Pharmacology & Therapeutics 203 (2019) 107394

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Roles of chitinase 3-like 1 in the development of cancer, neurodegenerative diseases, and inflammatory diseases

In Jun Yeo, Chong-Kil Lee, Sang-Bae Han, Jaesuk Yun *, Jin Tae Hong *

College of Pharmacy and Medical Research Center, Chungbuk National University, 194-31, Osongsaengmyeong 1-ro, Osong-eup, Cheongju-si, Chungbuk 28160, Republic of Korea

ARTICLE INFO

Available online 26 July 2019

Keywords:
Chitinase 3-like 1
Neurodegenerative diseases
Inflammatory disease
Cancer

ABSTRACT

Chitinase 3-like 1 (CHI3L1) is a secreted glycoprotein that mediates inflammation, macrophage polarization, apoptosis, and carcinogenesis. The expression of CHI3L1 is strongly increased by various inflammatory and immunological conditions, including rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, and several cancers. However, its physiological and pathophysiological roles in the development of cancer and neurodegenerative and inflammatory diseases remain unclear. Several studies have reported that CHI3L1 promotes cancer proliferation, inflammatory cytokine production, and microglial activation, and that multiple receptors, such as advanced glycation end product, syndecan-1/αVβ3, and IL-13Rα2, are involved. In addition, the pro-inflammatory action of CHI3L1 may be mediated via the protein kinase B and phosphoinositide-3 signaling pathways and responses to various pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, interleukin-6, and interferon-γ. Therefore, CHI3L1 could contribute to a vast array of inflammatory diseases. In this article, we review recent findings regarding the roles of CHI3L1 and suggest therapeutic approaches targeting CHI3L1 in the development of cancers, neurodegenerative diseases, and inflammatory diseases.

Contents

1. Introduction . . . 1
2. Chitinase-like proteins . . . 2
3. CHI3L1 and cancer . . . 4
4. CHI3L1 and neurodegenerative diseases . . . 8
5. CHI3L1 and inflammatory diseases . . . 11
6. Therapeutic approaches of CHI3L1 for treatment of diseases . . . 14
Acknowledgement . . . 15
References . . . 15

1. Introduction

CLPs, which are members of the glycoside hydrolase 18 gene family, are expressed by diverse species and play essential biological roles. CLPs bind to chitin by inducing conformational changes and are especially abundant in mammals, despite these species lacking endogenous chitin (Lee et al., 2011). CHI3L1, known as YKL-40 or BRP-39, is a CLP without chitinase enzymatic activity, for mutations in their active domains.

Abbreviations: AMCase, acidic mammalian chitinase; AD, Alzheimer's disease; Akt, protein kinase B; ALD, alcoholic liver disease; APP, amyloid precursor protein; Aβ, Amyloid beta; CHI3L1, Chitinase 3-like 1; CHID1, chitinase domain containing 1; CJD, Creutzfeldt-Jakob disease; CLPs, chitinase-like proteins; COPD, Chronic obstructive pulmonary disease; CXCL, chemokine (C-X-C motif) ligand; EC, endothelial cell; ERK, extracellular signal–regulated kinases; FAK, focal adhesion kinase; IFN-γ, interferon-γ; IL-13Rα2, interleukin-13 receptor α2 chain; IL-1β, interleukin-1β; IL-6, interleukin-6; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinases; MS, multiple sclerosis; NF-κB, nuclear transcription factor-kappa B; oviductin, OVGP1, oviductal glycoprotein 1; PI3K, phosphoinositide-3 kinae; PPARδ, peroxisome proliferator-activated receptor δ; P-tau, phosphorylated tau; RA, rheumatoid arthritis; RAGE, advanced glycation end product; STAT3, signal transducer and activator of transcription 3; TMEM219, transmembrane protein 219; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells.

* Corresponding authors.
E-mail addresses: jyun@chungbuk.ac.kr (J. Yun), jinthong@chungbuk.ac.kr (J.T. Hong).

https://doi.org/10.1016/j.pharmthera.2019.107394
0163-7258/

CHI3L1 is a heparin-, chitin-, and collagen-binding 40 kDa glycoprotein (Di Rosa, Tibullo, et al., 2016), and is expressed at high levels in numerous chronic inflammatory conditions (Low et al., 2015), where it acts as a lectin due to the presence of a preserved carbohydrate-binding domain. While a broad spectrum of cells are known to express CHI3L1, including macrophages, neutrophils, chondrocytes, synovial cells, osteoblasts, granulocytes, and vascular smooth muscle cells, the identity of its ligands has only recently began to be elucidated (Johansen et al., 1999; Kognole & Payne, 2017; Sanchez et al., 2018; Shao, 2013; Volck et al., 1998).

Recent studies have shown that CHI3L1 is associated with immune disease and cancer via regulation of various biologic processes, including oxidant injury response, apoptosis, Th1/Th2 inflammatory balance, and M2 macrophage differentiation (Chen, Zhang, Cao, & Zhang, 2018; Kim, Park, et al., 2018; Zhou et al., 2015). However, the exact role of CHI3L1 in inflammatory diseases remains controversial. Based on its ability to simultaneously decrease epithelial cell apoptosis while stimulating fibroproliferative repair, CHI3L1 is likely produced as a part of the protective response (Zhou et al., 2014).

Many studies have demonstrated that CHI3L1 mediates a number of pro-inflammatory effects. For example, CHI3L1 is strongly expressed by macrophages in inflammatory diseases such as rheumatoid arthritis, liver cirrhosis, diabetes, and asthma as well as in cases of tissue injury, as its secretion induces macrophage activation of inflammatory mediators (Di Rosa & Malaguarnera, 2016; Kumagai et al., 2016; Recklies, Ling, White, & Bernier, 2005; Tsai et al., 2014). Additionally, CHI3L1 has been shown to play a role in connective tissue cell growth, endothelial cell migration, and inhibition of mammary epithelial cell differentiation (Libreros, Garcia-Areas, & Iragavarapu-Charyulu, 2013).

CHI3L1 has the ability to bind to multiple receptors, inducing various cellular responses (He et al., 2013). Among these receptors, RAGE, syndecan-1/αVβ3, and IL-13Rα2 induce inflammasome activation, apoptosis, carcinogenesis, and tumor angiogenesis via binding to CHI3L1 (Subramaniam, Mizoguchi, & Mizoguchi, 2016). In previous studies, serum CHI3L1 levels were increased in various central nervous system diseases, including human immunodeficiency virus encephalitis, stroke, MS, traumatic brain injury, and glioblastoma, indicating that CHI3L1 could be involved in several neuroinflammatory diseases (Eurich, Segawa, Toei-Shimizu, & Mizoguchi, 2009; Hinsinger et al., 2015). Additionally, it has been shown that the expression of CHI3L1 can be regulated by various pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IFN-γ (Di Rosa & Malaguarnera, 2016).

Several inflammatory mediators, including monocyte chemoattractant protein-1 (MCP-1), are upregulated by CHI3L1 (Libreros & Iragavarapu-Charyulu, 2015). Conversely, CHI3L1 has also been shown to downregulate responses to inflammatory mediators, suggesting that it may be related to a feedback mechanism regulating inflammatory responses (Bohr et al., 2015). Therefore, CHI3L1 may play a role as an acute-phase reactant related to disease severity and mortality in various infections. Although several studies on CHI3L1 have been published, a systematic review of the various features and functions of the protein is lacking. In this review article, we discuss recent findings relating to CHI3L1's roles in the development of several diseases as well as therapeutic approaches.

2. Chitinase-like proteins

2.1. Members of Chitinase-like proteins

A systemic literature search identified 44 members of the mammalian chitinase protein family (Bussink, Speijer, Aerts, & Boot, 2007). Based on sequence homology, chitinases can be classified into two groups, namely families 18 and 19 of the glycoside hydrolases (Henrissat, 1991). Chitinases in which a substrate-assisted reaction mechanism is conserved belong to the glycoside hydrolase 18 gene family (Terwisscha Van Scheltinga et al., 1995; van Aalten et al., 2001), while gene family 19 members possess a fold-and-reaction mechanism similar to that of lysozyme (Bussink et al., 2007). This indicates that the evolution of genes occurs independently in each of these gene families.

A chitinolytic enzyme, chitotriosidase, was identified from the plasma of symptomatic patients with Gaucher disease, one of the most common lysosomal storage disorders, and shown to have a true chitinase activity. Moreover, another type of mammalian chitinase, the acidic mammalian chitinase (AMCase) family, was discovered, and the association between mammalian chitinase and susceptibility to fungal infection and pathophysiology of asthma has been reported.

Interestingly, chitinases lacking enzymatic activity have also been identified. These proteins are referred to as CLPs, and are homologous to active chitinase, have carbohydrate binding sites, and act as lectins. CLPs belong to family 18 of the glycoside hydrolases, and contain a triose-phosphate isomerase-barrel structure, one of the most versatile folds in nature, but lack the six cysteine residues responsible for true 'chitinases' ability to bind to chitin (Boot et al., 2001; Boot, Renkema, Strijland, van Zonneveld, & Aerts, 1995; Renkema et al., 1997). Among CLPs, CHI3L1 and OVGP1 are expressed in 11 mammals, while BP40 is specific for the artiodactyls. Other CLPs, such as CHI3L2, CHI3L3, CHI3L4, and brain chitinase-like protein 2, exist in specific species like primates and rodents.

2.2. General functions of Chitinase-like proteins

CLPs including CHI3L1 are expressed in extracellular matrix and secreted in response to immune activation (Catalan et al., 2016; Kzhyshkowska, Yin, Liu, Riabov, & Mitrofanova, 2016; Renkema et al., 1998; Sutherland, Maizels, & Allen, 2009). In this regard, these proteins may have a role in cancer development, tissue remodeling, and inflammatory conditions such as neurodegenerative diseases. For example, CLPs mediate T-helper 2 type inflammatory response (Lee et al., 2011), which is known to induce M2 macrophage activation. In addition, CHI3L4 (Ym2) mediates T-helper 2 type immune response (Muallem & Hunter, 2014). Polarization to M2 macrophages induces angiogenesis and this may exacerbate cancer development (Riabov et al., 2014). Furthermore, CHI3L1 also induces epithelial–mesenchymal transition, which is associated with cancer (Hao et al., 2017; Jefri, Huang, Huang, Tai, & Chen, 2015). Excessive expression of other CLPs such as OVGP1 is associated with ovarian cancers (Maines-Bandiera et al., 2010). These results suggest that CLPs may contribute to the development of cancers.

In addition, we also assume that CHI3L1 plays a critical role in tissue remodeling and regulation of immune response. CHI3L1 mediates tissue regenerative process and induces a balance between tissue remodeling and pathology (Sutherland, 2018). CHI3L1 also regulates liver fibrosis and contributes to fatty liver diseases such as non-alcoholic steatohepatitis (NASH) (Johansen et al., 1997; Johansen et al., 2000; Malaguarnera et al., 2006). TGF-β may mediate tissue remodeling induced by CHI3L1 at least in part (Lee et al., 2011). This tissue remodeling is not only induced by CHI3L1 but also CHI3L3 (Starossom et al., 2019). Additionally, immune responses of CHI3L2 are similar to those of CHI3L1. CHI3L2 also has a tissue remodeling function, because cartilage biogenesis and collagen expression are increased by this protein (Miyatake et al., 2013). These results suggest that CLPs are associated with tissue remodeling.

Another core function of CLPs is related to pathological processes in neurodegenerative diseases. Neurodegenerative diseases are highly related to inflammatory processes in the brain. We reported that CHI3L1 has an important role in Alzheimer's disease, which is mediated by NF-kB or STAT3 inhibition (Choi et al., 2018). The other CLPs including CHID1 also have pro-inflammatory functions. However, controversial results have been reported regarding the protective effects of CLPs during inflammation (Sutherland, 2018). Otherwise, CLPs are extensively expressed under chronic inflammatory conditions (Lee et al., 2011). This overexpression of CLPs may be responsible for the pathological

processes in various diseases. Therefore, we assume that CLPs may contribute to chronic neuroinflammation in neurodegenerative diseases.

We further analyzed gene-gene interactions of CLPs using a web-based prediction tool (https://genemania.org) (Warde-Farley et al., 2010). Among CLPs, CHI3L1, CHI3L2, CHID1, and OVGP1 are available in the web-based tool (Fig. 1). We identified 16 genes that are highly associated with CLPs (Table 1). Expectedly, several oncogenes such as ETS proto-oncogene 1, transcription factor, upstream transcription factor 1, and Spi-1 proto-oncogene were predicted as CLP-related genes. ETS proto-oncogene 1, transcription factor can induce angiogenesis in breast cancer (Furlan et al., 2019). Upstream transcription factor 1 regulates several cancers such as thyroid cancer and hepatocellular carcinoma (Yuan et al., 2016; Zhao et al., 2015). Spi-1 proto-oncogene is associated with cancers such as lymphoma (Goto et al., 2017; Seki et al., 2017). The gene-gene interaction network also showed that progesterone receptor is associated with CLPs. Progesterone receptor levels are negatively correlated with the expression of CHI3L1 in breast cancer (Kim, Das, Noreen, Coffman, & Hameed, 2007). OVGP1 and progesterone receptor interaction may have a role in ovarian cancer (Wang, Mavrogianis, & Fazleabas, 2009). The other cancer-related genes such as GALC, SP3, PAFAH1B1, RASA4, CD55, and RGS10 are predicted to interact with CLPs (Bivona et al., 2003; Cao et al., 2017; Essafi-Benkhadir et al.,

Table 1
CLP-related genes.

Gene	Description
PGR	progesterone receptor
CHIA	chitinase, acidic
CHIT1	chitinase 1
CTBS	chitobiase
ETS1	ETS proto-oncogene 1, transcription factor
SPI1	Spi-1 proto-oncogene
USF1	upstream transcription factor 1
GAA	glucosidase alpha, acid
SP3	Sp3 transcription factor
PAFAH1B1	platelet activating factor acetylhydrolase 1b regulatory subunit 1
MAN2B1	mannosidase alpha class 2B member 1
RASA4	RAS p21 protein activator 4
IDO1	indoleamine 2,3-dioxygenase 1
GALC	galactosylceramidase
MTRF1L	mitochondrial translational release factor 1 like
CD55	CD55 molecule (Cromer blood group)
CR2	complement component 3d receptor 2
UBE2W	ubiquitin conjugating enzyme E2 W (putative)
BRE	brain and reproductive organ-expressed (TNFRSF1A modulator)
RGS10	regulator of G-protein signaling 10

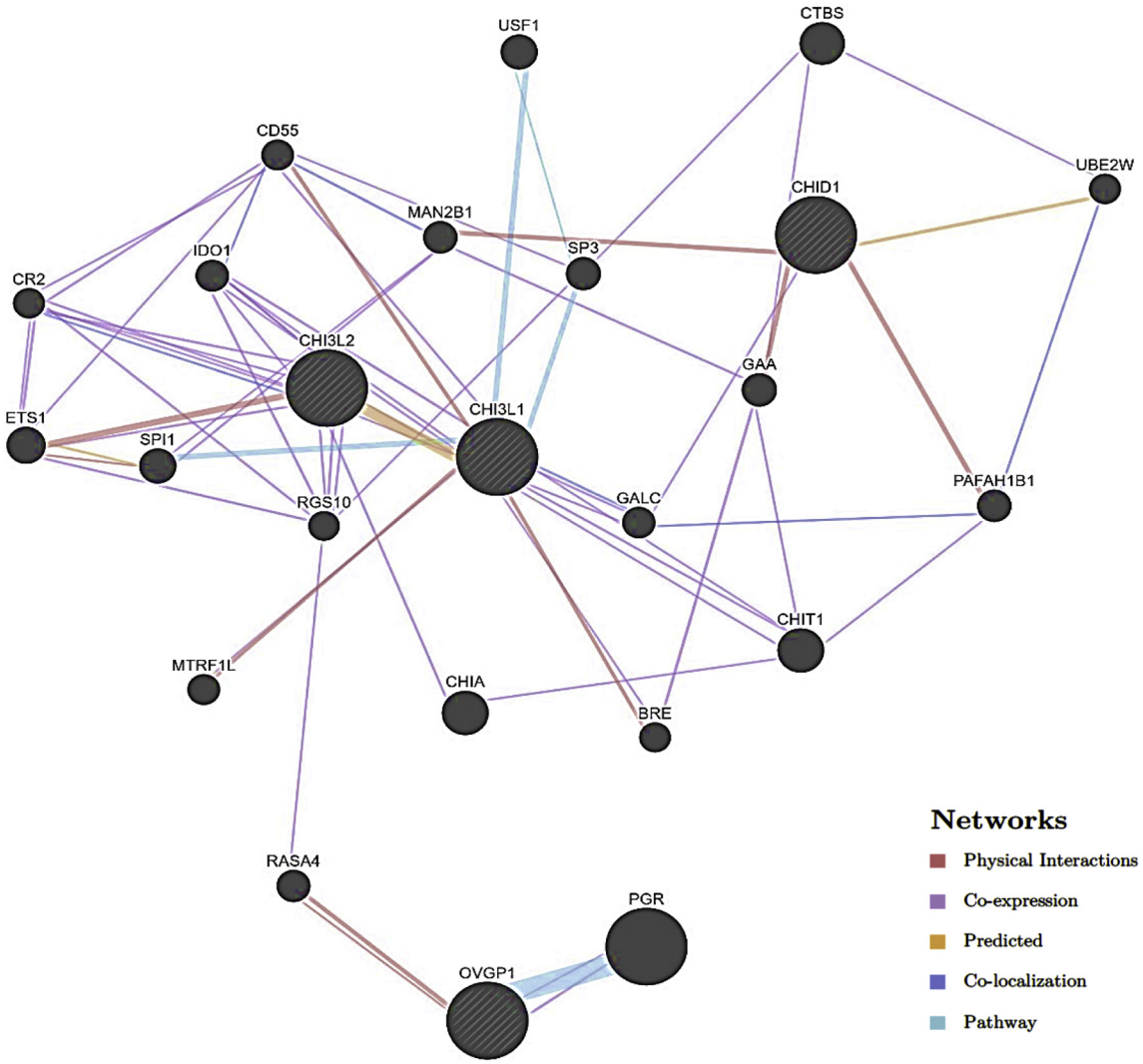

Fig. 1. Gene interaction network of CLP-related genes (see also Table 1). The gene-gene interaction network was generated by GeneMANIA (Warde-Farley et al., 2010). Color of lines represents the type of interaction in the network (right panel); physical interaction (pink), co-expression (purple), predicted (orange), co-localization (blue) and pathway (cyan). Sixteen genes are predicted to interact with CLPs.

2009; Hooks et al., 2010; Hooks & Murph, 2015; Liu, Xue, Li, Yang, & Peng, 2018; Zhang et al., 2017).

These gene-gene interactions may contribute to the regulation of immune response and tissue remodeling. Chitinase has a critical role in allergic inflammation process and tissue remodeling (Lee et al., 2011). Chitinase1 is released by activated macrophage and triggers tissue remodeling such as fibrosis (Kanneganti, Kamba, & Mizoguchi, 2012). IDO1, another CLP-related gene, is also related to immune response and T cell regulation (Spekker-Bosker et al., 2019). It inhibits structural vascular remodeling in the lungs (Xiao et al., 2013).

In addition, other CLP-related genes including MAN2B, MTRF1L1, CR2, and BRE are associated with the development of the nervous system and neurodegenerative diseases (Jang, Lee, Kim, & Ki, 2015; Michailidou et al., 2017; Pacitti & Bax, 2018; Wang, Li, et al., 2015). Spi-1 proto-oncogene also regulates neurodegenerative diseases such as Alzheimer's disease (Rustenhoven et al., 2018) by modulation of neuroinflammatory responses.

Regarding the possible core function of the 4 CLPs (CHI3L1, CHI3L2, CHID1, and OVGP1), we suggest that these genes have a critical role in tissue remodeling, cancer development, and neurodegeneration. Accordingly, we concentrated their functions.

Four CLPs have been identified in humans: CHI3L1, CHI3L2, oviductal glycoprotein 1 (oviductin, OVGP1), and chitinase domain containing 1 (CHID1) or SI-CLP. Unlike chitotriosidase and AMCase, CLPs do not contain the conserved additional chitin binding domain in which glutamic acid residue is substituted with tryptophan, leucine, or isoleucine (Fusetti, Pijning, Kalk, Bos, & Dijkstra, 2003; Hakala, White, & Recklies, 1993; Kzhyshkowska et al., 2016). These molecules have no ability to cleave chitin but are able to bind to it with high affinity. Chitin is a component of the cell walls of fungi, and activates innate immunity; however, the action of CLPs may not be limited to immune responses to fungal infection.

CHI3L1 is a 40 kDa mammalian glycoprotein and is also known as YKL-40 based on its three N-terminal amino acids namely tyrosine (Y), lysine (K), and leucine (L). Recently, several studies have revealed that CHI3L1 is a useful biomarker for various inflammatory diseases; however, its physiological role has not yet been fully elucidated. What is known is that CHI3L1 has regulatory activity on cell proliferation, adhesion, migration, and activation. Various cells, such as neutrophils, monocytes/macrophages, and osteoclasts, secrete CHI3L1 (Di Rosa, Szychlinska, Tibullo, Malaguarnera, & Musumeci, 2014), and the migration of macrophages and bronchial smooth muscle cells has been found to be associated with its expression (Libreros et al., 2012). Furthermore, CHI3L1 activates macrophages against infection by bacterial pathogens such as *S. pneumoniae*, and may have pathogen-specific affinity (Di Rosa, Distefano, Zorena, & Malaguarnera, 2016). CHI3L1 also regulates wide-ranging functions in immunity and extracellular matrix assembly in chronic inflammations and cancer. These functions may be mediated via interaction with several receptors, including RAGE, syndecan-1/αVβ3, and IL-13Rα2a.

Unlike CHI3L1, CHI3L2 (YKL-39) is not a glycoprotein, but is highly homologous to CHI3L1 in amino acid sequence (51%) (Di Rosa, Distefano et al., 2016) and has lectin properties (Schimpl et al., 2012). However, whether it displays chitinase activity remains controversial (Knorr, Obermayr, Bartnik, Zien, & Aigner, 2003; Schimpl et al., 2012). Human cartilage chondrocytes are known to secrete CHI3L2 during cartilage biogenesis. Furthermore, this protein enhances proliferation and type II collagen expression (Miyatake et al., 2013), acts as a growth factor, and induces differentiation. CHI3L2 is also associated with immune-response and inflammation in a manner similar to CHI3L1 (Lee et al., 2011).

