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Review article

Interleukin 34, from pathogenesis to clinical applications

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ABSTRACT

Interleukin-34 (IL-34) is a hematopoietic cytokine that was described for the first time in 2008 as a second ligand of CSF1R in addition to M-CSF. IL-34 and M-CSF share no sequence homology, but have similar functions, affecting the biology of myeloid cell lineage. In contrast to M-CSF, IL-34 shows unique signaling and expression patterns. Physiologically, IL-34 expression is restricted to epidermis and CNS, acting as a regulator of Langerhans cells and microglia, respectively. However, IL-34 expression can be induced and regulated by NF-κB under pathological conditions. Importantly, growing evidence indicates a correlation between IL-34 and disease severity, chronicity and progression. In addition to its promising roles as a novel diagnostic and prognostic biomarker of disease, IL-34 may also serve as a powerful target for therapeutic intervention. Here, we review the current knowledge regarding the emerging roles of IL-34 in disease, and focus on the clinical applications of IL-34 in medicine.

1. Introduction

Cytokines are a large family of small secreted proteins including interleukins, chemokines, lymphokines, interferons and tumor necrosis factors. Cytokines are produced by a broad range of cells and mediate autocrine and paracrine cell-cell signaling, thus play critical roles in communication between cells, tissues and organs in complex organisms. Through signaling via specific receptors, cytokines control major physiological functions at the cellular level (growth, proliferation and migration), in addition to essential biological process such as inflammation, immunity and angiogenesis. Due to their critical functions, cytokines are involved in a wide variety of pathological conditions including inflammation, infection, autoimmunity and cancer. Thus, cytokines have been considered as attractive therapeutic targets, diagnostic tools and novel biomarkers that help to predict disease progression and severity.

Interleukin 34 (IL-34) is a hematopoietic cytokine that acts as a Key regulator of survival, proliferation and differentiation of myeloid lineage cells including monocytes, macrophages and osteoclasts [1–3]. IL-34 was identified in 2008 as a second ligand of CSF1R, in addition to the previously well-known ligand, M-CSF [1]. IL-34 shares functional similarities with M-CSF, but also show different characteristics and unique signaling patterns [4–6]. In contrast to M-CSF, which is expressed in a wide range of cells and tissues, IL-34 is a specialized cytokine that show specific expression in the skin by keratinocytes, and the brain by neurons at the resting state, and play critical roles in the development and maintenance of Langerhans cells and microglia, respectively [7–9]. Despite of its absence at the protein level, IL-34 can be detected at mRNA levels in various tissues and organs [1]. Importantly, several reports have shown that IL-34 can be induced at both mRNA and protein levels in stressed cells, and this induction is regulated by NF-κB; the master regulator of inflammatory response [10,11]. This suggests the involvement of IL-34 in pathological conditions, and indeed there is growing evidence that IL-34 contributes to the etiology of various diseases including autoimmune disorders, infections, inflammation and cancer.

In this review, we summarize the current knowledge regarding the role of IL-34 in disease, with a special focus on the potential role of IL-34 as a novel diagnostic and prognostic biomarker of disease in medicine.

Abbreviations: anti-CCP, anti-cyclic citrullinated peptide antibody; BMI, body mass index; CCL20, CC chemokine ligand 20; C/EBPβ, CCAAT-enhancer-binding protein β; CRP, C-reactive protein; CSF1R, colony stimulating factor 1 receptor; DAS28, disease activity score 28; DMARDs, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate; ERK, extracellular-signal-regulated kinase; ESR, erythrocyte sedimentation rate; HOMA-IR, homeostasis model assessment for insulin resistance; hsCRP, high sensitivity C-reactive protein; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-17, interleukin-17; IL-23p19, interleukin-23p19; TJC, tender joint count; M-CSF, macrophage colony-stimulating factor; MMP-3, matrix metalloproteinase 3; NF-κB, nuclear factor kappa B; RANKL, receptor activator of nuclear factor κB ligand; RF, rheumatoid factor; RYGB, Roux-en-Y bypass surgery; SAT, sc adipose tissue; TAT, total abdominal adipose tissue; TGFβ1, transforming growth factor β1; TLR, Toll-like receptor; TNFα, tumor necrosis factor-α; VAT, visceral adipose tissue

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2. The role of IL-34 in autoimmune diseases

2.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder characterized by accumulation of inflammatory cells into the synovium resulting in joint destruction. Pro-inflammatory cytokines play major roles in the regulation of synovial inflammation. The contribution of IL-34 in RA pathogenesis has been strongly suggested in clinical studies [12–21]. IL-34 is produced by synovial fibroblasts in response to stimulation with pro-inflammatory cytokines such as TNFα and IL-1β, and has a potential role in amplifying the inflammatory cascade [12–14]. IL-34 is released into synovial fluids (SF) of RA patients where it can be detected at high levels compared with osteoarthritis patients (OA) or healthy controls [12–16]. A significant correlation between SF IL-34 with disease parameters is observed in RA patients including histological severity of synovitis, synovial hyperplasia disease activity score, and inflammatory intensity as measured by leucocyte count and cytokine concentrations such as IL-6, TGFβ1 and RANKL [12–16]. IL-34 can be also detected at high levels in the serum of RA patients than OA or controls [13–17]. Similarly, serum IL-34 correlates positively with disease activity index (TJC and DAS28), inflammation parameters (ESR and CRP), auto-antibody production (RF and anti-CCP), and concentrations of other inflammatory mediators such as IL-6, IL-17 and MMP-3 [13–17]. Importantly, a significant decrease in serum IL-34 can be observed upon successful treatment with DMARDs or TNFα antagonist therapy [12–21]. Collectively, IL-34 is suggested to serve as a promising biomarker to assess radiographic progression and predict good response upon successful treatment in RA patients, and additionally inhibition of IL-34 may provide a novel target for therapies of RA (Fig. 1).

