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Review Article

The loss of tolerance to CHI3L1 – A putative role in inflammatory bowel disease?

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ABSTRACT

The incidence of inflammatory bowel disease (IBD) is steadily increasing. IBD is characterized by chronic inflammation of the gastrointestinal tract and is divided into the two main entities Crohn's disease (CD) and ulcerative colitis (UC). Genetic predispositions, environmental factors and a dysregulated immune response are known to be involved at the beginning of IBD. However, their etiopathogenesis is not yet fully understood. Over the last ten years, there has been increasing evidence of the involvement of the member of the 18-glycosylhydrolase family chitinase-3-like protein 1 (CHI3L1) in IBD. CHI3L1 is associated with various diseases such as cancer and chronic inflammatory diseases including rheumatoid arthritis or IBD as well as neurological diseases where it can act as a chemoattractant, mitogen or growth factor. This review will focus on the role of autoimmunity to CHI3L1 in IBD in the context of its expression in inflamed colonic epithelia and interaction with intestinal microbiota. Further, it will provide insights into the interaction of CHI3L1 with different mechanisms of the innate and adaptive immune response in IBD.

1. Introduction

The incidence of inflammatory bowel diseases (IBDs) is increasing in countries that are developing western lifestyles, and IBD is most prevalent in industrialized countries affecting about one in 250 individuals [1]. However, the etiology of IBD is still elusive [2]. Based on pathological and clinical characteristics, IBD can be divided into two main entities, ulcerative colitis (UC) and Crohn's disease (CD). The latter is characterized by a transmural inflammation that leads to abscesses, fistulas and strictures and can affect the gastrointestinal tract from the mouth to the rectum. In contrast, UC is characterized by diffuse inflammation of the mucosa, locally restricted to the colon and rectum [3,4]. However, it is assumed that dysfunction of the intestinal mucosal barrier and dysregulation of the immune system, genetic predisposition and environmental factors play a significant role in the manifestation of IBD [5,6]. An increased leakiness of the epithelial barrier in combination with altered T cell regulation and function as well as impaired innate immunity may be triggers for mucosal inflammation in IBD [7–11]. In this article, we focus on the role of the 18-glycosylhydrolase member chitinase-3-like 1 protein (CHI3L1) in the pathophysiology of IBD.

2. Chitinase-3-like protein 1 (CHI3L1)

The 40 kDa glycoprotein CHI3L1 was first described in 1990 as a protein secreted by synovial cells and was referred to as human cartilage glycoprotein-39 (HC gp-39) [12] or YKL-40 due to its three N-terminal amino acids, Tyrosine (Y)- Lysine (K)- Leucine (L) [13]. Like other chitinases and chitinase-related proteins, CHI3L1 is a member of the 18-glycosylhydrolase family [14]. Although this group includes proteins such as chitotriosidase [15] and acidic mammalian chitinase (AMCase) [16], which are enzymatically active against chitin, CHI3L1 lacks chitinolytic activity due to an amino acid substitution in its catalytic region [14,17]. The gene for CHI3L1 consists of 10 exons, spanning 8 kb genomic DNA and is located on chromosome 1q31-q32 [18]. CHI3L1 is expressed by a variety of cells like synovial cells [12], chondrocytes [17], smooth muscle cells [19], colonic epithelial cells [20], osteosarcoma cells [21] as well as macrophages [14] and neutrophils [22].

Although CHI3L1 has no catalytic activity, it binds chitin, heparin,

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hyaluronan and collagen via a carbohydrate-binding motif (CBM) [23,24]. However, it was shown that the physiological ligands chitohexaose and hyaluronan bound CHI3L1 with a higher preference than heparin and collagen of types I, II and III. [25]. Depending on the site of CHI3L1 expression, CHI3L1 showed different effects on collagen. For example, CHI3L1 derived from cartilage had an inhibitory effect on type I collagen fibril formation. In contrast, CHI3L1, which was derived from chondrocytes, promoted the formation of fibrils and prevented the cleavage of type I collagen [25]. This was also reported for CHI3L1 derived from adipose tissue. Here it was expressed mainly in the stromal vascular fraction and had the same effect on collagen type I like CHI3L1 derived from chondrocytes [26].

The interaction with heparin was first described in 1990 when heparin-sepharose chromatography was used to isolate CHI3L1 [12]. Although CHI3L1 has a carbohydrate (heparin)-binding motif [27] it seems to be more likely that heparan sulfate proteoglycans are the physiological ligand for CHI3L1, since these proteoglycans are a component of the extracellular matrix and cell surface and play a role in cell adhesion and growth factor/cytokine action [28].

In accordance to this, it was reported that CHI3L1 was associated with tissue remodeling in vascular smooth muscle cells [19] and that it acted as a mitogen or growth factor to stimulate tissue remodeling in chondrocytes and synovial cells [29]. Here it was shown that CHI3L1 interacted with IGF-1 and could promote the growth of skin and fetal lung fibroblasts in a similar way to IGF-1. It appears that AKT-, ERK- and PKB-mediated signalling pathways are involved in the mitogenic function of CHI3L1 [30]. Furthermore, CHI3L1 acted as a chemoattractant in human umbilical vein vascular endothelial cells by stimulating cell migration and adhesion [31,32].

3. CHI3L1's interactions with the intestinal microbiota

A possible involvement of chronic bacterial infections in the pathogenesis of IBD has been investigated in several studies [33,34]. Antigens of *Listeria spp.*, *Streptococcus* and *Escherichia coli* (*E. coli*) were described in CD in granulomatous and peri-ulcerative lesions [35]. Especially *adherent invasive E. coli*(AIEC) which colonizes the terminal ileum of CD patients, was found in 21.7% of chronic lesions and 36.4% of early lesions [36]. AIEC survived in macrophages and intestinal epithelial cells while avoiding activation of apoptosis [36–38].

