Cytokine and Growth Factor Reviews 47 (2019) 43–53

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

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

Interleukin-34 as a promising clinical biomarker and therapeutic target for inflammatory arthritis

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ARTICLE INFO

Keywords:
Interleukin-34
Inflammatory arthritis
Rheumatoid arthritis
Knee osteoarthritis

ABSTRACT

Interleukin-34 (IL-34), recently identified as a novel inflammatory cytokine and the second ligand for colony-stimulating factor-1 receptor, is known to play regulatory roles in the development, maintenance, and function of mononuclear phagocyte lineage cells – especially osteoclasts. Regarding its primary effect on osteoclasts, IL-34 has been shown to stimulate formation and activation of osteoclasts, which in turn magnifies osteoclasts-resorbing activity. In addition to its role in osteoclastogenesis, IL-34 has been implicated in inflammation of synovium via augmenting production of inflammatory mediators, in which altered IL-34 expression is regulated by pro-inflammatory cytokines responsible for cartilage degradation. Indeed, IL-34 has been documented to be highly expressed in inflamed synovium of rheumatoid arthritis (RA) and knee osteoarthritis (OA) patients, which are recognized as inflammatory arthritis. Furthermore, a number of clinical studies demonstrated that IL-34 levels were significantly increased in the circulation and synovial fluid of patients with RA and knee OA. Its levels were also found to be positively associated with disease severity – especially radiographic severity of both RA and knee OA patients. Interestingly, emerging evidence has accumulated that functional blockage of IL-34 with specific antibody can alleviate the severity of inflammatory arthritis. It is therefore reasonable to speculate that IL-34 may be developed as a potential biomarker and a new therapeutic candidate for inflammatory arthritis. To date, there are numerous studies showing IL-34 involvement and association with many aspects of inflammatory arthritis. Herein, this review aimed to summarize the recent findings regarding regulatory role of IL-34 in synovial inflammation-mediated cartilage destruction and update the current comprehensive knowledge on usefulness of IL-34-based treatment in inflammatory arthritis – particularly RA and knee OA.

1. Introduction

Inflammatory arthritis is a leading cause of disability in elder people worldwide, which is becoming a major social economic burden and mainly composed of rheumatoid arthritis (RA) and osteoarthritis (OA). Although the etiology of each disease is somewhat different, it has been recognized that inflammation in the synovial membrane (synovitis) is a prominently pathologic event driving the progression of both RA and OA. This pathologic feature leads to debilitating and irreversible joint destruction in the patients, through which numerous pro-inflammatory

Abbreviations: 4E-BP, eukaryotic translation initiation factor 4E-binding proteins; Akt, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; Bcl-2/Bax, B-cell lymphoma-2- associated X; CCL-20, chemokine (C-C motif) ligand-20; CCP, cyclic citrullinated peptide; CD, cluster of differentiation; CRP, C-reactive protein; CSF-1R, colony-stimulating factor-1 receptor; CXCL-10, chemokine (C-X-C motif) ligand-10; DAS28, Joint Disease Activity Score; DCs, dendritic cells; ERK1/2, extracellular signal-regulated kinase 1/2; ESR, erythrocyte sedimentation rate; FAK, focal adhesion kinase; FLSs, fibroblast-like synoviocytes; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IL, interleukin; IP-10, interferon-inducible protein-10; JAK/STAT, Janus kinase/signal transducers and activators of transcription; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; M-CSF, macrophage-colony-stimulating factor; MiR-21, MicroRNA-21; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; NK, natural killer; OA, osteoarthritis; PI3K, phosphoinositide-3-kinase; PKB, protein kinase B; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; RF, rheumatoid factor; RPTP-ζ, receptor-like protein tyrosine phosphatase-zeta; S6K, ribosomal protein S6 kinase; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; Th1, type I helper T cell; TNF-α, tumor necrosis factor-alpha; Tregs, regulatory T cells; WOMAC, Western Ontario McMaster University Osteoarthritis Index

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https://doi.org/10.1016/j.cytogfr.2019.05.005
Received 2 April 2019; Accepted 9 May 2019
Available online 10 May 2019

cytokines and mediators secreted by resident joint and infiltrating immune cells participate cartilage degradation and excessive bone remodeling [1–3]. The morphological characteristics of synovitis commonly include hyperplasia of the synovial lining layer cells, infiltration of abundant numbers of leukocytes, and formation of new blood vessels [1]. Currently, there are no effective treatments that stop the progression of synovitis. As such, the majority of patients with inflammatory arthritis will suffer pain, swelling, as well as stiffness, and ultimately develop disability. These facts highlight the importance of not only developing more effective disease modifying treatments, but also identifying potential biomarkers to aid with earlier diagnosis to prolong the period before patients experience significant disability. In this context, elucidating the molecular mechanisms underlying the pathogenesis of inflammatory arthritis and their relevance to synovitis are of paramount importance for the discovery of new therapeutic targets. Interestingly, several biochemical factors, in particular, inflammatory cytokines have been considered as playing key roles in the development and progression of synovitis. For this reason, the ability of inflammatory cytokines to participate synovitis process attracts many researchers to explore their therapeutic potential for inflammatory arthritis.

Of various cytokines produced in the inflamed synovium, interleukin-34 (IL-34), a discovered inflammatory cytokine, is gaining increasing interest as a possible mediator for inflammatory arthritis. It has been identified that IL-34 as an alternative ligand for colony-stimulating factor-1 receptor (CSF-1R) shares functional similarities with CSF-1 (also known as macrophage-colony-stimulating factor; M-CSF) that regulates a variety of biological effects on several cells [4]; however, it has been suggested that these two molecules are not identical in signaling activation [5]. In fact, CSF-1 is the primary regulator of survival, proliferation, and differentiation of myeloid lineage cells including monocytes, macrophages, and osteoclasts [6]. Over the past years, emerging evidence indicates that IL-34 can substitute CSF-1 in osteoclastogenesis [7]. Regarding possible effect of IL-34 on osteoclasts, IL-34 has been investigated as to its role in bone resorption [8], which has been implicated in the pathology of inflammatory arthritis. Upon binding to CSF-1R and in concert with receptor activator of nuclear factor-kappa B ligand (RANKL), IL-34 regulates the differentiation and activation of osteoclasts responsible for bone erosion [9,10]. Besides osteoclastogenesis-induced bone degeneration, chronic inflammation of synovial joint can cause joint destruction via increasing release of RANKL and inflammatory cytokines. It has been shown that IL-34 exerts its synergistic effect with RANKL on inflammatory response-incited bone erosion. Strikingly, via the activation of CSF-1R, up-regulation of IL-34 expression has been reportedly regulated by tumor necrosis factor-alpha (TNF-α), which is an inflammatory cytokine known to influence joint destruction [11]. Indeed, several clinical studies demonstrated an increase in production in the systemic and local levels of IL-34 in RA patients [12–14]. From the above-mentioned findings, it seems likely that IL-34 may have an immense potential to be a biologically active stimulator of progressive joint degeneration and synovial inflammation.

