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REVIEW

Immunoregulatory properties of the cytokine IL-34

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Abstract Interleukin-34 is a cytokine with only partially understood functions, described for the first time in 2008. Although IL-34 shares very little homology with CSF-1 (CSF1, M-CSF), they share a common receptor CSF-1R (CSF-1R) and IL-34 has also two distinct receptors (PTP-ζ) and CD138 (syndecan-1). To make the situation more complex, IL-34 has also been shown as pairing with CSF-1 to form a heterodimer. Until now, studies have demonstrated that this cytokine is released by some tissues that differ to those where CSF-1 is expressed and is involved in the differentiation and survival of macrophages, monocytes, and dendritic cells in response to inflammation. The involvement of IL-34 has been shown in areas as diverse as neuronal protection, autoimmune diseases, infection, cancer, and transplantation. Our recent work has demonstrated a new and possible therapeutic role for IL-34 as a Foxp3$^+$ Treg-secreted cytokine mediator of transplant tolerance. In this review, we recapitulate most recent findings on IL-34 and its controversial effects on immune responses and address its immunoregulatory properties and the potential of targeting this cytokine in human.

Keywords Immune tolerance · Tregs · Ischemia reperfusion · Macrophages · Osteopetrosis · CSF-1(M-CSF)

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Introduction

The CSF-1/CSF-1R interaction delivers a well-characterized signaling cascade leading in hematopoietic cells to proliferation, differentiation, and function of the monocytic lineage. The discovery in 2008 of IL-34, identified by screening of human protein library as a protein involved in monocyte viability [1] and subsequently, as a new ligand of CSF-1R, has opened new perspectives. IL-34 actions have been rendered more complex by the discovery of receptors for IL-34, others than CSF-1R: the receptor-type protein-tyrosine phosphatase zeta (PTP-ζ), identified only in the brain and in the kidney [2, 3], and syndecan-1, with a broad distribution [4], altogether suggesting additional roles for IL-34. IL-34 is a 241 amino acid (aa) protein in humans that were originally characterized as a protein with no evident sequence similarity with other cytokines or proteins (26% sequence homology with CSF-1). IL-34 exists in two isoforms, differing by the addition of a glutamine inserted between position 80 and 81 in the 241 aa isoform, and generated by alternative splicing [5]. IL-34 is formed by four α-helix and disulfides bond that lead to the formation of a homodimeric protein, but the existence also of a heterodimeric protein between IL-34 and CSF-1, inducing a different signaling cascade in CSF-1R receptor, has been described, although the physiopathological significance of this discovery remains unclear [6]. Finally, IL-34 is a cytokine relatively conserved between species with 99.6% homology between human and chimpanzee and 72% between human, rat, or mouse [1]. Since 2008, studies have identified roles for IL-34 in areas as remote as neuronal protection, bone-degenerative diseases, delayed-type hypersensitivity, infection, cancer, and more recently transplantation.

Here, we summarize recent finding on IL-34 biology, signaling, and downstream effects and discuss in particular its controversial effect on immunity vs. immune tolerance (Table 1).

IL-34, a cytokine with a complex biology, which is a lot more than a substitute of CSF-1

Until recently, IL-34 was described as expressed in spleen, thymus, heart, brain, lung, liver, kidney, testis, prostate, ovary, small intestine, and colon [1]. Additional and more detailed expression has been described in "osteoclasts-like" bone giant cell tumors, osteoblasts but not osteoclasts [7], keratinocytes, hair follicles, proximal kidney cells, germ cells, neurons in the brain (cortex, hippocampus) as well as in the cerebrospinal fluid [8]. A weak expression of the protein in the spleen, especially in the red pulp, was also reported [1, 8]. Finally, expression in fibroblasts and synoviocytes from patients with rheumatoid arthritis has been described [9]. IL-34 and CSF-1 have partially non-overlapping expression. IL-34 but not CSF-1 is expressed by keratynocytes and neurons, whereas both cytokines share several other cellular sources [10] (Fig. 1).

IL-34 shares some partially overlapping actions with CSF-1, such as its effect on macrophages and neurons (Fig. 1). The CSF-1R is encoded by a proto-oncogen and has a tyrosine kinase activity, and ligation of CSF-1R induces the phosphorylation of a tyrosine residue of the CSF-1R cytoplasmic domain and its homodimerisation, and initiates a cascade of phosphorylation of other proteins, such as ERK1/2 (extracellular signal-regulated kinase) or AKT (protein kinase B) [11–13]. CSF-1R is expressed by dendritic cells (DCs) and macrophages, excluding $CD11c^{+}$ precursors of DCs. However, its expression has been described in $CD11c^{dim}B220^{+}$ plasmacytoid DCs using green fluorescent protein (GFP) transgenic mice (with GFP under control of CSF-1R promoter), in Langerhans cells, B cells, smooth muscle cells of the vessels, osteoclasts as well as trophoblast cell lineages, and to some extent granulocytes [14–20]. CSF-1R deficient mice and CSF-1-deficient rat toothless/toothless (tl/tl) both present a defect in macrophages, osteopetrosis, are toothless, and have growth retardation, low fertility, and skeletal defects, which cannot be compensated by CSF-1 administration [21, 22]. CSF-1R gene polymorphism has been demonstrated as a susceptibility marker of asthma with higher frequencies of two intronic polymorphisms and higher expression of CSF-1R on $CD14^{+}$ monocytes and neutrophils in asthmatic subjects than in normal controls [23]. CSF-1R gene expression was increased in inflammatory bowel disease (IBD) patients with colon cancer than in active chronic IBD [24].

Inhibition of CSF-1R has shown its involvement in proliferation and kidney graft infiltration by macrophages [25] and its potential in reducing macrophages proliferation and associated pathology in inflammatory arthritis [26] and myelin oligodendrocyte glycoprotein (MOG)-induced EAE in mice [27]. CSF-1R is also involved in induction of regulatory macrophages and it has been demonstrated that CSF-1R blockade using antibodies reduced resident tumor-associated macrophages (TAM) number in tumors [28] and exacerbate graft-versus-host disease (GVHD) following bone-marrow transplantation in mice [29].