In recent years, Emiko Mizoguchi's group has conducted extensive studies on the interaction of CHI3L1 with intestinal epithelia and bacteria. They showed an upregulated expression of CHI3L1 in colonic epithelial cells (CECs) and the lamina propria during different stages of inflammation in a murine colitis model and in patients with CD and UC [20]. This upregulation improved the adhesion and invasion of *Salmonella typhimurium* and AIEC, but not of non-pathogenic *E. coli* (DH5α) in CECs. Later, they showed that CHI3L1 bound to the chitin-binding protein 21 (CBP21) expressed by *Serratia marcescens* [39]. In potentially pathogenic *E. coli*, a corresponding CBP21 homologue, ChiA, was identified, which carried a unique amino acid motif in its chitin-binding domain that promoted adhesion of AIEC to CECs by N-glycosylated CHI3L1 [110]. Therefore, it has been suggested that CHI3L1 could improve the adhesion of CBP21- or ChiA-expressing bacteria to CECs [20,39]. Further it was shown by the same group that the CBM of CHI3L1 was critical for the activation of protein kinase B (Akt) signaling in CECs in vitro [24]. Akt signaling thus increased the secretion of pro-inflammatory cytokines TNF-α and IL-8 in CECs [24], which in turn triggered the accumulation, recruitment and activation of neutrophils [40–42]. Additionally, AIEC and mucosa-associated *E. coli* also induced TNF-α and IL-8, respectively [43].

4. CHI3L1 in intestinal epithelial cells

A critical factor for the development of inflammation in IBD is the impairment of the homeostasis between mucosal immunity and commensal bacteria [5]. Here, pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), which modulate the adaptive immune response by induction of anti-/pro-inflammatory genes [44], play an important role since they are essential for the recognition of highly conserved pathogen-associated molecular patterns [45]. Thus, TLR4 formed a complex with MD-2 (lymphocyte antigen 96, Lys-96) [46] and recognized lipopolysaccharide (LPS) molecules of Gram-negative bacteria (including commensals) that were bound to soluble CD14 [47,48]. In healthy individuals and intestinal epithelial cell lines (IECs), the expression of TLR4/MD-2 was downregulated and hardly detectable, probably contributing to the prevention of inappropriate activation by commensals [49,50]. In contrast, TLR4/MD-2 was upregulated in small intestine and colon biopsies of CD and UC patients and was induced by proinflammatory cytokines such as interferon gamma (IFNγ) and TNFα in IECs. The adapter protein MyD88, which interacts with the cytoplasmic region of TLRs, the so-called Toll/IL-1 receptor (TIR) domain, also plays an important role. However, activation of TLR4/MD-2 and subsequent MyD88-mediated signalling led to activation of the NF-kB signalling pathways [51]and thus to the upregulation of proinflammatory cytokines including TNFα, IL-1β, IL-2, IL-6, IL-12 and interferon gamma (IFNγ) or granulocyte colony stimulation factor (G-CSF) and granulocyte macrophage colony stimulation factor (GM-CSF) [52]. It has been shown that TNFα, IL-1β and IFNγ, but not LPS, upregulated the expression of CHI3L1 in CECs [20]. Interestingly, overall upregulated expression of CHI3L1 could be found in cells carrying the TLR4 mutations D299G or T399I [53]. These common “loss of function” mutations are associated with TLR4 hyporesponsivness to LPS and thus to a decreased NF-kB activation [54]. It is noteworthy that no endogenous CHI3L1 expression was found in HT-29 cells that did not carry a TLR4 mutation, but instead in SW480 and CaCo2 cells in which the D299G or T399I mutations of TLR4 were shown [55]. These data suggest that in IBD patients carrying the TLR4 mutation, an increased expression of CHI3L1 in the epithelium may contribute to increased bacterial adhesion and invasion. Nevertheless, the TLR4 mutation-independent upregulation of CHI3L1 by cytokines also seemed to increase bacterial adhesion and invasion and thus trigger an immune response [20,56].

5. CHI3L1 and macrophages

Macrophages contribute to the first line of host defense. They not only recycle cell debris generated by normal tissue homeostasis, but also remove pathogens and regulate the inflammatory process [57]. Intestinal macrophages are tolerant to foreign substances like antigens of commensal microbiota and food components by downregulating the relevant recognition receptors. The stimulation of PRRs and TLRs on macrophages caused a strong bactericidal activity but a low cytokine secretion to prevent against an undesired immune response [58–60]. In IBD patients, macrophages infiltrate and spread massively through the intestinal mucosa and submucosa [61]. In general, macrophages were divided into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages [62]. The activation and polarization of M1 or M2 macrophages is determined by chemokines. For example, IFNγ and LPS (via TLRs) activated macrophage polarization (M1 polarization), leading to the release of additional chemokines such as C-chemokine ligand 2 (CCL2, also known as monocytic chemotactic protein-1[MCP-1]) and numerous other interleukins [62–64]. In contrast, IL-10 induced M2 polarization while INFγ or LPS-dependent M1 polarization was inhibited. In IBD patients, the polarization of monocytes to anti-inflammatory M2 macrophages may be disturbed due to a defective TGFβ signalling that amplifies the inflammatory anergy of M2 macrophages [65,66].

CHI3L1 can mediate macrophage recruitment [67] and, although CHI3L1 was not upregulated by LPS in CECs, LPS (and INFγ) induced CHI3L1 expression in human macrophages [68]. However, in macrophages of tumor bearing mice, CHI3L1 induced the expression of CCL2,

Chemokine CX motif ligand 2 (CXCL2) and matrix metalloproteinase-9 (MMP-9) likely via the TLR4 receptor [64], an effect that could be inverted by chitin treatment [69]. MMP-9 is associated with inflammation and modulation of colonic epithelial permeability in IBD [70], and, like CCL2, with tumor progression and growth of metastasis [69]. Therefore, MMP-9 may also contribute to potentially CHI3L1-associated tissue destruction in IBD. CXCL2 may also participate in tumor progression by promoting angiogenesis [71], and it was also shown to mediate recruitment of neutrophils [72].

The exact mechanism of how CHI3L1 could take part in the macrophage-derived pathological effects of IBD and especially CD is still unclear. CD is characterized by impaired bacterial clearance which was linked to impaired cytokine secretion [73], *E. coli* infiltration into intestinal macrophages [74] and formation of granulomas resulting from ineffective elimination of invading pathogens [75,76]. However, LPS and CCL2 activation by CHI3L1 might provide a link of enhanced bacterial adhesion and invasion, following activation of macrophages. This could enhance destruction of the intestinal barrier by macrophage-secreted compounds and enhance macrophage infiltration, all of which were features of CD. In contrast, CHI3L1 may have an opposite effect in UC. CHI3L1 effected the T helper cell (Th) 2 response in mice pulmonary epithelium. Th2 can induce M2 macrophage activation in an alternative way [77] which in turn activates Wnt-signaling and a decrease of enterocyte differentiation in epithelial cells [78,79].