Accordingly, the main purpose of this article was to review a possible role of IL-34 in the development of inflammatory arthritis including RA and knee OA, highlighting its important mechanisms behind inflammatory process and cartilage destruction. In addition, we aimed to summarize an update on experimental and clinical studies that have been focused on the promising beneficial impacts of IL-34 on the treatment of synovitis associated with many aspects of inflammatory arthritis.

2. Interleukin-34 biology

2.1. Protein structure of interleukin-34

Human IL-34 encoded by the *IL-34* gene spanning on chromosome locus 16q22.1 is an N-glycosylated secreted protein and serves as the second ligand for CSF-1R, in which IL-34 possesses an expansive spectrum of biological functions in modulating the survival, proliferation, and differentiation of myeloid linage cells [15,16]. The translated IL-34 protein comprises 242 amino acids with a molecular mass of 39 kD. At the amino acid level, the first 182 amino acids contain predicted N-glycosylation sites at Asn76 and Asn100 positions, which are essential sites for regulation of IL-34 stability and accurate its folding and assembly. In addition, 6 cysteine residues are highly conserved across species, and 4 of these cysteines are vital positions for the formation of the intramolecular disulfide bonding. Additionally, the remaining ˜50 amino acid residues at the C terminal are found to be largely disordered and highly enriched with Pro-Ser-Thr amino acids, which are a typical characteristic of flexible O-linked-glycosylated mucin-like sequences [17–19].

The overall structure of IL-34 has been identified as a distinctive antiparallel four-helical bundle core fold consisting of 4 short helices: α1, α2, α3, and α4, which are integrally bundled to the core, 2 β-strands including β1 and β2 that link the helices, and unique terminal extensions used for receptor binding (αA, αB, αC, and αD). In addition, recent analysis of the IL-34 crystal structure combined with Fab fragments of CSF-1R proffers a structural rationale for their respective neutralizing and non-blocking properties, for which this information provides novel insights into their utility as therapeutic targets [17].

2.2. Interleukin-34 receptors

The biological functions of IL-34 are mainly mediated by IL-34 receptors, consisting of three predominant molecules: CSF-1R, receptor-like protein tyrosine phosphatase-zeta (RPTP-ζ), and syndecan-1. It is well-known that IL-34 shares some partially overlapping actions with CSF-1 via its interaction with CSF-1R [19]. The CSF-1R is a cell-surface protein encoded by the *CSF-1R* proto-oncogene and contains 5 immunoglobulin-like domains including D1–D5 [20], in which IL-34 binds this receptor at the cleft between D2 and D3 [21] and has a greater affinity for CSF-1R than CSF-1 [16]. Typically, CSF-1R is a member of the class III receptor tyrosine kinase family, and its expression has been discovered predominantly in monocytes, macrophages, osteoclasts, and monocytes-derived dendritic cells (DCs) as well as Langerhans cells. In addition to mononuclear phagocytic cells, the expression of CSF-1R is distributed not only in neuronal cells [22], but also in muscle precursors [23]. Given ubiquitous presence of CSF-1R throughout the body, IL-34 expression has been detected in several cell types [4], and it exerts pleiotropic biological activities in specific tissues and cells, such as myeloid cells, epithelial cells, endothelial cells, fibroblasts, neurons, and cancer cells [24]. Following the engagement of IL-34 with the extracellular domain of CSF-1R, this complex escalates the dimerization and autophosphorylation of specific tyrosine residues within the intracellular domain. The majority of phosphorylated residues afterwards result in the recruitment of several kinases and adaptor proteins known to persuade a variety of signaling pathways including extracellular signal-regulated kinase 1/2 (ERK1/2), signal transducer and activator of transcription 3 (STAT3), focal adhesion kinase (FAK), and serine/threonine protein kinase B (PKB, also known as Akt) [25]. These signal transduction pathways prompt the pleiotropic effects of IL-34-mediated CSF-1R on cellular differentiation, adhesion, migration, cytoskeletal organization, proliferation, as well as survival and subsequently regulate the expressions of specific genes [24]. For example, Boulakirba et al. [26] demonstrated the significant involvement of IL-34 binding to CSF-1R in regulation of macrophagic differentiation and polarization, through which IL-34 strengthened the expression and activation of adenosine monophosphate-activated protein kinase (AMPK)-1 and uridine kinase-like protein-1 being autophagy stimulating kinase 1 in monocytes, leading to the activation of Akt and caspase signaling pathways. It is comprehensible that IL-34-impeled appropriate signaling pathways is classically regulated by its own receptor like CSF-1R.

Apart from the transduction of IL-34/CSF-1R signaling pathway, IL-34 has been reported to be expressed in the brain where CSF-1R is disseminated with low expression, thereby leading to new insights concerning that IL-34 could stimulate proper signaling cascades via an alternative receptor. From knowledge on RPTP-ζ biology, as a chondroitin sulfate proteoglycan, RPTP-ζ is highly expressed in the central nervous system [27], and its activity induced by specific ligands takes fundamental parts in controlling cell proliferation, differentiation, communication, and adhesion – especially neurons [28]. Recently, there is supporting evidence that accentuates a RPTP-ζ chondroitin sulfate moieties-dependent action of IL-34. Mechanistically, IL-34 interacting with RPTP-ζ urges tyrosine phosphorylation of FAK and paxillin, which in turn restrains the intracellular signaling pathways including cellular proliferation, clonogenicity, and motility – particularly glioblastoma cells [29].

Aside from the interaction of IL-34 with RPTP-ζ, Segaliny et al. [30] identified additional receptors of IL-34 in other cell types and found that IL-34 bound chondroitin sulfates with low affinity in cells lacking both CSF-1R and RPTP-ζ. Among the proteoglycans with chondroitin sulphate chains, syndecan-1 can ameliorate the activity of IL-34-induced CSF-1R signaling, in which this mechanism leads to migration of myeloid cells. Notably, the activity of IL-34 mediated by CSF-1R was limited under low expression of syndecan-1, whereas overexpression of syndecan-1 has been shown to enhance the transduction of the IL-34/CSF-1R axis. Based on these previous findings, it is apparent that syndecan-1 may serve as a key regulator of IL-34 biology by regulating IL-34 bioavailability and modulating the binding affinity of IL-34 to CSF-1R. Since syndecan-1 is a sponge for extracellular matrix molecules and growth factors, with binding largely via heparan sulfate chains, it functions as an integral membrane protein and participates in cellular proliferation, migration, and matrix interactions [31]. It is conceivable that IL-34 interacting with its distinct receptors influences the stimulation of suitable signaling pathways becoming altered in disease development. The biological actions of IL-34 mediated through its own receptors in regulation of cellular functions in target tissues are illustrated in Fig. 1.