OVGP1 is an estrogen-regulated carbohydrate-rich glycoprotein secreted from oviductal epithelial cells (McBride, Boisvert, Bleau, & Kan, 2004). It contains threonine-, serine-, and proline-rich tandem repeats with O-glycosylation sites. OVGP1 plays a supportive role in fertilization and embryo development. Furthermore, it binds to human sperm via myosin heavy chain 9 (Kadam, D'Souza, Bandivdekar, & Natraj, 2006). OVGP1 is also associated with ovarian cancers and mucinous carcinomas (Maines-Bandiera et al., 2010).

CHID1 is a recently identified saccharide-binding protein that is reported to be a ligand for the multifunctional receptor stabilin-1. A variety of tissues express CHID1, and its expression is induced by activated macrophages in inflammatory diseases such as rheumatoid arthritis. Furthermore, in human macrophages, IL-4 and dexamethasone have been found to increase CHID1 expression, while IFN-γ diminishes its upregulated expression (Kzhyshkowska, Gratchev, & Goerdt, 2007). Interestingly, dexamethasone-induced expression is found only in CHID1, and not in other CLPs. The findings described above indicate that CLPs may differ in terms of the mechanisms regulating their expression.

Of the human CLPs, CHI3L1 shows responses to pro-inflammatory cytokines and displays binding capacities for several receptors that are associated with various inflammatory diseases and cancer. The general properties of CLPs are summarized in Table 2, and their roles are illustrated in Fig. 2.

2.3. Regulation of CHI3L1 expression

A mechanism underlying the regulation of transcription or release of CHI3L1 is not fully known yet; however, the general regulatory pathway of CHI3L1 expression is presented in Fig. 3. A variety of diseases are associated with increased expression levels of CHI3L1 in patients (Table 3).

A number of mediators, including IL-13, IL-6, IL-1β, and IFN-γ, have been reported to regulate CHI3L1 expression in cells such as macrophages, osteoclasts, Kupffer cells, epithelial cells, and chondrocytes. Recently, STAT3 and RelB/p50 complexes were proposed to play an important role in cytokine-induced CHI3L1 expression. However, the underlying mechanism remains largely unknown (Bhardwaj et al., 2015; Kim, Park, et al., 2018). The CHI3L1 promoter sequence contains binding sites for PU.1, Sp1, Sp3, USF, AML-1, and C/EBP proteins. Among these transcription factors, Sp1 was identified as having a critical role in transcriptional regulation of CHI3L1 for macrophage differentiation. CHI3L1 expression is also regulated by miRNAs such as miR-24 and miR-449a in aortic vascular inflammation, osteomyelitis, and hepatitis (Deng et al., 2017; Jin et al., 2015; Maegdefessel et al., 2014; Sarma et al., 2012). Recently, we reported that miR-342-3p regulates CHI3L1 expression in vascular inflammation and atherosclerosis (Jung, Park, et al., 2018). Semaphorin 7a and β-1 integrin have been found to regulate the expression of CHI3L1 in pulmonary melanoma metastasis (Ma et al., 2015). In addition, RIG-like helicase regulation has an inhibitory role in CHI3L1 expression via Semaphorin 7a and β-1 integrin. Interestingly, miRNA-449a decreased the expression of IL-6 receptor in osteosarcoma (Deng et al., 2018).

These findings indicate that the expression of CHI3L1 is regulated by inflammation and immune response mediators in cancer and inflammatory diseases. However, CHI3L1 can also regulate the transcription levels of IL-6, IL-8, IL-12, IFN-γ, TNF-α, CXCL9, CXCL11, and IL-18, consequently modulating immunity and tissue repair in various diseases (Dela Cruz et al., 2012; Kawada et al., 2012; Li, Liu, et al., 2017; Li, Lu, et al., 2017; Libreros et al., 2012; Marion et al., 2016).

3. CHI3L1 and cancer

The high expression level of CHI3L1 is accompanied by poor prognosis in cancer. Several studies have suggested that CHI3L1 may be a new biomarker for several cancers, including glioblastoma, osteosarcoma, colorectal cancer, lung adenocarcinoma, breast cancer, and cervical cancer (Fuksiewicz et al., 2018; Mitsuhashi et al., 2009; Rusak et al., 2018; Steponaitis et al., 2016; Thorn et al., 2016; Yan et al., 2013). The tumor microenvironment including blood vessels, immune cells, fibroblasts, endothelial cell, cytokines, growth factor, signaling molecules, and extracellular matrix contributes to relapse and metastasis. In cancer cells,

Table 2
Properties of CLP isoforms.

	CHI3L1	CHI3L2	OVGP1	CHID1
Glycoprotein	Yes	No	Yes	Yes
Expressed sites	Various cells including neutrophils, monocytes/macrophages, and osteoclasts	Human cartilage chondrocytes	Oviductal epithelial cell	Macrophages and neutrophils
Function	Regulation of cell proliferation, adhesion, migration, and activation Activation of macrophages Regulation of immune-response in inflammation and cancer	Cartilage biogenesis Type II collagen expression Similar to CHI3L1 in immune-response	Supportive role in fertilization and embryo development	A ligand for the multifunctional receptor stabilin-1
Dexamethasone-induced expression	No	No	No	Yes
Associated disease	Various inflammatory diseases and cancers	Similar to CHI3L1 in immune and inflammatory disease	Ovarian cancers, mucinous carcinomas	Inflammatory diseases (Rheumatoid arthritis)

altered environmental conditions and cellular morphologies often involve tumor growth and resistance to chemotherapy. Increased microvessel density, reactive oxygen species, type 2 immunity, and vascular endothelial growth factor (VEGF) in cancer cells may promote tumor development and progression. As CHI3L1 has a role in a wide variety of functions related to immunity, inflammation, and extracellular matrix assembly, it can regulate microenvironmental conditions that are associated with tumor growth, metastasis, and response to therapy.

3.1. Roles of CHI3L1 in cancer development

Changes in the expression of CHI3L1 have been associated with diagnosis of cancer; however, the roles it plays have not been extensively studied. Although the relationship between CHI3L1 and poor prognosis remains controversial (Erturk, Tas, Serilmez, Bilgin, & Yasasever, 2017; Xu, Yu, et al., 2014), several studies have suggested that increased CHI3L1 expression promotes metastasis and progression of cancer.

Immune response and cytokines may mediate the regulatory activity of CHI3L1 on cancer development. A recent study showed that decreased expression of CHI3L1 in T cells inhibits lung metastasis via activation of the Th1 response, and by increasing IFN-γ, TNF-α, and IL-2 levels (Kim, Park, et al., 2018). In gastric and breast cancer, M2 macrophage-secreted CHI3L1 can activate interleukin-13 receptor α2 chain (IL-13Rα2) and stimulate the MAPK signaling pathway, resulting in the expression of metalloproteinase genes associated with cancer progression (Chen, Zhang, Wang, & Zhang, 2017).

Other studies suggest that the CHI3L1-associated signal pathway is associated with cancer development. In cholangiocarcinoma cell lines, CHI3L1 promotes tumor growth and migration via the Akt/Erk-mediated pathway (Thongsom et al., 2016). Knock-down of CHI3L1 reduced invasion and migration of prostate cancer, while overexpression increased the anchorage-independent growth of cells, and induced more invasion and migration (Jeet, Tevz, Lehman, Hollier, & Nelson, 2014). Oxidative stress is another possible mechanism underlying CHI3L1-related cancer progression. CHI3L1 may contribute to colitis-associated carcinoma by increasing reactive oxygen species and oxidative DNA damage (Ma et al., 2014).

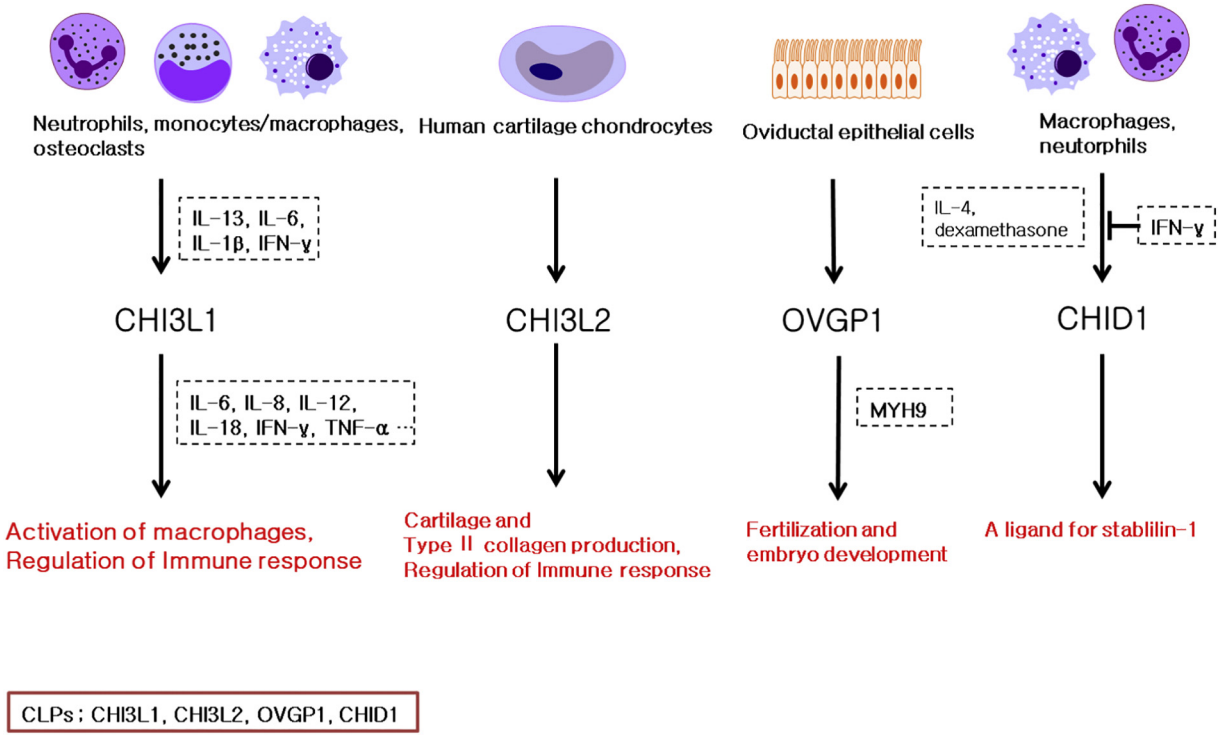

Fig. 2. The roles of CLPs. Four CLPs have been identified in humans. Various cells, such as neutrophils, monocytes/macrophages, cartilage chondrocytes, and epithelial cells produce CLPs (see also Table 2). Several interleukins such as IL-13, IL-6, and IL-1β stimulate CHI3L1 production, while IFN-γ inhibits CHID1 expression. CHI3L1 regulates immune responses via the regulation of actions of cytokines including IL-6, IL-8, IL-12, IL-18, IFN-γ, and TNF-α. CHI3L2 is also associated with immune-response and inflammation in a manner similar to that of CHI3L1. OVGP1 binds to myosin heavy chain 9 and has a supportive role in fertilization and embryo development. CHID1 is a ligand for the multifunctional receptor stabilin-1.

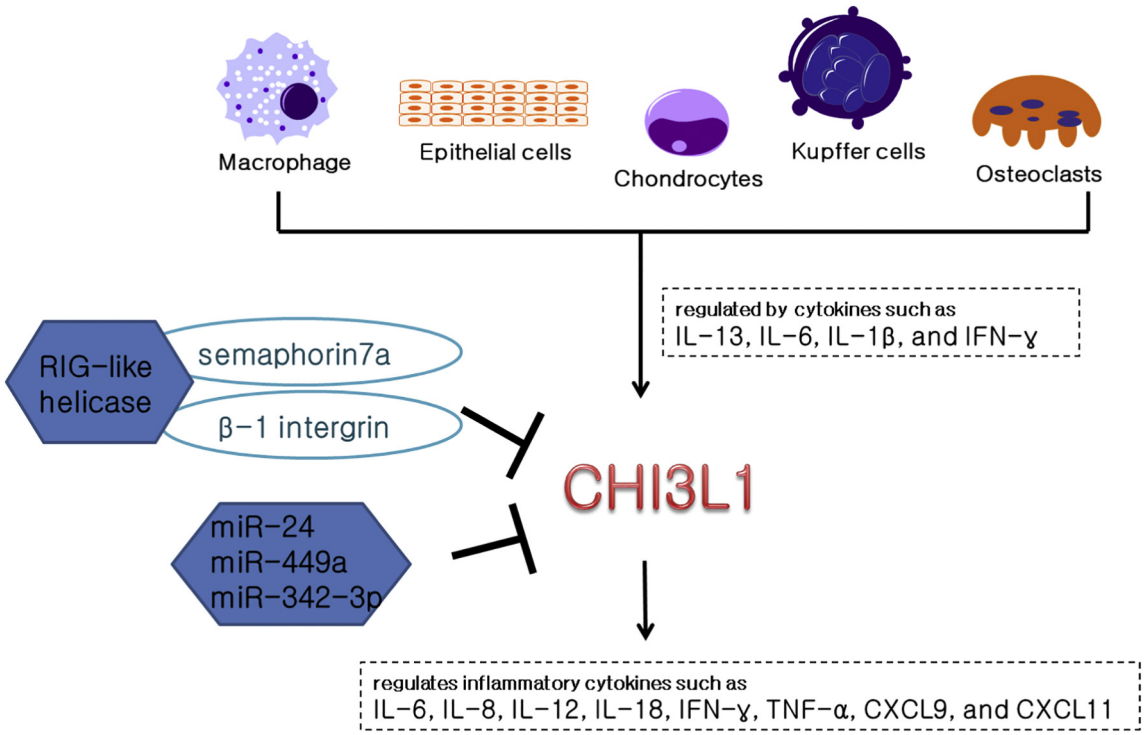

Fig. 3. General regulatory pathways of CHI3L1 expression. Increased expression of CHI3L1 is observed in patients with various cancers, immunological diseases, and neurodegenerative diseases. A number of mediators, including IL-13, IL-6, IL-1β, and IFN-γ induce CHI3L1 expression in cells such as macrophages, osteoclasts, Kupffer cells, epithelial cells, and chondrocytes. RIG-like helicase inhibits CHI3L1 expression via Semaphorin 7a and β-1 integrin. CHI3L1 expression is also regulated by miRNAs such as miR-342-3p. CHI3L1 can also increase the transcription levels of IL-6, IL-8, IL-12, IFN-γ, TNF-α, CXCL9, CXCL11, and IL-18,

A collection of studies have suggested a possible role of CHI3L1 in cancer development and progression. One recent study showed that CHI3L1 derived from cancer-associated fibroblasts mediates breast cancer growth and metastasis (Cohen et al., 2017). In addition, decreased expression of CHI3L1 resulted in tumor suppression in endometrial cancer cells (Libreros et al., 2013). Creation of an immunosuppressive microenvironment is also suggested as a possible mechanism of CHI3L1-induced cancer promotion. Especially, CHI3L1 mediates tumor progression and metastasis via the regulation of type 2 immunity, including macrophage recruitment and reprogramming to an M2-like phenotype (Cohen et al., 2017). Mutant CHI3L1 expression decreased development and vessel formation in breast cancer cells (Ngernyuang, Shao, Suwannarurk, & Limpaiboon, 2018). Furthermore, VEGF may have a synergistic effect with CHI3L1 on endothelial cell angiogenesis and tumor malignancy in human glioblastoma (Francescone et al., 2011), and CHI3L1 expression was followed by VEGF production in osteosarcoma cells (Salvatore et al., 2017). CHI3L1 has also been found to induce angiogenesis and the formation of vasculogenic mimicry in cervical cancer patients (Ngernyuang et al., 2018). These results suggest that CHI3L1 has a promotive role in angiogenesis and the regulation of the cell microenvironment in cancer.

Furthermore, in circulating tumor cells from patients with extensive small cell lung cancer, CHI3L1 was expressed and mediated invasion and tumor progression via the regulation of macrophages and inflammation (Hamilton & Rath, 2017). It is also reported that CHI3L1 is associated with disease risk and poor survival, and demonstrated a pathophysiological role in disease initiation and drug resistance in multiple myeloma patients (Nielsen et al., 2017). In gliomas, anisomycin-induced decreases in CHI3L1 expression are associated with the attenuation of aggressive features of cancer (Heiland et al., 2017). In addition, STAT3 inhibitor inhibited the glioblastoma cell line through regulation of CHI3L1 expression (Miyata et al., 2017). The relationship between cancer development and CHI3L1 is summarized in Table 4.

3.2. Expression of CHI3L1 in human cancer patients

Increased expression of CHI3L1 has commonly been observed in the tissues or plasma of patients with various types of cancer, and is, for example, significantly upregulated in non-small cell lung cancer tissue (Wang, Cai, et al., 2015). It has therefore been suggested as a poor prognostic marker. In human glioblastoma samples, elevated expression of CHI3L1 was reported in glioblastoma patients with poorer rates of survival (Francescone et al., 2011). A recent study showed that 58% of subventricular zone type II glioblastomas (45 out of 77 samples) expressed CHI3L1 (Batista et al., 2016). However, another study suggested that CHI3L1-expressed glioblastoma multiforme is linked to subventricular zone types IV and V (Pina Batista et al., 2015). In addition, CHI3L1 was expressed at high levels in human astrocytoma as well as in glioblastoma tissues (Steponaitis et al., 2016). CHI3L1 was highly expressed in human papillary thyroid carcinoma tissues, and was associated with tumor size, lymph node metastasis, and invasion (Luo et al., 2017). It is also associated with poor prognosis in melanoma patients. Interestingly, tumor-associated macrophages expressed CHI3L1 at significantly higher levels than melanoma cells, and may induce high serum levels of CHI3L1 in melanoma patients (Krogh et al., 2016). Elevated serum CHI3L1 correlated with short survival in cholangiocarcinoma, but the cancer cells themselves expressed low levels of CHI3L1 (Thongsom et al., 2016). CHI3L1 seems to be expressed in early endometrial cancer, and is suggested as a prognostic marker in detection of high risk patients (Kemik et al., 2016). CHI3L1 in the colon is detectable during colorectal cancer; however it is rare in the colons of healthy individuals (Chen et al., 2011; Petersson, Bucht, Granberg, & Stark, 2006). Serum CHI3L1 was higher in subjects at risk of colorectal cancer, and was suggested as a biomarker to predict colorectal cancer (Johansen et al., 2015).

Contrary to what was reported in the previously mentioned studies, in one study, a high CHI3L1 tumor cell/matrix ratio was found to be

Table 3
Summary of diseases associated with increased CHI3L1 levels.

Pathological conditions	Diseases type	References
Inflammatory conditions	Pneumonia, rheumatoid arthritis, Kawasaki disease, asthma, COPD, coronary artery disease, periodontitis, diabetes, cellulitis, intracerebral hemorrhage, psoriasis, obesity-associated inflammation, Behcet's disease, hepatic fibrosis, acute kidney injury, and atopic dermatitis	(Baran et al., 2018; Bilen, Altinkaynak, Sebin, Aksoy, & Akcay, 2016; Erturk et al., 2015; Hall, Stern, Cantley, Elias, & Parikh, 2014; Harvey, Whaley, & Eberhardt, 2000; Jiang, Zhang, Wang, & Yang, 2014; Kido et al., 2015; Kim, Ahn, Kim, Kim, & Kim, 2017; Kunz et al., 2015; Mathiasen et al., 2011; Salomon, Matusiak, Nowicka-Suszko, & Szepietowski, 2017; Thomsen et al., 2015; Usemann et al., 2016; Wang, Hsiao, Tsai, Yeh, & Yang, 2013; Zheng, Cai, Zhao, Zhu, & Liu, 2005).
Cancers	Breast cancer, colon cancer, epithelial ovarian carcinoma, uterine leiomyomas, hepatocellular carcinoma, lung cancer, squamous cell carcinoma of the head and neck, anal carcinoma, papillary thyroid carcinoma, gastric cancer, osteosarcoma, cholangiocarcinoma, astrocytoma, multiple myeloma, renal cell carcinoma, colitis-associated carcinoma, prostate cancer, uterine cervical cancer, glial tumors, and pancreatic cancer	(Catalan et al., 2016; Chen, Zhang, et al., 2017; Guo, Wang, & Wei, 2016; Joob, Wiwanitkit, & Tin, 2015; Kazakova et al., 2014; Luo et al., 2017; Ma et al., 2014; Mitsuhashi et al., 2009; Mylin et al., 2015; Ozdemir, Cicek, & Kaya, 2012; Roslind et al., 2008; Schultz et al., 2013; Shao et al., 2011; Stawerski, Wagrowska-Danilewicz, Stasikowska-Kanicka, & Danilewicz, 2011; Thongsom et al., 2016; Thorn, Daugaard, Christensen, Christensen, & Petersen, 2016; Vaananen, Kallio, et al., 2017; Yang, Yang, Tao, & Jin, 2014; Zhang et al., 2010; Zhu et al., 2012)
Immunological diseases, neuropsychological disorders, and neurodegenerative diseases	Acute graft-versus-host disease, suicidal ideation, depression, schizophrenia, and Alzheimer's disease	(Chung, Tallerico, & Seeman, 2003; Johansson et al., 2017; Morup et al., 2011; Rymo et al., 2017; Wennstrom et al., 2015).

positively correlated with longer overall survival in human osteosarcoma patients (Thorn et al., 2016). Furthermore, it was reported that serological CHI3L1 was not significantly associated with risk of subsequent primary cancer (Hvolris et al., 2016). Further research on CHI3L1 expression in serum or immune cell-related microenvironments is required. These results suggest that the expression of CHI3L1 varies in tumor cells and microenvironments, and its presence depends on the stage of the cancer.

3.3. Signaling pathway of CHI3L1 in the development of cancer

The roles of CHI3L1 in signaling pathways for the development of cancers is illustrated in Fig. 4. CHI3L1 is associated with several signal pathways in the process of cancer development. CHI3L1 plays a regulatory role in cancer microenvironment and immune-responses. Therefore, several studies investigating the signaling pathway of CHI3L1 in immune cells have been conducted recently. One such study revealed that CHI3L1 was expressed at significant levels in Th2 cells, and that it modulated cytokine production, including that of IL-2, IFN-γ, and IL-4 (Kim, Park, et al., 2018). A basic helix-loop-helix family member, Twist1, was proposed as a target molecule of CHI3L1 in T cells. CHI3L1 deficiency upregulated IFN-γ signaling mediated by decreased Twist1 expression. These results suggest that IFN-γ signaling may play an important role in antitumor activity in CHI3L1 knock-out T cells.

Angiogenesis is a possible result of cancer progression associated with CHI3L1. CHI3L1 elevated both VEGF and angiogenesis through FAK^{397} and ERK-1/ERK-2 activity (Francescone et al., 2011). Especially, membrane receptors syndecan-1 and integrin αvβ5 were identified as trigger molecules in CHI3L1 signaling cascades. CHI3L1 binds to RAGE and induces proliferation of cancer cells, with the ERK1/2-MAPK pathway playing a role in the RAGE-CHI3L1 downstream signal cascade. Furthermore, CHI3L1 is able to increase the expression levels of MMP9, CCL2, and CXCL2 via syndecan-1 (Kzhyshkowska et al., 2016).