2.2. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease, characterized by the development of anti-nuclear antibodies. Although the exact etiology of SLE is still unclear, chronic inflammation mediated by anti-nuclear antibodies is implicated in the major complications frequently observed in SLE patients. IL-34 was identified among a limited number of cytokines and chemokines that were increased in kidney of three independent mouse models of lupus nephritis, indicating a potential role of IL-34 in SLE pathogenesis [22]. Consistent with this, serum IL-34 shows high levels in SLE patients compared to healthy controls, and remarkably correlates with the accumulation of SLE clinical features including malar rash/discoid rash, alopecia, oral or nasal ulcers, serositis, arthritis, active nephritis, CNS lupus, vasculitis, fever, thrombocytopenia, leukopenia and anemia [23]. Moreover, serum IL-34 correlates positively with the systemic lupus erythematosus disease activity index, anti-double-stranded DNA antibody titers and CRP levels, but inversely with complement 3 [23]. Importantly, serum IL-34 is significantly decreased after successful treatment of SLE [23]. Together, serum IL-34 may serve as a helpful diagnostic and therapeutic biomarker for SLE, showing elevated levels in the serum of treatment-naive SLE patients, which are significantly decreased after effective treatment (Fig. 1).

2.3. Sjogren's syndrome

Sjogren's syndrome (SS) is a systemic chronic autoimmune disease characterized by a connective tissue disease associated with keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth), and usually accompanies other autoimmune disorders such as rheumatoid arthritis and lupus. A major feature of SS is the upregulation of pro-inflammatory cytokines which results in enhanced infiltration of plasma cells and lymphocytes into secretory glands leading to fibrosis and decreased secretory function. Several studies have emphasized the critical role of monocytes in the expansion of inflammatory infiltrate in SS [24]. As a pro-inflammatory cytokine that affects monocytes biology, IL-34 may contribute to SS pathogenesis. In clinical samples, IL-34 was found to be highly expressed in the inflamed salivary glands of primary Sjogren's syndrome patients (p-SS) and correlated with increased expression of pro-inflammatory cytokines such as TNFα, IL-1β, IL-17 and IL-23p19 [24]. Importantly, high expression of IL-34 is accompanied by the expansion of pro-inflammatory $CD14^{bright}CD16^{+}$ monocytes in salivary glands; an observation supported by an evidence from in *vitro* studies where IL-34 stimulation of peripheral blood mononuclear cells resulted in the expansion of $CD14^{+}CD16^{-}$ and $CD14^{bright}CD16^{+}$ monocytes [24]. Together, IL-34 is suggested to play important roles in the pathogenesis of salivary gland inflammation, and may serve as a biomarker to indicate disease severity, and a potential therapeutic approach to p-SS treatment (Fig. 1).

2.4. Psoriasis and psoriatic arthritis

Psoriasis (Ps) is a chronic autoimmune disease characterized by patches of abnormal skin. Chronic inflammation in Ps results in the development of psoriatic arthritis (PsA) in 30% of Ps patients, which frequently associates with progressive joint damage, osteoclastogenesis and bone erosions. Pro-inflammatory cytokines such as TNFα, IL-1β and IL-12 play important roles in the immunopathogenicity of Ps/PsA by promoting systemic inflammation. The role of IL-34 in Ps/PsA has been recently suggested by the increased levels of serum IL-34 in Ps/PsA patients than healthy controls, with remarkable higher levels in PsA compared to Ps patients [25]. Furthermore, a range of bone pathologies is observed in PsA patients, which are related to over-activated osteoclastogenesis [25]. In this context, serum IL-34 levels importantly correlate with elevated numbers of circulating osteoclast precursors (OCPs), consistent with its critical roles in osteoclastogenesis [25]. These initial findings indeed indicate an important role for IL-34 in the etiology of Ps/PsA, suggesting it as a potent biomarker to monitor disease activity, and a potential therapeutic target to control inflammation and bone erosion in Ps/PsA patients (Fig. 1).

3. The role of IL-34 in metabolic diseases

3.1. Obesity

Obesity is a leading preventable cause of death worldwide, with increasing rates in adults and children. Obesity is a medical condition characterized by excess body fat and a state of low-grade chronic inflammation associated with increased serum levels of pro-inflammatory cytokines and acute phase proteins. Chronic inflammation is involved in the pathogenesis of obesity-associated complications such as insulin resistance and type II diabetes. Because of metabolic dysregulation and cellular stress, adipocytes release several factors that recruit macrophages into adipose tissues [26]. Adipose tissues-infiltrated macrophages mediate chronicity and correlates positively with BMI [26]. As a cytokine that dominates in chronic inflammation and affects macrophage biology, IL-34 is strongly suggested to have a role in the pathogenesis of obesity. Indeed, IL-34 expression can be detected in adipose tissues, which is remarkably enhanced upon exposure to pro-inflammatory cytokines such as TNFα and IL-1β [27]. Importantly, high levels of IL-34 can be observed in the serum of obese patients compared to controls (normal-weight healthy controls), which correlates positively with insulin resistance-related metabolic parameters including BMI, systolic BP, fasting plasma insulin, HOMA-IR, serum leptin, hsCRP, TAT, VAT and SAT, with higher levels of IL-34 in VAT compared to SAT [27]. Another interesting observation is that serum IL-34 is decreased after RYGB-induced weight loss [27]. Together, IL-34 is suggested to play important roles in the pathogenesis of obesity and obesity-associated complications, suggesting IL-34 as a novel biomarker for diagnosis and therapeutic monitoring in obese patients (Fig. 1).

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