6. CHI3L1 and neutrophils

Neutrophils migrate to the site of inflammation and serve as the first line of immune response in the acute phase of inflammation. However, it is thought that a defective neutrophil regulation in IBD plays an important role in the onset or manifestation of IBD. Neutrophil dysregulation leads to damage of the intestinal mucosal barrier caused by the infiltration of neutrophils into the inflamed mucosa and the accumulation of pathogens, such as bacteria, that are not phagocytosed by neutrophils [80,81]. Although the migration of neutrophils into the intestinal mucosa is a characteristic of IBD, there are differences between CD and UC [82]. While in UC the infiltration and accumulation of neutrophils were increased and correlated with disease activity [83], in CD, a disturbed neutrophil recruitment was described [84]. At the site of inflammation neutrophils roll along the intestinal surface and interact loosely with so-called P-Selctins [85]. Neutrophils are then activated by various chemokines such as IL-8 [40]. It is noteworthy that IL-8 varies in IBD. It has been shown that the production of IL-8 and thus the accumulation of neutrophils is reduced in the intestines of CD patients [86]. In contrast, IL-8 is overexpressed in the intestinal tissue of UC patients and correlates with the severity of the disease and the neutrophil number [87]. In neutrophils, CHI3L1 is stored in specific granules and during recruitment and activation of neutrophils, CHI3L1 is co-mobilized with lactoferrin, a known antigenic target of anti-neutrophil cytoplasmic antibodies (ANCA) commonly found in IBD patients [22]. These data suggest a disparate role of CHI3L1 in neutrophil function in IBD. In UC, an increased expression of CHI3L1 in intestinal epithelial cells and the resulting upregulation of IL-8 may explain an increased neutrophil recruitment, accumulation and infiltration. However, activated neutrophils release various molecules, including matrix metalloproteinases (MMPs). One of the most important MMPs is MMP-9, which correlates with endoscopic, clinical and histological activities in UC but not CD [88]. MMP9 contributes to the infiltration of neutrophils in inflammatory processes by degradation of collagen [89]. The release of collagen fragments, which have a chemotactic effect on neutrophils, recruited more neutrophils, which secreted more MMP, resulting in a kind of "positive feedback loop" [90]. In addition, MMP-9 can cleave IL-8, resulting in a truncated, more active form of IL-8, that potentiated neutrophil recruitment and MMP-9 secretion [91] and would explain increased neutrophil infiltration and intestinal tissue destruction [70] in UC patients. Since CHI3L1 has already been shown to induce secretion of MMP9, CHI3L1 may also contribute to this positive feedback effect.

7. Loss of tolerance to CHI3L1 – just an epiphenomenon of IBD?

The data discussed here show that CHI3L1 can play an important role in the etiopathogenesis of IBD. However, it is unclear whether CHI3L1 can directly contribute to the development of IBD or whether its upregulation in, for example, CECs is an epiphenomenon.

In this context, the previous report on the loss of tolerance to CHI3L1, to be associated with IBD and in particular CD, provides further evidence of CHI3L1's involvement in the pathophysiology of IBD [92]. If CHI3L1 interacts with pathogenic bacteria via CBP21 or ChiA, the resulting immune response against these bacteria may also trigger a tolerance break against CHI3L1. The loss of tolerance to other glycoproteins interacting with the microbiota, such as glycoprotein 2 and its possible role in IBD pathophysiology, was recently demonstrated [93–95]. In contrast to GP2, expression of CHI3L1 was shown in immune cells and especially in neutrophils [14,18,96]. Furthermore, CHI3L1 is expressed in dendritic cells (DCs) [97], upregulated in macrophages [68] and overexpressed in B lymphocytes (B cells) of tumor-bearing mice [69]. Macrophages and DCs, but also B cells, are antigen-presenting cells affecting the subsequent immune response [98,99]. However, T cells, can be activated by antigen-presentation mediated by the T-cell receptor (TCR)/CD3 complex. After interaction of this receptor complex with antigen/ major histocompatibility complex as ligand, additional chemokine signals are required to define T-cell polarization in subsets such as Th1, Th2 or Th17 [9,10]. These subsets are involved differently in IBD. CD is traditionally associated with Th1 and UC with Th2. Recent findings suggest that Th17 is associated with the development of autoimmunity in IBD. Activated T cells have the ability to induce clonal expansion of B cells [100] that are hyperactivated in IBD [101]. Distinct signals result in a class switch of immunoglobulins to IgA which are directed against the presented antigen [102]. IgA and especially secretory IgA (sIgA) are capable of directly clearing microbial antigens and pathogens [103]. In context with the loss of tolerance to CHI3L1 in IBD, sIgA directed against CHI3L1 and microbial antigens may attenuate CHI3L1-induced bacterial adhesion and migration and thus reduce the downstream immune response. Interestingly, elevated levels of sIgA in CD in contrast to UC was recently demonstrated [104] (Fig. 1). kHowever, this mechanism needs to be demonstrated experimentally and could address aspects of upregulated CHI3L1 in other parts of intestinal immunity. Noteworthy is that CHI3L1 has been identified as an antigenic target in patients with rheumatoid arthritis [105,106]. It is shown that APCs present CHI3L1 to T cells, and downstream signaling leads to a much stronger pro-inflammatory response of monocytes and suppresses the anti-inflammatory T cell response [107–109]. These data may underline that CHI3L1 may act similarly in IBD.

8. Conclusion

CHI3L1 is a glycoprotein associated with various diseases such as IBD. It affects different components of the innate and adaptive immune response but its physiological function is not yet fully understood. However, it is unclear whether CHI3L1 affects IBD through mechanisms such as increased bacterial adhesion and invasion or upregulated expression in different cell types such as immune cells. The loss of tolerance to CHI3L1 could be considered an epiphenomenon of inflammation in IBD. However, autoantibodies against CHI3L1, in particular sIgA, may contribute to the onset and course of IBD. Future research is needed to answer these questions and to investigate the pathological features of CHI3L1 in IBD and other diseases.