3. Multifaceted biological roles of interleukin-34

Considerable studies shed light on IL-34's biological activities in regulating an exceptional range of physiological and pathological processes including cell differentiation, proliferation, survival, adhesion, migration, inflammation, and immune response through the triggering of CSF-1R signaling cascades [23,32–34].

3.1. Cell differentiation

It has been apprehended that IL-34 can substitute for CSF-1 entirely for inducing the differentiation of monocytes into immunosuppressive macrophages [35,36]. Besides, through the activation of ERK1/2, Akt, AMPK, and autophagy signaling cascades, IL-34-activated CSF-1R has been shown to provoke the differentiation and polarization of macrophages [26]. Furthermore, the IL-34/CSF-1R signaling stimulates the polarization of Kupffer cells into an M2-phenotype of macrophage that exhibits decreased expressions of pro-inflammatory cytokines including IL-12 and increased expressions of immunosuppressive cytokines such as arginase-1, IL-10, and transforming growth factor-beta 1 (TGF-β1). These downstream effects are mediated by a wide variety of signaling pathways including the induction of phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) pathway, the enhancement of the phosphorylation of mammalian target of rapamycin (mTOR), ribosomal protein S6 kinase (S6K), as well as eukaryotic translation initiation factor 4E-binding proteins (4E-BP), and the suppression of p65 and p38 mitogen-activated protein kinase (MAPK) activities [37]. In addition to the differentiation of macrophages and Kupffer cells from monocytes, experimental studies have established that IL-34, but not CSF-1, plays a possible role in controlling the differentiation of splenocytes into follicular DCs-induced monocytic cells via CSF-1R signaling-elicited B-cell activity [38]. Additionally, a study by Booker et al. revealed an alternative effect of IL-34 on modulating the differentiation of leukemia cell lines into monocyte-like cells mediated through the janus kinase/signal transducers and activators of transcription (JAK/STAT) and PI3K/Akt pathways. Regarding this, IL-34 has been shown to alter the expressions of cell surface markers of myeloid lineage cells and display functional capabilities to phagocytize foreign particles and to perform respiratory burst activity [39]. Taken together, the above-mentioned observations

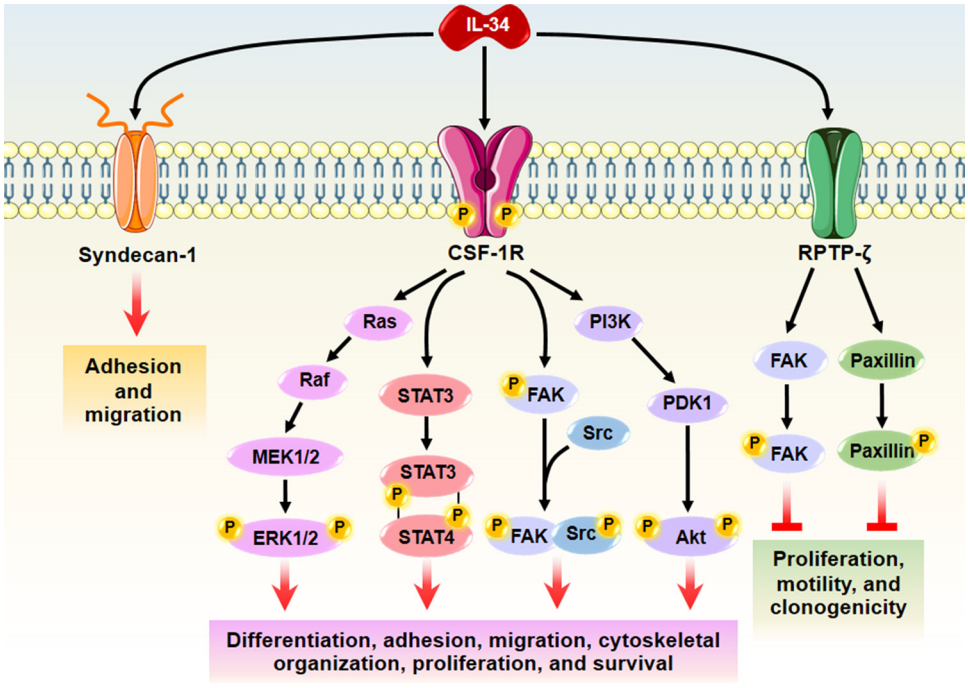

Fig. 1. The biological effects of interleukin-34 mediated by its own receptors. IL-34 interacts with CSF-1R to prompt a number of signaling pathways that regulate cellular differentiation, adhesion, migration, cytoskeletal organization, proliferation, and survival. IL-34 also suppresses numerous cellular functions including proliferation, motility, and clonogenicity through its binding to RPTP-ζ. The IL-34/syndecan-1 axis has been shown to stimulate adhesion and migration in several cells – especially macrophage.
Abbreviations: CSF-1R, colony-stimulating factor-1 receptor; FAK, focal adhesion kinase; IL-34, interleukin-34; MEK, MAPK kinase; PDK, pyruvate dehydrogenase kinase; PI3K, phosphoinositide-3-kinase; RPTP-ζ, receptor-like protein tyrosine phosphatase-zeta; STAT, signal transducer and activator of transcription

indicate a potential effect of IL-34-mediated CSF-1R signaling on regulation of cellular differentiation.

3.2. Cell proliferation and survival

The binding of IL-34 to CSF-1R has been reported to activate the proliferation and survival of myeloid lineage cells including bone marrow cells, monocytes, macrophages, osteoclasts, and microglia [40,41]. In parallel with its effects on myeloid cells proliferation, IL-34/CSF-1R axis can promote proliferation of other cell types including endothelial cells, fibroblasts, and cancerous cells. Furthermore, acting via CSF-1R, IL-34 directly stimulates proliferation of endothelial colony forming cells [30,39]. Instead, it has been documented to quell the proliferation of glioblastoma cells through its interaction with RPTP-ζ [29]. Moreover, the triggering of ERK1/2 and Akt signaling pathways mediated by IL-34/CSF-1R axis reportedly results in cancerous survival, thereby contributing to chemoresistance in lung and colon cancer cells, in addition to malignant pleural mesothelioma cells [42–44].