CSF-1 ligation to CSF-1R is only based on saline bonds, while IL-34 ligation to CSF-1R needs hydrophobic amino acids and hydrogen bonds, suggesting a rather specific structure and chemical constraints supporting a co-evolution of CSF-1R with IL-34 rather than CSF-1 [10]. However, affinity of IL-34 for the receptor CSF-1R is stronger than CSF-1 for CSF-1R; indeed, IL-34 recruits two domains of CSF-1R, while CSF-1 recruits only one [1, 30]. Signal transduction through CSF-1R after ligation by IL-34 involves a stronger but shorter phosphorylation of ERK1/2 and AKT than CSF-1 and decreases CSF-1R expression, leading to differentiated macrophages with distinct morphology (few aggregates vs. many large aggregates with CSF-1) and phenotype (less CD54 expression and monocyte chemoattractant protein-1 (MCP-1/CCL2) production, more HLA-DR expression, and eotaxin-2 production) [31]. In addition, it has been reported that IL-34 and CSF-1 have different levels of expression in different organs.

Since IL-34 acts through the same receptor as CSF-1, therapies directed to block CSF-1R could be viewed as sufficient to neutralize the effects of IL-34; however, more recently, it has been described that IL-34 binds to other receptors through low affinity interactions with chondroitin sulphate chains, such as PTP-ζ [2] and syndecan-1 [4]. Thus, blocking of CSF-1R is not expected to inhibit the actions of IL-34 through these other receptors but blockade of these receptors and not of CSF1-R has not been reported yet. PTP-ζ is expressed as a cell surface or as a soluble receptor by neural progenitors, glia, glioblastoma, B cells, and kidney tubular cells [2, 3, 32]. Activation of PTP-ζ leads to increased tyrosine phosphorylation of several transduction pathways and is upregulated in many human cancers (such as lung and prostate cancers) in chronic oxidative stress in kidney cells and regulates their proliferation and metastasis [3, 33–37]. PTP-ζ has other ligands, such as pleiotrophin [38], the cell surface protein contactin [39], and the extracellular matrix protein tenascin-R [40]. The role of IL-34 binding on PTP-ζ remains unexplored. IL-34 binding to syndecan-1 modulates the IL-34-induced CSF-1R signaling pathways, and IL-34 induced the migration of myeloid cells in a syndecan-1-dependent manner [4]. Syndecan-1 is expressed by many cancers [41], like

