Kingfisher Biotech Circular

IL-34: The brains behind CSF-1R pathology in the brain and skin?

In humans, loss or gain of function in CSF-1R has been associated with many inflammatory conditions and cancers, due to its role in the maintenance of mononuclear phagocytes. In particular, the CSF-1R ligand IL-34 plays a key role in maintaining the tissue resident macrophages of the skin and brain, thus being critical to antimicrobial and other inflammatory responses at these sites. IL-34, along with CSF-1, has also been implicated in the inflammation of rheumatoid arthritis and Sjögrens, as well as a poor prognosis in many malignancies.

Interleukin-34 (IL-34) is a homodimeric cytokine identified by high throughput screening of human recombinant secreted factors. (1) It contains no known conserved domains and has no sequence homology with other cytokines. IL-34 is recognized by colony-stimulating factor 1 receptor (CSF-1R). CSF-1R also binds CSF-1, also called macrophage colony-stimulating factor (M-CSF). Both IL-34 and CSF-1 are involved in the survival, proliferation and differentiation of mononuclear phagocytes, including monocytes, macrophages, dendritic cells, Langerhans cells, microglia and osteoclasts. However, their expression profiles, binding interactions with CSF-1R, and resulting functions differ. (2, 3, 4)

IL-34, like CSF-1, stimulates phosphorylation of extracellular signal-regulated kinase-1 and -2 (ERK1/2) in monocytes to promote monocyte survival and macrophage differentiation. (1) However, IL-34-deficient mice lack Langerhans cells and most microglia, whereas CSF-1 null mice retain these cell types. (5, 6) In contrast, CSF-1 null mice display more severe deficiencies in osteoclasts, monocytes and total macrophages, except in the spleen, where IL-34 is highly expressed. (7, 8) Interestingly, CSF-1-dependent expression of IL-34 rescues the CSF-1 null phenotype, suggesting these functional differences are due primarily to differential expression profiles. (2) However, a novel IL-34 receptor expressed on neural progenitors and glial cells, receptor-type protein-tyrosine phosphatase zeta (PTP-ζ), may contribute to the differences observed in the brain. (9)

IL-34 sequence is highly conserved among vertebrates, and even orthologs as distant as avian IL-34 are functionally similar. (10) Human recombinant IL-34 has shown at least partial cross-reactivity in mouse, swine, and feline CSF-1R expressing cells, and murine IL-34 had some activity with both swine and feline CSF-1R, although it does not stimulate human CSF-1R (2, 11, 12). These cross-reactivity studies suggest an opportunity to study the role of CSF-1R and test therapeutic candidates in additional animal models for which IL-34 may not yet be commercially available.

Thus, both IL-34 and CSF-1 act on mononuclear phagocyte lineage cells through CSF-1R, although differential expression patterns for these cytokines result in different cell-specific effects. In particular, IL-34 plays a prominent role in development and maintenance of Langerhans cells, and maintenance of microglia. Loss or stimulation of these tissue resident macrophages by IL-34 dysregulation is implicated in cancer prognosis and many inflammatory pathologies, including rheumatoid arthritis and Sjögrens syndrome. (13) IL-34 is evolutionarily conserved and exhibits some cross-reactivity between species, underlining its critical role in the development of a functional immune system.

References

1. H. Lin *et al.*, Science 320, 807 (2008).
2. S. Wei *et al.*, J. Leukoc. Biol. 88, 495 (2010).
3. X. Ma *et al.*, Structure 20, 676 (2012).
4. H. Liu *et al.*, Biochim. Biophys. Acta 1824, 938 (2012).
5. Y. Wang *et al.*, Nat. Immunol. 13, 753 (2012).
6. M. Greter *et al.*, Immunity 37, 1050 (2012).
7. T. Yamamoto *et al.*, Cell Tissue Res. 332, 245 (2008).
8. Y. Nakamichi *et al.*, Proc. Natl. Acad. Sci. 109, 10006 (2012).
9. S. Nandi *et al.*, J. Biol. Chem. 288, 21972 (2013).
10. V. Garceau *et al.*, J. Leukoc. Biol. 87, 753 (2010).
11. D.J. Gow *et al.*, Cytokine 60, 793 (2012).
12. D.J. Gow *et al.*, Cytokine 61, 630 (2013).
13. Y. Nakamichi *et al.*, J. Bone Miner. Metab. (2013). [epub ahead of print] PMID: 23740288

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