3.3. Cell adhesion and migration

Nowadays, many studies have been focused on investigating the possible functions of IL-34 in cellular adhesion and migration. Among others, Segaliny et al. explored whether IL-34 possesses a direct effect of monocyte adhesion to the endothelium and remarked that IL-34 promoted the adhesion of cluster of differentiation (CD) 14^+ monocytes to endothelial cell precursors and $CD34^+$ hematopoietic stem cells to activated human umbilical cord monolayers [45]. Specially, Segaliny et al. attempted to elucidate the possible action of IL-34 mediated through syndecan-1 in cell migration, and they also found that IL-34/syndecan-1 signaling cascade stimulated the migration of myeloid cells including THP-1 cells being a human monocytic cell line and M2a macrophages, in which the blockage of syndecan-1 with anti-syndecan-1 antibody suppressed the activity of IL-34-induced migration of those cells [43,45].

3.4. Inflammation

Given that IL-34 is considered to be a novel inflammatory cytokine, the involvement of IL-34 in inflammatory response has been proved by previous studies that unveiled overexpression of IL-34 induced by inflammatory stimuli via promoting nuclear factor-kappa B (NF-κB) signal transduction pathway in various cells, leading to increasing the production of pro-inflammatory cytokines and chemical stressors [40]. Consistent with this, a number of *in vitro* studies depicted that IL-34 expression was decreased in cells treated with specific inhibitors of NF-κB [11,46], indicating the possible influence of IL-34-mediated NF-κB signaling in response to inflammation. As NF-κB is a transcription factor acting as a dominant regulator of the inflammatory signaling pathways, it is not surprising that IL-34 has been reportedly implicated in inflammatory process in various pathological conditions such as coronary artery disease [47], chronic apical periodontitis [48], and chronic liver disease [49]. For instance, IL-34 expression was found to be increased in inflamed ileum of patients with inflammatory bowel disease (IBD) and in a mouse model of experimental colitis. In human, it has been shown that IL-34 expression in intestinal epithelial cells is regulated by tumor necrosis factor-alpha (TNF-α) via the NF-κB pathway [32]. These previous findings indicate that IL-34 could serve as an additional modulator of inflammation in IBD. Moreover, colon epithelial cells stimulated with IL-34 reportedly increase the expressions of pro-inflammatory cytokines including TNF-α, IL-6, and chemokine (C-C motif) ligand-20 (CCL-20) via the ERK1/2 signaling [50,51]. Besides its inflammatory effect on IBD, IL-34 can induce the release of IL-6 being pro-inflammatory cytokine and chemokines including IL-8, interferon-inducible protein-10 (IP-10), chemokine (C-X-C motif) ligand-10 (CXCL-10), and monocyte chemotactic protein-1 (MCP-1) in human whole blood [52]. These previous findings are important evidence supporting a significant role of IL-34 in an inflammatory reaction contributing to several diseases, by which IL-34 augments the production of pro-inflammatory cytokines and enriches the infiltration of inflammatory lymphocytes via the stimulation of inflammatory pathways – particularly NF-κB signaling cascade.

3.5. Immune response

With such its potent effect on inflammation, IL-34 can activate a complex signaling network involving various types of cells and molecules known to regulate innate and adaptive immune responses during inflammation. Several studies delineated that IL-34 prompted monocytes differentiation into M2-polarized Mφs macrophages, which are characterized by enriched immunosuppressive abilities to aggravate the protective responses of natural killer (NK) and T cells to pathogen [35,43]. These previous findings provide further evidence that favors an alternative action of IL-34 as an immunosuppressive cytokine responsible for inflammation-medicated immune deregulation. Supporting this, Boulakirba et al. reported a potential role of IL-34-induced Mφs differentiation in regulating a protective response of T cells, importantly affected by stimuli available at the local microenvironment, in which altered expressions of cytokines/chemokines in IL-34-differentiated Mφ macrophages depend on their polarization status, resulting in alterations of type 1 helper T cell (Th1) polarization [26]. Furthermore, Bézie et al. established a direct link between IL-34-differentiated Mφs and regulatory T cells (Tregs)-mediated immune tolerance [53]. Pathophysiologically, IL-34 activates the abilities of $CD4^+$ and $CD8^+$ Tregs to prevent allograft from acute and chronic rejection both *in vivo* and *in vitro* models through the polarization of monocytes towards M2 macrophages [54,55]. The aforementioned findings indicate that IL-34 appears to have a suppressive effect on the innate and adaptive immune responses through escalating the expressions of cytokines/chemokines and rendering Mφs differentiation into dissimilar phenotypes.

4. Pathological roles of interleukin-34 and its feasibility as a novel biomarker in inflammatory arthritis

Although in the steady state, IL-34 expression has been detected predominantly in the brain and skin [41], several lines of evidence uncover IL-34 expression in several cells and tissues – particularly fibroblast-like synoviocytes (FLSs) and the synovial membrane [12–14]. In this regard, IL-34 would be a molecular predictor for the pathophysiology of synovium, which may be involved in the onset of inflammatory forms of arthritis including RA and knee OA. The pleiotropic biological effects of IL-34-mediated inflammation and destruction on the joint are demonstrated in Fig. 2.

4.1. Pathological roles of interleukin-34 in rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease of the joints, which is mainly characterized by synovial inflammation and hyperplasia, potentially leading to the progression of cartilage and bone destruction. It has been suggested that pro-inflammatory cytokines take a critical role in the regulation of synovial inflammation, by which IL-1β and TNF-α being pivotal mediators of inflammatory process stimulate the production of numerous cytokines, metalloproteases, and chemokines in synovial fibroblasts [1]. With regard to the pleiotropic actions of IL-34 in inflammation, numerous studies unveiled that both IL-1β and TNF-α prompted IL-34 expression in FLSs isolated from RA patients [12,14], suggesting the pathological role of IL-34 as a downstream effector of pro-inflammatory cytokines in synovial inflammation of RA. Correspondingly, Chemel et al. revealed that IL-34 was ubiquitously detected in the synovial sublining and intimal lining layer from patients with RA, and its expression was associated with the severity of synovial inflammation in the patients [12]. Furthermore, IL-34 has