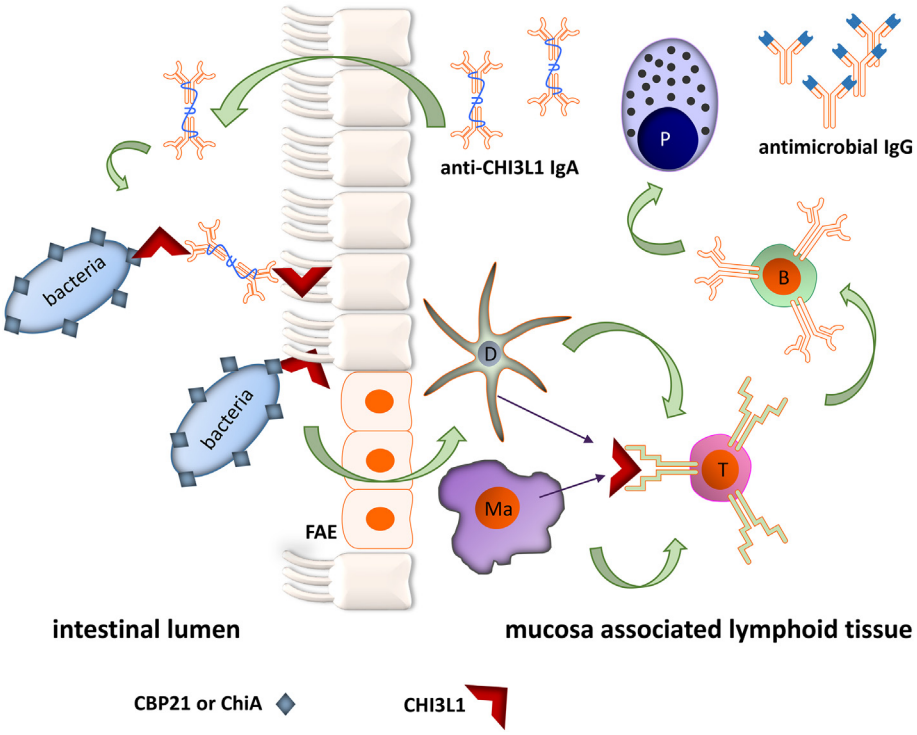

Fig. 1. Putative pathophysiological function of CHI3L1. Under inflammatory conditions, expression of CHI3L1 is upregulated in intestinal epithelial cells and improves adhesion of CBP21 or ChiA expressing microorganisms. Microbial antigens are processed in follicle-associated epithelium (FAE), delivered to antigen-presenting cells (APCs) such as dendritic cells (D), B cells (B) and macrophages (Ma), resulting in an immune response. CHI3L1 is expressed in dendritic cells and macrophages, the latter showing increased CHI3L1 expression after induction by bacterial lipopolysaccharide. CHI3L1 could be processed by these APCs as an antigen, leading to activation of T cells (T). Activated T cells induce clonal expansion of B cells and, together with different signals, can induce a class switch of B cells immunoglobulins to IgA, which is transported as secretory IgA into the intestinal lumen. Under normal conditions, IgA would contribute to the elimination of microbes, but in connection with the loss of tolerance to CHI3L1 in IBD, IgA could participate in the CHI3L1-mediated improved adhesion and invasion of potentially pathogenic microorganisms. FAE, follicle-associated epithelium; D, dentritic cells; M, microfold cells of follicle-associated epithelium; B, B-cells; Ma, macrophages; T, T-cells; CBP21, chitin-binding protein 21.

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Conflict of interest

Dirk Roggenbuck is a shareholder of GA Generic Assays and Medipan GmbH and has a managerial position in both companies. All other authors declare that they have no conflict of interest.

References

[1] S.C. Ng, H.Y. Shi, N. Hamidi, et al., Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies, Lancet 390 (2017) 2769–2778, https://doi.org/10.1016/S0140-6736(17)32448-0.

[2] D.C. Baumgart, S.R. Carding, Inflammatory bowel disease: cause and immunobiology, Lancet 369 (2007) 1627–1640, https://doi.org/10.1016/S0140-6736(07)60750-8.

[3] K. Conrad, D. Roggenbuck, M.W. Laass, Diagnosis and classification of ulcerative colitis, Autoimmun. Rev. 13 (2014) 463–466, https://doi.org/10.1016/j.autrev.2014.01.028.

[4] M.W. Laass, D. Roggenbuck, K. Conrad, Diagnosis and classification of Crohn's disease, Autoimmun. Rev. 13 (2014) 467–471, https://doi.org/10.1016/j.autrev.2014.01.029.

[5] R.J. Xavier, D.K. Podolsky, Unravelling the pathogenesis of inflammatory bowel disease, Nature 448 (2007) 427–434, https://doi.org/10.1038/nature06005.

[6] D. Knights, K.G. Lassen, R.J. Xavier, Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome, Gut 62 (2013), https://doi.org/10.1136/gutjnl-2012-303954.

[7] S. Zeissig, N. Bürgel, D. Günzel, et al., Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease, Gut 56 (2007) 61–72, https://doi.org/10.1136/gut.2006.094375.

[8] M. Ramasundara, S.T. Leach, D.A. Lemberg, A.S. Day, Defensins and inflammation: the role of defensins in inflammatory bowel disease, J. Gastroenterol. Hepatol. 24 (2009) 202–208, https://doi.org/10.1111/j.1440-1746.2008.05772.x.

[9] Z.-J. Liu, P.K. Yadav, J.-L. Su, et al., Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease, World J Gastroenterol: WJG 15 (2009) 5784–5788, https://doi.org/10.3748/wjg.15.5784.

[10] M.F. Neurath, S. Finotto, L.H. Glimcher, The role of Th1/Th2 polarization in mucosal immunity, Nat. Med. 8 (2002) 567–573, https://doi.org/10.1038/nm0602-567.

[11] A. Geremia, P. Biancheri, P. Allan, et al., Innate and adaptive immunity in inflammatory bowel disease, Autoimmun. Rev. 13 (2014) 3–10, https://doi.org/10.1016/j.autrev.2013.06.004.