Interestingly, CHI3L1 expression in mice is directly associated with increased vulnerability to infection by microbes such as *Salmonella* and *Escherichia coli*, as it enhances bacterial adhesion and invasion. Bacterial/epithelial interaction may play a role in the increased susceptibility to carcinogenesis and tumor cell expansion in Japanese mice (*Mus musculus molossinus)* (Low et al., 2013). One mechanism underlying CHI3L1's effect in bacterial infection is the binding of microbes to the N-glycosylated asparagine of CHI3L1 (Low et al., 2013). Furthermore, microbe-released factors can promote tumor cell expansion (Bhatt, Redinbo, & Bultman, 2017). Therefore, further investigation of intestinal microbiota and CHI3L1 interaction is required to elucidate the mechanism of CHI3L1 during the development of colorectal cancer.

Malignant glioblastomas are brain tumors closely associated with CHI3L1. Tumor angiogenesis plays an important role in glioblastoma prognosis. Vascular endothelial cells can sprout and mediate the process of tumor angiogenesis. VEGF is an angiogenic factor capable of enhancing glioblastoma vascularization. CHI3L1 has been found to directly induce VEGF and VEGF receptor 2 expression in glioblastoma-derived cell line U87 and endothelial cells, respectively (Faibish, Francescone, Bentley, Yan, & Shao, 2011; Francescone et al., 2011). In endothelial cells, the membrane-bound protein syndecan-1 is suggested as a receptor mediating CHI3L1-induced angiogenesis. Syndecan-1 is a cellular surface heparan sulfate that binds to CHI3L1 by means of an adjacent membrane-associated protein, integrin αvβ3. This coupling facilitates a signaling pathway of FAK^{861} to MAP kinase ERK 1 and 2, consequently activating angiogenesis in endothelial cells (Kawada et al., 2012). Activation of the FAK^{861} signaling pathway also promotes VEGF expression.

Furthermore, CHI3L1 is able to induce activation of the PI_3K-AKT pathway in U87 cells (Faibish et al., 2011; Francescone et al., 2011)

Table 4
Summary of the relationship between CHI3L1 and cancer development.

Cancer type	Results	Mechanisms	Reference
Gastric and breast cancer	Expression of metalloproteinase genes	Activation of IL-13Rα2 and stimulation of MAPK signaling pathway	(Chen, Zhang, et al., 2017)
Cholangiocarcinoma	Promotion of tumor growth and migration	Akt/Erk-mediated pathway	(Thongsom et al., 2016)
Breast cancer	Tumor progression and metastasis	Type 2 immunity such as macrophage recruitment and reprogramming to an M2-like phenotype	(Cohen et al., 2017)
Glioblastoma, Osteosarcoma	Endothelial cell angiogenesis and tumor malignancy Growth of glioblastoma cell line	VEGF production STAT3 pathway	(Francescone et al., 2011) (Salvatore et al., 2017) (Miyata et al., 2017)
Small cell lung cancer	Invasion and tumor progression	Regulation of macrophages and inflammation	(Hamilton & Rath, 2017)

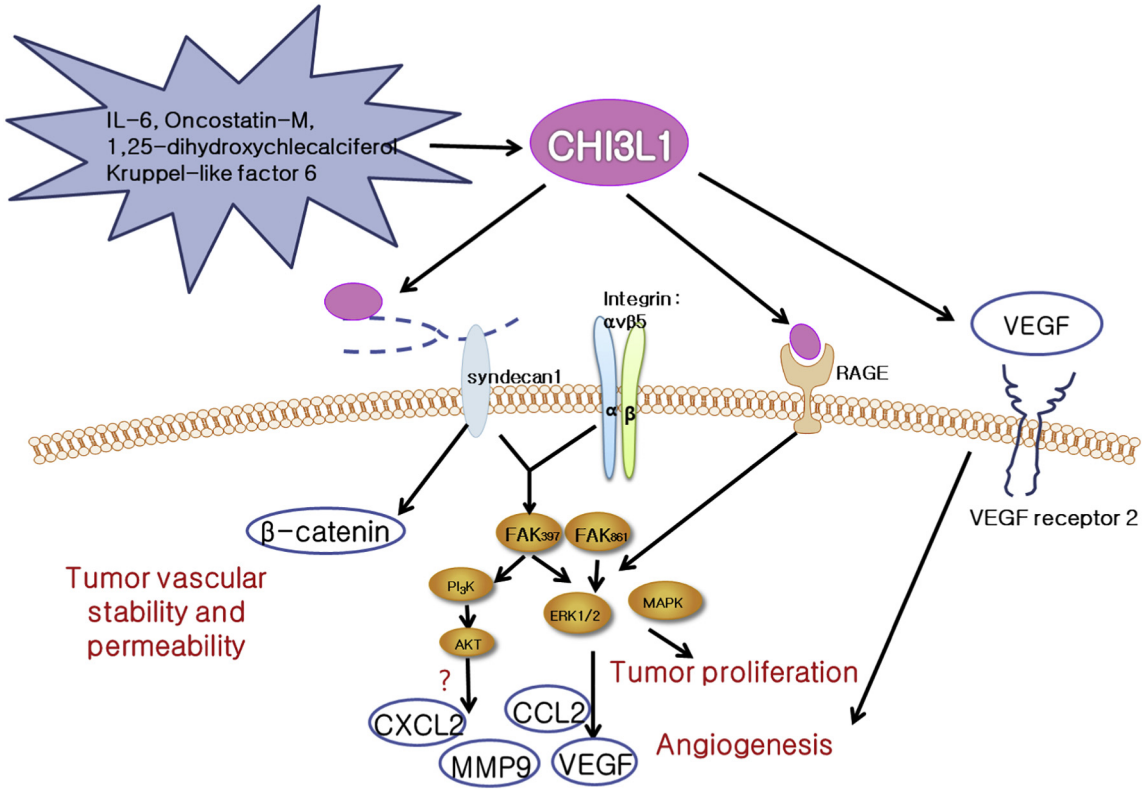

Fig. 4. The roles of CHI3L1 in signaling pathways for the development of cancers. Cytokines, transcription factors, and active vitamin D3 metabolite increase CHI3L1 expression in various cancer cells. The membrane receptors syndecan-1 and integrin αvβ5 trigger CHI3L1 signaling cascades and elevate both VEGF and angiogenesis through FAK^{397} and ERK-1/ERK-2 activity. CHI3L1 also directly induces VEGF and VEGF receptor 2 expression. CHI3L1 binds to RAGE and induces proliferation of cancer cells with the ERK1/2-MAPK pathway. Furthermore, CHI3L1 is able to activate β-catenin and increase the expression levels of MMP9, CCL2, and CXCL2 via syndecan-1.

and is capable of binding to IL-13Rα2 in macrophages (He et al., 2013). These signaling pathways protect against cell death by irradiation and mediate melanoma lung metastasis, respectively (Faibish et al., 2011; Francescone et al., 2011; Ma et al., 2015). MEK1/2 and the PI3K signal pathways also mediate CHI3L1 function in glioblastoma (Yao et al., 2015). However, the association of IL-13Rα2 and angiogenesis in glioblastoma has not yet been fully elucidated, and further study is required.

Tumor vascular stability and permeability are correlated with CHI3L1 expression in glioblastoma patients (Pinet et al., 2016). CHI3L1 induces the activation of β-catenin and cytoskeleton protein smooth muscle actin coordination via syndecan-1, which regulates vascular permeability and stability in endothelial cell-derived pericytes/smooth muscle cells (Pinet et al., 2016). Furthermore, we recently reported that CHI3L1 mediates endothelial cell inflammation and vascular smooth muscle cell activation, which in turn exacerbates atherosclerosis (Jung, Park, et al., 2018). These pro-atherogenic effects of CHI3L1 are induced via monocyte-endothelial cell adhesion, inflammatory gene expression, and reduced NO generation in endothelial cells, and are accompanied by enhanced vascular smooth muscle cell proliferation and migration (Jung, Park, et al., 2018). As microRNA 342-3p inhibits CHI3L1-induced vascular inflammation, further study into its effects on angiogenesis in glioblastoma is required.

Similarly, CHI3L1 is highly expressed in small cell lung cancer circulating tumor cells. CHI3L1 may play a role in the regulation of VEGF, MMP9, and cadherin expression in small cell lung cancer circulating tumor cells (Hamilton, Rath, & Ulsperger, 2015). Inhibition of CHI3L1 expression by miR-125-3p-mediated upregulation of USF1 has been reported to suppress lung cancer metastasis (Kim, Yun, et al., 2018). In human fibroblasts, CHI3L1 acts in a manner similar to insulin-like growth factor-1, and increases the expression of MMP1 and extracellular matrix remodeling (Salvatore, Focaroli, Teti, Mazzotti, & Falconi, 2015). These findings suggest that CHI3L1 regulates the tumor microenvironment and stroma reactivity via angiogenesis and the inflammation-related signaling pathway.

Several studies have investigated the upstream signaling pathway of CHI3L1. Cytokines, including IL-6, regulate CHI3L1 secretion in macrophages (Xing et al., 2017). A complex of nuclear factor I-X3 and STAT3 binds to the promoter of CHI3L1 and induces transcription (Singh, Bhardwaj, Wilczynska, Dumur, & Kordula, 2011). Furthermore, a vital factor, active vitamin D3 metabolite (1,25-dihydroxychlecalciferol, 1,25 D), has been shown to stimulate CHI3L1 expression in osteoblasts (Mansell et al., 2016). Meanwhile, inhibitors targeting AP1, MEK, Sp1, and STAT3 inhibited 1,25 D-induced CHI3L1 expression. STAT3 signaling is also associated with the expression of CHI3L1 in glioblastoma (Natesh et al., 2015). An IL-6 family cytokine, oncostatin-M, induces CHI3L1 expression in mesenchymal glioblastoma via oncostatin-M receptor and STAT3. In addition, a transcription factor, Kruppel-like factor 6 binds to CHI3L1 promoter and increases its expression in glioblastoma stem cells (Yao et al., 2015).

Hormone levels, which are associated with cancer development, also affect CHI3L1 levels. Testosterone regulates CHI3L1 expression in breast cancer cell lines and positively correlates with CHI3L1 in nipple aspiration fluid of breast cancer patients (Shidfar et al., 2016).

4. CHI3L1 and neurodegenerative diseases

Elevated levels of CHI3L1 are routinely detected in patients with various neurodegenerative diseases, including Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease (Hall et al., 2016; Melah et al., 2016; Quintana et al., 2018; Sanfilippo et al., 2017). In the brain, activated microglia produce CHI3L1 and mediate neuroinflammation and neural damage. CHI3L1 is expressed in activated microglia and reactive astrocytes and is therefore a biomarker of

neuroinflammation and microglial activation. Hippocampal neurons also express CHI3L1 in response to neuronal injury (Long et al., 2016).

4.1. Roles of CHI3L1 in the development of neurodegenerative diseases

The relationship between CHI3L1 and neurodegenerative disease is summarized in Table 5. Serum CHI3L1 levels have been found to be increased in various central nervous system diseases, including human immunodeficiency virus encephalitis, stroke, multiple sclerosis, traumatic brain injury, and glioblastoma, indicating that the protein could be associated with neuroinflammatory diseases (Eurich et al., 2009; Hinsinger et al., 2015). However, no pathophysiological roles of CHI3L1 in this regard have yet been elucidated. Alzheimer's disease, the most common cause of dementia, can be characterized by difficulties in memory, language, problem-solving, and other cognitive abilities required to perform everyday activities (Calderon-Garciduenas & Duyckaerts, 2017). Amyloid beta (Aβ) accumulation, the neuropathological hallmark of AD, leads to synaptic dysfunction and neurodegeneration in critical brain regions involved in cognition and memory (Ali, Yoon, Shah, Lee, & Kim, 2015; Cai & Tammineni, 2017). Inflammation is an important factor in the pathogenesis of AD. Increased levels of CHI3L1 have been detected in CSF from AD patients (Muszynski, Groblewska, Kulczynska-Przybik, Kulakowska, & Mroczko, 2017). The pattern of CSF CHI3L1 overlaps extensively with that of P-tau and Aβ1-42 in AD patients, suggesting that CHI3L1 is associated with the inflammatory process of neurodegeneration in AD (Alcolea et al., 2015). Additionally, chitinases, as well as CHI3L1, are produced in the brains of late-onset AD patients during neuroinflammation (Querol-Vilaseca et al., 2017). In an animal study, the levels of chitinase 1 proteins increased significantly in a time-dependent manner in APP/PS1 mice aged 22 months, compared to those in age-matched wild-type mice, indicating that chitinase 1 is associated with disease progression in AD (Xiao et al., 2016). The mechanism may involve secretion of CHI3L1 by activated microglia and astrocytes accelerating macrophage infiltration, angiogenesis, and neuronal death associated with neuroinflammation (Bonneh-Barkay et al., 2012). Additionally, the upregulation of chitinase neuromolecules is associated with increased neuroinflammation (Querol-Vilaseca et al., 2017).

One in six humans will suffer at least one stroke in their lifetime (Seshadri et al., 2006). Ischemic stroke causes thrombotic or embolic occlusion of major cerebral arteries and their branches. In a general population study, elevated CHI3L1 was found to be associated with a 34% increase in triglyceride levels, and with increased risk of ischemic stroke (Kjaergaard et al., 2015). Furthermore, circulatory CHI3L1 serum levels were elevated in cases of acute ischemic stroke compared to those in controls in a study involving human patients (Park et al., 2012). Comparison of CHI3L1 transcription in different chronic infarct levels showed that there is focal and temporal expression of CHI3L1 in astrocytes with injury. Furthermore, in acute stages, maximal CHI3L1 induction was initiated with ischemic changes in visible neurons along with a prominent endothelium and early neutrophilic infiltration, and then diminished at the chronic stages. These differences in CHI3L1 transcription at different stages of pathology imply that acute inflammation induces CHI3L1 expression in astrocytes proximal to the lesion and that, as inflammation resolves, CHI3L1 expression is diminished (Bonneh-Barkay, Wang, Starkey, Hamilton, & Wiley, 2010). It was suggested that significantly higher serum levels of CHI3L1 are a risk factor of atherosclerosis for stroke, the triggering of inflammatory responses, and positive vascular dementia (Xu et al., 2016). Furthermore, it is known that CHI3L1 can induce macrophage activation and matrix degradation within the atherosclerotic lesion (Di Rosa & Malaguarnera, 2016).

CHI3L1 has also been implicated in the pathogenesis of MS. MS is a type of demyelinating autoimmune disease of the CNS, and is accompanied by white matter lesions in the brain with neuronal damage and astroglial activation (Bonneh-Barkay, Wang, et al., 2010). Much effort has been put into identifying biomarkers for MS, and into predicting and treating disease progression. Diagnosis using CSF could trace the characteristics or patterns of the brain (Stoeck et al., 2012). In a previous study, CSF CHI3L1 levels were found to be associated with conversion to MS in patients presenting with clinically isolated syndrome. It is known that CHI3L1 and CHI3L2 induce proliferation and apoptosis during MS relapse (El Ayoubi & Khoury, 2017). Furthermore, it has been found that patients with progressive forms of MS have the highest plasma levels of CHI3L1 compared with relapsing-remitting MS patients and healthy controls (Varhaug et al., 2018).

Parkinson's disease is pathologically characterized by dopaminergic neurodegeneration in the substantia nigra, and consequent depletion of dopamine in the striatum (Kitada et al., 2009). CSF biomarkers including α-synuclein, neurofilament light, tau, and phosphorylated tau (P-tau) are associated with Parkinson's disease. CHI3L1 also increases in PD, and is associated with cognitive decline (Hall et al., 2016). CHI3L1 is expressed in the process of astrocyte and microglia-mediated inflammation, an important pathogenesis of PD, similarly to in other neurological disorders such as traumatic brain injury, stroke, MS, amyotrophic lateral sclerosis, and AD. Microglia activation, especially, has been observed in several brain regions and is associated with motor symptoms. CHI3L1 augments inflammation via the regulation of pro-inflammatory cytokine secretion (Chen, Jiao, et al., 2017; Llorens et al., 2017; Rocha, Ribeiro, Furr-Stimming, & Teixeira, 2016). Therefore, CHI3L1 may play a role in the worsening of cognitive function in PD.

CHI3L1 is also detected in CJD. Prion pathology is abundant in the thalamus at pre-clinical stages of sporadic CJD, and spreads over other brain regions, including the hippocampus and cortex, in the clinical stages of prion disease. CHI3L1 immunoreactivity correlated with prion pathology at the pre-clinical disease stage in an Rocky Mountain Laboratory strain prion-infected mice model (Llorens et al., 2017). This study also demonstrated CHI3L1 levels to be positively correlated with CSF tau. These results suggest that CHI3L1 is associated with the pre-clinical and early stages of sporadic CJD.

Table 5
Summary of the relationship between CHI3L1 and neurodegenerative diseases.

Disease type	Results	Mechanisms	Reference
Alzheimer's disease	Aβ accumulation and synaptic dysfunction in critical brain regions Neuron death associated with neuroinflammation Amyloidogenesis and memory loss	CHI3L1 is overlapped with P-tau and Aβ1-42 in AD patients, associating with inflammatory process Accelerating the macrophages infiltration, astrocyte activation NF-κB signaling pathway	(Alcolea et al., 2015) (Bonneh-Barkay et al., 2012) (Choi et al., 2018)
Ischemic stroke	Increasing risk of ischemic stroke Neutrophilic infiltration and acute inflammation	Increase in triglyceride levels Astrocytes activation	(Kjaergaard, Johansen, Bojesen, & Nordestgaard, 2015) (Bonneh-Barkay, Wang, et al., 2010)
Multiple sclerosis	Conversion to MS	Increasing of apoptosis	(El Ayoubi & Khoury, 2017)
Parkinson's disease	Cognitive decline and inflammation	Astrocytes and microglia activation, Increasing pro-inflammatory cytokines secretion	(Hall et al., 2016)

CHI3L1 is also upregulated in other neuroinflammatory conditions, including human immunodeficiency virus infection, encephalitis, and amyotrophic lateral sclerosis. Generally, elevated levels of CHI3L1 are detected in astrocytes involved in inflammatory responses, indicating reactive gliosis (Bonneh-Barkay, Wang, et al., 2010). However, in contrast to what is described in other inflammatory diseases, CHI3L1 expression is not abundant in macrophage/microglia in the brain (Arion, Unger, Lewis, Levitt, & Mirnics, 2007; Lee et al., 2009; Yang et al., 2008). Additionally, not all CHI3L1-positive cells are co-localized with GFAP-stained cells in the brain in sCJD and AD (Llorens et al., 2017). Therefore, further studies are needed to elucidate a clear role for CHI3L1 in reactive gliosis during neuroinflammatory responses.

4.2. Signaling pathway of CHI3L1 in neurodegenerative diseases

The roles of CHI3L1 in the signaling pathways of neurodegenerative diseases are illustrated in Fig. 5. While CHI3L1 is considered a biochemical marker in various neurodegenerative diseases, its expression patterns and the mechanisms underlying its roles in the human brain remain unclear. Some studies have suggested that CHI3L1 is expressed in astrocytes in a variety of acute neuroinflammatory conditions, such as traumatic brain injury or multiple sclerosis (Bonneh-Barkay, Zagadailov, et al., 2010; Canto et al., 2015). Other studies, however, support the idea that CHI3L1 is also expressed in macrophage/microglia cell types in these conditions (Canto et al., 2015; Hinsinger et al., 2015). A recent study reported that CHI3L1 was detected in astrocytes, but not in neurons or microglia, in postmortem human frontal cortexes from healthy controls and AD patients (Querol-Vilaseca et al., 2017). Another research suggested that CHI3L1 is highly expressed in the astrocytes of sCJD-related animal brains and is associated with elevated pro-inflammatory mediators, IL-1β and TNF-α, in microglia (Llorens et al., 2017). Pro-inflammatory cytokines such as IL-1β and IL-6 increased in astrocytes, and synergistically induced the elevation of CHI3L1 expression through a STAT3 dependent-mechanism (Bhardwaj et al., 2015). A recent study showed that secreted cytokines from activated microglia induced reactive astrocytes in neurodegenerative diseases (Liddelow et al., 2017). These findings suggest that elevated levels of CHI3L1 in astrocytes may promote infiltration of immune cells and induce a pro-inflammatory response, in turn, stimulating astrogliosis and CHI3L1 expression. The mechanism by which CHI3L1 functions in astrocyte-microglia cross-talk during neurodegeneration remains to be clarified.