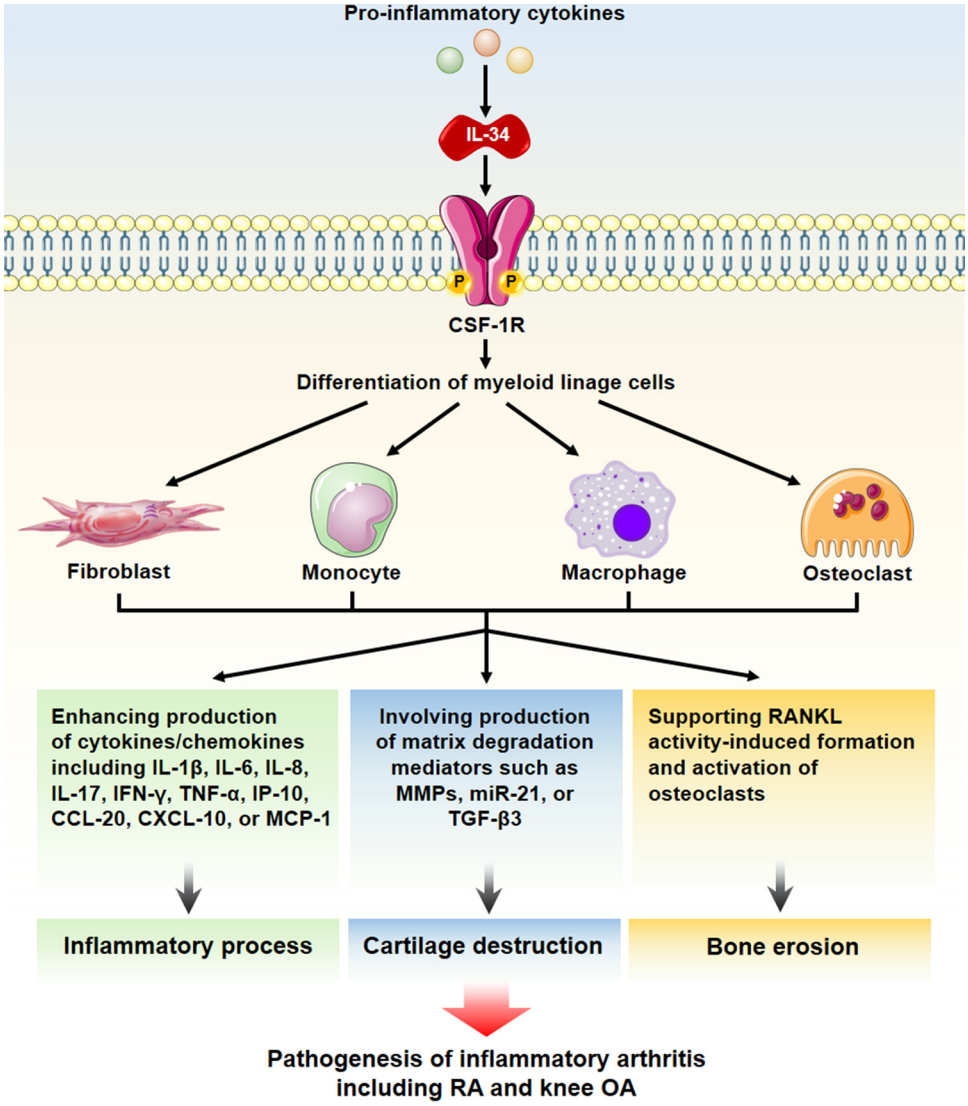

Fig. 2. The pathological roles of interleukin-34 in inflammatory arthritis. IL-34 exerts biological effects mediated through the activation of downstream mediators responsible for joint inflammation and cartilage destruction on inflammatory arthritis including RA and knee OA.
Abbreviations: CCL-20, chemokine (C-C motif) ligand-20; CSF-1R, colony-stimulating factor-1 receptor; CXCL-10, chemokine (C-X-C motif) ligand-10; IFN-γ, interferon-gamma; IL, interleukin; IP-10, interferon-inducible protein-10; MCP-1, monocyte chemotactic protein-1; MiR-21, microRNA-21; MMPs, matrix metalloproteinases; RANKL, receptor activator of nuclear factor-kappa B ligand; TGF-β3, transforming growth factor-beta 3; TNF-α, tumor necrosis factor-alpha

been shown to promote the expression of IL-6 in RA FLSs via JNK/P38/NF-κB signaling pathway, in which activation of FLSs is a keystone step that aggravates RA progression [56]. Similarly, results from an experimental study by Zhang et al. substantiate the role of IL-34 as an inflammatory modulator of RA pathology, in which IL-34 upsurges mRNA expressions of *TNF-α* and *IL-17* in synovial tissues of collagen-induced arthritis mice [57]. Interestingly, through the phosphorylation of STAT3, in RA FLSs, IL-34 reportedly increases the expression of microRNA-21 (miR-21) contributing to cartilage destruction, whereas the functional inhibition of miR-21 expression has been shown to mitigate B-cell lymphoma-2- associated X (Bcl-2/Bax) ratio that results in FLSs resistance to apoptosis. These effects have been previously reversed by the suppression of CSF-1R activity, implying that the inhibition of IL-34-induced CSF-1R can mitigate FLSs proliferation, subsequently alleviating the accumulation of inflammatory cytokines [58].

Apart from its probable effect on synovial inflammation, IL-34 has been proposed to exert alternative properties in regulating the production of autoimmune-related components including pro-inflammatory cytokines and chemokines, importantly participating in RA pathogenesis. More recently, IL-34 was found to trigger IL-6 expression in monocyte-like cell line (THP-1) co-cultured with RA $CD4^+$ cells, and this effect was impeded by CSF-1R antagonist [56]. This previous finding supports Eda's investigation, which noted a significant decline in the ability of IL-34 to influence the production of chemokines by a CSF-1R kinase inhibitor like GW2580 [52], indicating the possible influence of IL-34 interacting with CSF-1R in modulating the release of autoimmune-related components responsible for inflammation in RA.

Besides synovial inflammation-mediated immune deregulation, osteoclastogenesis induced by pro-inflammatory cytokines is well-established as an important mechanism implicated in the pathogenesis of RA [59]. It is now appreciated that chronic inflammation stimulates osteoclasts formation and a subsequent increase in their resorbing activity. Regardless of bone resorption, in response to RANKL and CSF-1 activities, osteoclasts differentiated from monocyte/macrophage haematopoietic lineage cells undergo an activation process, and they break down the tissue in bones and release the minerals including calcium into the circulation [9]. This emphasizes the possibility of RANKL and CSF-1 as key modulators of osteoclastogenesis. As IL-34 serves as an alternative ligand for CSF-1R and exerts its role in synovial inflammation, a growing body of evidence indicates a chief action of IL-34 in regulation of osteoclastogenesis, possibly involved in RA pathogenesis. In recent years, Chen et al. reported that recombinant mouse IL-34 combined with RANKL stimulated osteoclasts differentiation from splenocytes and bone marrow cells in a dose-dependent manner, and these cells exhibited bone resorbing activity. The investigators further showed that the systematic administration of IL-34 in mouse urged the differentiation of osteoclasts from peripheral blood mononuclear cells, which in turn reduced bone mass [60]. In line with these previous

Table 1
Summary of studies on the association between interleukin-34 levels and clinical parameters in various types of inflammatory arthritis.