[12] P. Nyirkos, E.E. Golds, Human synovial cells secrete a 39 kDa protein similar to a bovine mammary protein expressed during the non-lactating period, Biochem. J. 269 (1990) 265–268, https://doi.org/10.1042/bj2690265.

[13] J.S. Johansen, H.S. Jensen, P.A. Price, A new biochemical marker for joint injury. Analysis of YKL-40 in serum and synovial fluid, Br. J. Rheumatol. 32 (1993) 949–955.

[14] G.H. Renkema, R.G. Boot, F.L. Au, et al., 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, Eur. J. Biochem. 251 (1998) 504–509, https://doi.org/10.1046/j.1432-1327.1998.2510504.x.

[15] C.E. Hollak, S. van Weely, M.H. van Oers, J.M. Aerts, Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease, J. Clin. Invest. 93 (1994) 1288–1292, https://doi.org/10.1172/JCI117084.

[16] R.G. Boot, E.F.C. Blommaart, E. Swart, et al., Identification of a Novel Acidic Mammalian Chitinase Distinct from Chitotriosidase, J. Biol. Chem. 276 (2001) 6770–6778, https://doi.org/10.1074/jbc.M009886200.

[17] B.E. Hakala, C. White, A.D. Recklies, Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family, J. Biol. Chem. 268 (1993) 25803–25810.

[18] M. Rehli, S.W. Krause, R. Andreesen, Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation, Genomics 43 (1997) 221–225, https://doi.org/10.1006/geno.1997.4778.

[19] L.M. Shackelton, D.M. Mann, A.J.T. Millis, Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling, J. Biol. Chem. 270 (1995) 13076–13083, https://doi.org/10.1074/jbc.270.22.13076.

[20] E. Mizoguchi, Chitinase 3–like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells, Gastroenterology 130 (2006) 398–411, https://doi.org/10.1053/j.gastro.2005.12.007.

[21] J.S. Johansen, M.K. Williamson, J.S. Rice, P.A. Price, Identification of proteins secreted by human osteoblastic cells in culture, J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 7 (1992) 501–512, https://doi.org/10.1002/jbmr.5650070506.

[22] C. Nordenbaek, J.S. Johansen, P. Junker, et al., YKL-40, a matrix protein of specific granules in neutrophils, is elevated in serum of patients with community-acquired pneumonia requiring hospitalization, J. Infect. Dis. 180 (1999) 1722–1726, https://doi.org/10.1086/315050.

[23] A.A. Kognole, C.M. Payne, Inhibition of mammalian glycoprotein YKL-40 identification of the physiological ligand, J. Biol. Chem. 292 (2017) 2624–2636, https://doi.org/10.1074/jbc.M116.764985.

[24] C.-C. Chen, V. Llado, K. Eurich, et al., Carbohydrate-binding motif in Chitinase 3-like 1 (CHI3L1/YKL-40) specifically activates Akt signaling pathway in colonic epithelial cells, Clin. Immunol. Orlando, FL 140 (2011) 268–275, https://doi.org/10.1016/j.clim.2011.04.007.

[25] H.F. Bigg, R. Wait, A.D. Rowan, T.E. Cawston, The mammalian chitinase-like lectin, YKL-40, binds specifically to type I collagen and modulates the rate of type I