Table 1 Biological and pathophysiological studies with IL-34

Pathophysiological situation	Model	Species	Major findings	References
Biology and targets of IL-34	Monocytes, THP1 cell line	Human	Identification of IL-34 Identification of CSF1-R as a receptor for IL-34 Kd of IL-34 to CSF-1R = 1 pM (Kd of CSF-1 to CSF-1R = 34 pM)	[1]
	Monocytic THP1 and J774A.1 cell lines	Human and mouse	IL-34 and CSF-1 are distinct in biological activity and signal activation IL-34 and CSF-1 both support cell growth or survival IL-34 and CSF-1 are different in the ability to induce chemokines production, morphological change in THP1 cells and migration of J774A.1 cells IL-34 induced a stronger but transient tyrosine phosphorylation of CSF-1 and downstream molecules, and rapidly downregulated CSF-1	[31]
	Macrophages	Human	Generation of M2 macrophages = CSF-1, ≠GM-CSF-1	[105]
	Macrophages	Mouse	huIL-34 was much less active at stimulating mouse macrophage proliferation than huCSF-1 Overexpression of muIL-34 rescued defects of Csf1op/op mice CSF-1 and IL-34 similarly activate CSF-1R tyrosine phosphorylation and ERK1/2 activation	[5]
	KO for IL-34	Mouse	Keratynocytes produce IL-34 that maintains LCs IL-34 is a non-redundant cytokine for the development of LCs during embryo-genesis and homeostasis in the adult skin Inflammation-induced repopulation of LCs is dependent on CSF-1, once inflammation is resolved, LC survival is again IL-34-dependent	[8, 93]
	Skin	Mouse	IL-34 produced in skin epidermis of the embryo promotes the final differentiation of LCs precursors Adult LCs required IL-34 to continually self-renew in the steady-state During skin damage, LCs regeneration depended on CSF-1 produced by infiltrating neutrophils	[110]
	PBMCs	Human	IL-34 and CSF-1 ↗ IL-6, CXCL10, CXCL8 and CCL2	[111]
	IL-34 and CSF-1 interactions	Human	Hybrid structural approach reveal bivalent binding of human IL-34 to CSF-1R with similarities to the CSF-1:CSF-1R complex C-terminal region of IL-34 is heavily glycosylated and can be proteolytically cleaved from the IL-34:hCSF-1R complex	[112]
	Monocytes	Human	Transcriptional profiling of monocytes induced by IL-34 or CSF-1 has 75% similarity with dampened effect on 25% of them by IL-34 A major ≠ in CCR2 expression repressed by CSF-1	[113]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Folicular dendritic cell line	Mouse	Cell line produce both CSF-1 and IL-34, but only IL-34 was responsible for mononuclear phagocytes generation	[114]
	KO for IL-34	Mouse	Keratinocytes produce IL-34 that maintains LCs Neurons produce IL-34 that maintains microglia	[8]
	Syndecan-1	Human	IL-34 binds to chondroitin sulphate chains on syndecan-1 and this modulates the IL-34-induced CSF-1R signaling pathways IL-34 induced the migration of myeloid cells in a syndecan-1 dependent manner	[4]
	Macrophages	Human	IL-34 and CSF-1 bind CSF-1R through different interfaces IL-34 ↗ association stability with CSF-1R than CSF-1	[30]
	PTP-z	Human and mouse	IL-34 binds to chondroitin sulphate chains on PTP-z is ($K_d \sim 10^{-7}$ M) PTP-z is primarily expressed on neural progenitors, glial cells and human glioblastomas IL-34 inhibited the proliferation, clonogenicity and motility of glioma cells	[2]
	IL-34 and CSF-1 interactions	Human	IL-34 and CSF-1 showed additive effects on cellular proliferation or viability Heteromeric interaction between CSF-1 and IL-34 was confirmed by surface plasmon resonance and proximity ligation assays	[6]
Neuronal protection	Alzheimer's disease	Mouse	Neurons primarily produce IL-34 and microglia expresses the CSF-1R IL-34 promoted microglial proliferation clearance of soluble oligomeric amyloid and production of the antioxidant enzyme HO-1 Neuronal protection by IL-34 was dependent on HO-1	[90]
	KO for IL-34	Mouse	Neurons produce IL-34 that maintains microglia Microglia and their yolk sac precursors develop independently of IL-34 but rely on it for their maintenance in the adult brain	[8, 93]
	Neural development	Mouse	In the CNS, IL-34 exhibited a broader regional expression than CSF-1 High levels of IL-34 in the absence of CSF-1R expression IL-34 > CSF-1 to suppress neural progenitor self-renewal and enhance neuronal differentiation	[115]
	Neuronal toxicity	Mouse	Neurons express CSF-1R CSF-1 and IL-34 strongly reduced excitotoxin-induced neuronal cell loss and gliosis	[92]
	Blood–brain barrier	Mouse	IL-34 ↗ endothelial cell protection IL-34 ↗ tight junction proteins	[91]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Peripheral nerve injury	Rat	IL-34 constitutively expressed in the spinal cord IL-34 not affected by nerve injury in contrast to CSF-1	[116]
	Induction of microglia from monocytes	Human	Human monocytes cultured with GCSF-1 and IL-34 showed microglial characteristics	[88]
Bone physiology	Gingival fibroblasts	Human	IL-34 expressed by gingival fibroblasts ↗ by TNFa and IL-1	[53]
	Osteoclasts	Human and mouse	IL-34 together with RANKL induced the formation of osteoclasts Systemic administration of IL-34 to mice increases the proportion of $CD11b^+$ cells and reduces trabecular bone mass	[55]
	Osteoblasts	Mouse	TNF-alpha induces IL-34 in an osteoblast cell line	[54]
Autoimmunity and Inflammation	Rheumatoid arthritis	Human	IL-34 ↗ in synovial fluid, synovial fibroblasts and sera of RA vs. OA IL-34 ↗ by TNF-alpha IL-34 in sera ↘ by RA treatment	[59]
	Rheumatoid arthritis	Human	IL-34 was expressed in 24/27 biopsies from RA patients Significant correlation between IL-34 expression and synovitis severity and the total leukocyte count in the synovial fluid IL-34 expression by the synovial fibroblasts ↗ by TNF-alpha and IL-1β	[9]
	Rheumatoid arthritis	Human	Synovial fluid IL-34 levels were higher in patients with RA than in those with OA and were positively associated with IL-6 levels in serum from patients with RA and OA Synovial fluid IL-34 concentration correlated significantly with IL-6 and RANKL levels only in RA Serum levels of IL-34 were not correlated with radiographic joint damage in RA and were positively correlated with rheumatoid factor and anti-citrullinated antibody titers	[56]
	Rheumatoid arthritis	Human	IL-34 ↗ in synovial fluid, synovial fibroblasts and sera of RA vs. OA IL-34 in sera ↘ by anti-TNFalpha treatment IL-34 ↗ IL-17 production by PBMCs	[60]
	Rheumatoid arthritis	Human	IL-34 in sera ↗ vs. OA IL-34 serum levels correlated with: rheumatoid factor, erythrocyte sedimentation rate and C-reactive protein levels but not disease activity Serum IL-34 levels were an independent risk factor for radiographic progression	[61]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Rheumatoid arthritis	Human	Synovial fluid IL-34 levels were significantly higher in patients with RA with high Disease Activity Score IL-34 stimulation strengthened the activation of p-STAT3, resulting in increment of miR-21 expression CSF-1R participated in the biological functions of IL-34 in RA	[58]
	Rheumatoid arthritis	Human	IL-34 level in serum phase III > phase II	[57]
	Rheumatoid arthritis	Human	CSF-1 and IL-34 expression was similar in RA and psoriatic arthrititis synovial tissue, but lower in controls CSF-1 expression was observed in the synovial sublining, and IL-34 in the sublining and the intimal lining layer. Anti-CSF1R Ab significantly reduced IL-6 and other inflammatory mediator production in RA synovial explants, and paw swelling and joint destruction in CIA	[117]
	Rheumatoid arthritis, Psoriatic arthritis and osteoarthritis	Human	CSF-1 and IL-34 express at same level in RA and PsA tissues, but lower in OA CSF-1 expression in synovial sublining IL-34 expression in sublining and intimal layer No effect of IL-34 and CSF-1 addition or neutralization in inflammatory mediators production Blockade of receptor CSF-1R reduced RA and CIA	[65]
	Rheumatoid arthritis	Human	IL-34 serum level < 194 pg/ml predicts a good response to TNF-alpha antagonist treatment to RA at 3 months	[62]
	Atopic dermatitis		IL-34 is decreased in lesional zones	[87]
	Inflammatory bowel diseases	Human	↗ *IL-34* expression in inflamed areas ↗ IL-34 expression by TNF-alpha and TLR ligands in lamina propia mononuclear cells and ↘ by infliximab IL-34 ↗ TNF-alpha and IL-6 synthesis by mucosal explants	[68]
	Inflammatory bowel diseases	Human mouse	*IL-34* in ileum, *CSF1* in colon ↗ *IL-34* in CD and UC ↗ *CSF1* in CD TNFa ↗ *IL-34* and *CSF1* in epithelial cells, NFkb-dependent only for *IL-34* Mo-treated with IL-34 showed expression of IL-10 whereas CSF-1 ↘ expression DSS model: ↗ *IL-34* and *CSF1*	[69]
	Inflammatory bowel diseases	Human	IL-34 increased CCL20 production by an epithelial cell line through an ERK1/2-dependent mechanism	[118]
	Obesity, metabolic syndrome	Human	↗ in serum of obese women IL-34 expressed by adipocytes and ↗ by TNFα IL-34 ↗ insulin resistance	[72]
	Type 2 diabetes GWAS studies	Human	IL-34 SNP 5′ UTR associated with type 2 diabetes	[71]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Type 2 diabetes	Human	IL-34 has more discriminatory power than C-reactive protein (CRP) for the risk of diabetic complications	[73]
	Non-alcoholic fatty liver disease	Human	IL-34 increased with the progression of fibrosis and was an independent marker for liver fibrosis	[119]
	Sjogren's syndrome	Human	IL-34 was overexpressed in inflamed salivary glands of Sjogren's syndrome and associated with ↗ expression of TNF-α, IL-1β, IL-17 and IL-23p19 IL-34 expression was accompanied by the expansion of $CD14^{bright}CD16^{+}$ monocytes in salivary glands	[66]
Infection	Parasites, macrophages	Teleost fish	IL-34, CSF-1 and the isoform CSF-2 are differentially expressed in tissues and cell lines Lack of induction of IL-34, but not of CSF-1 and CSF-2 expression by PAMPs, inflammatory cytokines and a parasitic proliferative kidney disease model in rainbow trout macrophages	[120]
	Hepatitis C virus	Human	IL-34 and CSF-1 correlated with fibrosis IL-34 produced by hepatocytes IL-34 induces profibrogenic macrophages IL-34 ↗ collagen 1 by hepatic stellate cells	[83]
	Viral infection, macrophages	X. laevis	IL-34 and CSF-1 different tissue expression IL-34 vs. CSF-1 Mo: ↘ phagocytic, ↘ susceptible to infection, ↗ antiviral, ↗ type I IFN, ↗ NADPH	[100]
	Influenza A	Human PBMCs	IL-34 ↗ in influenza A patients IL-22 ↗ *IL-34* IL-34 ↘ *IL-22*	[84]
	SIV, Mo	Macaque microglia and human Mo	IL-34 and CSF-1 ↗ $CD163^{+}$ cells in CNS IL-34 produced by neurons and CSF-1 by neurons and $CD163^{+}$ Mo IL-34 and CSF-1 act through CSF-1R	[121]
	SIV, Mo	Macaque and human	IL-34 and CSF-1 ↗ HIV production by SIV^{+} microglia through CSF-1R	[85]
	Macrophages/Candida	Mouse	IL-34 ↘ TNF-alpha production by M1 macrophages challenged with *C. albicans* by the inhibition of expression of TLR2 and Dectin-1	[86]
	Monocytes	X. laevis	IL-34 vs. CSF-1 Mo: ↘ iNOs, ↘ phagocytic activity, ↘ bactericidal activity, ↗ arginase-1, ↗ NADPH, ↗ antiviral activity	[101]
Transplantation	Organ transplantation	Human and rat	IL-34 was expressed and played a role in the suppressive function of both $CD8^{+}$ and $CD4^{+}$ rat and human Tregs In a rat cardiac allograft model treatment with IL-34 promoted allograft tolerance that mediated by induction of tolerogenic macrophages and Tregs Human macrophages cultured with IL-34 expanded and increased the suppressive capacity of $CD8^{+}$ and $CD4^{+}$ $Foxp3^{+}$ Tregs	[51]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Kidney ischemia/Reperfusion injury	Human and mouse	Renal I/R was reduced in IL-34-KO mice IL-34, CSF1-R and PTPζ were upregulated in the kidney after I/R in mice and in kidney transplant patients	[3]
Cancer	bone giant cell tumor	Human	IL-34 is expressed in Giant cell tumors IL-34 promotes osteoclastogenesis	[7]
	Mammary cancer	Human and mouse	Cytotoxic therapies induce mammary cancer cells to produce CSF-1 and IL-34 Blockade of CSF-1R- improved survival of mammary tumor-bearing mice with decreased vessel density and appearance of $CD8^+$ antitumor immune responses	[81]
	Differentiation of T cells by macrophages	Human	CSF-1- or IL-34-treated macrophages and TAM switch memory but not naive $CD4^+$ T cells into conventional Th17 cells, expressing or not IFN-gamma via membrane IL-1α	[102]
	Teratoma	Mouse	ES cells produce IL-34 but not CSF-1 IL-34 ↗ M2 macrophages IL-34 ↗ neo-angiogenesis	[80]
	Liver metastasis	Human	miR-28-5p down-regulation in HCCs correlated with tumor metastasis, recurrence, and poor survival IL-34 is a direct target of miR-28-5p Effects of miR-28-5p deficiency on HCC growth and metastasis are dependent on IL-34-mediated TAM infiltration miR-28-5p-IL-34-macrophage-positive feedback loop modulates HCC metastasis In clinical HCC samples, miR-28-5p levels were inversely correlated with IL-34 expression and the number of TAMs	[82]
	Tumor cells and macrophages	Human	IL-34 binds to chondroitin sulphate chains on syndecan-1 and this modulates the IL-34-induced CSF-1R signaling pathways IL-34 induced the migration of myeloid cells in a syndecan-1 dependent manner	[4]
	Osteosarcoma	Human and mouse	IL-34 produced by osteosarcoma cells IL-34 ↗: osteosarcoma development, M2 macrophages, neo-angiogenesis and monocyte adhesion to ECs	[79]
	Several solid cancers	Fish, amphibians, birds, mammals	IL-34 exists in all species with similar gene organization In human IL-34 gene: 32 SNPs causing missense mutations, 3 exonic splicing enhancer SNPs and 20 SNPs causing nonsense mutations ↘ IL-34 expression correlated with poor survival in NSCLC, blood cancer and colorectal cancer ↗ IL-34 expression correlated with poor survival in adenocarcinoma and brain cancer	[122]

