The multifactorial roles of IL-34 in immune responses

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Abstract: Interleukin 34 (IL-34), a newly identified interleukin that is functionally similar to macrophage colony-stimulating factor (M-CSF), stimulates and persists the survival, differentiation, migration and function of various myeloid mononuclear cells and macrophages. These cells express IL-34 receptor, colony-stimulating factor 1 receptor (CSF1R, CD115). IL-34 forcefully combines to CSF1R and then recruits macrophage and monocyte which secret TNF and IL-6 to initiate the innate or adaptive immune responses. The high serum level of IL-34 was observed in many inflammatory and autoimmune diseases that are linked to the unique pro-inflammatory role of IL-34 in immune responses. In addition, IL-34 is considered to be a pro-inflammatory cytokine in anti-virus infection. Nonetheless, IL-34 also exerts an immunosuppressive reinforcement expressed in Treg that involves in the immunoregulatory role. Here, we conduct a systematic review to update the roles of IL-34 in immune responses.

Keywords: Interleukin 34 (IL-34); macrophage; immune responses

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Introduction

Interleukin 34 (IL-34) is a newly discovered cytokine that regulates the survival, differentiation and function of macrophage, osteoclast as well as microglia. Like other cytokines (1-15), it exerts its roles in target cells depending upon its receptor distribution. Although several receptors of IL-34 have been identified, the colony-stimulating factor 1 receptor (CSF1R, also called CD115) is a major one. However, CSF1R also binds with its archetypical ligand colony stimulating factor 1 (CSF-1), or called macrophage colony stimulating factor (M-CSF), for mediating mononuclear phagocyte, especially participates in the development of macrophage, dendritic cell, Langerhans and microglia (16). In CSF1-KO mice, Langerhans and microglia are unaffected, but they are absent in CSF1R-deficient mice. It suggests CSF1 is a dispensable cytokine for the development of Langerhans and microglia, and IL-34, alternative ligand of CSF1R, is nonredundant for differentiation of myeloid progenitor cell in the skin and central nervous system (CNS) (17). In 2009, Wei et al. (18) revealed IL-34, like CSF1, phosphorylates the membrane receptor CSF1R tyrosine phosphorylation, enhances the proliferation and viability in CSF1R+ macrophage via activating intracellular signaling pathway MAPK and ERK1/2. Additionally, IL-34 was identified as osteoclastogenic cytokine product by multiple myeloma cells that promote osteoclast formation and deteriorate osteolytic disease in multiple myeloma (19). Indeed, the osteoclast formation usually needs RANKL and M-CSF (20,21). Thus, IL-34 can directly initiate macrophage and monocyte responses as a pro-inflammatory agent by...
combining its receptor CSF-1. Nonetheless, IL-34 can be produced by regulatory cells (22) and then plays a role in suppressing immune responses. It is clear now that Treg cells are a crucial negative player that regulates immune balance and prevention of autoimmune and inflammatory diseases (23-31).

Source of IL-34

It is well known that IL-34 is a cytokine mainly produced by macrophage, monocyte, and microglia (32). Additionally, it is also produced by synovial fibroblasts in rheumatoid arthritis (RA) and hepatocytes in hepatitis virus infection. As synovial fibroblast plays a critical role in the pathogenesis of rheumatoid arthritis (33-37), this is likely that IL-34 serves as an inflammatory cytokine to participate in inflammation. In addition, IL-34 has also been found to be expressed in regulatory T cell (Treg) and IL34+ Treg has stronger immunoregulatory capacity (22). Thus, IL-34 could be a double sword that plays a different role under the distinct conditions and environments.

IL-34 in infection immunity

IL-34 has been recognized as an anti-virus cytokine during infection with influenza A virus (IAV) (38), hepatitis B virus (HBV) (39,40), hepatitis C virus (HCV) (41), human immunodeficiency virus (HIV) (42), that is produced in response to virus infection by inhibiting virus replication accompanied infiltration of macrophage in peripheral tissue or microglia in CNS. Virus infection is a critical cause of immune responses, and interleukins are secreted during the host’s anti-virus process that plays a different role in different tissues depending upon the types of virus-infection. For example, IL-22 is one of IL-10 family members to play a role in inhibiting inflammatory responses, was enhanced in IAV infected patients to induce IL-34 production that feedbacks to regulate IL-22 expression (38). In HCV-infection, IL-34 from hepatocytes around liver lesion can drive the existing macrophages to secret chemokine ligands (CCLs) and chemokine receptors (CCRs) to recruit monocytes and macrophages, to release platelet-derived growth factor (PDGF), and transforming growth factor beta (TGF-β) that induce liver fibrosis (41). The detailed descriptions of the anti-virus immune responses of IL-34 are summarized in Table 1 and Figure 1.