Publications	Year	Study Design	Subjects	Significant results
Rheumatoid arthritis				
Wang et al. [56]	2017	Case-control study	168 RA patients and 84 healthy controls	RA patients exhibited significantly higher serum IL-34 levels than healthy controls, and its serum levels were associated with clinical variables in the patients.
Chemel et al. [12]	2017	Cross-sectional study	20 RA patients, 3 OA patients, and 4 other inflammatory arthritis	Synovial fluid IL-34 levels were markedly reduced in RA patients. Its levels in joint fluid were also associated with total leukocyte counts of RA patients.
Yang et al. [58]	2016	Case-control study	30 RA patients, 20 OA patients, and 20 healthy controls	An increase in synovial fluid IL-34 levels was found in advanced RA patients who had high DAS28 score. Furthermore, there was a positive correlation between synovial fluid IL-34 levels and DAS28 scores of RA patients.
Chang et al. [61]	2015	Case-control study	100 serum RA patients, 36 serum AS patients, 59 serum healthy controls, 18 joint fluid RA patients, and 19 OA patients	Serum IL-34 levels were remarkably increased in RA patients compared to controls, and joint fluid IL-34 levels were considerably higher in RA patients than in OA patients. Moreover, serum IL-34 levels were associated with outcome parameters – especially radiographic severity of the patients.
Zhang et al. [62]	2015	Prospective cohort study	83 RA patients and 35 healthy controls	Serum IL-34 levels were significantly increased in RA patients before treatment with TNF-α inhibitor, while its serum levels were also markedly declined in the patients after therapy initiation at 4 weeks. Moreover, serum IL-34 levels were correlated with inflammatory cytokines, MMP-3, and anti-CCP antibodies in RA patients at baseline.
Moon et al. [13]	2013	Case-control study	113 serum RA patients, 56 serum OA patients, 36 serum healthy controls, 36 synovial fluid RA patients, and 24 synovial fluid OA patients	Serum IL-34 levels were significantly higher in RA patients than in OA patients and healthy controls. Besides, its levels in synovial fluid were considerably increased in RA patients compared with OA patients. Particularly, serum and joint fluid IL-34 levels were associated with IL-6, RANKL, and clinical variables in RA patients.
Tian et al. [63]	2013	Case-control study	125 serum RA patients, 40 serum OA patients, 55 serum healthy controls, and 11 synovial fluid RA patients	RA patients had significantly increased IL-34 levels in both serum and synovial fluid, as compared with OA patients and serum controls. In addition, a marked reduction in serum IL-34 levels was observed in RA patients who received anti-TNF treatment.
Hwang et al. [14]	2012	Cross-sectional study	RA patients and OA patients	An elevation of synovial fluid IL-34 levels weas found in RA patients, and its circulating levels were also declined in the patients treated with disease-modifying anti-rheumatic drugs.
Chemel et al. [12]	2012	Cross-sectional study	20 RA patients, 3 OA patients, and 4 other inflammatory arthritis	An increment of synovial fluid IL-34 levels associated with the disease severity was found in RA patients.
Knee osteoarthritis				
Wang et al. [75]	2018	Case-control study	182 Knee OA patients and 69 healthy controls	Knee OA patients had significantly higher serum IL-34 levels than healthy controls, and synovial fluid IL-34 levels were remarkably increased paired plasma samples of the patients. Notably, synovial fluid IL-34 levels were found to be related to radiographic severity and WOMAC scores in knee OA patients.

Abbreviation: AS, ankylosing spondylitis; DAS28, disease Activity Score, IL-34: interleukin-34, IL-6: interleukin-6; OA, osteoarthritis; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; TNF-α, tumor necrosis factor alpha; WOMAC, Western Ontario McMaster University Osteoarthritis Index.

findings, a study by Hwang et al. illustrated that IL-34 secreted by RA FLSs treated with TNF-α induced chemotactic migration of peripheral blood mononuclear cells and eventually stimulated osteoclasts differentiation, and the functional aggravation of IL-34 with its specific antibody alleviated osteoclasts formation [14]. Collectively, these provide novel information that attests an additional role of IL-34 in regulating bone erosion contributing to RA pathology.

4.1.1. Interleukin-34 as a biochemical marker for rheumatoid arthritis

Given that IL-34 has been shown to play predominant roles in synovial inflammation and bone erosion, possibly implicated in RA pathology, whether IL-34 levels are associated with the severity of RA remains to be determined. A large number of studies have been focused on investigating the possible relationship of IL-34 concentrations in the circulation and joint fluid with clinical parameters of RA patients, as summarized in Table 1. First, a case-control study of 168 RA patients and 84 healthy controls by Wang et al. demonstrated that serum IL-34 levels in RA patients were significantly greater than that in healthy controls, and its serum levels were found to be positively associated with clinical variables including c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (CCP) antibody titers in the patients [56]. In addition, strong evidence for a possible correlation between synovial fluid IL-37 levels and inflammatory parameters in RA was recently described by Chemel et al. The authors reported that an increase in synovial fluid IL-34 concentrations was associated with the total leukocyte counts of RA patients [12]. This information supports a study of Yang and coworkers showing that advanced RA patients who had a high 28-joint Disease Activity Score (DAS28 ≥ 3.2) showed remarkably greater synovial fluid IL-34 levels than the patients with a lower DAS28 (DAS28 < 3.2). Particularly, there was a positive correlation between IL-34 levels in synovial fluid and DAS28 scores [58]. In 2015, Chang et al. measured serum and synovial fluid IL-34 levels in RA patients and healthy controls and also observed that serum IL-34 levels were markedly higher in RA patients than in controls, and joint fluid IL-34 levels were considerably increased in RA patients compared with OA patients. When determining the correlation between circulating IL-34 levels and clinical parameters in RA patients, serum IL-34 levels were found to be positively associated with RF, current smoking, ESR, CRP, DAS28 scores, and radiographic severity of RA patients [61]. Besides, Zhang et al. added another piece of supporting data, demonstrating that serum IL-34 levels were significantly increased in RA patients compared to healthy controls, but were markedly decreased in the patients during therapy. They also found that there were significant associations of serum IL-34 levels with ESR, CRP, IL-6, IL-8, TNF-α, matrix metalloproteinase-3 (MMP-3), anti-CCP antibodies, and disease severity in RA patients [62]. In 2013, Moon et al. revealed that RA patients had a significantly higher serum IL-34 levels than OA patients and healthy controls, and joint fluid IL-34 levels were remarkably elevated in RA patients as compared to OA patients. The authors also reported the positive associations of serum and synovial fluid IL-34 levels with IL-6 and RANKL levels in RA patients, and its serum levels were positively related to RF and anti-CCP antibody titers in RA patients [13]. Likewise, when Tian et al. analyzed serum and synovial fluid IL-34 levels in RA patients, OA patient, and healthy controls, they reported an increase in serum and synovial fluid IL-34 levels in RA patients. Furthermore, the investigators found that serum levels of IL-34 were decreased in RA patients receiving anti-TNF treatment [63]. This study supports a previous report, in which synovial fluid IL-34 levels were substantially increased in RA patients, and circulating IL-34 levels were significantly declined in RA patients who were treated with disease-modifying antirheumatic drugs (DMARDs) [14]. Additionally, the findings of Chemel et al. provide support to an elevation in synovial fluid IL-34 levels in RA patients and a significant relationship between IL-34 levels and RA severity [12]. All of these previous findings support the notion that IL-34 has the classical actions including a potential capacity to induce synovial inflammation-mediated bone erosion and therefore may link its role to the pathogenesis of RA.