Table 1 (continued)

Pathophysiological situation	Model	Species	Major findings	References
	Metastases and microglia	Human and mouse	Macrophage-induced metastases was reduced by anti-CSF-1 treatment while microglia-induced invasion was reduced to a lower extend Lung and breast brain metastases express CSF-1 and IL-34	[109]
	Differentiation monoblastic leukemias to monocyte-like cells	Human	Induction of IL-1α and β production Induction of CD64 and CD86, CD14 and CD68 expression Induction of endocytosis and respiratory burst activities	[123]

GWAS genome-wide association studies, *IBD* inflammatory bowel diseases, *I/R* ischemia/reperfusion injury, *Mo* macrophages, *LCs* Langerhans cells, *RA* rheumatoid arthritis, *OA* osteoarthritis, *NSCLC* non-small cell lung cancer

myeloma [42], melanoma [43, 44], and pancreas carcinomas [45]. Through chondroitin sulphate chains, syndecan-1 is a co-receptor for growth factors, such as epidermal growth factor [46], hepatocyte growth factor [47], vascular endothelial growth factor [48], Wnt factors [49], or members of the transforming growth factors [50]. Syndecan-1 exhibits a stimulatory or inhibitory role on IL-34 actions, probably depending on its expression levels. A low/moderate level of syndecan-1 may sequestrate IL-34 at the cell surface through its chondroitin sulphate chains, limiting the interaction between IL-34 and the CSF-1R. In contrast, the overexpression of syndecan-1 may increase the proximity between the CSF-1R, favoring the effects of IL-34. More recently, to add another level of complexity, the heterodimeric interaction of IL-34 with CSF-1 has been described by surface plasmon resonance and proximity ligation assays. Such heterodimer showed additive effects on cell proliferation and viability [6].