CHI3L1 has the ability to bind RAGE, contributing to various cellular responses with enhanced activation of the NF-κB, MAPK, and β-catenin signaling pathways (Low et al., 2015). NF-κB is well-documented as a transcription factor regulating β-secretase in brain cells, inducing neuronal cell death with accumulation of Aβs (Snow & Albensi, 2016). The activation of NF-κB, especially constitutively activated NF-κB in chronic inflammatory patients, is a factor in a wide variety of human diseases, including AD, PD, rheumatoid arthritis, cancer, and asthma (Gupta, Sundaram, Reuter, & Aggarwal, 2010; Shih, Wang, & Yang, 2015). Several investigations have detected activated NF-κB in the brains of AD patients (Snow & Albensi, 2016). Disruption of NF-κB in p65 knockout cells reduced expression of β-site APP-cleaving enzyme 1, contributing to Aβ generation. NF-κB p50 subunit deletion leads to memory deficits through reduction of neurogenesis and protection of hippocampal neurons *in vivo* (Chen et al., 2012; Rolova et al., 2016). When applied extracellularly to cultured neurons, Aβs, the main amyloid plaque, can exert pro-apoptotic effects by activating the NF-κB pathway, but may also enhance the intracellular production of Aβ peptides (Shih et al., 2015). NF-κB has been suggested to play an important role in neuroinflammatory responses in neurons and astrocytes. Upregulation of NF-κB enhances pro-inflammatory/inflammatory stimuli in AD neuropathology (Zhang & Jiang, 2015), while its inactivation reduces cellular Aβ generation, as the promotor for the β-site APP-cleaving enzyme 1 gene contains functional NF-κB

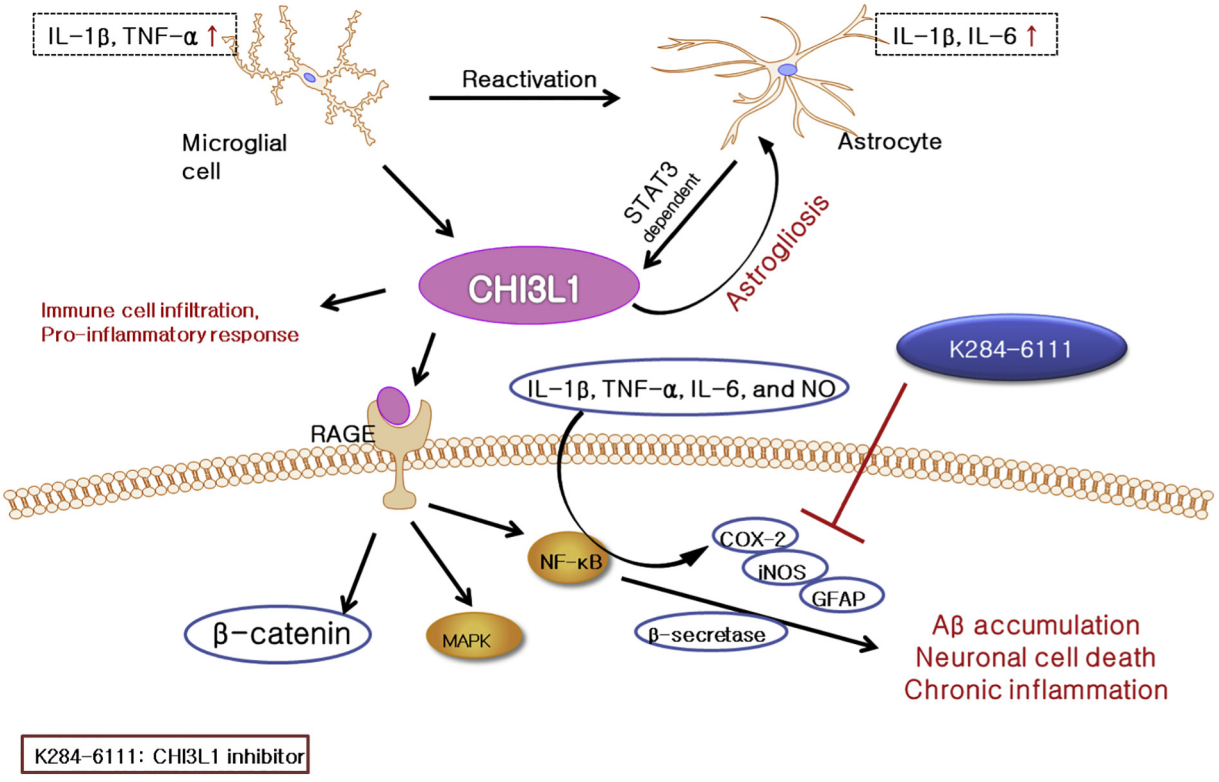

Fig. 5. The roles of CHI3L1 in the signaling pathways of neurodegenerative diseases. Pro-inflammatory cytokines such as IL-1β and IL-6 induce the elevation of CHI3L1 expression through a STAT3 dependent-mechanism in astrocytes. CHI3L1 in astrocytes may promote infiltration of immune cells and stimulate astrogliosis and CHI3L1 expression. Inflammation-induced CHI3L1 activates the NF-κB, MAPK, and β-catenin signaling pathways via RAGE. A CHI3L1 inhibitor, K284-6111 inhibited NF-κB activation and expression of NF-κB-related neuroinflammatory genes including COX-2, iNOS, and GFAP in the AD animal brain.

binding elements. Therefore, regulation of NF-κB plays a key role in Aβ-associated AD pathogenesis.

CHI3L1 interacts synergistically with pro-inflammatory cytokines to activate NF-κB signaling (Tran et al., 2014b, 2014a). Moreover, the expression of the *CHI3L1* gene induces proliferation in various cell lines, and stimulates endothelial cell migration (Johansen, 2006). Inflammation-induced CHI3L1 efficiently activates the NF-κB signaling pathway and enhances the secretion of IL-1β, IL-6, and TNF-α, suggesting the presence of a positive feedback loop in the pro-inflammatory cascade (Hamilton & Rath, 2017; Schimpl et al., 2012; Wang, Tan, Yu, & Tan, 2015). Recently, we showed that a CHI3L1 inhibitor, K284-6111, inhibited not only NF-κB activation and NF-κB-related neuroinflammatory gene expression, including that of COX-2, iNOS, GFAP, and Iba-1, but also that of inflammatory cytokines such as NO, TNF-α, IL-1β, and IL-6 in the AD animal brain (Choi et al., 2018). Additionally, K284-6111 inhibited the translocation of a p65 subunit in microglial BV-2 cells and cultured astrocytes. Thus, inactivation of NF-κB by K284-6111 induced significant neuroprotective effects in the AD animal brain through an anti-neuroinflammatory mechanism. We also showed that K284-6111 directly binds to CHI3L1, with a docking model revealing a strong protein binding affinity (−9.7 kcal/mol) to Arg263, Thr293, Glu290, Lys289, Thr288, Phe287, Leu356, Trp352, Trp99, Asn100, Phe58, Glu36, Arg35, Tyr34, Trp31, and Trp69. K284-6111 also bound to cell lysates containing CHI3L1 from B16F10 in a pull-down assay. It was also illustrated that K284-6111 has an anti-inflammatory effect in LPS-induced microglial BV-2 cells and cultured astrocytes, via inhibition of NF-κB-mediated CHI3L1 activation. This inhibitory pathway was accompanied by decreased levels of Aβ1-42, *CHI3L1* mRNA, and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 (Choi et al., 2018). These results suggest that CHI3L1 activation followed by stimulation of the NF-κB signaling pathway contribute to neuroinflammation and amyloidogenesis.

5. CHI3L1 and inflammatory diseases

Inflammation is a complex biological self-defense reaction of the immune system triggered by tissue damage, infection, or toxic compounds (Ishii, 2015). CHI3L1 expression is increased in a variety of inflammatory and chronic diseases including obesity, diabetes, nephropathy disease, rheumatoid arthritis, inflammatory bowel disease, cancer, coronary arterial diseases, and acute ischemic stroke (Hobaus et al., 2018; Johansen, Schultz, & Jensen, 2009; Kamba, Lee, & Mizoguchi, 2013; Lee et al., 2012; Persson et al., 2012; Schernthaner, Hobaus, & Brix, 2016; Turkyilmaz et al., 2013; Xu, Ma, et al., 2014). CHI3L1 is also associated with immune response and inflammation in instances of acute infection by viruses and bacteria (Breyne, Steenbrugge, Demeyere, Vanden Berghe, & Meyer, 2017; Chen, Jiao, et al., 2017; Peluso et al., 2017).

NF-κB is a well-characterized transcription factor and plays an important role in the initiation and progression of inflammation through the production of various cytokines and prostaglandins (Kunsch & Medford, 1999). In addition, CHI3L1 secreted from cells under conditions of inflammation induces NF-κB activation, which is important for the expression of inflammatory proteins. Furthermore, CHI3L1 can stimulate pro-inflammatory mediators (Libreros et al., 2012) and may play a role in type 2 helper cell-mediated inflammation. Therefore, these reports suggest that CHI3L1 is involved in inflammation-related disease.

5.1. Roles of CHI3L1 in the development of inflammatory diseases

The relationship between CHI3L1 and inflammatory diseases is summarized in Table 6. Elevated levels of CHI3L1 are associated with various inflammatory diseases including pneumonia, RA, Kawasaki disease, asthma, COPD, coronary artery disease, periodontitis, diabetes, cellulitis, intracerebral hemorrhage, psoriasis, obesity-associated inflammation, Behcet's disease, hepatic fibrosis, acute kidney injury, and atopic dermatitis.

RA is an autoimmune disease that induces chronic inflammation of the joints. Several studies have suggested that CHI3L1 is a candidate autoantigen for inducing autoimmune response in RA (Steenbakkers et al., 2003; Tsark et al., 2002; van Bilsen et al., 2004; van Lierop et al., 2007; Vos et al., 2000). RA patients show high levels of circulating CHI3L1, with concentrations in synovial fluid being higher than those in plasma (Johansen, Jensen, & Price, 1993; Volck et al., 2001). Articular chondrocytes, synovial cells, infiltrated macrophages, and neutrophils can produce CHI3L1 in RA joints. In addition, the levels of pro-inflammatory mediators such as MMP-3, IL-6, IFN-γ, and TNF-α, were found to be correlated with those of CHI3L1 in RA, with anti-rheumatic treatment reducing CHI3L1 levels in RA patients (Cope et al., 1999; Houseman et al., 2012; Mottonen et al., 1999; Vaananen, Vuolteenaho, et al., 2017). These findings suggest that CHI3L1 may play a role in the development of RA.

Obesity induces a chronic inflammatory state with elevated levels of several inflammatory mediators (Cao, 2014). Various cytokines, including IL-1, IL-6, and TNF-α, increase during this inflammatory response. Pathological states including insulin resistance and islet β-cell dysfunction may contribute to the disease activity of diabetes, and CHI3L1 is associated with this chronic inflammation. The immune response is critically involved in obesity and insulin resistance. Infiltrated macrophages are observed in obesity-associated inflammation (Lackey & Olefsky, 2016), and peripheral blood mononuclear cells in obesity released high levels of TNF-α, IFN-γ, and IL-2 (Dicker, Salook, Marcoviciu, Djaldetti, & Bessler, 2013). Furthermore, upregulation of CHI3L1 in peripheral blood mononuclear cells exacerbate inflammation in obesity, and high levels of CHI3L1 are associated with insulin resistant markers (Nielsen et al., 2008). In type 2 diabetes patients, CHI3L1 is expressed at a high level, and correlates with metabolic syndrome, dyslipidemia, and glycemic parameters such as HbA1c, albuminuria, and fasting glucose (Cabrera, Henschel, & Hessner, 2016; Downs & Faulkner, 2015; Nielsen et al., 2008; Rathcke, Persson, Tarnow, Rossing, & Vestergaard, 2009; Rathcke & Vestergaard, 2006). These reports suggest that CHI3L1 plays a critical role in the pathophysiological states of obesity and diabetes.

CHI3L1 is also associated with the pathology of atherosclerosis in diabetes patients (Aguilera et al., 2015). CHI3L1 was found to be secreted from differentiated macrophages in early-stage atherosclerosis lesions (Boot et al., 1999; Rehli et al., 2003), as well as from VSMCs during hyper cholesterol-induced coronary atherosclerotic plaque development in swine (Rocchiccioli et al., 2015). A recent study reported that CHI3L1 inhibited the atherosclerotic response induced by LPS in human umbilical vein endothelial cells (Jung, Kim, et al., 2018). However, CHI3L1 may have a dual action in inflammatory responses, depending on inflammatory states. Acute inflammatory responses have been studied using LPS models and can be used to elucidate the role of CHI3L1 in inflammation. Knock-down of elevated CHI3L1 expression associated with the atherosclerotic aorta and endothelial dysfunction was found to suppress the progression of these characteristics in a mouse model (Bakirci et al., 2015; Gong, Xing, Zheng, & Xing, 2014; Jafari, Elias, & Mohsenin, 2014; Maegdefessel et al., 2014; Ridker, Chasman, Rose, Loscalzo, & Elias, 2014; Rocchiccioli et al., 2015). These data suggest that CHI3L1 is associated with the development of vascular inflammation and atherosclerosis, adding to its potential role as a circulating biomarker for inflammation.

Based on the above findings, we investigated whether CHI3L1 mediated the observed increased vascular inflammation, arterial wall thickening, and atherosclerosis in APPsw Tg mice by performing supplementation and knock-down analyses. Briefly, recombinant human CHI3L1 (rhCHI3L1) treatment resulted in pro-atherogenic effects *in vitro*, as measured by monocyte-EC adhesion, inflammatory gene expression, and reduced NO generation in ECs along with enhanced VSMC proliferation and migration, whereas CHI3L1 knock-

Table 6
Summary of the relationship between CHI3L1 and inflammatory diseases.

Disease type	Results	Mechanisms	Reference
Rheumatoid arthritis	Autoimmune response Chronic inflammation	CHI3L1 is an auto-antigen Production of CHI3L1 in RA joints by articular chondrocytes, synovial cells, and infiltrated macrophages Mediation of pro-inflammatory such as MMP-3, IL-6, IFN-γ, and TNF-α correlated with CHI3L1 in RA	(Steenbakkers et al., 2003; Tsark et al., 2002; van Bilsen et al., 2004; van Lierop et al., 2007; Vos et al., 2000) (Cope et al., 1999; Houseman et al., 2012; Mottonen et al., 1999; Vaananen Vuolteenaho, et al., 2017)
Chronic obstructive pulmonary disease (COPD)	Promoting wound healing in oxidant-induced lung injury Protection from inflammatory cell apoptosis and cell death	Regulation of adaptive Th2 immunity, apoptosis, macrophage activation and fibrosis Inhibition of Fas expression	(Lee et al., 2011) (Lee et al., 2009)
Obesity-associated inflammation	Insulin resistance (Diabetes) Chronic inflammation	Increasing of various cytokines such as IL-1, IL-6, and TNF-α in an inflammatory response Infiltrated macrophage	(Di Rosa & Malaguarnera, 2016) (Nielsen et al., 2008)
Osteomyelitis	Bone destruction	Reducing of Notch signaling	(Chen, Jiao et al., 2017)
Atherosclerosis	Development of atherosclerotic plaque and vascular inflammation	Enhancing endothelial cell inflammation and VSMC migration and proliferation	(Jung, Park, et al., 2018)

down yielded the opposite effects, and also inhibited atherosclerotic plaque development and vascular inflammation *in vivo* (Jung, Park, et al., 2018). Taken together, our findings suggest that upregulated levels of CHI3L1 contribute to the development of atherosclerosis in the artery of the APPsw Tg mouse. We demonstrated that CHI3L1 plays a key role as a pro-atherogenic factor in vascular inflammation and atherosclerosis development in APPsw Tg mice through the enhancement of EC inflammation and VSMC migration and proliferation (Jung, Park, et al., 2018). In addition, CHI3L1 has also been found to be associated with other inflammatory diseases such as chronic liver inflammation. Analysis of the Human Protein Atlas revealed that CHI3L1 is abundantly expressed in hepatocytes and hepatic stellate cells (www.proteinatlas.org) (Uhlen et al., 2015). Fibrosis, chronic hepatitis C, and hepatitis B are reported to be associated with the elevated expression levels of CHI3L1 (Kumagai et al., 2016; Tao et al., 2014). Especially, inflammation is tightly linked to the development of alcoholic liver disease (ALD), which induces severe liver injuries including steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (Sugimoto & Takei, 2017). ALD patients showed higher serum CHI3L1 levels than did healthy controls (Johansen et al., 2000; Nøjgaard et al., 2003). However, the role of CHI3L1 in the development of ALD is not yet fully understood. Therefore, we studied the function of CHI3L1 in ethanol-induced liver injury. We observed that CHI3L1 knockout inhibited liver injury through regulation of triglyceride synthesis and oxidative stress in ethanol-treated mice (Lee, Han, et al., 2019).

Hepatic fibrosis with tissue inflammation also represents a progression of NASH/nonalcoholic fatty liver disease (NAFLD). It has been proposed that CHI3L1 is a non-invasive serum biomarker for diagnosis of these life-threating liver diseases (Cho et al., 2014; Kori, Gov, & Arga, 2019; Paschetta et al., 2015). Serum CHI3L1 levels showed a good correlation with severity of liver fibrosis in NAFLD patients (Kumagai et al., 2016). Therefore, we assume that CHI3L1 plays an important role in the development of ALD and NASH/NAFLD.

In contrast to its roles in the induction of disease, CHI3L1 plays a protective role in several inflammatory diseases. COPD is associated with various immune cells and inflammatory mediators. Immune cells, including macrophages, dendritic cells, neutrophils, and T lymphocytes increase in number in COPD (Rovina, Koutsoukou, & Koulouris, 2013). Lung chitinolytic activity is upregulated in COPD, and chitin induces innate inflammation, which can be blocked by acidic mammalian chitinase (AMCase) (Lalaker, Nkrumah, Lee, Ramanathan, & Lane, 2009; Letuve et al., 2010). AMCase reportedly also reduces Th2 inflammatory conditions and the activity of IL-13 (Zhu et al., 2004). CHI3L1 may promote wound healing in oxidant-induced lung injury via the regulation of adaptive Th2 immunity, apoptosis, macrophage activation, and fibrosis (Lee et al., 2011). Antigen-induced Th2 responses were significantly inhibited in CHI3L1 knock-out mice, and were rescued by epithelial CHI3L1. IL-13-induced inflammation and fibrosis were also reduced by the absence of CHI3L1. Furthermore, CHI3L1 showed a protective effect against inflammatory cell apoptosis and cell death with the inhibition of Fas expression (Lee et al., 2009). COPD patients and smokers have high circulating levels of CHI3L1, while non-smokers do not (Matsuura et al., 2011). This suggests that CHI3L1 plays a role in the regulation of pulmonary inflammation.

Infiltration of polymorphonuclear cells and macrophages is a normal inflammatory response to kidney injury. In this inflammatory state, CHI3L1 is expressed at high levels in macrophages and promotes the repair process (Montgomery et al., 2017). CHI3L1 is therefore considered an important growth and survival factor in renal tubular repair. Furthermore, CHI3L1 reduces tubular cell apoptosis and promotes proliferative repair in kidney injury (Puthumana et al., 2017). However, excessive expression of CHI3L1 has profibrotic activity, and induces maladaptive kidney repair.

CHI3L1 protein is expressed in colonic epithelial cells and macrophages in the inflamed colon of colitis (Chen, Pekow, et al., 2011; Mizoguchi, 2006). In inflammatory bowel disease, highly expressed CHI3L1 induces the proliferation of intestinal epithelial cells, which may promote cell survival (Low et al., 2015). However, elevated levels of CHI3L1 are pathogenic in that they are involved in hyperproliferation and contribute to colitis-associated cancer. The dual function of CHI3L1 in idiopathic pulmonary fibrosis has been suggested previously (Turn & Kolliputi, 2014). Low levels of CHI3L1 in the acute inflammatory state or injury, and elevated levels in the chronic inflammatory state or recovery period, both result in pathological responses in inflammatory bowel disease and idiopathic pulmonary fibrosis.

In inflammatory disease, CHI3L1's role may be complicated, and dependent on both the disease and the inflammatory state, such as acute injury and recovery.

5.2. Signal pathway of CHI3L1 in the development of inflammatory diseases

The roles of CHI3L1 in the signaling pathways for the development of inflammatory diseases are illustrated in Fig. 6. CHI3L1 is considered a pro-inflammatory molecule as it induces the NF-κB and TGF-β signaling pathway in various pathological process (Jung, Park, et al., 2018; Lee et al., 2009; Matsuura et al., 2011; Sohn et al., 2010). However, this molecule also prevents apoptosis and promotes fibrosis. During the acute phase of inflammation or injury in the colon, low levels of CHI3L1 exacerbate the inflammatory response and consequently induce chronic colitis. The mechanism underlying CHI3L1's action in this regard is not well understood. However, a damage-associated molecular protein, S100A9, is involved in the reduced inflammation induced by CHI3L1, which negatively regulates the action of S100A9 by competitively binding to RAGE in chronic colitis (Low et al., 2015).

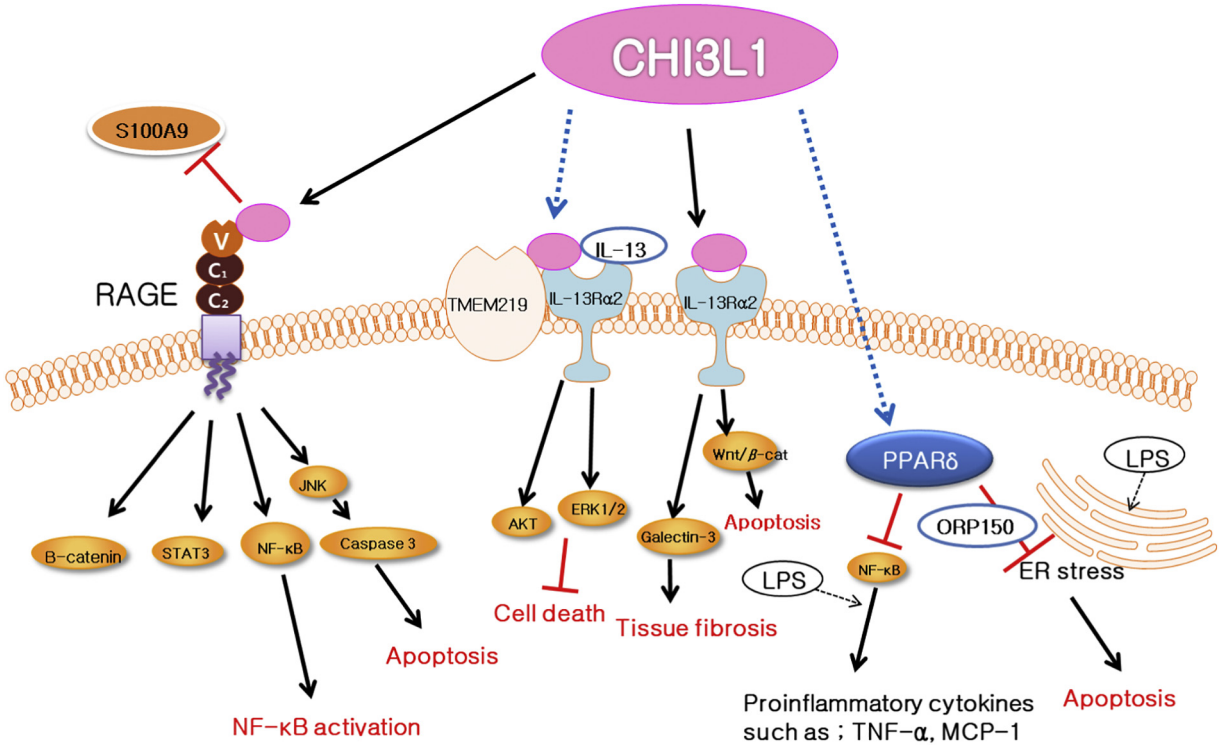

Fig. 6. The roles of CHI3L1 in the signaling pathways for the development of inflammatory diseases. Activation of RAGE by CHI3L1 induces the pro-inflammatory signaling pathway such as, STAT3, caspase 3, and NF-κB in various pathological process. However, CHI3L1-induced inhibition of S100A9 action is involved in reduced inflammation through competitive binding of CHI3L1 to RAGE in the chronic colitis. Interestingly, CHI3L1 binds to its receptors in two ways, depending on the association of TMEM219. A multimeric CHI3L1 receptor composed of IL-13Rα2 and TMEM219 can bind to CHI3L1 and reduce cell death by activating Erk1/2 and Akt signaling. However, CHI3L1 binding to IL-13Rα2 in the absence of TMEM219 induces apoptotic responses via stimulation of Wnt/β-catenin signaling. CHI3L1 also has a protective role in inflammation through the regulation of TNF-α and in MCP-1 release induced by LPS via PPARδ-mediated signaling.