Even though former clinical studies have demonstrated a close association of IL-34 levels with RA severity, the exact mechanism responsible for increases in circulating and synovial fluid IL-34 levels in RA patients remains uncertain. The possible explanation for these findings might be attributed to augmented IL-34 synthesis, which surpassed it clearance. In this context, high levels of IL-34 may be implicated in a defensive response of the body to fight against inflammation and further bone erosion. From previous reports regarding its significant association with RA severity, it is apparent that IL-34 levels may serve as a potential indicator for the development and progression of RA.

4.2. Pathological roles of interleukin-34 in osteoarthritis

Osteoarthritis (OA) is one of the most common rheumatic disorders related to a degenerative joint, and it is most common in the elderly where the patients will develop severe pain as well as declined physical activity and eventually require total knee replacement (TKR) [64]. The increasing rates of TKR means that there is a desperate need to improve diagnosis and treatment of the disease. As a consequence, an increased understanding of what causes joint destruction in knee OA could lead to identifying potential biomarkers and new therapeutic targets. Although the specific order of pathologic alterations occurring in knee OA is far less clear, mounting evidence indicates that inflammatory and destructive responses of the synovium induced by the resultant pro-inflammatory mediators are the cornerstone events of OA pathogenesis [65,66]. From this, the products of degraded cartilage fragments released into the synovial cavity are likely to initiate synovial inflammation in OA, through which plentiful cells located in the synovial membrane including synovial fibroblasts, macrophages, and chondrocytes produce inflammatory cytokines, such as IL-1β and TNF-α [67]. These cytokines modulate the production of the proteolytic enzymes responsible for cartilage breakdown and degradation [68]. As synovial inflammation is directly linked to clinical symptoms and also reflects joint destruction in OA, it is noteworthy that treating key aspects of synovial inflammation holds great promise not only for painlessness but also for prevention of structural modification in the patients. It is therefore important to understand the cellular and molecular mechanisms associated with synovial inflammation that may provide a novel biomarker to aid in better diagnosis of OA severity. Considering the pathogenesis of OA characterized by synovial inflammation that is quite similar to RA pathology, the important roles of IL-34 in osteoclastogenesis and synovial inflammation have made it a novel therapeutic target and biomarker for synovitis in knee OA. As mentioned previously, IL-34 is able to substitute for CSF-1 to support RANKL-induced differentiation of monocytes into osteoclasts via the activation of CSF-1R, which in turn increases the capability of osteoclasts to stimulate bone resorption, thereby providing the plausible relevance of IL-34 to physiological and developmental OA. With its fundamental function in osteoclastogenesis, IL-34 has been recognized as a downstream effector of synovial inflammation. In general, pro-inflammatory cytokines have a chief action in promoting synovial inflammation in knee OA by heightening the release of inflammatory mediators, matrix metalloproteases, and chemokines in FLSs into the synovial fluid of knee OA [65–68], which further damage surrounding tissues of the joint. This lays emphasis on the involvement of pro-inflammatory cytokines in synovial inflammation and supports our own study, in which significantly increased levels of pro-inflammatory cytokine like IL-6 were found in synovial fluid and plasma samples of knee OA patients, and its levels were positively correlated with radiographic severity of knee OA [69]. In addition to alterations in local and systemic production of IL-6 in knee OA patients, our laboratory also investigated *IL-6* polymorphisms in knee OA patients and found that the *IL-6* −174 G/C polymorphism GC genotype was significantly associated with a higher risk

of knee OA in Thai population [70]. Our previous observations indicate that IL-6 plays a vital role in inflammatory process involving OA development. In regard to the effect of IL-34 on inflammation, cumulative data from experimental studies denoted that IL-34 knock-down mice attenuated the severity of inflammatory arthritis [71], in which the biological function of IL-34-mediated inflammation is governed by pro-inflammatory cytokines including TNF-α and IL-1β in human osteoblasts [11]. These cytokines enhance the secretion and expression of IL-34 through the activation of NF-κB and JNK signaling pathways. In conjunction with these previous findings, our laboratory determined whether *IL-34* expression is regulated by pro-inflammatory cytokine in FLSs isolated from knee OA patients and investigated *IL-34* mRNA expression in the inflamed synovium compared with the non-inflamed synovium obtained from knee OA patients who underwent total knee replacement. Our unpublished result showed that *IL-34* expression was significantly up-regulated in dose-and time-dependent manners in OA FLSs stimulated with TNF-α, when compared with untreated OA FLSs. Furthermore, our additional findings demonstrated that *IL-34* mRNA expression was remarkably increased in the inflamed synoivum of knee OA patients, and its mRNA expression was closely associated with circulating protein levels in the patients (unpublished data). This is important evidence that confirms the biological action of IL-34 as a downstream effector of pro-inflammatory cytokines-induced synovial inflammation in knee OA.

Along with the inflammation of synovium towards cartilage degradation, osteophyte formation is one of the most common features of knee OA, which is mediated by increased activity of osteoblasts through the activation of Wnt signaling that regulates the differentiation of mesenchymal progenitor cells into osteoblasts [72]. Due to the effect of IL-34 on stimulating the differentiation and function of osteoclasts, IL-34 has been proposed to act as a substitute for osteoblast-producing M-CSF responsible for osteoclasts formation. The involvement of IL-34 in osteoblasts has been verified by Yu and colleagues' study, which noted that IL-34 expression was up-regulated by TNF-α through the induction of NF-κB activity in mouse MC3T3-E1 osteoblastic cells [46]. Furthermore, Eda et al. reported that pro-inflammatory cytokines such as IL-1β and TNF-α enhanced IL-34 expression in human osteoblasts via JNK and p44/42 MAPK signaling pathways [11], in which osteoblasts have been reportedly involved in the distribution of osteoclast precursors in the bone [73]. More recently, macrophage dysfunction has been proposed as the prominently pathologic feature that drives the progression of knee OA [74], in which IL-34 is able to regulate the differentiation and function of macrophage, possibly implicated in the deterioration of macrophage function. All of these findings indicate that aberrant IL-34 levels may be induced in the site of bone destruction in knee OA patients and would be of great value for its usefulness as a novel biomarker and a promising target of therapeutic agents in bone-related diseases.