So far, it was thought that IL-34 played mainly a role in the differentiation and survival of microglia and Langerhans cells in the brain and in the skin, respectively. This vision on the actions of IL-34 was recently expanded with the description of its specific and restricted expression by $CD4^+$ and $CD8^+$ $Foxp3^+$ Tregs [51]. This suggests a role for IL-34 in immune tolerance, and at least in an organ transplantation model through actions on macrophages. This report from our group provided the first description of co-expression of Foxp3 and IL-34 in $CD4^+$ and $CD8^+$ Tregs from healthy human individuals, and also at least by $CD8^+$ Tregs from rat. Such expression had not been looked for or evidenced in mice or humans before and emerged from deoxyribonucleic acid (DNA) microarray analysis of $CD8^+$ Tregs in a model of organ transplantation tolerance in the rat compared to $CD8^+$ Tregs from naive animals [52]. In this model, we observed that one of the most upregulated genes was IL-34. IL-34 produced by $CD8^+$ Treg-suppressed $CD4^+$ T effector cells in vitro and treatment in vivo prolonged cardiac allografts [51]. Further analysis revealed that IL-34 is also expressed in human and specifically by $Foxp3^+$ Tregs (half of them) and both $CD4^+$ and $CD8^+$ Tregs [51]. However, IL-34-deficient mice failed to demonstrate major autoimmune lesions [8], probably because IL-34 is expressed by half of the $Foxp3^+$ Tregs in healthy individuals, and Tregs secrete other cytokines, such as IL-10, IL-35, and TGFβ that might compensate for the lost of IL-34 activity. In addition, and to the best of our knowledge, there are no reports on the impact of IL-34 deficiency on autoimmune models in mice and these models could show an increase in lesions vs. controls. Finally, differences between rats and mice cannot be excluded, and to address this point, IL-34 deficient rats have been generated and are under analysis.

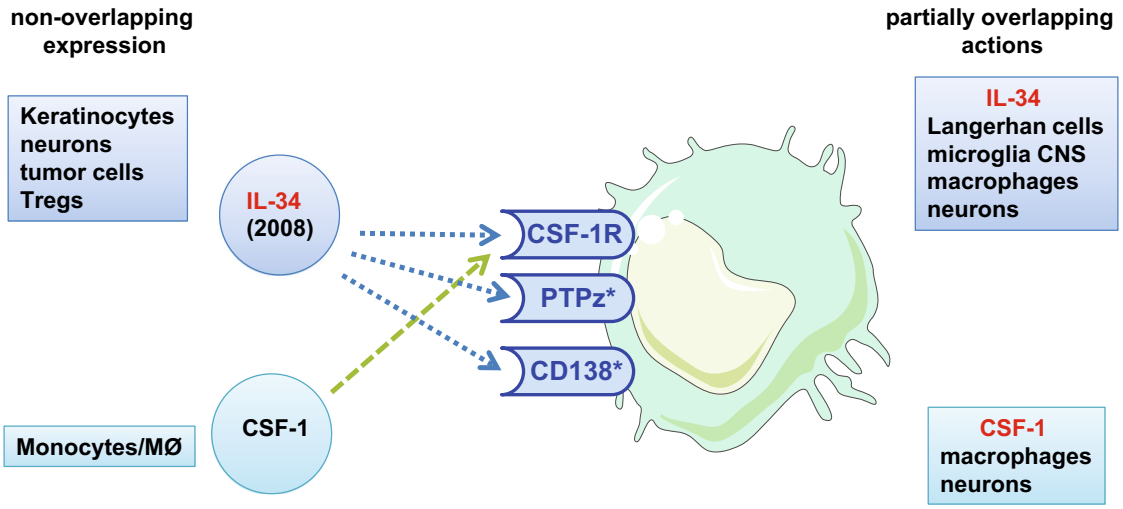

Fig. 1 IL-34, a cytokine described in 2008, and CSF-1 have non-overlapping expression in cells. While CSF-1 only binds to CSF-1R, IL-34 binds to CSF-1R, PTPz, and CD138. IL-34 and CSF-1 binding to CSF-1R result in partially overlapping actions in some cell subsets. *Asterisk* chondroitin sulphate chains on protein-tyrosine-phosphatase zeta (PTP-z) and CD138

Yin and yang of IL-34

IL-34 and inflammatory diseases

IL-34 expression has been correlated with several inflammatory diseases in patients and in animal models involving monocytes/macrophages over-proliferation, such as rheumatoid arthritis (Table 1). IL-34 is expressed by gingival fibroblasts in human and osteoblasts in human and mouse [53, 54]. Systemic administration of IL-34 to mice increases the proportion of $CD11b^{+}$ cells in bone and reduces trabecular bone mass [55]. High level of IL-34 in synovial fluids, synovial fibroblasts, and serum has been reported in patients suffering from rheumatoid arthritis (RA). Indeed, IL-34 overexpression correlates with the presence of autoantibodies (rheumatoid factors) in serum and in synovial fluid of patients [56], with the synovitis severity [9] and with the stage of RA development [57]. In addition, IL-34 levels were significantly higher in synovial fluids of RA patients with a high disease severity score [58]. The high IL-34 expression was reduced by anti-RA treatments [59, 60]. Furthermore, a correlation analysis suggested IL-34 as a biomarker of RA progression [61] and as a predictive marker of TNF-alpha antagonist therapy efficiency (better prognosis if <194.12 pg/ml of IL-34 in serum at 3 month treatment) [62]. Dysregulation of osteoclastogenesis promoted by IL-34 was associated with RA inflammation [55], despite of the absence of osteopetrosis symptoms in IL-34-deficient mice (probably due to a compensation by CSF-1) [8]. In this context, blockade of IL-34 should reduce osteoclastogenesis and thus inflammation symptoms. However, this strategy should be associated with a CSF-1 blockade to avoid compensatory effect as IL-34-deficient mice showed no osteopetrosis [8]. In CSF-1-deficient mice, the osteoclast deficiency is compensated over time by IL-34-responsive cells originating from the spleen [63]. Both IL-34 and CSF-1 are upregulated in RA synovium [64]; however, exogenous addition of IL-34 or CSF-1 or blockade with IL-34 or anti-CSF-1 Abs had no effect on RA synovial inflammatory mediator production [65].