Overexpression of RAGE activates STAT3-, β-catenin-, and NF-κB-signaling, which are known downstream pathways of CHI3L1 (Chen, Llado, Eurich, Tran, & Mizoguchi, 2011; Chen, Pekow, et al., 2011; Tran et al., 2014b, 2014a). CHI3L1 binding to RAGE induces the common pro-inflammatory signaling pathway, consequently stimulating phosphorylation of MAPK p42/p44, p38, JNK, STAT3, and caspase-3 p17 (p17's cleaved active caspase-3 form) (Low et al., 2015). These results suggest that the elevated levels of CHI3L1 induce the activation of inflammatory signaling pathways via RAGE.

In addition to RAGE, several CHI3L1-binding molecules have been identified, including IL-13Rα2, prostaglandin D2 receptor (also called CRTH2), and type I collagen (Bigg, Wait, Rowan, & Cawston, 2006; He et al., 2013; Iwata et al., 2009; Zhou et al., 2015). ERK and AKT signaling is activated through the binding of CHI3L1 and IL-13Rα2. CHI3L1 also stimulates Wnt/β-catenin signaling. IL-13 is able to stimulate macrophage MAPK and AKT through the IL-13Rα2-mediated CHI3L1 pathway (He et al., 2013). TGF-β1 activation is also induced by CHI3L1/IL-13Rα2-dependent mechanisms (Lee et al., 2009). In addition, CHI3L1 and IL-13 form a multimeric complex with IL-13Rα2 (He et al., 2013). IL-13Rα2 may mediate CHI3L1-induced MAPK, AKT, and Wnt/β-catenin signaling pathways, consequently regulating inflammatory responses.

CHI3L1 also has a protective effect against inflammation (Gorgens, Eckardt, Elsen, Tennagels, & Eckel, 2014). Recently, PPARδ-dependent pathway has been put forward as a candidate signaling pathway of CHI3L1 (Jung, Kim, et al., 2018). In this study, CHI3L1 reduced TNF-α and MCP-1 release induced by LPS via PPARδ-mediated signaling. The 150-kDa oxygen-regulated protein is also associated with the protective effect of CHI3L1 on endoplasmic reticulum stress through PPARδ-mediated signaling.

Fibrosis could be triggered by inflammation. CHI3L1 plays a role in pulmonary fibrosis by binding to and activating the chemokine receptor homologous molecule on the surfaces of Th2 lymphocytes (CRTH2, prostaglandin D2 receptor 2). Activation of this molecule induces profibrotic signaling in lung injury (He et al., 2013; Lee et al., 2016; Zhou et al., 2014; Zhou et al., 2015). Transient expression of CHI3L1 activates IL13Ra2-dependent PI_3K signaling during acute repair processes, reducing tubular cell death. Hermansky–Pudlak syndrome (HPS) is an inherited disorder that is associated with severe pulmonary fibrosis. A recent study suggested that elevated expression of CHI3L1 resulting from injury increases the levels of Galectin-3 that exacerbates tissue fibrosis by interacting with CHI3L1 and its receptor IL-13Rα2 in HPS epithelial cells (Zhou et al., 2018).

In the inflammation process, CHI3L1 and its receptor binding pattern are very important. For example, CHI3L1 is reported to bind to its receptors in two ways, depending on the association of TMEM219. This molecule is a cell death receptor and regulates CHI3L1 and its receptor signaling pathway activation. A multimeric CHI3L1 receptor composed of IL-13Rα2 and TMEM219 can bind to CHI3L1 and reduce epithelial cell death by activating Erk1/2 and Akt signaling (He et al., 2013). However, CHI3L1 binding to IL-13Rα2 in the absence of TMEM219 stimulates Wnt/β-catenin signaling, which, in turn, induces apoptotic responses (Lee et al., 2016).

CHI3L1 is also associated with the inflammatory response to infection by microorganisms. Aberrant STAT3 activation, induced by bacterial infection, has been demonstrated in CHI3L1 knock-out mice, with the finding that activation of CHI3L1 and IL-6 can stimulate the STAT3 signaling pathway synergistically by means of a NF-κB/MAPK-dependent mechanism in bacterial infectious colitis (Tran et al., 2014). In addition, in *Staphylococcus aureus*-induced osteomyelitis, CHI3L1 is involved in bone destruction. Elevated levels of CHI3L1 were observed in an *S. aureus*-induced murine model of osteomyelitis. CHI3L1 increased pro-inflammatory cytokines and reduced Notch signaling, which worsened bone destruction (Chen, Jiao, et al., 2017). A recent study showed that CHI3L1 modulated the expression of pro-

inflammatory cytokines, such as IL-1β, IL-6, and RANTES/CCL5, via the regulation of caspase activity in *E. coli*-infected mammary glands (Breyne et al., 2018).

6. Therapeutic approaches of CHI3L1 for treatment of diseases

From the findings of many clinical and non-clinical studies, CHI3L1 has been sufficiently verified as a promising treatment target in a variety of diseases. Several studies have demonstrated that CHI3L1 plays an important role in the progression of cancer.

Inhibition of CHI3L1 by caffeine has been shown to reduce tumor progress in colitis-associated carcinoma via regulation of oxidative stress (Ma et al., 2014). Caffeine has protective effects against inflammatory bowel disease through the inhibition of CHI3L1, AKT-, and PI_3K-signaling pathway (Lee, Low, Kamba, Llado, & Mizoguchi, 2014). In addition, oxidation-induced DNA damage is reduced by caffeine via the inhibition of CHI3L1. CHI3L1 was proposed as a target for colitis-associated carcinoma (Ma et al., 2014). In glioblastoma, downregulation of CHI3L1 expression induces sensitization to PI_3K/AKT pathway inhibitors (Wang et al., 2018). Furthermore, another CHI3L1 inhibitor, theophylline, has been suggested to exert antitumor activity. This pan-chitinase inhibitor targets CHI3L1 and also regulates PI_3K/AKT pathway. Theophylline inhibits the proliferation of human rectal cancer SW480 cells through G1 phase cell cycle arrest and downregulation of angiopoietin-2 (Peng et al., 2018). Therefore, caffeine and theophylline may have a beneficial effect in cancer treatment by regulating the PI_3K/AKT pathway.

Furthermore, CHI3L1 inhibits apoptosis of human ovarian cancer cells by interfering with the action of paclitaxel through regulation of Mcl-l expression (Chiang et al., 2015). In brain tumor models, anti-CHI3L1 antibody combined with irradiation was suggested as a synergistic treatment method for inhibition of tumor vascularization and progression (Faibish et al., 2011; Shao et al., 2014). These data indicated that CHI3L1 could be a target for the treatment of drug resistant cancers.

The therapeutic targeting of CHI3L1 has also been studied for the inhibition of metastasis. In lung metastasis, the siRNA complex for CHI3L1 significantly enhances anti-tumor immunity, such as TH1 and CTL response and inhibits melanoma lung metastasis (Kim, Park, et al., 2018). Another study reported that CHI3L1 is associated with breast cancer metastasis (Libreros et al., 2012). Chitin (β-(1–4)-poly-N-acetyl D-glucosamine) can block CHI3L1's action and inhibit breast cancer metastasis via production of IFN-γ and reduction of CCL2, CXCL2, and MMP-9 expression. According to the aforementioned studies, angiogenesis induced by CHI3L1 is critical for cancer cell resistance. Recently, the heparin-binding motif of CHI3L1 has been reported to be associated with microvascularization in cancer. Point mutations in the heparin binding domain of CHI3L1 resulted in decreased angiogenic activity. Furthermore, anti-CHI3L1 antibody targeting heparin-binding residues prevented angiogenesis in breast cancer model (Ngernyuang, Shao, et al., 2018).

Ischemia-reperfusion injury is a major problem in the transplantation of steatotic liver disease. CHI3L1 has been proposed as a therapeutic target of boratezomib in this condition (Tiriveedhi et al., 2014). Bortezomib is a selective inhibitor of 26S proteasome and has a NF-kB inhibitory action. However, this drug inhibited CHI3L1 expression and MMP activation in steatotic liver ischemia-reperfusion injury models. In addition, suppressed CHI3L1 expression is correlated with the downregulation of NF-kB and its downstream signaling pathways such as the pro-inflammatory (IL-1β, TNF-α and IFN-γ) and pro-fibrotic (VEGF, TGF-β, HGF, bFGF) cascades. The STAT3 and mTOR pathway is also associated with the therapeutic application of CHI3L1 in cancer (Miyata et al., 2017). According to a previous study, mTOR is downstream of STAT3/CHI3L1. Therefore, dual inhibitors such as rapamycin (mTOR inhibitor) and STX-0119 (STAT3/CHI3L1 inhibitor) were suggested for glioma treatment.

CHI3L1 is also a promising target for the treatment of various inflammatory diseases. In RA, CHI3L1 promoted production of IL-18 in osteoblasts and angiogenesis in endothelial progenitor cells, which are critical to the pathogenesis of RA (Li, Liu, et al., 2017). CHI3L1 shRNA transfection reduced vessel formation *in vivo*, and miR-590-3p inhibited CHI3L1-induced endothelial progenitor cells tube formation and migration through regulation of the FAK/PI_3K/Akt pathway for IL-18 production (Li, Liu, et al., 2017). CHI3L1 is also implicated in another inflammatory-related disease, atherosclerosis, Interestingly, APP is associated with vascular diseases and CHI3L1 may promote EC inflammation and VSMC activation (Jung, Park, et al., 2018). Based on this involvement, we recently demonstrated that microRNA 342-3p targeting CHI3L1 reduced inflammatory response in arterial endothelium and inhibited the development of atherosclerosis in APPsw-Tg mice (Jung, Park, et al., 2018). In addition, microRNA targeting CHI3L1 can be applied for the treatment of osteomyelitis induced by *S. aureus* (Jin et al., 2015). The study reporting this finding demonstrated that miR-24 reduced osteoblast apoptosis, abnormal bone formation, and mineralization induced by *S. aureus* by inhibiting the expression of CHI3L1.

Furthermore, obesity has an inflammatory pathology and is associated with asthma (Brumpton, Langhammer, Romundstad, Chen, & Mai, 2013). High fat diet and allergen exposure increased the expression of CHI3L1 in white adipose tissue and lung tissue with Th2 inflammation (Ahangari et al., 2015). The inflammatory response was decreased in CHI3L1 knockout mice. Therefore, avoidance of fatty foods, in combination with inhibitors of CHI3L1 or its receptor(s), has been proposed as a novel preventive and/or therapeutic strategy for treating obesity and asthma-related inflammation (Ahangari et al., 2015). These data indicated that targeting CHI3L1 may have potentially beneficial effects for the treatment of inflammatory diseases.

Based on our studies on the roles of CHI3L1 in various inflammatory diseases including Alzheimer's diseases, atherosclerosis, liver injury, and cancer, to the best of our knowledge, our previous report (Choi et al., 2018) is the first to show that CHI3L1 inhibitor attenuates memory dysfunction and neuroinflammation in AD animal models. In our previous study, we screened CHI3L1 inhibitors using 3D chemical database analysis with X-ray structure-based virtual screening (Fig. 7). We identified 11 candidates as CHI3L1 inhibitors from 14 million chemical databases (data not shown). Among the 11 candidates, we evaluated the efficacy of 2-((3-[2-(1-cyclohexen-1-yl)ethyl]-6,7-dimethoxy-4-oxo-3,4-dihydro-2-quinazolinyl)sulfanyl)-N-(4-ethylphenyl)butanamide (K284-6111) in an AD animal model.

We observed that K284-6111 inhibited NF-κB activation and NF-κB-related neuroinflammatory gene expression, including COX-2, iNOS, GFAP, and Iba-1, and also inflammatory cytokines such as NO, TNF-α, IL-1β, and IL-6, in the AD animal brain (Choi et al., 2018). Additionally, K284-6111 inhibited the translocation of the p65 subunit in microglial BV-2 cells and cultured astrocytes. Thus, inactivation of NF-κB by K284-6111 induced significant neuroprotective effects in the AD animal brain through an anti-neuroinflammatory mechanism. We also observed that K284-6111 directly binds to CHI3L1 with a high protein binding affinity (-9.7 kcal/mol) to Arg263, Thr293, Glu290, Lys289, Thr288, Phe287, Leu356, Trp352, Trp99, Asn100, Phe58, Glu36, Arg35, Tyr34, Trp31, and Trp69, in a docking model. K284-6111 also bound to CHI3L1 in cell lysates from B16F10 in a pull-down assay. In addition to this, it was illustrated that K284-6111 has an anti-inflammatory effect in LPS-induced microglial BV-2 cells and cultured astrocytes through inhibition of NF-κB-mediated CHI3L1 activation. This inhibitory pathway of NF-κB was accompanied by decreased Aβ1-42 levels, as well as lowered levels of *CHI3L1* mRNA and pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These results suggest that CHI3L1 deactivation followed by inhibition of the NF-κB signaling pathway could be a target for treating neuroinflammatory diseases such as AD.

We also observed that downregulation of CHI3L1 decreased lung tumor development and metastasis (Kim, Yun, et al., 2018; Lee, Kim,

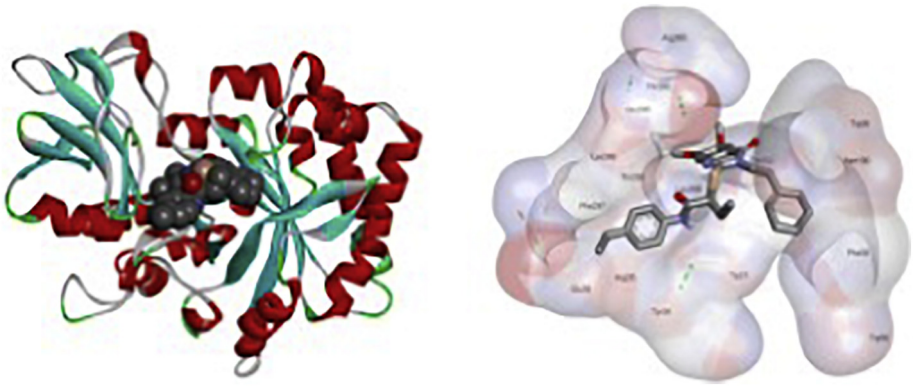

Fig. 7. Docking model of K384-6111; reproduction of a figure from our previous report (J Neuroinflammation. 2018; 15: 224. Choi et al., 2018). We observed that K284-6111 directly binds to CHI3L1 with a high protein binding affinity (-9.7 kcal/mol) to Arg263, Thr293, Glu290, Lys289, Thr288, Phe287, Leu356, Trp352, Trp99, Asn100, Phe58, Glu36, Arg35, Tyr34, Trp31, and Trp69 in a docking model.

et al., 2019). Furthermore, these therapeutic effects of CHI3L1 antagonism could be potentiated by NF-kB or STAT3 inhibition. We found that STAT3 and NF-kB activity is regulated by CHI3L1 expression. Collectively, simultaneous downregulation of CHI3L1 protein activity, NF-kB- and STAT3- pathways by the binding of inhibitors, anti-CHI3L1 antibody, or siRNA is a novel therapeutic strategy for treating various inflammatory diseases.

In conclusion, CHI3L1 plays a pro-inflammatory role in cancers, neurodegenerative diseases, and inflammatory diseases. However, other roles for CHI3L1 have also been proposed in different disease types and inflammatory states, and these remain controversial. It remains to be determined how the interplay and regulatory behavior of CHI3L1 vary with respect to acute/chronic inflammation, non-immune cells/immune cells, cytokine production/angiogenesis, and multimeric receptor complex binding. Investigation of novel therapeutic strategies targeting CHI3L1 will open new avenues for the future treatment of cancers, neurodegenerative diseases, and inflammatory disease.

Declaration of Competing Interest

The authors declare that there are no conflict of interest.

Acknowledgement

This work was supported by National Research Foundation of Korea (NRF) grants funded by the Korean Government (MSIP) (MRC2017R1A5A2015541). Reproduced by permission from Springer Nature: *Journal of Neuroinflammation* (Choi et al., 2018), copyright (2018).

References

van Aalten, D. M., Komander, D., Synstad, B., Gaseidnes, S., Peter, M. G., & Eijsink, V. G. (2001). Structural insights into the catalytic mechanism of a family 18 exo-chitinase. *Proceedings of the National Academy of Sciences of the United States of America 98*, 8979–8984.

Aguilera, E., Serra-Planas, E., Granada, M. L., Pellitero, S., Reverter, J. L., Alonso, N., et al. (2015). Relationship of YKL-40 and adiponectin and subclinical atherosclerosis in asymptomatic patients with type 1 diabetes mellitus from a European Mediterranean population. *Cardiovascular Diabetology 14*, 121.

Ahangari, F., Sood, A., Ma, B., Takyar, S., Schuyler, M., Qualls, C., et al. (2015). Chitinase 3-like-1 regulates both visceral fat accumulation and asthma-like Th2 inflammation. *American Journal of Respiratory and Critical Care Medicine 191*, 746–757.

Alcolea, D., Vilaplana, E., Pegueroles, J., Montal, V., Sanchez-Juan, P., Gonzalez-Suarez, A., et al. (2015). Relationship between cortical thickness and cerebrospinal fluid YKL-40 in predementia stages of Alzheimer's disease. *Neurobiology of Aging 36*, 2018–2023.

Ali, T., Yoon, G. H., Shah, S. A., Lee, H. Y., & Kim, M. O. (2015). Osmotin attenuates amyloid beta-induced memory impairment, tau phosphorylation and neurodegeneration in the mouse hippocampus. *Scientific Reports 5*, 11708.

Arion, D., Unger, T., Lewis, D. A., Levitt, P., & Mirnics, K. (2007). Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. *Biological Psychiatry 62*, 711–721.

Bakirci, E. M., Unver, E., Degirmenci, H., Kivanc, T., Gunay, M., Hamur, H., et al. (2015). Serum YKL-40/chitinase 3-like protein 1 level is an independent predictor of atherosclerosis development in patients with obstructive sleep apnea syndrome. *Türk Kardiyoloji Derneği Arşivi 43*, 333–339.

Baran, A., Mysliwiec, H., Szterling-Jaworowska, M., Kiluk, P., Swiderska, M., & Flisiak, I. (2018). Serum YKL-40 as a potential biomarker of inflammation in psoriasis. *The Journal of Dermatological Treatment 29*, 19–23.

Batista, K., Costa, B., Pablo, I., Vega, I. F., Morales, J., Alvarez, A. V., et al. (2016). Analysis of Olig2 and YKL-40 expression: a clinicopathological/immunohistochemical study for the distinction between subventricular zone II and III glioblastomas. *Folia Neuropathologica 54*, 31–39.

Bhardwaj, R., Yester, J. W., Singh, S. K., Biswas, D. D., Surace, M. J., Waters, M. R., et al. (2015). RelB/p50 complexes regulate cytokine-induced YKL-40 expression. *Journal of Immunology 194*, 2862–2870.

Bhatt, A. P., Redinbo, M. R., & Bultman, S. J. (2017). The role of the microbiome in cancer development and therapy. *CA: A Cancer Journal for Clinicians 67*, 326–344.

Bigg, H. F., Wait, R., Rowan, A. D., & Cawston, T. E. (2006). The mammalian chitinase-like lectin, YKL-40, binds specifically to type I collagen and modulates the rate of type I collagen fibril formation. *Journal of Biological Chemistry 281*, 21082–21095.

Bilen, H., Altinkaynak, K., Sebin, E., Aksoy, H., & Akcay, F. (2016). Serum YKL-40 and MDA levels in Behcet disease. *Journal of the Pakistan Medical Association 66*, 1299–1302.

van Bilsen, J. H., van Dongen, H., Lard, L. R., van der Voort, E. I., Elferink, D. G., Bakker, A. M., et al. (2004). Functional regulatory immune responses against human cartilage glycoprotein-39 in health vs. proinflammatory responses in rheumatoid arthritis. *Proceedings of the National Academy of Sciences of the United States of America 101*, 17180–17185.

Bivona, T. G., Perez De Castro, I., Ahearn, I. M., Grana, T. M., Chiu, V. K., Lockyer, P. J., et al. (2003). Phospholipase Cgamma activates Ras on the Golgi apparatus by means of RasGRP1. *Nature 424*, 694–698.

Bohr, S., Patel, S. J., Vasko, R., Shen, K., Golberg, A., Berthiaume, F., et al. (2015). The Role of CHI3L1 (Chitinase-3-Like-1) in the pathogenesis of infections in burns in a mouse model. *PLoS ONE 10*, e0140440.

Bonneh-Barkay, D., Bissel, S. J., Kofler, J., Starkey, A., Wang, G., & Wiley, C. A. (2012). Astrocyte and macrophage regulation of YKL-40 expression and cellular response in neuroinflammation. *Brain Pathology 22*, 530–546.

Bonneh-Barkay, D., Wang, G., Starkey, A., Hamilton, R. L., & Wiley, C. A. (2010). In vivo CHI3L1 (YKL-40) expression in astrocytes in acute and chronic neurological diseases. *Journal of Neuroinflammation 7*, 34.

Bonneh-Barkay, D., Zagadailov, P., Zou, H., Niyonkuru, C., Figley, M., Starkey, A., et al. (2010). YKL-40 expression in traumatic brain injury: an initial analysis. *Journal of Neurotrauma 27*, 1215–1223.

Boot, R. G., Blommaart, E. F., Swart, E., Ghauharali-van der Vlugt, K., Bijl, N., Moe, C., et al. (2001). Identification of a novel acidic mammalian chitinase distinct from chitotriosidase. *The Journal of Biological Chemistry 276*, 6770–6778.

Boot, R. G., Renkema, G. H., Strijland, A., van Zonneveld, A. J., & Aerts, J. M. (1995). Cloning of a cDNA encoding chitotriosidase, a human chitinase produced by macrophages. *Journal of Biological Chemistry 270*, 26252–26256.

Boot, R. G., van Achterberg, T. A., van Aken, B. E., Renkema, G. H., Jacobs, M. J., Aerts, J. M., et al. (1999). Strong induction of members of the chitinase family of proteins in atherosclerosis: chitotriosidase and human cartilage gp-39 expressed in lesion macrophages. *Arteriosclerosis, Thrombosis, and Vascular Biology 19*, 687–694.

Breyne, K., Steenbrugge, J., Demeyere, K., Lee, C. G., Elias, J. A., Petzl, W., et al. (2018). Immunomodulation of host chitinase 3-like 1 during a mammary pathogenic escherichia coli infection. *Frontiers in Immunology 9*, 1143.