collagen fibril formation, J. Biol. Chem. 281 (2006) 21082–21095, https://doi.org/10.1074/jbc.M601153200.
[26] T. Iwata, M. Kuwajima, A. Sukeno, et al., YKL-40 secreted from adipose tissue inhibits degradation of type I collagen, Biochem. Biophys. Res. Commun. 388 (2009) 511–516, https://doi.org/10.1016/j.bbrc.2009.08.024.
[27] N. Ngernyuang, W. Yan, L.M. Schwartz, et al., A heparin binding motif rich in arginine and lysine is the functional domain of YKL-40, Neoplasia N Y N 20 (2017) 182–192, https://doi.org/10.1016/j.neo.2017.11.011.
[28] F. Fusetti, T. Pijning, K.H. Kalk, et al., Crystal structure and carbohydrate-binding properties of the human cartilage glycoprotein-39, J. Biol. Chem. 278 (2003) 37753–37760, https://doi.org/10.1074/jbc.M303137200.
[29] F. De Ceuninck, S. Gaufillier, A. Bonnaud, et al., YKL-40 (Cartilage gp-39) induces proliferative events in cultured chondrocytes and synoviocytes and increases glycosaminoglycan synthesis in chondrocytes, Biochem. Biophys. Res. Commun. 285 (2001) 926–931, https://doi.org/10.1006/bbrc.2001.5253.
[30] A.D. Recklies, C. White, H. Ling, The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways, Biochem. J. 365 (2002) 119–126, https://doi.org/10.1042/BJ20020075.
[31] K.M. Malinda, L. Ponce, H.K. Kleinman, et al., Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells, Exp. Cell Res. 250 (1999) 168–173, https://doi.org/10.1006/excr.1999.4511.
[32] K.C. Nishikawa, A.J.T. Millis, gp38k (CHI3L1) is a novel adhesion and migration factor for vascular cells, Exp. Cell Res. 287 (2003) 79–87, https://doi.org/10.1016/S0014-4827(03)00069-7.
[33] R.B. Sartor, Role of commensal enteric bacteria in the pathogenesis of immune-mediated intestinal inflammation: lessons from animal models and implications for translational research, J. Pediatr. Gastroenterol. Nutr. 40 (2005).
[34] C. Schultsz, M. Moussa, R. van Ketel, et al., Frequency of pathogenic and enteroadherent Escherichia coli in patients with inflammatory bowel disease and controls, J. Clin. Pathol. 50 (1997) 573–579.
[35] Y. Liu, H.J. van Kruiningen, A.B. West, et al., Immunocytochemical evidence of Listeria, Escherichia coli, and Streptococcus antigens in Crohn's disease, Gastroenterology 108 (1995) 1396–1404.
[36] A. Darfeuille-Michaud, J. Boudeau, P. Bulois, et al., High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease, Gastroenterology 127 (2004) 412–421, https://doi.org/10.1053/j.gastro.2004.04.061.
[37] A. Darfeuille-Michaud, C. Neut, N. Barnich, et al., Presence of adherent Escherichia coli strains in ileal mucosa of patients with Crohn's disease, Gastroenterology 115 (1998) 1405–1413.
[38] J. Boudeau, A.-L. Glasser, E. Masseret, et al., Invasive ability of an Escherichia coli strain isolated from the ileal mucosa of a patient with Crohn's disease, Infect. Immun. 67 (1999) 4499–4509.
[39] M. Kawada, C.-C. Chen, A. Arihiro, et al., Chitinase 3-like-1 enhances bacterial adhesion to colonic epithelial cells through the interaction with bacterial chitin-binding protein, Lab. Investig. 88 (2008) 883–895, https://doi.org/10.1038/labinvest.2008.47.
[40] M. Baggiolini, A. Walz, S.L. Kunkel, Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils, J. Clin. Invest. 84 (1989) 1045–1049.
[41] S.J. Van Deventer, Tumour necrosis factor and Crohn's disease, Gut 40 (1997) 443–448.
[42] A. Szkaradkiewicz, R. Marciniak, I. Chudzicka-Strugała, et al., Proinflammatory cytokines and IL-10 in inflammatory bowel disease and colorectal cancer patients, Arch. Immunol. Ther. Exp. 57 (2009) 291–294, https://doi.org/10.1007/s00005-009-0031-z.
[43] N. Rolhion, A. Darfeuille-Michaud, Adherent-invasive Escherichia coli in inflammatory bowel disease, Inflamm. Bowel Dis. 13 (2007) 1277–1283, https://doi.org/10.1002/ibd.20176.
[44] R. Medzhitov, P. Preston-Hurlburt, C.A.J. Jr, A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity, Nature 388 (1997) 394–397, https://doi.org/10.1038/41131.
[45] R. Suresh, D.M. Mosser, Pattern recognition receptors in innate immunity, host defense, and immunopathology, Adv. Physiol. Educ. 37 (2013) 284–291, https://doi.org/10.1152/advan.00058.2013.
[46] R. Shimazu, S. Akashi, H. Ogata, et al., MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4, J. Exp. Med. 189 (1999) 1777–1782.
[47] B.S. Park, D.H. Song, H.M. Kim, et al., The structural basis of lipopolysaccharide recognition by the TLR4–MD-2 complex, Nature 458 (2009) 1191–1195, https://doi.org/10.1038/nature07830.
[48] J. Pugin, C.C. Schürer-Maly, D. Leturcq, et al., Lipopolysaccharide activation of human endothelial and epithelial cells is mediated by lipopolysaccharide-binding protein and soluble CD14, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 2744–2748.
[49] M.T. Abreu, P. Vora, E. Faure, et al., Decreased expression of toll-like receptor-4 and MD-2 correlates with intestinal epithelial cell protection against dysregulated proinflammatory gene expression in response to bacterial lipopolysaccharide, J. Immunol. 167 (2001) 1609–1616, https://doi.org/10.4049/jimmunol.167.3.1609.
[50] E. Cario, D.K. Podolsky, Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease, Infect. Immun. 68 (2000) 7010–7017.
[51] K. Takeda, S. Akira, TLR signaling pathways, Semin. Immunol. 16 (2004) 3–9.
[52] T.S. Blackwell, J.W. Christman, The role of nuclear factor- κ B in cytokine gene regulation, Am. J. Respir. Cell Mol. Biol. 17 (1997) 3–9, https://doi.org/10.1165/ajrcmb.17.1.f132.