Similarly, IL-34 overexpression has been linked to other autoimmune diseases for its role as stimulator of monocyte proliferation (Table 1). For example, IL-34 is highly expressed in inflamed salivary glands from patients affected by Sjogren's syndrome, characterized by a high expression of inflammatory cytokine, such as TNF-α or IL-17 and expansion of pro-inflammatory $CD14^{bright}CD16^{+}$ monocytes [66]. IL-34 has also been involved in IBD, where monocytes might play a major role [67]. A positive correlation was observed between inflammation levels, IL-34 overexpression in ileon's inflamed mucosa from patients affected by Crohn's disease or by ulcerative colitis [68, 69], and monocytes number supporting the inflammation [70]. IL-34 and CSF-1 are upregulated or in blood and urine of patients with lupus nephritis [64]. A positive correlation has been reported between high IL-34 level expression and the insulin-resistant type II diabetes chronic inflammation and susceptibility [71–73]. The cause and effect relationship should also be considered, since pancreatic islets infiltration by macrophages remains unclear [74, 75]. Finally, in obesity, IL-34 is expressed by adipocytes and

increased in serum of obese women, and IL-34 increases insulin resistance [72].

Despite these observations, some pro-inflammatory cytokines, such as TNFα, play a major role in the pathogenesis of inflammatory diseases and we should consider the possibility that IL-34 could be increased as an inhibitory mechanism initiated as a consequence of acute or chronic inflammation, instead of a cause of the disease, and could thus be used as an inhibitory mechanism of inflammation. In IBD, IL-34 overexpression was suggested to coincide with protective IL-10 producing macrophages contributing to the integrity of the intestinal epithelium [69]. In addition, CSF-1 and CSF-1R deficient mice both display defective proliferation of colon epithelial cells [76], thus arguing for a protective functions of both CSF-1 and IL-34 on survival and proliferation of colon epithelial cells in IBD. IL-34 transgenic mice do not show exacerbated inflammatory responses [77]. Finally, IL-34 in these pathologies could facilitate macrophages differentiation and migration in the spleen to injured tissues for healing of lesions, as the spleen appears to be a source and site of storage of monocytes for rapid deployment to regulate inflammation [78].

An emerging role for IL-34 in immune tolerance

Many studies showed a positive correlation between high IL-34 expression level and tumor development (Table 1). For giant cell tumors of bone, the pathogenesis results directly from the supporting/proliferative action of IL-34 on osteoclastogenesis [7]. In other types of tumors, IL-34 is rather involved in TAM recruitment [79]. Indeed, IL-34 promotes the survival and the differentiation of type 2 macrophages which are important for teratoma development after ES cells graft, and promote neo-angiogenesis [80]. Produced in response to cytotoxic therapies in mammary cancer, IL-34 would also participate to cancer recurrence through TAM recruitment [81]. Indeed, a higher IL-34 level has been associated with shorter survival and time to recurrence [82]. Blockade of CSF-1R improves survival of mammary tumor-bearing mice with decreased vessel density and appearance of antitumor $CD8^+$ cell immune responses.

IL-34 also allows and even promotes some pathogens persistence (Table 1). IL-34 has been reported highly expressed in serum of chronically Hepatitis C (HCV)-infected patients and correlating with fibrosis [83]. IL-34 differentiates monocytes into profibrogenic type 2 macrophages in liver lesions, preventing destruction of hepatic stellate cells by NK cells, and thus increasing collagen 1 [83]. Besides, IL-34 is highly expressed in serum of influenza A virus-infected patients by the IL-22 inflammatory cytokine-producing cells and acts in an autocrine/paracrine manner to control IL-22 production [84]. IL-34 would help human immunodeficiency virus (HIV)-infected microglial cells to survive as a reservoir for the virus in brain [85]. Notably in skin, IL-34 inhibits *C. albicans* pattern recognition receptors (PRRs) expression by M1 macrophages, maintaining mucosal and dermal skin tolerance to the fungal infection [86]. Otherwise, IL-34 is less expressed in atopic dermatitis skin lesions than in non-lesional skin [87]. The higher expression of IL-34 in non-inflamed lesions suggests the inhibition of inflammatory cascade propagation from lesioned to non-lesioned skin [87].

Furthermore, IL-34 has an immune protective role in brain (Table 1). In vitro, IL-34 has been described to induce monocyte differentiation into cells with microglial characteristics [88]. Produced by neurons, IL-34 promotes microglia proliferation and beta oligomeric amyloid degradation, increases heme oxygenase-1 and TGF-beta production and decreases oxidative stress [89, 90]. Moreover, IL-34 restores hemato-encephalic barrier by acting on endothelial cells and tight junction proteins [91] and decreases neuronal toxicity in mice [92]. Microglia and their yolk sac precursors rely on IL-34 for their maintenance in adult brain [93].

Finally, our group was the first to report the expression of IL-34 by $Foxp3^+CD4^+$ and $CD8^+$ Tregs and to demonstrate IL-34 involvement in human and rat Treg-mediated suppressive function. We demonstrated also IL-34 capacity to induce in vivo and in vitro $CD4^+$ and $CD8^+$ Tregs through monocytes polarization toward M2-type macrophages to protect allograft from acute and chronic rejection [51, 94] (Table 1). Accordingly, although IL-34 was not investigated, Conde et al. demonstrated that CSF-1/CSF1-R interactions differentiated monocytes into $CD209^+$ (DC-SIGN) macrophages able to induce $CD4^+$ Tregs and transplantation tolerance [95].