4.2.1. Interleukin-34 as a biochemical marker for knee osteoarthritis

Even though there are, to date, a number of diagnostic approaches for OA development such as tissue histology, MRI, or clinical findings, it has been suggested that these tools are inadequate for early identification of OA severity. In order to achieve an early and timely detection of the disease, a circulating biomarker is thought to be a possible diagnostic adjunct. Consequently, the possible influence of molecules taking a possible part in inflammatory response has great potential to become diagnostic biomarkers for OA.

Owing to the involvement of IL-34 in OA pathogenesis, IL-34 would be used as a biochemical indicator for synovial inflammation and bone degeneration in knee OA patients. This hypothesis has been addressed by a case-control study of 182 knee OA patients and 69 healthy controls conducted by Wang et al. [75]. The authors measured IL-34 levels in serum and joint fluid of knee OA patients and determined whether its levels are associated with radiographic and symptomatic severity of the patients. They also reported that IL-34 levels in synovial fluid were considerably greater than that in paired serum samples of knee OA patients, and its synovial fluid levels were positively associated with radiographic severity and scores of knee pain and disability including Western Ontario McMaster University Osteoarthritis Index (WOMAC) in knee OA patients. Besides, main result from our own research provides support to a significantly positive correlation of plasma and synovial fluid IL-34 levels with radiographic severity of knee OA patients (unpublished data). This finding suggests that IL-34 levels could be used as a biochemical predictor of knee OA severity. The possible association of IL-34 levels in the circulation and synovial fluid with the disease severity in knee OA patients is described in Table 1.

In the light of these considerations, it is tempting to postulate that an increase in synovial fluid IL-34 levels in knee OA might be presumably attributable to either enriched secretion of IL-34 residing in extracellular matrix responsible for injured arthritic and synovial tissues, raised IL-34 clearance, which in turn exceeded its synthesis, or both. Nonetheless, the precise mechanisms regulating IL-34 production not only IL-34 increment in the circulation but also its enhancement in synovial fluid of knee OA patients remain to be elucidated further.

5. Interleukin-34-targeted treatment for inflammatory arthritis

Given that accumulating data derived from both humans and mouse models associate the regulatory functions of IL-34 with synovial inflammation and osteoclastogenesis, which are both central mechanisms of inflammatory arthritis, increases in circulating and synovial fluid IL-34 levels and its agonists could be an alternative therapeutic option for the protection and therapy of inflammatory arthritis. Due to the biological effect of IL-34 mostly mediated by CSF-1R, the option to selectively block either IL-34 or CSF-1R may provide more efficiency in the design of therapeutic strategies for inflammatory arthritis including RA and knee OA.

Based on the results from experimental studies, the blockade of IL-34 by administration of anti-CSF-1R antibody has been recently shown to impede bone and cartilage destruction and relieve pain-related behaviors in an adjuvant arthritis model [76–78]. In accordance with these findings, Ohno et al. reported that anti-CSF-1R-neutralized IL-34 activity not only inhibited the accumulation of both inflammatory cells and osteoclasts in arthritis mouse model, but also alleviated the production of pro-inflammatory cytokines including TNF-α, interferon-γ (IFN-γ), IL-1β, and IL-6 [79]. Furthermore, several studies revealed that oral CSF-1R inhibitors consisting of GW2580, Ki20227, and PLX3397 exerted their defensive effects against bone erosion in arthritis mouse models [80,81]. More importantly, additional research showed that inhibiting the action of IL-34 by a specific antibody diminished osteoclasts differentiation and formation, which in turn constrained their resorbing activity [14]. From the above-mentioned findings, it appears that specific inhibition of the IL-34/CSF-1R pathway might serve as anti-inflammatory or anti-osteolytic agents against arthritis in preclinical models, and the rigorous identification of new drugs that target IL-34 in the treatment of inflammatory arthritis is presently even more important. However, due to the lack of clinical data concerning human toxicity, it remains to be seen whether clinical trials will ultimately bear out this premise, and further studies assessing the toxic and off-target effects of IL-34 inhibitors will be necessary to determine the practicability and clinical efficiency of IL-34 for practical applications.

6. Conclusions

Considerable research conducted over the past several years has demonstrated the multifaceted and potentially contradicting functions of IL-34 in regulating a range of biological functions of myeloid lineage cells – especially osteoclasts. With regard to its dominant role as a novel regulator of osteoclasts formation, IL-34 has been shown to possess a crucial role in bone destruction, which is one of the most pathologic events driving the onset and development of inflammatory arthritis.

The possible involvement of IL-34 in inflammatory and destructive responses has emerged from studies in cell cultures and animal models, in addition to clinical investigations. Indeed, experimental studies evidence the multiple effects of IL-34 on stimulating the differentiation of osteoclasts and further intensifying their resorbing activity through specific signal transduction pathways. Besides its effect on osteoclastogenesis, IL-34 has been recognized as a downstream effector of pro-inflammatory cytokines-induced synovial inflammation, in which its overexpression in FLSs isolated from patients with inflammatory arthritis including RA and knee OA is regulated by these cytokines. Importantly, the blockage of IL-34 and/or CSF-1R has been demonstrated to attenuate the severity of inflammatory arthritis in animal models, suggesting the targeting of IL-34/CSF-1R as a potentially effective therapy for inflammatory arthritis – especially RA and knee OA. Regulatory roles of IL-34 in osteoclastogenesis and synovial inflammation have been verified by clinical studies that link increased IL-34 levels in the circulation and joint fluid to the disease severity in inflammatory arthritis including RA and knee OA. Based on these observations, IL-34 could serve as a biochemical indicator and an alternative therapeutic target for synovial inflammation and bone degeneration. Since current data on the precise aspect of IL-34 in inflammatory arthritis have mostly been obtained from murine arthritis models, further research should focus on human systems to comprehensively elucidate the therapeutic potential of IL-34 in RA and knee OA.

Conflicts of interest

The authors declare that they have no competing interests regarding the publication of this paper.

Acknowledgements

This review is supported by Mahidol University, the Ratchadapiseksompotch Fund (RA61/104, Faculty of Medicine, Chulalongkorn University), and the Research Chair grant from National Science and Technology Development Agency (NSTDA).

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