[53] A. Eyking, B. Ey, M. Rünzi, et al., Toll-like receptor 4 variant D299G induces features of neoplastic progression in Caco-2 intestinal cells and is associated with advanced human colon cancer, Gastroenterology 141 (2011) 2154–2165, https://doi.org/10.1053/j.gastro.2011.08.043.
[54] N.C. Arbour, E. Lorenz, B.C. Schutte, et al., TLR4 mutations are associated with endotoxin hyporesponsiveness in humans, Nat. Genet. 25 (2000) 187–191, https://doi.org/10.1038/76048.
[55] A. Kamba, I.-A. Lee, E. Mizoguchi, 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, Curr. Mol. Med. 13 (2013) 1110–1121.
[56] L.A. Edwards, M. Bajaj-Elliott, N.J. Klein, et al., Bacterial-epithelial contact is a key determinant of host innate immune responses to enteropathogenic and enteroaggregative Escherichia coli, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0027030.
[57] J. Cole, J. Aberdein, J. Jubrail, D.H. Dockrell, Chapter four - the role of macrophages in the innate immune response to Streptococcus pneumoniae and Staphylococcus aureus: mechanisms and contrasts, in: R.K. Poole (Ed.), Advances in Microbial Physiology, Academic Press, 2014, pp. 125–202.
[58] P.D. Smith, L.E. Smythies, M. Mosteller-Barnum, et al., Intestinal macrophages lack CD14 and CD89 and consequently are down-regulated for LPS- and IgA-mediated activities, J. Immunol. 167 (2001) 2651–2656, https://doi.org/10.4049/jimmunol.167.5.2651.
[59] L.E. Smythies, M. Sellers, R.H. Clements, et al., Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity, J. Clin. Invest. 115 (2005) 66–75, https://doi.org/10.1172/JCI200519229.
[60] J. Rugtveit, A. Bakka, P. Brandtzaeg, Differential distribution of B7.1 (CD80) and B7.2 (CD86) costimulatory molecules on mucosal macrophage subsets in human inflammatory bowel disease (IBD), Clin. Exp. Immunol. 110 (1997) 104–113, https://doi.org/10.1046/j.1365-2249.1997.5071404.x.
[61] Y.R. Mahida, S. Patel, P. Gionchetti, et al., Macrophage subpopulations in lamina propria of normal and inflamed colon and terminal ileum, Gut 30 (1989) 826–834.
[62] A. Mantovani, A. Sica, S. Sozzani, et al., The chemokine system in diverse forms of macrophage activation and polarization, Trends Immunol. 25 (2004) 677–686, https://doi.org/10.1016/j.it.2004.09.015.
[63] H. Darmani, J.L. Harwood, J. Parton, S.K. Jackson, Macrophage activation by lipopolysaccharide, interferon-γ and interleukin-4: effect of fatty acid metabolism, Mediat. Inflamm. 4 (1995) 25–30, https://doi.org/10.1155/S0962935195000056.
[64] W. Fang, D. Bi, R. Zheng, et al., Identification and activation of TLR4-mediated signalling pathways by alginate-derived guluronate oligosaccharide in RAW264.7 macrophages, Sci. Rep. 7 (2017), https://doi.org/10.1038/s41598-017-01868-0.
[65] G. Monteleone, A. Kumberova, N.M. Croft, et al., Blocking Smad7 restores TGF-β1 signaling in chronic inflammatory bowel disease, J. Clin. Invest. 108 (2001) 601–609.
[66] L.E. Smythies, R. Shen, D. Bimczok, et al., inflammation anergy in human intestinal macrophages is due to Smad-induced IκBα expression and NF-κB inactivation, J. Biol. Chem. 285 (2010) 19593–19604, https://doi.org/10.1074/jbc.M109.069955.
[67] M. Kawada, H. Seno, K. Kanda, et al., Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer, Oncogene 31 (2012) 3111–3123, https://doi.org/10.1038/onc.2011.498.
[68] J. Kzhyshkowska, S. Mamidi, A. Gratchev, et al., Novel stabilin-1 interacting chitinase-like protein (SI-CLP) is up-regulated in alternatively activated macrophages and secreted via lysosomal pathway, Blood 107 (2006) 3221–3228, https://doi.org/10.1182/blood-2005-07-2843.
[69] S. Libreros, R. Garcia-Areas, Y. Shibata, et al., Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: decreased tumor metastasis in a breast cancer model, Int. J. Cancer 131 (2012) 377–386, https://doi.org/10.1002/ijc.26379.
[70] P. Nighot, R. Al-Sadi, M. Rawat, et al., Matrix metalloproteinase 9-induced increase in intestinal epithelial tight junction permeability contributes to the severity of experimental DSS colitis, Am. J. Physiol. Gastrointest. Liver Physiol. 309 (2015) G988–G997, https://doi.org/10.1152/ajpgi.00256.2015.
[71] C.L. Addison, D.A. Arenberg, S.B. Morris, et al., The CXC chemokine, monokine induced by interferon-gamma, inhibits non-small cell lung carcinoma tumor growth and metastasis, Hum. Gene Ther. 11 (2000) 247–261, https://doi.org/10.1089/10430340050015996.
[72] B. Moser, I. Clark-Lewis, R. Zwahlen, M. Baggiolini, Neutrophil-activating properties of the melanoma growth-stimulatory activity, J. Exp. Med. 171 (1990) 1797–1802.
[73] A.M. Smith, F.Z. Rahman, B. Hayee, et al., Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease, J. Exp. Med. 206 (2009) 1883–1897, https://doi.org/10.1084/jem.20091233.
[74] T.R. Elliott, N.B. Rayment, B.N. Hudspith, et al., Lamina propria macrophage phenotypes in relation to Escherichia coli in Crohn's disease, BMC Gastroenterol. 15 (2015), https://doi.org/10.1186/s12876-015-0305-3.
[75] H. Rotterdam, B.I. Korelitz, S.C. Sommers, Microgranulomas in grossly normal rectal mucosa in Crohn's disease, Am. J. Clin. Pathol. 67 (1977) 550–554.
[76] M.G. Cook, M.F. Dixon, An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis, Gut 14 (1973) 255–262.
[77] S. Gordon, F.O. Martinez, Alternative activation of macrophages: mechanism and