Targeting IL-34 in the clinic? (Fig. 2)

Tolerogenic IL-34 in patients with deleterious inflammatory responses

First, IL-34 is a promising tool for inducing tolerance in solid organ transplanted patients. As CSF-1, IL-34 has been reported as capable of inhibiting T-cell proliferation in response to allogeneic stimulation in vitro, and treatment of rats with a viral vector encoding for IL-34 efficiently prolonged cardiac allograft survival [51]. Moreover, short-term IL-34 treatment was sufficient to induce potent antigen-specific Tregs in vivo through early M2 macrophage polarization mediating altogether long-term tolerance to the allograft. These results suggest that a short period treatment of transplanted patients with IL-34 protein could be sufficient to induce tolerance and to replace or at least reduce

large spectral and lifelong immunosuppressive treatments. Recently, the expression of PTPζ by the kidney in mice and human was described and a role in mice was suggested for IL-34 in mediating macrophage infiltration during experimental kidney ischemia–reperfusion [96]. These results are in contradiction with the protective action of CSF-1 from kidney injury acting on tubular cells and macrophages [97, 98]. This potential controversial action of IL-34 highlights the need for a more thorough analysis on the role of IL-34 in ischemia reperfusion in other models [37]. In humans, an increased expression of tubular IL-34 was found in a cohort of 17 kidney patients with acute rejection in the 6 months following transplantation compared with controls. Analysis of a larger cohort of transplanted patients with different outcomes at different timings will determine the importance of IL-34 in promoting macrophage accumulation in the graft and the most appropriate treatment window. A potential deleterious action of IL-34 on kidney tubular cells highlights the need for a more thorough analysis in new models of kidney injury not only in mice but also in other species. In addition, a thorough analysis of macrophages skewing to repair vs. profibrotic macrophages in the kidney would improve our understanding of the action of IL-34 in this setting.

The capacity of IL-34 to instruct efficient and rapid myeloid reconstitution following myelosuppressive chemotherapy and hematopoietic stem cell (HSC) transplantation could be beneficial to defense against opportunistic pathogens while preserving the graft-versus-leukemia effect. Indeed, CSF-1 treatment showed shortening recovery time of myeloid cells without influencing the relapse of leukemia or GVHD in mice studies [29, 99] and treatment with CSF-1 inhibited GVHD [29]. Similarly, IL-34 has been shown to improve monocyte viability [1] and macrophage growth [10]. Thus, IL-34 treatment could be used as myeloid growth factor and as an inhibitor of GVHD after hematopoietic stem cells (HSC) transplantation.

IL-34 treatment could be used for preventing skin lesions in atopic dermatitis diseases. Indeed, the lower expression of IL-34 in wounded epidermis and its expression co-localization with $CD163^+$ macrophages suggest a role in inhibiting the propagation of inflammatory cascade through macrophage M2 polarization [87].

Many evidences of a neuroprotective role suggest the use of IL-34 as therapeutic tool for brain diseases, such as Alzheimer disease and multiple sclerosis. IL-34 has been shown to promote degradation of oligomeric amyloid beta and production of the immunoregulatory cytokines heme oxygenase-1 (HO-1) and TGF-beta, reducing oxidative stress and neuronal toxicity [89, 90], as well as for restoring hematoencephalique barrier integrity through tight junction protein production, which were downregulated by pro-inflammatory cytokines [91]. Indeed, systemic administration of IL-34 strongly reduced excitotoxin-induced neuronal cell loss and gliosis in mice model of Alzheimer's disease [92]. Nevertheless, there have not been until now reports on the effect of IL-34 in animal models of multiple sclerosis or in patients with this disease.

Finally, IL-34 could have antiviral properties due to a lower susceptibility to infection of IL-34-derived macrophages. Indeed, IL-34 administration significantly prolonged Frog Virus 3-challenged animal survival from which IL-34-derived macrophages exhibited significantly greater in vitro anti-ranaviral activity [100, 101].

IL-34-derived M2 macrophages and optimized Treg cell therapy

It has been reported that IL-34 induces type 2 macrophages polarization. Indeed, culture of human monocytes with IL-34-induced regulatory M2 expressing high level of IL-10 and low levels of IL-12 [102]. Moreover, M2 macrophages have a key role in IL-34-mediated induction of tolerance to cardiac allograft in the rat, since tolerance was not established after macrophages depletion [51]. More detailed phenotypic and functional analysis is still necessary to fully characterize these tolerogenic IL-34-induced M2 macrophages.

Interestingly, tolerogenic macrophages have already been assessed for cell therapy in a clinical pilot study in kidney-transplanted patients. Indeed, donor-derived regulatory macrophages infusion to these patients was associated with graft survival with minimal immunosuppression without signs of graft rejection at 1 year [103]. Thus, macrophage polarization by IL-34 cytokine could be considered for future macrophages-based tolerogenic therapies.

Furthermore, M2 macrophages are known to convert effector cells in $CD4^+$ Tregs [104]. Recently, we have shown the higher efficiency for expanding both human $CD8^+$ and $CD4^+$ Tregs in vitro using IL-34-differentiated macrophages compared to macrophages without IL-34 [51]. Our results also showed a higher suppressive function of Tregs expanded with IL-34-macrophages compared to without. Moreover, tolerance to allograft induced by IL-34 overexpression in rat was mediated by both $CD8^+$ and $CD4^+$ Tregs. Thus, IL-34-differentiated macrophages should also be considered for in vitro Treg cell expansion in a cell-therapy aim.

It should be noted that other cytokines can associate with IL-34 to induce even more potent regulatory cells. First, IL-34 and CSF-1 could have an additive effect on regulatory cells differentiation [6]. IL-6 has been shown to potentiate IL-34 induced differentiation of immunosuppressive macrophages [105]. Finally, IFNγ has been closely related to Tregs function [52, 106, 107] and regulatory macrophage differentiation with CSF-1 [108].