Taken together, role IL-34 exerts in the infection remains to be further studied, existing researches focus only on viral infections but not on bacterial, fungal, and parasitic infection. These studies demonstrate that IL-34 requires the responses of monocyte and macrophage in inflammation initiated by the virus to exert its function, but the triggering mechanism of initial IL-34 expression is still elusive. Interestingly, A contradictory phenomenon was reported that IL-34 is enhanced in IAV-infection while decreased in HBV-infection (38,40). Alternatively, IL-34 functional differences may be related to the timing and specific tissue localization.

IL-34 in autoimmune diseases

Autoimmune diseases are a systemic disease characterized by excessive immune responses involving many immune tissues, cells and interleukins (43-47). The high serum level of IL-34 was observed in many autoimmune diseases (48-53). Indeed, the involvement of IL-34 has been assessed in the initiation and development of autoimmune inflammation. Many correlation-studies assessed the serum level of IL-34 and suggested IL-34 is a positive biomarker for autoimmune response. Osteoclasts are the potent drivers and effector cells...
that participated in both inflammatory and erosion of bone and cartilage in rheumatoid arthritis (RA). The serum level of IL-34 was higher in RA patients than osteoarthritis patients, more than healthy control, and was positively accompanied with a higher radiographic progression and rheumatoid factors expression (54-56). The maturation of osteoclastogenesis is successfully induced by the supernatants of tumor necrosis factor-α (TNF-α) stimulated periodontal ligament cells added to the differentiation medium of human peripheral blood monocytes/macrophage cells with the receptor activator of nuclear factor kappa-B ligand (RANKL) in vitro, but the number of osteoclast was decreased after the anti-IL-34 IgG was added to the cultures (57). Obviously, the high expression of IL-34 in RA patients is inseparable from its ability to promote the differentiation of monocytes, especially osteoclasts, and thus participates in the development of RA.

High serum level of IL-34 was also observed in patients with systemic lupus erythematosus (SLE), and the worse the clinical features and the higher IL-34 expression (48,58). The SLE is a systemic autoimmune disease characterized by a large number of activated autoreactive T, B cells and followed by immune dysfunction (59-63). However, abnormal secretion of many cytokines can lead to immune dysfunction, but how the IL34 is involved in the course of SLE remains to be unclear and deserves a deep study in the future.

**IL-34 in transplant immunity**

Induction of transplant tolerance provides an efficiently therapy in both the acute rejection and the chronic allograft dysfunction (64-66). The therapy of anti-graft immunity has benefited from the development of Tregs and immune-suppressive monocytes in both experimental allograft-models and transplantation-patients (67,68). Yet, it is still unclear how IL-34 regulates Tregs and suppressive monocytes and how the balance of pro-inflammatory and anti-inflammatory role of IL-34 is regulated. Recently, IL-34 was demonstrated as a key mediator as it was highly expressed in CD8+CD45RC<sup>+</sup> Tregs and regulatory macrophages (69,70). In fact, Treg cells and M2 macrophage have an outstanding anti-inflammation role in organ transplantation and other diseases (71-77). Bezie and

Figure 1 Roles of IL-34 in different tissues and immune-microenvironment.
colleagues has found that CD8+CD45RClo Tregs expressed a high level of IL-34. IL-34-treated macrophages when co-cultured with allogeneic PBMCs, significantly increased the percentage and number of Foxp3+CD8+CD45RClo and Foxp3+CD4+CD45RClo Tregs. Importantly, the IL-34-expanded Foxp3+CD8+CD45RClo Tregs showed an enhanced immunosuppressive capability (22), as shown in Figure 1. Moreover, long-term transplant survival was successfully established in rat cardiac allograft model by IL-34 overexpression to expand Foxp3+CD8+CD45RClo Tregs that promotes macrophage to easily migrate into graft, then exhausts the autoreactive effect T cells and inhibits the production of autoantibody.

Concluding remarks

IL-34 is functionally similar to CSF-1, playing a key role in development and function of mononuclear lineage cells. However, its effect is strongly determined by timing and sources. It is yet unclear what is its exact role in the diseases and patients. The further study is strongly suggested.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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