functions, Immunity 32 (2010) 593–604, https://doi.org/10.1016/j.immuni.2010.05.007.
[78] J. Cosín-Roger, D. Ortiz-Masiá, S. Calatayud, et al., The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD, Mucosal Immunol. 9 (2016) 986–998, https://doi.org/10.1038/mi.2015.123.
[79] J. Cosín-Roger, D. Ortiz-Masiá, S. Calatayud, et al., M2 macrophages activate wnt signaling pathway in epithelial cells: relevance in ulcerative colitis, PLoS One 8 (2013) e78128, , https://doi.org/10.1371/journal.pone.0078128.
[80] O. Wéra, P. Lancellotti, C. Oury, The dual role of neutrophils in inflammatory bowel diseases, J. Clin. Med. 5 (2016), https://doi.org/10.3390/jcm5120118.
[81] G.X. Zhou, Z.J. Liu, Potential roles of neutrophils in regulating intestinal mucosal inflammation of inflammatory bowel disease, J. Dig. Dis. 18 (2017) 495–503, https://doi.org/10.1111/1751-2980.12540.
[82] D. Muthas, A. Reznichenko, C.A. Balendran, et al., Neutrophils in ulcerative colitis: a review of selected biomarkers and their potential therapeutic implications, Scand. J. Gastroenterol. 52 (2017) 125–135, https://doi.org/10.1080/00365521.2016.1235224.
[83] F. Costa, M.G. Mumolo, L. Ceccarelli, et al., Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease, Gut 54 (2005) 364–368, https://doi.org/10.1136/gut.2004.043406.
[84] J.H. Wandall, V. Binder, Leucocyte function in Crohn's disease. Studies on mobilisation using a quantitative skin window technique and on the function of circulating polymorphonuclear leucocytes in vitro, Gut 23 (1982) 173–180.
[85] Gironella M, Mollà M, Salas A, et al The role of P-selectin in experimental colitis as determined by antibody immunoblockade and genetically deficient mice. J. Leukoc. Biol. 72:56–64. doi: https://doi.org/10.1189/jlb.72.1.56.
[86] D.J. Marks, M.W. Harbord, R. MacAllister, et al., Defective acute inflammation in Crohn's disease: a clinical investigation, Lancet 367 (2006) 668–678, https://doi.org/10.1016/S0140-6736(06)68265-2.
[87] K. Mitsuyama, A. Toyonaga, E. Sasaki, et al., IL-8 as an important chemoattractant for neutrophils in ulcerative colitis and Crohn's disease, Clin. Exp. Immunol. 96 (1994) 432–436.
[88] K. Farkas, Z. Saródi, A. Bálint, et al., The diagnostic value of a new fecal marker, matrix metalloprotease-9, in different types of inflammatory bowel diseases, J. Crohns Colitis 9 (2015) 231–237, https://doi.org/10.1093/ecco-jcc/jjv005.
[89] X. Xu, P.L. Jackson, S. Tanner, et al., a self-propagating matrix metalloprotease-9 (MMP-9) dependent cycle of chronic neutrophilic inflammation, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0015781.
[90] P.J. Koelink, S.A. Overbeek, S. Braber, et al., Collagen degradation and neutrophilic infiltration: a vicious circle in inflammatory bowel disease, Gut 63 (2014) 578–587, https://doi.org/10.1136/gutjnl-2012-303252.
[91] Steen P.E.V. Den, P. Proost, A. Wuyts, et al., Neutrophil gelatinase B potentiates interleukin-8 tenfold by aminoterminal processing, whereas it degrades CTAP-III, PF-4, and GRO-α and leaves RANTES and MCP-2 intact, Blood 96 (2000) 2673–2681.
[92] C. Deutschmann, Identification of chitinase 3 like-1-protein as a neutrophil autoantigenic target in inflammatory bowel diseases and autoimmune liver disorders, Oral Presentation at the 13thDresden Symposium on Autoantibodies, September 27–30, 2017, Dresden, 2017.
[93] D. Roggenbuck, G. Hausdorf, L. Martinez-Gamboa, et al., Identification of GP2, the major zymogen granule membrane glycoprotein, as the autoantigen of pancreatic antibodies in Crohn's disease, Gut 58 (2009) 1620–1628, https://doi.org/10.1136/gut.2008.162495.
[94] L. Komorowski, B. Teegen, C. Probst, et al., Autoantibodies against exocrine pancreas in Crohn's disease are directed against two antigens: the glycoproteins CUZD1 and GP2, J. Crohns Colitis 7 (2013) 780–790, https://doi.org/10.1016/j.crohns.2012.10.011.
[95] D. Roggenbuck, D. Reinhold, D.C. Baumgart, et al., Chapter two - autoimmunity in crohn's disease—a putative stratification factor of the clinical phenotype, in: G.S. Makowski (Ed.), Advances in Clinical Chemistry, Elsevier, 2016, pp. 77–101.
[96] B. Volck, P.A. Price, J.S. Johansen, et al., YKL-40, a mammalian member of the chitinase family, is a matrix protein of specific granules in human neutrophils, Proc. Assoc. Am. Physicians 110 (1998) 351–360.
[97] M. Di Rosa, P. Castrogiovanni, G. Musumeci, et al., Expression and localization of CHI3L1 in monocyte derived dendritic cells, Ital. J. Anat. Embryol. 122 (2017) 80, https://doi.org/10.13128/IJAE-21472.
[98] G.J. Randolph, C. Jakubzick, C. Qu, Antigen presentation by monocytes and monocyte-derived cells, Curr. Opin. Immunol. 20 (2008) 52–60, https://doi.org/10.1016/j.coi.2007.10.010.
[99] X. Chen, P.E. Jensen, The role of B lymphocytes as antigen-presenting cells, Arch. Immunol. Ther. Exp. 56 (2008) 77, https://doi.org/10.1007/s00005-008-0014-5.
[100] K.M. Smith, L. Pottage, E.R. Thomas, et al., Th1 and Th2 CD4+ T Cells provide help for B cell clonal expansion and antibody synthesis in a similar manner in vivo, J. Immunol. 165 (2000) 3136–3144, https://doi.org/10.4049/jimmunol.165.6.3136.
[101] A.M. Noronha, Y. Liang, J.T. Hetzel, et al., Hyperactivated B cells in human inflammatory bowel disease, J. Leukoc. Biol. 86 (2009) 1007–1016, https://doi.org/10.1189/jlb.0309203.
[102] S. Fagarasan, K. Kinoshita, M. Muramatsu, et al., *In situ* class switching and differentiation to IgA-producing cells in the gut lamina propria, Nature 413 (2001) 639–643, https://doi.org/10.1038/35098100.
[103] N.J. Mantis, N. Rol, B. Corthésy, Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut, Mucosal Immunol. 4 (2011) 603–611, https://doi.org/10.1038/mi.2011.41.
[104] C. Deutschmann, M. Sowa, J. Murugaiyan, U. Roesler, N. Röber, K. Conrad, M.W. Laass, D.P. Bogdanos, N. Sipeki, M. Papp, S. Rödiger, D. Roggenbuck, P. Schierack, Identification of Chitinase-3-like protein 1 as a novel neutrophil antigenic target in Crohn's disease, J. Crohns Colitis (2018) (accepted December).
[105] G.S. Panayi, Targeting of cells involved in the pathogenesis of rheumatoid arthritis, Rheumatol. Oxf. Engl. 38 (Suppl. 2) (1999) 8–10.
[106] Hueber W, Kidd BA, Tomooka BH, et al Antigen microarray profiling of autoantibodies in rheumatoid arthritis. Arthritis Rheum. 52:2645–2655. doi: https://doi.org/10.1002/art.21269.
[107] E.C. Tsark, W. Wang, Y.-C. Teng, et al., Differential MHC class II-mediated presentation of rheumatoid arthritis autoantigens by human dendritic cells and macrophages, J. Immunol. 169 (2002) 6625–6633, https://doi.org/10.4049/jimmunol.169.11.6625.
[108] J.H.M. Van Bilsen, H. Van Dongen, L.R. Lard, et al., Functional regulatory immune responses against human cartilage glycoprotein-39 in health vs. proinflammatory responses in rheumatoid arthritis, Proc. Natl. Acad. Sci. 101 (2004) 17180–17185, https://doi.org/10.1073/pnas.0407704101.
[109] Cope AP, Patel SD, Hall F, et al T cell responses to a human cartilage autoantigen in the context of rheumatoid arthritis–associated and nonassociated HLA–DR4 alleles. Arthritis Rheum. 42:1497–1507.
[110] D. Low, H.T. Tran, I.-A. Lee, N. Dreux, A. Kamba, H.-C. Reinecker, A. Darfeuille-Michaud, N. Barnich, E. Mizoguchi, Chitin-Binding Domains of Escherichia coli chiA Mediate Interactions With Intestinal Epithelial Cells in Mice with Colitis, Gastroenterology 145 (2013) 602–612, https://doi.org/10.1053/j.gastro.2013.05.017 e9.