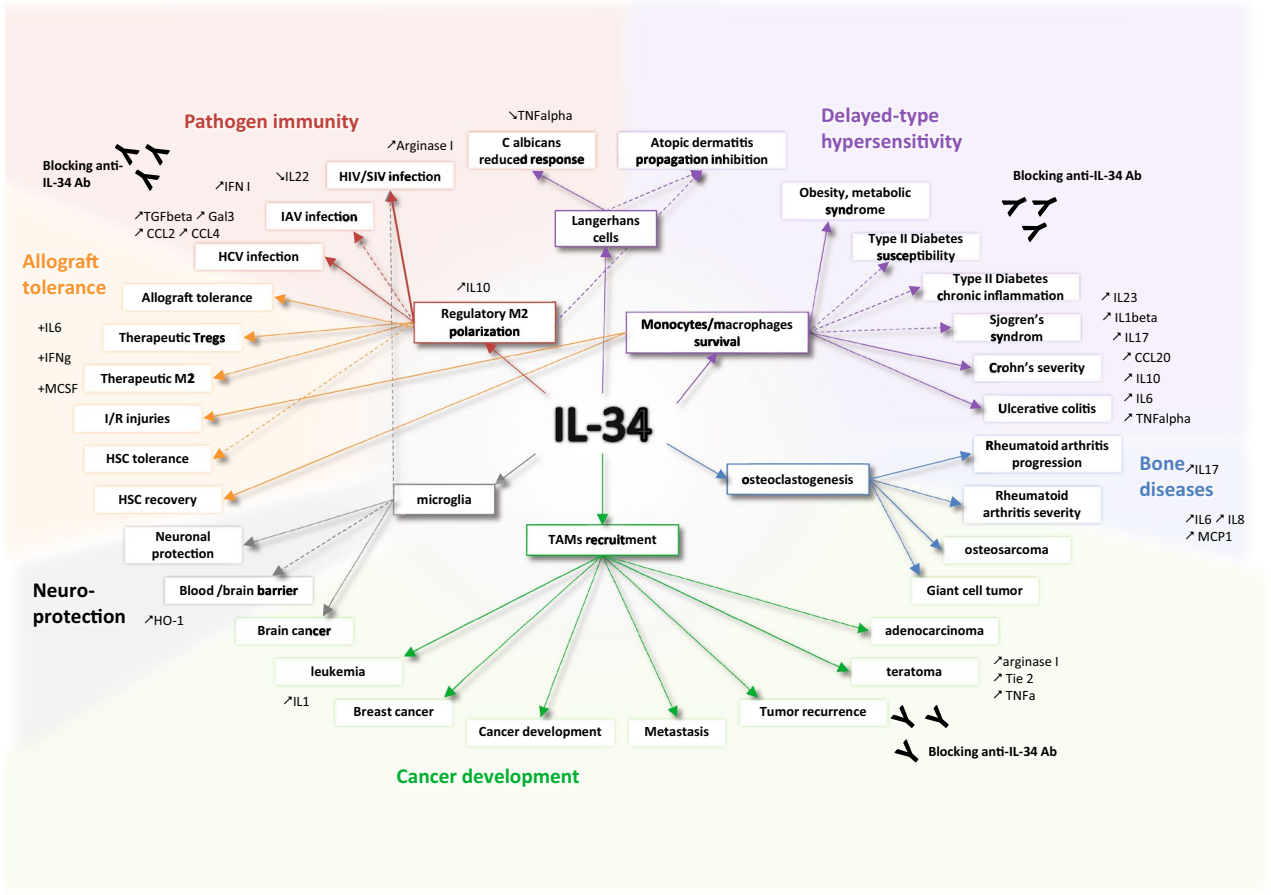

Fig. 2 Therapeutic applications of IL-34 and antagonist potential of blocking anti-IL-34 Ab

Unwanted tolerance could be abrogated by IL-34 inhibition

In cancer, the tolerogenic role of IL-34 is an unwanted effect. Bone giant cell tumor characterized by over-osteoclastogenesis is promoted by IL-34 [7]. Blocking of IL-34 action could stop tumor progression by reducing osteoclasts proliferation and survival signal to these cells. TAMs are major players in the inhibition of antitumor immune responses, and IL-34 and CSF-1 have both been shown to actively participate in CSF-1R-dependent TAM infiltration in the tumor. Indeed, blocking of CSF1R signaling, in combination with paclitaxel, slowed primary tumor and metastasis development improving survival of mammary tumor-bearing mice [81]. Similarly, anti-CSF-1 treatment of cells was efficient to prevent tumor colonization by monocyte-derived cells. However, this effect could be annihilated by the adding of IL-34 [109]. These results highlight the potential of targeting CSF-1R pathway for inhibiting TAMs recruitment, but also suggest the requirement of blocking both IL-34 and CSF-1 to efficiently/definitely control TAMs recruitment. This could be obtained by targeting the CSF-1R but IL-34 could still have actions through its other receptors. An alternative strategy could be to use recombinant bispecific anti-CSF-1 and anti-IL-34 antibodies that would neutralize both cytokines. Thus, for applications, such as cancer, blocking of CSF-1R, CSF-1, and/or IL-34 seems an interesting approach. Blocking of IL-34 or CSF-1 with MAbs can neutralize the other one at least partially, since heterodimers of both molecules can be formed [50]. Nevertheless, the proportion of hetero vs. homodimers is not known. Blocking CSF-1R would eliminate the action of both CSF-1 and IL-34 through this receptor but not IL-34 actions through PTPzeta and/or syndecan-1. PTPzeta is expressed by glioma, astrocytoma, and neuroblastoma cells [35, 36], and IL-34 is produced by astrocytes. CSF-1 has been implicated in increasing lung and brain metastases, and brain metastases express CSF-1 and IL-34 [109], and thus glioma and brain metastasis of CSF-1R$^+$ or PTPzeta$^+$ or syndecan-1$^+$ cancers are areas of particular interest.

Following the same reasoning and since IL-34 is produced by keratinocytes and that melanoma are PTPzeta$^+$

[44] and syndecan-1$^+$ [43], treatment with IL-34 would be particularly relevant. If IL-34 plays a role in the biology of PTPzeta$^+$ [33–36] and/or syndecan-1$^+$ tumors [41, 42, 45], then anti-IL-34 neutralizing antibodies could be an interesting approach.

Positive correlations between IL-34 overexpression in patients and pathogens infections have been reported. High level of IL-34 would promote infection of patients by influenza A virus [84], HIV [85], HCV [83], and C. albicans [86] and could contribute to the generation of anti-inflammatory M2 macrophage polarization. Blocking of IL-34 would thus be helpful to activate the immune response against pathogens.

Conclusions

Thus, although IL-34 and CSF-1 share effects, the two cytokines are not equivalent (Fig. 1) and IL-34 is potentially pathogenic in inflammatory pathophysiological situations, such as IBD and RA, although a possible increase as a suppressive mechanism to inhibit inflammation cannot be ruled out. IL-34 has a distinct pathogenic role in cancer (Table 1; Fig. 2). In general, IL-34 favors the generation of tolerogenic macrophages, such as TAM/M2 macrophages which inhibit immune responses and favor tumor growth. In infectious models, IL-34 has been associated with increase pathogenic burden. Therefore, in light of these studies, neutralizing IL-34 would be desirable to increase immune responses in cancer and infectious diseases and delivering IL-34 could be used to decrease immune responses in autoimmunity and solid organ transplantation or GVHD.

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