Breyne, K., Steenbrugge, J., Demeyere, K., Vanden Berghe, T., & Meyer, E. (2017). Preconditioning with lipopolysaccharide or lipoteichoic acid protects against staphylococcus aureus mammary infection in mice. *Frontiers in Immunology 8*, 833.

Brumpton, B., Langhammer, A., Romundstad, P., Chen, Y., & Mai, X. M. (2013). General and abdominal obesity and incident asthma in adults: The HUNT study. *European Respiratory Journal 41*, 323–329.

Bussink, A. P., Speijer, D., Aerts, J. M., & Boot, R. G. (2007). Evolution of mammalian chitinase(-like) members of family 18 glycosyl hydrolases. *Genetics 177*, 959–970.

Cabrera, S. M., Henschel, A. M., & Hessner, M. J. (2016). Innate inflammation in type 1 diabetes. *Translational Research: The Journal of Laboratory and Clinical Medicine 167*, 214–227.

Cai, Q., & Tammineni, P. (2017). Mitochondrial aspects of synaptic dysfunction in alzheimer's disease. *Journal of Alzheimer's Disease 57*, 1087–1103.

Calderon-Garciduenas, A. L., & Duyckaerts, C. (2017). Alzheimer disease. *Handbook of Clinical Neurology 145*, 325–337.

Canto, E., Tintore, M., Villar, L. M., Costa, C., Nurtdinov, R., Alvarez-Cermeno, J. C., et al. (2015). Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. *Brain 138*, 918–931.

Cao, H. (2014). Adipocytokines in obesity and metabolic disease. *Journal of Endocrinology 220*, T47–T59.

Cao, S., Lu, X., Wang, L., Qian, X., Jin, G., & Ma, H. (2017). The functional polymorphisms of LIS1 are associated with acute myeloid leukemia risk in a han chinese population. *Leukemia Research 54*, 7–11.

Catalan, V., Gomez-Ambrosi, J., Rodriguez, A., Ramirez, B., Izaguirre, M., Hernandez-Lizoain, J. L., et al. (2016). Increased obesity-associated circulating levels of the extracellular matrix proteins osteopontin, chitinase-3 like-1 and tenascin c are associated with colon cancer. *PLoS ONE 11*, e0162189.

Chen, C. C., Llado, V., Eurich, K., Tran, H. T., & Mizoguchi, E. (2011). Carbohydrate-binding motif in chitinase 3-like 1 (CHI3L1/YKL-40) specifically activates Akt signaling pathway in colonic epithelial cells. *Clinical Immunology 140*, 268–275.

Chen, C. C., Pekow, J., Llado, V., Kanneganti, M., Lau, C. W., Mizoguchi, A., et al. (2011). Chitinase 3-like-1 expression in colonic epithelial cells as a potentially novel marker for colitis-associated neoplasia. *American Journal of Pathology 179*, 1494–1503.

Chen, C. H., Zhou, W., Liu, S., Deng, Y., Cai, F., Tone, M., et al. (2012). Increased NF-kappaB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. *International Journal of Neuropsychopharmacology 15*, 77–90.

Chen, X., Jiao, J., He, X., Zhang, J., Wang, H., Xu, Y., et al. (2017). CHI3L1 regulation of inflammation and the effects on osteogenesis in a staphylococcus aureus-induced murine model of osteomyelitis. *FEBS Journal 284*, 1738–1747.

Chen, Y., Zhang, S., Cao, J., & Zhang, X. (2018). Shrimp antiviral mja-miR-35 Targets CHI3L1 in human M2 macrophages and suppresses breast cancer metastasis. *Frontiers in Immunology 9*, 2071.

Chen, Y., Zhang, S., Wang, Q., & Zhang, X. (2017). Tumor-recruited M2 macrophages promote gastric and breast cancer metastasis via M2 macrophage-secreted CHI3L1 protein. *Journal of Hematology & Oncology 10*, 36.

Chiang, Y. C., Lin, H. W., Chang, C. F., Chang, M. C., Fu, C. F., Chen, T. C., et al. (2015). Overexpression of CHI3L1 is associated with chemoresistance and poor outcome of epithelial ovarian carcinoma. *Oncotarget 6*, 39740–39755.

Cho, S. J., Echevarria, G. C., Lee, Y. I., Kwon, S., Park, K. Y., Tsukiji, J., et al. (2014). YKL-40 is a protective biomarker for fatty liver in world trade center particulate matter-exposed firefighters. *Journal Mol Biomark Diagn*, 5.

Choi, J. Y., Yeo, I. J., Kim, K. C., Choi, W. R., Jung, J. K., Han, S. B., et al. (2018). K284-6111 prevents the amyloid beta-induced neuroinflammation and impairment of recognition memory through inhibition of NF-kappaB-mediated CHI3L1 expression. *Journal of Neuroinflammation 15*, 224.

Chung, C., Tallerico, T., & Seeman, P. (2003). Schizophrenia hippocampus has elevated expression of chondrex glycoprotein gene. *Synapse 50*, 29–34.

Cohen, N., Shani, O., Raz, Y., Sharon, Y., Hoffman, D., Abramovitz, L., et al. (2017). Fibroblasts drive an immunosuppressive and growth-promoting microenvironment in breast cancer via secretion of chitinase 3-like 1. *Oncogene 36*, 4457–4468.

Cope, A. P., Patel, S. D., Hall, F., Congia, M., Hubers, H. A., Verheijden, G. F., et al. (1999). T cell responses to a human cartilage autoantigen in the context of rheumatoid arthritis-associated and nonassociated HLA-DR4 alleles. *Arthritis and Rheumatism 42*, 1497–1507.

Dela Cruz, C. S., Liu, W., He, C. H., Jacoby, A., Gornitzky, A., Ma, B., et al. (2012). Chitinase 3-like-1 promotes streptococcus pneumoniae killing and augments host tolerance to lung antibacterial responses. *Cell Host & Microbe 12*, 34–46.

Deng, N., Li, L., Gao, J., Zhou, J., Wang, Y., Wang, C., et al. (2018). Hsa_circ_0009910 promotes carcinogenesis by promoting the expression of miR-449a target IL6R in osteosarcoma. *Biochemical and Biophysical Research Communications 495*, 189–196.

Deng, X., Liu, Y., Luo, M., Wu, J., Ma, R., Wan, Q., et al. (2017). Circulating miRNA-24 and its target YKL-40 as potential biomarkers in patients with coronary heart disease and type 2 diabetes mellitus. *Oncotarget 8*, 63038–63046.

Di Rosa, M., Distefano, G., Zorena, K., & Malaguarnera, L. (2016). Chitinases and immunity: Ancestral molecules with new functions. *Immunobiology 221*, 399–411.

Di Rosa, M., & Malaguarnera, L. (2016). Chitinase 3 Like-1: An emerging molecule involved in diabetes and diabetic complications. *Pathobiology 83*, 228–242.

Di Rosa, M., Szychlinska, M. A., Tibullo, D., Malaguarnera, L., & Musumeci, G. (2014). Expression of CHI3L1 and CHIT1 in osteoarthritic rat cartilage model. A morphological study. *European Journal of Histochemistry 58*, 2423.

Di Rosa, M., Tibullo, D., Saccone, S., Distefano, G., Basile, M. S., Di Raimondo, F., et al. (2016). CHI3L1 nuclear localization in monocyte derived dendritic cells. *Immunobiology 221*, 347–356.

Dicker, D., Salook, M. A., Marcoviciu, D., Djaldetti, M., & Bessler, H. (2013). Role of peripheral blood mononuclear cells in the predisposition of obese individuals to inflammation and infection. *Obesity Facts 6*, 146–151.

Downs, C. A., & Faulkner, M. S. (2015). Toxic stress, inflammation and symptomatology of chronic complications in diabetes. *World Journal of Diabetes 6*, 554–565.

El Ayoubi, N. K., & Khoury, S. J. (2017). Blood biomarkers as outcome measures in inflammatory neurologic diseases. *Neurotherapeutics 14*, 135–147.

Erturk, A., Cure, E., Cure, M. C., Parlak, E., Kurt, A., & Ogullar, S. (2015). The association between serum YKL-40 levels, mean platelet volume, and c-reactive protein in patients with cellulitis. *Indian Journal of Medical Microbiology 33*(Suppl), 61–66.

Erturk, K., Tas, F., Serilmez, M., Bilgin, E., & Yasasever, V. (2017). Clinical significance of serum Ykl-40 (chitinase-3-like-1 protein) as a biomarker in melanoma: An analysis of 112 turkish patients. *Asian Pacific Journal of Cancer Prevention 18*, 1383–1387.

Essafi-Benkhadir, K., Grosso, S., Puissant, A., Robert, G., Essafi, M., Deckert, M., et al. (2009). Dual role of Sp3 transcription factor as an inducer of apoptosis and a marker of tumour aggressiveness. *PLoS ONE 4*, e4478.

Eurich, K., Segawa, M., Toei-Shimizu, S., & Mizoguchi, E. (2009). Potential role of chitinase 3-like-1 in inflammation-associated carcinogenic changes of epithelial cells. *World Journal of Gastroenterology 15*, 5249–5259.

Faibish, M., Francescone, R., Bentley, B., Yan, W., & Shao, R. (2011). A YKL-40-neutralizing antibody blocks tumor angiogenesis and progression: a potential therapeutic agent in cancers. *Molecular Cancer Therapeutics 10*, 742–751.

Francescone, R. A., Scully, S., Faibish, M., Taylor, S. L., Oh, D., Moral, L., et al. (2011). Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. *Journal of Biological Chemistry 286*, 15332–15343.

Fuksiewicz, M., Kotowicz, B., Rutkowski, A., Achinger-Kawecka, J., Wagrodzki, M., & Kowalska, M. M. (2018). The assessment of clinical usage and prognostic value of YKL-40 serum levels in patients with rectal cancer without distant metastasis. *Technology in Cancer Research & Treatment 17*, 1533033818765209.

Furlan, A., Vercamer, C., Heliot, L., Wernert, N., Desbiens, X., & Pourtier, A. (2019). Ets-1 drives breast cancer cell angiogenic potential and interactions between breast cancer and endothelial cells. *International Journal of Oncology 54*, 29–40.

Fusetti, F., Pijning, T., Kalk, K. H., Bos, E., & Dijkstra, B. W. (2003). Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39. *Journal of Biological Chemistry 278*, 37753–37760.

Gong, Z., Xing, S., Zheng, F., & Xing, Q. (2014). Increased expression of chitinase 3-like 1 in aorta of patients with atherosclerosis and suppression of atherosclerosis in apolipoprotein E-knockout mice by chitinase 3-like 1 gene silencing. *Mediators of Inflammation 2014*, 905463.

Gorgens, S. W., Eckardt, K., Elsen, M., Tennagels, N., & Eckel, J. (2014). Chitinase-3-like protein 1 protects skeletal muscle from TNFalpha-induced inflammation and insulin resistance. *Biochemical Journal 459*, 479–488.

Goto, H., Kariya, R., Kudo, E., Okuno, Y., Ueda, K., Katano, H., et al. (2017). Restoring PU.1 induces apoptosis and modulates viral transactivation via interferon-stimulated genes in primary effusion lymphoma. *Oncogene 36*, 5252–5262.

Guo, W., Wang, J., & Wei, H. (2016). Serum YKL-40 level positively correlates with uterine leiomyomas. *Reproductive Sciences 23*, 1559–1564.

Gupta, S. C., Sundaram, C., Reuter, S., & Aggarwal, B. B. (2010). Inhibiting NF-kappaB activation by small molecules as a therapeutic strategy. *Biochimica et Biophysica Acta 1799*, 775–787.

Hakala, B. E., White, C., & Recklies, A. D. (1993). Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. *Journal of Biological Chemistry 268*, 25803–25810.

Hall, I. E., Stern, E. P., Cantley, L. G., Elias, J. A., & Parikh, C. R. (2014). Urine YKL-40 is associated with progressive acute kidney injury or death in hospitalized patients. *BMC Nephrology 15*, 133.

Hall, S., Surova, Y., Ohrfelt, A., Swedish Bio, Finder Study, Blennow, K., Zetterberg, H., et al. (2016). Longitudinal measurements of cerebrospinal fluid biomarkers in parkinson's disease. *Movement Disorders 31*, 898–905.

Hamilton, G., & Rath, B. (2017). Circulating tumor cell interactions with macrophages: Implications for biology and treatment. *Translation of Lung and Cancer Research 6*, 418–430.

Hamilton, G., Rath, B., & Ulsperger, E. (2015). How to target small cell lung cancer. *Oncoscience 2*, 684–692.

Hao, H., Wang, L., Chen, H., Xie, L., Bai, T., Liu, H., et al. (2017). YKL-40 promotes the migration and invasion of prostate cancer cells by regulating epithelial mesenchymal transition. *American Journal of Translational Research 9*, 3749–3757.

Harvey, S., Whaley, J., & Eberhardt, K. (2000). The relationship between serum levels of YKL-40 and disease progression in patients with early rheumatoid arthritis. *Scandinavian Journal of Rheumatology 29*, 391–393.

He, C. H., Lee, C. G., Dela Cruz, C. S., Lee, C. M., Zhou, Y., Ahangari, F., ... Elias, J. A. (2013). Chitinase 3-like 1 regulates cellular and tissue responses via IL-13 receptor α2. *Cell Reports 4*, 830–841.

Heiland, D. H., Ferrarese, R., Claus, R., Dai, F., Masilamani, A. P., Kling, E., et al. (2017). c-Jun-N-terminal phosphorylation regulates DNMT1 expression and genome wide methylation in gliomas. *Oncotarget 8*, 6940–6954.

Henrissat, B. (1991). A classification of glycosyl hydrolases based on amino acid sequence similarities. *Biochemical Journal 280*(Pt 2), 309–316.

Hinsinger, G., Galeotti, N., Nabholz, N., Urbach, S., Rigau, V., Demattei, C., et al. (2015). Chitinase 3-like proteins as diagnostic and prognostic biomarkers of multiple sclerosis. *Multiple Sclerosis 21*, 1251–1261.

Hobaus, C., Tscharre, M., Herz, C. T., Pesau, G., Wrba, T., Koppensteiner, R., et al. (2018). YKL-40 levels increase with declining ankle-brachial index and are associated with long-term cardiovascular mortality in peripheral arterial disease patients. *Atherosclerosis 274*, 152–156.

Hooks, S. B., Callihan, P., Altman, M. K., Hurst, J. H., Ali, M. W., & Murph, M. M. (2010). Regulators of G-Protein signaling RGS10 and RGS17 regulate chemoresistance in ovarian cancer cells. *Molecular Cancer 9*, 289.

Hooks, S. B., & Murph, M. M. (2015). Cellular deficiency in the RGS10 protein facilitates chemoresistant ovarian cancer. *Future Medicinal Chemistry 7*, 1483–1489.

Houseman, M., Potter, C., Marshall, N., Lakey, R., Cawston, T., Griffiths, I., et al. (2012). Baseline serum MMP-3 levels in patients with Rheumatoid Arthritis are still independently predictive of radiographic progression in a longitudinal observational cohort at 8 years follow up. *Arthritis Research & Therapy 14*, R30.

Hvolris, M. H., Piper, T. B., Hammer, E., Jorgensen, L. N., Olsen, J., Rahr, H. B., et al. (2016). Increased serological cancer-associated biomarker levels at large bowel endoscopy and risk of subsequent primary cancer (dagger). *Scandinavian Journal of Gastroenterology 51*, 860–865.

Ishii, T. (2015). Close teamwork between Nrf2 and peroxiredoxins 1 and 6 for the regulation of prostaglandin D2 and E2 production in macrophages in acute inflammation. *Free Radical Biology and Medicine 88*, 189–198 Part B.

Iwata, T., Kuwajima, M., Sukeno, A., Ishimaru, N., Hayashi, Y., Wabitsch, M., et al. (2009). YKL-40 secreted from adipose tissue inhibits degradation of type I collagen. *Biochemical and Biophysical Research Communications 388*, 511–516.

Jafari, B., Elias, J. A., & Mohsenin, V. (2014). Increased plasma YKL-40/chitinase-3-like-protein-1 is associated with endothelial dysfunction in obstructive sleep apnea. *PLoS ONE 9*, e98629.

Jang, M. A., Lee, S. H., Kim, N., & Ki, C. S. (2015). Frequency and spectrum of actionable pathogenic secondary findings in 196 korean exomes. *Genetics in Medicine 17*, 1007–1011.

Jeet, V., Tevz, G., Lehman, M., Hollier, B., & Nelson, C. (2014). Elevated YKL40 is associated with advanced prostate cancer (PCa) and positively regulates invasion and migration of PCa cells. *Endocrine-Related Cancer 21*, 723–737.

Jefri, M., Huang, Y. N., Huang, W. C., Tai, C. S., & Chen, W. L. (2015). YKL-40 regulated epithelial-mesenchymal transition and migration/invasion enhancement in non-small cell lung cancer. *BMC Cancer 15*, 590.

Jiang, Y. X., Zhang, G. H., Wang, Z. M., & Yang, H. (2014). Serum YKL-40 levels as a prognostic factor in patients with intracerebral hemorrhage. *Clinical Biochemistry 47*, 302–306.

Jin, T., Lu, Y., He, Q. X., Wang, H., Li, B. F., Zhu, L. Y., et al. (2015). The role of microRNA, miR-24, and Its target CHI3L1 in osteomyelitis caused by staphylococcus aureus. *Journal of Cellular Biochemistry 116*, 2804–2813.

Johansen, J. S. (2006). Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. *Danish Medical Bulletin 53*, 172–209.

Johansen, J. S., Christensen, I. J., Jorgensen, L. N., Olsen, J., Rahr, H. B., Nielsen, K. T., et al. (2015). Serum YKL-40 in risk assessment for colorectal cancer: a prospective study of 4,496 subjects at risk of colorectal cancer. *Cancer Epidemiology, Biomarkers and Prevention 24*, 621–626.

Johansen, J. S., Christoffersen, P., Moller, S., Price, P. A., Henriksen, J. H., Garbarsch, C., et al. (2000). Serum YKL-40 is increased in patients with hepatic fibrosis. *Journal of Hepatology 32*, 911–920.

Johansen, J. S., Jensen, H. S., & Price, P. A. (1993). A new biochemical marker for joint injury. Analysis of YKL-40 in serum and synovial fluid. *British Journal of Rheumatology 32*, 949–955.

Johansen, J. S., Moller, S., Price, P. A., Bendtsen, F., Junge, J., Garbarsch, C., et al. (1997). Plasma YKL-40: A new potential marker of fibrosis in patients with alcoholic cirrhosis? *Scandinavian Journal of Gastroenterology 32*, 582–590.

Johansen, J. S., Schultz, N. A., & Jensen, B. V. (2009). Plasma YKL-40: A potential new cancer biomarker? *Future Oncology (London, England) 5*, 1065–1082.

Johansen, J. S., Stoltenberg, M., Hansen, M., Florescu, A., Horslev-Petersen, K., Lorenzen, I., et al. (1999). Serum YKL-40 concentrations in patients with rheumatoid arthritis: Relation to disease activity. *Rheumatology (Oxford, England) 38*, 618–626.

Johansson, V., Jakobsson, J., Fortgang, R. G., Zetterberg, H., Blennow, K., Cannon, T. D., et al. (2017). Cerebrospinal fluid microglia and neurodegenerative markers in twins concordant and discordant for psychotic disorders. *European Archives of Psychiatry and Clinical Neuroscience 267*, 391–402.

Joob, B., Wiwanitkit, V., & Tin, S. S. (2015). YKL-40 and non-small cell lung cancer. *Tüberküloz ve Toraks 63*, 145–146.

Jung, T. W., Park, H. S., Choi, G. H., Kim, D., Jeong, J. H., & Lee, T. (2018). Chitinase-3-like protein 1 ameliorates atherosclerotic responses via PPARdelta-mediated suppression of inflammation and ER stress. *Journal of Cellular Biochemistry 119*, 6795–6805.

Jung, Y. Y., Kim, K. C., Park, M. H., Seo, Y., Park, H., Park, M. H., et al. (2018). Atherosclerosis is exacerbated by chitinase-3-like-1 in amyloid precursor protein transgenic mice. *Theranostics 8*, 749–766.

Kadam, K. M., D'Souza, S. J., Bandivdekar, A. H., & Natraj, U. (2006). Identification and characterization of oviductal glycoprotein-binding protein partner on gametes: epitopic similarity to non-muscle myosin IIA, MYH 9. *Molecular Human Reproduction 12*, 275–282.

Kamba, A., Lee, I. A., & Mizoguchi, E. (2013). Potential association between TLR4 and chitinase 3-like 1 (CHI3L1/YKL-40) signaling on colonic epithelial cells in inflammatory bowel disease and colitis-associated cancer. *Current Molecular Medicine 13*, 1110–1121.

Kanneganti, M., Kamba, A., & Mizoguchi, E. (2012). Role of chitotriosidase (chitinase 1) under normal and disease conditions. *Journal of Epithelial Biology & Pharmacology 5*, 1–9.

Kawada, M., Seno, H., Kanda, K., Nakanishi, Y., Akitake, R., Komekado, H., et al. (2012). Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer. *Oncogene 31*, 3111–3123.

Kazakova, M. H., Staneva, D. N., Koev, I. G., Staikov, D. G., Mateva, N., Timonov, P. T., et al. (2014). Protein and mRNA levels of YKL-40 in high-grade glioma. *Folia Biologica (Praha) 60*, 261–267.

Kemik, P., Saatli, B., Yildirim, N., Kemik, V. D., Deveci, B., Terek, M. C., et al. (2016). Diagnostic and prognostic values of preoperative serum levels of YKL-40, HE-4 and DKK-3 in endometrial cancer. *Gynecologic Oncology 140*, 64–69.

Kido, J., Bando, Y., Bando, M., Kajiura, Y., Hiroshima, Y., Inagaki, Y., et al. (2015). YKL-40 level in gingival crevicular fluid from patients with periodontitis and type 2 diabetes. *Oral Diseases 21*, 667–673.

Kim, D. H., Park, H. J., Lim, S., Koo, J. H., Lee, H. G., Choi, J. O., et al. (2018). Regulation of chitinase-3-like-1 in T cell elicits Th1 and cytotoxic responses to inhibit lung metastasis. *Nature Communications 9*, 503.

Kim, K. C., Yun, J., Son, D. J., Kim, J. Y., Jung, J. K., Choi, J. S., et al. (2018). Suppression of metastasis through inhibition of chitinase 3-like 1 expression by miR-125a-3p-mediated up-regulation of USF1. *Theranostics 8*, 4409–4428.

Kim, K. Y., Ahn, Y., Kim, D. Y., Kim, H. S., & Kim, D. S. (2017). Elevated serum YKL-40 levels in patients with kawasaki disease. *Biomarkers 22*, 326–330.

Kim, S. H., Das, K., Noreen, S., Coffman, F., & Hameed, M. (2007). Prognostic implications of immunohistochemically detected YKL-40 expression in breast cancer. *World Journal of Surgical Oncology 5*, 17.

Kitada, T., Pisani, A., Karouani, M., Haburcak, M., Martella, G., Tscherter, A., et al. (2009). Impaired dopamine release and synaptic plasticity in the striatum of parkin-/- mice. *Journal of Neurochemistry 110*, 613–621.

Kjaergaard, A. D., Johansen, J. S., Bojesen, S. E., & Nordestgaard, B. G. (2015). Elevated plasma YKL-40, lipids and lipoproteins, and ischemic vascular disease in the general population. *Stroke 46*, 329–335.

Knorr, T., Obermayr, F., Bartnik, E., Zien, A., & Aigner, T. (2003). YKL-39 (chitinase 3-like protein 2), but not YKL-40 (chitinase 3-like protein 1), is up regulated in osteoarthritic chondrocytes. *Annals of the Rheumatic Diseases 62*, 995–998.

Kognole, A. A., & Payne, C. M. (2017). Inhibition of mammalian glycoprotein YKL-40: identification of the physiological ligand. *Journal of Biological Chemistry 292*, 2624–2636.

Kori, M., Gov, E., & Arga, K. Y. (2019). Novel genomic biomarker candidates for cervical cancer as identified by differential co-expression network analysis. *OMICS: A Journal of Integrative Biology 23*, 261–273.

Krogh, M., Christensen, I., Bouwhuis, M., Johansen, J. S., Norgaard, P., Schmidt, H., et al. (2016). Prognostic and predictive value of YKL-40 in stage IIB-III melanoma. *Melanoma Research 26*, 367–376.

Kumagai, E., Mano, Y., Yoshio, S., Shoji, H., Sugiyama, M., Korenaga, M., et al. (2016). Serum YKL-40 as a marker of liver fibrosis in patients with non-alcoholic fatty liver disease. *Scientific Reports 6*, 35282.

Kunsch, C., & Medford, R. M. (1999). Oxidative stress as a regulator of gene expression in the vasculature. *Circulation Research 85*, 753–766.

Kunz, L. I., van't Wout, E. F., van Schadewijk, A., Postma, D. S., Kerstjens, H. A., Sterk, P. J., et al. (2015). Regulation of YKL-40 expression by corticosteroids: effect on pro-inflammatory macrophages in vitro and its modulation in COPD in vivo. *Respiratory Research 16*, 154.

Kzhyshkowska, J., Gratchev, A., & Goerdt, S. (2007). Human chitinases and chitinase-like proteins as indicators for inflammation and cancer. *Biomarker Insights 2*, 128–146.

Kzhyshkowska, J., Yin, S., Liu, T., Riabov, V., & Mitrofanova, I. (2016). Role of chitinase-like proteins in cancer. *Biological Chemistry 397*, 231–247.

Lackey, D. E., & Olefsky, J. M. (2016). Regulation of metabolism by the innate immune system. *Nature Reviews Endocrinology 12*, 15–28.

Lalaker, A., Nkrumah, L., Lee, W. K., Ramanathan, M., & Lane, A. P. (2009). Chitin stimulates expression of acidic mammalian chitinase and eotaxin-3 by human sinonasal epithelial cells in vitro. *American Journal of Rhinology & Allergy 23*, 8–14.

Lee, C. G., Da Silva, C. A., Dela Cruz, C. S., Ahangari, F., Ma, B., Kang, M. J., et al. (2011). Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. *Annual Review of Physiology 73*, 479–501.

Lee, C. G., Hartl, D., Lee, G. R., Koller, B., Matsuura, H., Da Silva, C. A., et al. (2009). Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. *The Journal of Experimental Medicine 206*, 1149–1166.

Lee, C. M., He, C. H., Nour, A. M., Zhou, Y., Ma, B., Park, J. W., et al. (2016). IL-13Ralpha2 uses TMEM219 in chitinase 3-like-1-induced signalling and effector responses. *Nature Communications 7*, 12752.

Lee, D. H., Han, J. H., Lee, Y. S., Jung, Y. S., Roh, Y. S., Yun, J. S., et al. (2019). Chitinase-3-like-1 deficiency attenuates ethanol-induced liver injury by inhibition of sterol regulatory element binding protein 1-dependent triglyceride synthesis. *Metabolism 95*, 46–56.

Lee, D. H., Kim, K. C., Hwang, C. J., Park, K. R., Jung, Y. S., Kim, S. Y., et al. (2019). Decreased lung tumor development in swapp mice through the downregulation of CHI3L1 and STAT 3 activity via the upregulation of miRNA342-3p. *Molecular Therapy–Nucleic Acids 16*, 63–72.

Lee, I. A., Low, D., Kamba, A., Llado, V., & Mizoguchi, E. (2014). Oral caffeine administration ameliorates acute colitis by suppressing chitinase 3-like 1 expression in intestinal epithelial cells. *Journal of Gastroenterology 49*, 1206–1216.

Lee, J. H., Kim, S. S., Kim, I. J., Song, S. H., Kim, Y. K., In Kim, J., et al. (2012). Clinical implication of plasma and urine YKL-40, as a proinflammatory biomarker, on early stage of nephropathy in type 2 diabetic patients. *Journal of Diabetes and its Complications 26*, 308–312.

Letuve, S., Kozhich, A., Humbles, A., Brewah, Y., Dombret, M. C., Grandsaigne, M., et al. (2010). Lung chitinolytic activity and chitotriosidase are elevated in chronic obstructive pulmonary disease and contribute to lung inflammation. *American Journal of Pathology 176*, 638–649.

Li, T. M., Liu, S. C., Huang, Y. H., Huang, C. C., Hsu, C. J., Tsai, C. H., et al. (2017). YKL-40-Induced Inhibition of miR-590-3p Promotes Interleukin-18 Expression and Angiogenesis of Endothelial Progenitor Cells. *International Journal of Molecular Sciences*, 18.

Li, Z., Lu, H., Gu, J., Liu, J., Zhu, Q., Lu, Y., et al. (2017). Chitinase 3-like-1-deficient splenocytes deteriorated the pathogenesis of acute graft-versus-host disease via regulating differentiation of tfh cells. *Inflammation 40*, 1576–1588.

Libreros, S., Garcia-Areas, R., & Iragavarapu-Charyulu, V. (2013). CHI3L1 plays a role in cancer through enhanced production of pro-inflammatory/pro-tumorigenic and angiogenic factors. *Immunologic Research 57*, 99–105.

Libreros, S., Garcia-Areas, R., Shibata, Y., Carrio, R., Torroella-Kouri, M., & Iragavarapu-Charyulu, V. (2012). Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: decreased tumor metastasis in a breast cancer model. *International Journal of Cancer 131*, 377–386.

Libreros, S., & Iragavarapu-Charyulu, V. (2015). YKL-40/CHI3L1 drives inflammation on the road of tumor progression. *Journal of Leukocyte Biology 98*, 931–936.

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature 541*, 481–487.

van Lierop, M. J., den Hoed, L., Houbiers, J., Vencovsky, J., Ruzickova, S., Krystufkova, O., et al. (2007). Endogenous HLA-DR-restricted presentation of the cartilage antigens human cartilage gp-39 and melanoma inhibitory activity in the inflamed rheumatoid joint. *Arthritis and Rheumatism 56*, 2150–2159.

Liu, D. G., Xue, L., Li, J., Yang, Q., & Peng, J. Z. (2018). Epithelial-mesenchymal transition and GALC expression of circulating tumor cells indicate metastasis and poor prognosis in non-small cell lung cancer. *Cancer Biomarkers 22*, 417–426.

Llorens, F., Thune, K., Tahir, W., Kanata, E., Diaz-Lucena, D., Xanthopoulos, K., et al. (2017). YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. *Molecular Neurodegeneration 12*, 83.

Long, X., Hu, H., Li, S., Chen, M., Cai, J., & Song, B. (2016). Hippocampal YKL-40 expression in rats after status epilepticus. *Epilepsy Research 125*, 52–57.

Low, D., Subramaniam, R., Lin, L., Aomatsu, T., Mizoguchi, A., Ng, A., et al. (2015). Chitinase 3-like 1 induces survival and proliferation of intestinal epithelial cells during chronic inflammation and colitis-associated cancer by regulating S100A9. *Oncotarget 6*, 36535–36550.

Low, D., Tran, H. T., Lee, I. A., Dreux, N., Kamba, A., Reinecker, H. C., et al. (2013). Chitin-binding domains of Escherichia coli ChiA mediate interactions with intestinal epithelial cells in mice with colitis. *Gastroenterology 145*(602-612), e609.

Luo, D., Chen, H., Lu, P., Li, X., Long, M., Peng, X., et al. (2017). CHI3L1 overexpression is associated with metastasis and is an indicator of poor prognosis in papillary thyroid carcinoma. *Cancer Biomarkers 18*, 273–284.

Ma, B., Herzog, E. L., Lee, C. G., Peng, X., Lee, C. M., Chen, X., et al. (2015). Role of chitinase 3-like-1 and semaphorin 7a in pulmonary melanoma metastasis. *Cancer Research 75*, 487–496.

Ma, J. Y., Li, R. H., Huang, K., Tan, G., Li, C., & Zhi, F. C. (2014). Increased expression and possible role of chitinase 3-like-1 in a colitis-associated carcinoma model. *World Journal of Gastroenterology 20*, 15736–15744.

Maegdefessel, L., Spin, J. M., Raaz, U., Eken, S. M., Toh, R., Azuma, J., et al. (2014). miR-24 limits aortic vascular inflammation and murine abdominal aneurysm development. *National Communation 5*, 5214.

Maines-Bandiera, S., Woo, M. M., Borugian, M., Molday, L. L., Hii, T., Gilks, B., et al. (2010). Oviductal glycoprotein (OVGP1, MUC9): a differentiation-based mucin present in serum of women with ovarian cancer. *International Journal of Gynecological Cancer 20*, 16–22.

Malaguarnera, L., Di Rosa, M., Zambito, A. M., dell Ombra, N., Di Marco, R., & Malaguarnera, M. (2006). Potential role of chitotriosidase gene in nonalcoholic fatty liver disease evolution. *American Journal of Gastroenterology 101*, 2060–2069.

Mansell, J. P., Cooke, M., Read, M., Rudd, H., Shiel, A. I., Wilkins, K., et al. (2016). Chitinase 3-like 1 expression by human (MG63) osteoblasts in response to lysophosphatidic acid and 1,25-dihydroxyvitamin D3. *Biochimie 128-129*, 193–200.

Marion, C. R., Wang, J., Sharma, L., Losier, A., Lui, W., Andrews, N., et al. (2016). Chitinase 3-like 1 (Chil1) regulates survival and macrophage-mediated Interleukin-1beta and tumor necrosis factor alpha during pseudomonas aeruginosa pneumonia. *Infection and Immunity 84*, 2094–2104.

Mathiasen, A. B., Harutyunyan, M. J., Jorgensen, E., Helqvist, S., Ripa, R., Gotze, J. P., et al. (2011). Plasma YKL-40 in relation to the degree of coronary artery disease in patients with stable ischemic heart disease. *Scandinavian Journal of Clinical and Laboratory Investigation 71*, 439–447.

Matsuura, H., Hartl, D., Kang, M. J., Dela Cruz, C. S., Koller, B., Chupp, G. L., et al. (2011). Role of breast regression protein-39 in the pathogenesis of cigarette smoke-induced inflammation and emphysema. *American Journal of Respiratory Cell and Molecular Biology 44*, 777–786.

McBride, D. S., Boisvert, C., Bleau, G., & Kan, F. W. (2004). Detection of nascent and/or mature forms of oviductin in the female reproductive tract and post-ovulatory oocytes by use of a polyclonal antibody against recombinant hamster oviductin. *Journal of Histochemistry and Cytochemistry 52*, 1001–1009.

Melah, K. E., Lu, S. Y., Hoscheidt, S. M., Alexander, A. L., Adluru, N., Destiche, D. J., et al. (2016). Cerebrospinal fluid markers of alzheimer's disease pathology and microglial activation are associated with altered white matter microstructure in asymptomatic adults at risk for alzheimer's disease. *Journal of Alzheimer's Disease 50*, 873–886.

Michailidou, I., Naessens, D. M., Hametner, S., Guldenaar, W., Kooi, E. J., Geurts, J. J., et al. (2017). Complement C3 on microglial clusters in multiple sclerosis occur in chronic but not acute disease: Implication for disease pathogenesis. *Glia 65*, 264–277.

Mitsuhashi, A., Matsui, H., Usui, H., Nagai, Y., Tate, S., Unno, Y., et al. (2009). Serum YKL-40 as a marker for cervical adenocarcinoma. *Annals of Oncology 20*, 71–77.

Miyata, H., Ashizawa, T., Iizuka, A., Kondou, R., Nonomura, C., Sugino, T., et al. (2017). Combination of a STAT3 inhibitor and an mtor inhibitor against a temozolomide-resistant glioblastoma cell line. *Cancer Genomics & Proteomics 14*, 83–91.

Miyatake, K., Tsuji, K., Yamaga, M., Yamada, J., Matsukura, Y., Abula, K., et al. (2013). Human YKL39 (chitinase 3-like protein 2), an osteoarthritis-associated gene, enhances proliferation and type II collagen expression in ATDC5 cells. *Biochemical and Biophysical Research Communications 431*, 52–57.

Mizoguchi, E. (2006). Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. *Gastroenterology 130*, 398–411.

Montgomery, T. A., Xu, L., Mason, S., Chinnadurai, A., Lee, C. G., Elias, J. A., et al. (2017). Breast regression protein-39/chitinase 3-like 1 promotes renal fibrosis after kidney injury via activation of myofibroblasts. *Journal of the American Society of Nephrology 28*, 3218–3226.

Morup, A. M., Kornblit, B., Johansen, J. S., Masmas, T. N., Madsen, H. O., Vindelov, L., et al. (2011). The prognostic value of YKL-40 concentrations in nonmyeloablative conditioning allogeneic hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation 17*, 1299–1307.

Mottonen, T., Hannonen, P., Leirisalo-Repo, M., Nissila, M., Kautiainen, H., Korpela, M., et al. (1999). Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *FIN-RACo trial group Lancet 353*, 1568–1573.

Muallem, G., & Hunter, C. A. (2014). ParadYm shift: Ym1 and Ym2 as innate immunological regulators of IL-17. *Nature Immunology 15*, 1099–1100.

Muszynski, P., Groblewska, M., Kulczynska-Przybik, A., Kulakowska, A., & Mroczko, B. (2017). YKL-40 as a potential biomarker and a possible target in therapeutic strategies of alzheimer's disease. *Current Neuropharmacology 15*, 906–917.

Mylin, A. K., Abildgaard, N., Johansen, J. S., Heickendorff, L., Kreiner, S., Waage, A., et al. (2015). Serum YKL-40: a new independent prognostic marker for skeletal complications in patients with multiple myeloma. *Leukemia and Lymphoma 56*, 2650–2659.

Natesh, K., Bhosale, D., Desai, A., Chandrika, G., Pujari, R., Jagtap, J., et al. (2015). Oncostatin-M differentially regulates mesenchymal and proneural signature genes in gliomas via STAT3 signaling. *Neoplasia 17*, 225–237.

Ngernyuang, N., Shao, R., Suwannarurk, K., & Limpaiboon, T. (2018). Chitinase 3 like 1 (CHI3L1) promotes vasculogenic mimicry formation in cervical cancer. *Pathology 50*, 293–297.

Ngernyuang, N., Yan, W., Schwartz, L. M., Oh, D., Liu, Y. B., Chen, H., et al. (2018). A heparin binding motif rich in arginine and lysine is the functional domain of YKL-40. *Neoplasia 20*, 182–192.

Nielsen, A. R., Erikstrup, C., Johansen, J. S., Fischer, C. P., Plomgaard, P., Krogh-Madsen, R., et al. (2008). Plasma YKL-40: a BMI-independent marker of type 2 diabetes. *Diabetes 57*, 3078–3082.

Nielsen, K. R., Rodrigo-Domingo, M., Steffensen, R., Baech, J., Bergkvist, K. S., Oosterhof, L., et al. (2017). Interactions between SNPs affecting inflammatory response genes are associated with multiple myeloma disease risk and survival. *Leukemia and Lymphoma 58*, 2695–2704.

Nøjgaard, C., Johansen, J. S., Christensen, E., Skovgaard, L. T., Price, P. A., & Becker, U. (2003). Serum levels of YKL-40 and PIIINP as prognostic markers in patients with alcoholic liver disease. *Journal of Hepatology 39*, 179–186.

Ozdemir, E., Cicek, T., & Kaya, M. O. (2012). Association of serum YKL-40 level with tumor burden and metastatic stage of prostate cancer. *Urology Journal 9*, 568–573.

Pacitti, D., & Bax, B. E. (2018). The development of an in vitro cerebral organoid model for investigating the pathomolecular mechanisms associated with the central nervous system involvement in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *Nucleosides, Nucleotides & Nucleic Acids 37*, 603–617.

Park, H. Y., Jun, C. D., Jeon, S. J., Choi, S. S., Kim, H. R., Choi, D. B., et al. (2012). Serum YKL-40 levels correlate with infarct volume, stroke severity, and functional outcome in acute ischemic stroke patients. *PLoS ONE 7*, e51722.

Paschetta, E., Belci, P., Alisi, A., Liccardo, D., Cutrera, R., Musso, G., et al. (2015). OSAS-related inflammatory mechanisms of liver injury in nonalcoholic fatty liver disease. *Mediators of Inflammation 2015*, 815721.

Peluso, M. J., Valcour, V., Phanuphak, N., Ananworanich, J., Fletcher, J. L., Chalermchai, T., et al. (2017). Immediate initiation of cART is associated with lower levels of cerebrospinal fluid YKL-40, a marker of microglial activation, in HIV-1 infection. *Acquired Immune Deficiency Syndrome 31*, 247–252.

Peng, H., Su, Q., Lin, Z. C., Zhu, X. H., Peng, M. S., & Lv, Z. B. (2018). Potential suppressive effects of theophylline on human rectal cancer SW480 cells in vitro by inhibiting YKL-40 expression. *Oncology Letters 15*, 7403–7408.

Persson, F., Rathcke, C. N., Gall, M. A., Parving, H. H., Vestergaard, H., & Rossing, P. (2012). High YKL-40 levels predict mortality in patients with type 2 diabetes. *Diabetes Research and Clinical Practice 96*, 84–89.

Petersson, M., Bucht, E., Granberg, B., & Stark, A. (2006). Effects of arginine-vasopressin and parathyroid hormone-related protein (1-34) on cell proliferation and production of YKL-40 in cultured chondrocytes from patients with rheumatoid arthritis and osteoarthritis. *Osteoarthritis and Cartilage 14*, 652–659.

Pina Batista, K. M., Vega, I. F., de Eulate-Beramendi, S. A., Morales, J., Kurbanov, A., Asnel, D., et al. (2015). Prognostic significance of the markers IDH1 and YKL40 related to the subventricular zone. *Folia Neuropathologica 53*, 52–59.

Pinet, S., Bessette, B., Vedrenne, N., Lacroix, A., Richard, L., Jauberteau, M. O., et al. (2016). TrkB-containing exosomes promote the transfer of glioblastoma aggressiveness to YKL-40-inactivated glioblastoma cells. *Oncotarget 7*, 50349–50364.

Puthumana, J., Hall, I. E., Reese, P. P., Schroppel, B., Weng, F. L., Thiessen-Philbrook, H., et al. (2017). YKL-40 associates with renal recovery in deceased donor kidney transplantation. *Journal of the American Society of Nephrology 28*, 661–670.

Querol-Vilaseca, M., Colom-Cadena, M., Pegueroles, J., San Martin-Paniello, C., Clarimon, J., Belbin, O., et al. (2017). YKL-40 (Chitinase 3-like I) is expressed in a subset of astrocytes in Alzheimer's disease and other tauopathies. *Journal of Neuroinflammation 14*, 118.

Quintana, E., Coll, C., Salavedra-Pont, J., Munoz-San Martin, M., Robles-Cedeno, R., Tomas-Roig, J., et al. (2018). Cognitive impairment in early stages of multiple sclerosis is associated with high cerebrospinal fluid levels of chitinase 3-like 1 and neurofilament light chain. *European Journal of Neurology 25*, 1189–1191.

Rathcke, C. N., Persson, F., Tarnow, L., Rossing, P., & Vestergaard, H. (2009). YKL-40, a marker of inflammation and endothelial dysfunction, is elevated in patients with type 1 diabetes and increases with levels of albuminuria. *Diabetes Care 32*, 323–328.

Rathcke, C. N., & Vestergaard, H. (2006). YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. *Inflammation Research 55*, 221–227.

Recklies, A. D., Ling, H., White, C., & Bernier, S. M. (2005). Inflammatory cytokines induce production of CHI3L1 by articular chondrocytes. *Journal of Biological Chemistry 280*, 41213–41221.

Rehli, M., Niller, H. H., Ammon, C., Langmann, S., Schwarzfischer, L., Andreesen, R., et al. (2003). Transcriptional regulation of CHI3L1, a marker gene for late stages of macrophage differentiation. *Journal of Biological Chemistry 278*, 44058–44067.

Renkema, G. H., Boot, R. G., Au, F. L., Donker-Koopman, W. E., Strijland, A., Muijsers, A. O., et al. (1998). Chitotriosidase, a chitinase, and the 39-kDa human cartilage glycoprotein, a chitin-binding lectin, are homologues of family 18 glycosyl hydrolases secreted by human macrophages. *European Journal of Biochemistry 251*, 504–509.

Renkema, G. H., Boot, R. G., Strijland, A., Donker-Koopman, W. E., Van Den Berg, M., Muijsers, A. O., et al. (1997). Synthesis, sorting, and processing into distinct isoforms of human macrophage chitotriosidase. *European Journal of Biochemistry 244*, 279–285.

Riabov, V., Gudima, A., Wang, N., Mickley, A., Orekhov, A., & Kzhyshkowska, J. (2014). Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis. *Frontiers in Physiology 5*, 75.

Ridker, P. M., Chasman, D. I., Rose, L., Loscalzo, J., & Elias, J. A. (2014). Plasma levels of the proinflammatory chitin-binding glycoprotein YKL-40, variation in the chitinase 3-like 1 gene (CHI3L1), and incident cardiovascular events. *Journal of the American Heart Association 3*, e000897.

Rocchiccioli, S., Cecchettini, A., Ucciferri, N., Terreni, M., Viglione, F., Trivella, M. G., et al. (2015). Site-Specific secretome map evidences VSMC-related markers of coronary atherosclerosis grade and extent in the hypercholesterolemic swine. *Disease Markers 2015*, 465242.

Rocha, N. P., Ribeiro, F. M., Furr-Stimming, E., & Teixeira, A. L. (2016). Neuroimmunology of huntington's disease: revisiting evidence from human studies. *Mediators of Inflammation 2016*, 8653132.

Rolova, T., Dhungana, H., Korhonen, P., Valonen, P., Kolosowska, N., Konttinen, H., et al. (2016). Deletion of nuclear factor kappa b p50 subunit decreases inflammatory response and mildly protects neurons from transient forebrain ischemia-induced damage. *Aging and Disease 7*, 450–465.

Roslind, A., Johansen, J. S., Christensen, I. J., Kiss, K., Balslev, E., Nielsen, D. L., et al. (2008). High serum levels of YKL-40 in patients with squamous cell carcinoma of the head and neck are associated with short survival. *International Journal of Cancer 122*, 857–863.

Rovina, N., Koutsoukou, A., & Koulouris, N. G. (2013). Inflammation and immune response in COPD: where do we stand? *Mediators of Inflammation 2013*, 413735.

Rusak, A., Jablonska, K., Piotrowska, A., Grzegrzolka, J., Nowak, A., Wojnar, A., et al. (2018). The Role of CHI3L1 expression in angiogenesis in invasive ductal breast carcinoma. *Anticancer Research 38*, 3357–3366.

Rustenhoven, J., Smith, A. M., Smyth, L. C., Jansson, D., Scotter, E. L., Swanson, M. E. V., et al. (2018). PU.1 regulates Alzheimer's disease-associated genes in primary human microglia. *Molecular Neurodegeneration 13*, 44.

Rymo, I., Kern, S., Bjerke, M., Zetterberg, H., Marlow, T., Blennow, K., et al. (2017). CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. *Acta Psychiatrica Scandinavica 135*, 351–357.

Salomon, J., Matusiak, L., Nowicka-Suszko, D., & Szepietowski, J. C. (2017). Chitinase-3-like protein 1 (YKL-40) reflects the severity of symptoms in atopic dermatitis. *Journal of Immunology Research 2017*, 5746031.

Salvatore, V., Focaroli, S., Teti, G., Mazzotti, A., & Falconi, M. (2015). Changes in the gene expression of co-cultured human fibroblast cells and osteosarcoma cells: the role of microenvironment. *Oncotarget 6*, 28988–28998.

Salvatore, V., Teti, G., Focaroli, S., Mazzotti, M. C., Mazzotti, A., & Falconi, M. (2017). The tumor microenvironment promotes cancer progression and cell migration. *Oncotarget 8*, 9608–9616.

Sanchez, C., Mazzucchelli, G., Lambert, C., Comblain, F., DePauw, E., & Henrotin, Y. (2018). Comparison of secretome from osteoblasts derived from sclerotic versus non-sclerotic subchondral bone in OA: A pilot study. *PLoS ONE 13*, e0194591.

Sanfilippo, C., Longo, A., Lazzara, F., Cambria, D., Distefano, G., Palumbo, M., et al. (2017). CHI3L1 and CHI3L2 overexpression in motor cortex and spinal cord of sALS patients. *Molecular and Cellular Neurosciences 85*, 162–169.

Sarma, N. J., Tiriveedhi, V., Subramanian, V., Shenoy, S., Crippin, J. S., Chapman, W. C., et al. (2012). Hepatitis c virus mediated changes in miRNA-449a modulates inflammatory biomarker YKL40 through components of the NOTCH signaling pathway. *PLoS ONE 7*, e50826.

Schernthaner, G. H., Hobaus, C., & Brix, J. (2016). YKL-40 and its complex association with metabolic syndrome, obesity, and cardiovascular disease. *Anatolian Journal of Cardiology 16*, 959.

Schimpl, M., Rush, C. L., Betou, M., Eggleston, I. M., Recklies, A. D., & van Aalten, D. M. (2012). Human YKL-39 is a pseudo-chitinase with retained chitooligosaccharide-binding properties. *Biochemical Journal 446*, 149–157.

Schultz, N. A., Christensen, I. J., Werner, J., Giese, N., Jensen, B. V., Larsen, O., et al. (2013). Diagnostic and prognostic impact of circulating YKL-40, IL-6, and CA 19.9 in patients with pancreatic cancer. *PLoS ONE 8*, e67059.

Seki, M., Kimura, S., Isobe, T., Yoshida, K., Ueno, H., Nakajima-Takagi, Y., et al. (2017). Recurrent SPI1 (PU.1) fusions in high-risk pediatric T cell acute lymphoblastic leukemia. *Nature Genetics 49*, 1274–1281.

Seshadri, S., Beiser, A., Kelly-Hayes, M., Kase, C. S., Au, R., Kannel, W. B., et al. (2006). The lifetime risk of stroke: Estimates from the framingham study. *Stroke 37*, 345–350.

Shao, R. (2013). YKL-40 acts as an angiogenic factor to promote tumor angiogenesis. *Frontiers in Physiology 4*, 122.

Shao, R., Cao, Q. J., Arenas, R. B., Bigelow, C., Bentley, B., & Yan, W. (2011). Breast cancer expression of YKL-40 correlates with tumour grade, poor differentiation, and other cancer markers. *British Journal of Cancer 105*, 1203–1209.

Shao, R., Francescone, R., Ngernyuang, N., Bentley, B., Taylor, S. L., Moral, L., et al. (2014). Anti-YKL-40 antibody and ionizing irradiation synergistically inhibit tumor vascularization and malignancy in glioblastoma. *Carcinogenesis 35*, 373–382.

Shidfar, A., Fatokun, T., Ivancic, D., Chatterton, R. T., Khan, S. A., & Wang, J. (2016). Protein biomarkers for breast cancer risk are specifically correlated with local steroid hormones in nipple aspirate fluid. *Hormones & Cancer 7*, 252–259.

Shih, R. H., Wang, C. Y., & Yang, C. M. (2015). NF-kappaB signaling pathways in neurological inflammation: A mini review. *Frontiers in Molecular Neuroscience 8*, 77.

Singh, S. K., Bhardwaj, R., Wilczynska, K. M., Dumur, C. I., & Kordula, T. (2011). A complex of nuclear factor I-X3 and STAT3 regulates astrocyte and glioma migration through the secreted glycoprotein YKL-40. *Journal of Biological Chemistry 286*, 39893–39903.

Snow, W. M., & Albensi, B. C. (2016). Neuronal gene targets of nf-kappab and their dysregulation in alzheimer's disease. *Frontiers in Molecular Neuroscience 9*, 118.

Sohn, M. H., Kang, M. J., Matsuura, H., Bhandari, V., Chen, N. Y., Lee, C. G., et al. (2010). The chitinase-like proteins breast regression protein-39 and YKL-40 regulate hyperoxia-induced acute lung injury. *American Journal of Respiratory and Critical Care Medicine 182*, 918–928.

Spekker-Bosker, K., Ufermann, C. M., Maywald, M., Zimmermann, A., Domrose, A., Woite, C., et al. (2019). hCMV-mediated immune escape mechanisms favor pathogen growth and disturb the immune privilege of the eye. *International Journal of Molecular Sciences*, 20.

Starossom, S. C., Campo Garcia, J., Woelfle, T., Romero-Suarez, S., Olah, M., Watanabe, F., et al. (2019). Chi3l3 induces oligodendrogenesis in an experimental model of autoimmune neuroinflammation. *Nature Communications 10*, 217.

Stawerski, P., Wagrowska-Danilewicz, M., Stasikowska-Kanicka, O., & Danilewicz, M. (2011). Increased tissue immunoexpression of YKL-40 protein in high grade serous ovarian cancers. *Pathology, Research and Practice 207*, 573–576.

Steenbakkers, P. G., Baeten, D., Rovers, E., Veys, E. M., Rijnders, A. W., Meijerink, J., et al. (2003). Localization of MHC class II/human cartilage glycoprotein-39 complexes in synovia of rheumatoid arthritis patients using complex-specific monoclonal antibodies. *Journal of Immunology 170*, 5719–5727.

Steponaitis, G., Skiriute, D., Kazlauskas, A., Golubickaite, I., Stakaitis, R., Tamasauskas, A., et al. (2016). High CHI3L1 expression is associated with glioma patient survival. *Diagnostic Pathology 11*, 42.

Stoeck, K., Sanchez-Juan, P., Gawinecka, J., Green, A., Ladogana, A., Pocchiari, M., et al. (2012). Cerebrospinal fluid biomarker supported diagnosis of Creutzfeldt-Jakob disease and rapid dementias: a longitudinal multicentre study over 10 years. *Brain 135*, 3051–3061.

Subramaniam, R., Mizoguchi, A., & Mizoguchi, E. (2016). Mechanistic roles of epithelial and immune cell signaling during the development of colitis-associated cancer. *Cancer Research Front 2*, 1–21.

Sugimoto, K., & Takei, Y. (2017). Pathogenesis of alcoholic liver disease. *Hepatology Research 47*, 70–79.

Sutherland, T. E. (2018). Chitinase-like proteins as regulators of innate immunity and tissue repair: helpful lessons for asthma? *Biochemical Society Transactions 46*, 141–151.

Sutherland, T. E., Maizels, R. M., & Allen, J. E. (2009). Chitinases and chitinase-like proteins: potential therapeutic targets for the treatment of T-helper type 2 allergies. *Clinical and Experimental Allergy 39*, 943–955.

Tao, H., Yang, J. J., Shi, K. H., Huang, C., Zhang, L., Lv, X. W., et al. (2014). The significance of YKL-40 protein in liver fibrosis. *Inflammation Research 63*, 249–254.

Terwisscha Van Scheltinga, A. C., Armand, S., Kalk, K. H., Isogai, A., Henrissat, B., & Dijkstra, B. W. (1995). Stereochemistry of chitin hydrolysis by a plant chitinase/lysozyme and X-ray structure of a complex with allosamidin: evidence for substrate assisted catalysis. *Biochemistry 34*, 15619–15623.

Thomsen, S. B., Gjesing, A. P., Rathcke, C. N., Ekstrom, C. T., Eiberg, H., Hansen, T., et al. (2015). Associations of the Inflammatory Marker YKL-40 with Measures of Obesity and Dyslipidaemia in Individuals at High Risk of Type 2 Diabetes. *PLoS ONE 10*, e0133672.

Thongsom, S., Chaocharoen, W., Silsirivanit, A., Wongkham, S., Sripa, B., Choe, H., et al. (2016). YKL-40/chitinase-3-like protein 1 is associated with poor prognosis and promotes cell growth and migration of cholangiocarcinoma. *Tumour Biology 37*, 9451–9463.

Thorn, A. P., Daugaard, S., Christensen, L. H., Christensen, I. J., & Petersen, M. M. (2016). YKL-40 protein in osteosarcoma tumor tissue. *Acta Pathologica, Microbiologica et Immunologica Scandinavica 124*, 453–461.

Tiriveedhi, V., Upadhya, G. A., Busch, R. A., Gunter, K. L., Dines, J. N., Knolhoff, B. L., et al. (2014). Protective role of bortezomib in steatotic liver ischemia/reperfusion injury through abrogation of MMP activation and YKL-40 expression. *Transplant Immunology 30*, 93–98.

Tran, H. T., Lee, I. A., Low, D., Kamba, A., Mizoguchi, A., Shi, H. N., ... Mizoguchi, E. (2014b). Chitinase 3-like 1 synergistically activates IL6-mediated STAT3 phosphorylation in intestinal epithelial cells in murine models of infectious colitis. *Inflammatory Bowel Diseases 20*, 835–846.

Tran, H. T., Lee, I. A., Low, D., Kamba, A., Mizoguchi, A., Shi, H. N., et al. (2014a). Chitinase 3-like 1 synergistically activates IL6-mediated STAT3 phosphorylation in intestinal epithelial cells in murine models of infectious colitis. *Inflammatory Bowel Diseases 20*, 835–846.

Tsai, Y., Ko, Y., Huang, M., Lin, M., Wu, C., Wang, C., et al. (2014). CHI3L1 polymorphisms associate with asthma in a Taiwanese population. *BMC Medical Genetics 15*, 86.

Tsark, E. C., Wang, W., Teng, Y. C., Arkfeld, D., Dodge, G. R., & Kovats, S. (2002). Differential MHC class II-mediated presentation of rheumatoid arthritis autoantigens by human dendritic cells and macrophages. *Journal of Immunology 169*, 6625–6633.

Turkyilmaz, A. K., Devrimsel, G., Kirbas, A., Cicek, Y., Karkucak, M., Capkin, E., et al. (2013). Relationship between pulse wave velocity and serum YKL-40 level in patients with early rheumatoid arthritis. *Rheumatology International 33*, 2751–2756.

Turn, C. S., & Kolliputi, N. (2014). Two sides of a coin: the dual roles of chitinase 3-like 1 in idiopathic pulmonary fibrosis. *Lung 192*, 825–827.

Uhlen, M., Fagerberg, L., Hallstrom, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., et al. (2015). Proteomics. Tissue-based map of the human proteome. *Science 347*, 1260419.

Usemann, J., Frey, U., Mack, I., Schmidt, A., Gorlanova, O., Roosli, M., et al. (2016). CHI3L1 polymorphisms, cord blood YKL-40 levels and later asthma development. *BMC Pulmonary Medicine 16*, 81.

Vaananen, T., Kallio, J., Vuolteenaho, K., Ojala, A., Luukkaala, T., Hamalainen, M., et al. (2017). High YKL-40 is associated with poor survival in patients with renal cell carcinoma: A novel independent prognostic marker. *Scandinavian Journal of Urology 51*, 367–372.

Vaananen, T., Vuolteenaho, K., Kautiainen, H., Nieminen, R., Mottonen, T., Hannonen, P., et al. (2017). Glycoprotein YKL-40: A potential biomarker of disease activity in rheumatoid arthritis during intensive treatment with csDMARDs and infliximab. Evidence from the randomised controlled NEO-RACo trial. *PLoS ONE 12*, e0183294.

Varhaug, K. N., Barro, C., Bjornevik, K., Myhr, K. M., Torkildsen, O., Wergeland, S., et al. (2018). Neurofilament light chain predicts disease activity in relapsing-remitting MS. *Neurol Neuroimmunol Neuroinflamm 5*, e422.

Volck, B., Johansen, J. S., Stoltenberg, M., Garbarsch, C., Price, P. A., Ostergaard, M., et al. (2001). Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Involvement of YKL-40 in the joint pathology. *Osteoarthritis and Cartilage 9*, 203–214.

Volck, B., Price, P. A., Johansen, J. S., Sorensen, O., Benfield, T. L., Nielsen, H. J., et al. (1998). YKL-40, a mammalian member of the chitinase family, is a matrix protein of specific granules in human neutrophils. *Proceedings of the Association of American Physicians 110*, 351–360.

Vos, K., Miltenburg, A. M., van Meijgaarden, K. E., van den Heuvel, M., Elferink, D. G., van Galen, P. J., et al. (2000). Cellular immune response to human cartilage glycoprotein-39 (HC gp-39)-derived peptides in rheumatoid arthritis and other inflammatory conditions. *Rheumatology (Oxford, England) 39*, 1326–1331.

Wang, C., Mavrogianis, P. A., & Fazleabas, A. T. (2009). Endometriosis is associated with progesterone resistance in the baboon (Papio anubis) oviduct: Evidence based on the localization of oviductal glycoprotein 1 (OVGP1). *Biology of Reproduction 80*, 272–278.

Wang, G., Li, Y., Wang, X. Y., Chuai, M., Yeuk-Hon Chan, J., Lei, J., et al. (2015). Misexpression of BRE gene in the developing chick neural tube affects neurulation and somitogenesis. *Molecular Biology of the Cell 26*, 978–992.

Wang, H. L., Hsiao, P. C., Tsai, H. T., Yeh, C. B., & Yang, S. F. (2013). Usefulness of plasma YKL-40 in management of community-acquired pneumonia severity in patients. *International Journal of Molecular Sciences 14*, 22817–22825.

Wang, W. Y., Tan, M. S., Yu, J. T., & Tan, L. (2015). Role of pro-inflammatory cytokines released from microglia in alzheimer's disease. *Annals Translation Medicine 3*, 136.

Wang, X. W., Cai, C. L., Xu, J. M., Jin, H., & Xu, Z. Y. (2015). Increased expression of chitinase 3-like 1 is a prognosis marker for non-small cell lung cancer correlated with tumor angiogenesis. *Tumour Biology 36*, 901–907.

Wang, Y., Wong, C. W., Yan, M., Li, L., Liu, T., Or, P. M., et al. (2018). Differential regulation of the pro-inflammatory biomarker, YKL-40/CHI3L1, by PTEN/Phosphoinositide 3-kinase and JAK2/STAT3 pathways in glioblastoma. *Cancer Letters 429*, 54–65.

Warde-Farley, D., Donaldson, S. L., Comes, O., Zuberi, K., Badrawi, R., Chao, P., et al. (2010). The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. *Nucleic Acids Research 38*, W214–w220.

Wennstrom, M., Surova, Y., Hall, S., Nilsson, C., Minthon, L., Hansson, O., et al. (2015). The inflammatory marker YKL-40 is elevated in cerebrospinal fluid from patients with alzheimer's but not parkinson's disease or dementia with lewy bodies. *PLoS ONE 10*, e0135458.

Xiao, Q., Shi, R., Yang, W., Zou, Y., Du, Y., Zhang, M., et al. (2016). Time-dependent increase of chitinase1 in APP/PS1 double transgenic mice. *Neurochemical Research 41*, 1604–1611.

Xiao, Y., Christou, H., Liu, L., Visner, G., Mitsialis, S. A., Kourembanas, S., et al. (2013). Endothelial indoleamine 2,3-dioxygenase protects against development of pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine 188*, 482–491.

Xing, S., Zheng, X., Zeng, T., Zeng, M. S., Zhong, Q., Cao, Y. S., et al. (2017). Chitinase 3-like 1 secreted by peritumoral macrophages in esophageal squamous cell carcinoma is a favorable prognostic factor for survival. *World Journal of Gastroenterology 23*, 7693–7704.

Xu, C. H., Yu, L. K., & Hao, K. K. (2014). Serum YKL-40 level is associated with the chemotherapy response and prognosis of patients with small cell lung cancer. *PLoS ONE 9*, e96384.

Xu, X., Ma, H., Xu, J., Huang, H., Wu, X., Xiong, Y., et al. (2014). Elevation in circulating YKL-40 concentration in patients with cerebrovascular disease. *Bosnian Journal of Basic Medical Sciences. Udruzenje Basicnih Mediciniskih Znanosti 14*, 120–124.

Xu, Y., Wang, Q., Liu, Y., Cui, R., Lu, K., & Zhao, Y. (2016). Association between Helicobacter pylori infection and carotid atherosclerosis in patients with vascular dementia. *Journal of the Neurological Sciences 362*, 73–77.

Yan, C., Ding, X., Wu, L., Yu, M., Qu, P., & Du, H. (2013). Stat3 downstream gene product chitinase 3-like 1 is a potential biomarker of inflammation-induced lung cancer in multiple mouse lung tumor models and humans. *PLoS ONE 8*, e61984.

Yang, M. S., Morris, D. W., Donohoe, G., Kenny, E., O'Dushalaine, C. T., Schwaiger, S., et al. (2008). Chitinase-3-like 1 (CHI3L1) gene and schizophrenia: genetic association and a potential functional mechanism. *Biological Psychiatry 64*, 98–103.

Yang, Y., Yang, J. J., Tao, H., & Jin, W. S. (2014). YKL-40 and EGFR is a good biomarker for predicting nodal metastasis in anal carcinoma. *Colorectal Disease 16*, 69.

Yao, Y. L., Ma, J., Wang, P., Xue, Y. X., Li, Z., Zhao, L. N., et al. (2015). miR-101 acts as a tumor suppressor by targeting Kruppel-like factor 6 in glioblastoma stem cells. *CNS Neuroscience & Therapeutics 21*, 40–51.

Yuan, Q., Bu, Q., Li, G., Zhang, J., Cui, T., Zhu, R., et al. (2016). Association between single nucleotide polymorphisms of upstream transcription factor 1 (USF1) and susceptibility to papillary thyroid cancer. *Clinical Endocrinology 84*, 564–570.

Zhang, F., & Jiang, L. (2015). Neuroinflammation in alzheimer's disease. *Neuropsychiatric Disease and Treatment 11*, 243–256.

Zhang, W., Kawanishi, M., Miyake, K., Kagawa, M., Kawai, N., Murao, K., et al. (2010). Association between YKL-40 and adult primary astrocytoma. *Cancer 116*, 2688–2697.

Zhang, Y., Zhang, Z., Cao, L., Lin, J., Yang, Z., & Zhang, X. (2017). A common CD55 rs2564978 variant is associated with the susceptibility of non-small cell lung cancer. *Oncotarget 8*, 6216–6221.

Zhao, X., Wang, T., Liu, B., Wu, Z., Yu, S., & Wang, T. (2015). Significant association between upstream transcription factor 1 rs2516839 polymorphism and hepatocellular carcinoma risk: A case-control study. *Tumour Biology 36*, 2551–2558.

Zheng, M., Cai, W. M., Zhao, J. K., Zhu, S. M., & Liu, R. H. (2005). Determination of serum levels of YKL-40 and hyaluronic acid in patients with hepatic fibrosis due to schistosomiasis japonica and appraisal of their clinical value. *Acta Tropica 96*, 148–152.

Zhou, Y., He, C. H., Herzog, E. L., Peng, X., Lee, C. M., Nguyen, T. H., et al. (2015). Chitinase 3-like-1 and its receptors in Hermansky-Pudlak syndrome-associated lung disease. *Journal of Clinical Investigation 125*, 3178–3192.

Zhou, Y., He, C. H., Yang, D. S., Nguyen, T., Cao, Y., Kamle, S., et al. (2018). Galectin-3 Interacts with the CHI3L1 axis and contributes to hermansky-pudlak syndrome lung disease. *Journal of Immunology 200*, 2140–2153.

Zhou, Y., Peng, H., Sun, H., Peng, X., Tang, C., Gan, Y., et al. (2014). Chitinase 3-like 1 suppresses injury and promotes fibroproliferative responses in Mammalian lung fibrosis. *Science Translational Medicine 6*, 240ra276.

Zhu, C. B., Chen, L. L., Tian, J. J., Su, L., Wang, C., Gai, Z. T., et al. (2012). Elevated serum YKL-40 level predicts poor prognosis in hepatocellular carcinoma after surgery. *Annals of Surgical Oncology 19*, 817–825.

Zhu, Z., Zheng, T., Homer, R. J., Kim, Y. K., Chen, N. Y., Cohn, L., et al. (2004). Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. *Science 304*, 1678–1682.