Kingfisher Biotech Circular

M-CSF: More than just a macrophage growth factor

M-CSF (also called CSF-1) has long been known to induce macrophage differentiation in culture. However, studies in CSF-1-deficient (op/op) mice highlight the varied roles of M-CSF in everything from development and fertility, to bone remodeling and tissue repair, to immune surveillance.

M-CSF (macrophage colony-stimulating factor) is a well-described homodimeric cytokine, believed to be secreted by proteolytic cleavage of a membrane-bound precursor, and has 3 differentially spliced isoforms. (1) M-CSF is recognized by CSF-1R, which is expressed on the surface of mononuclear phagocytes. (2) IL34 is the only other known ligand of CSF-1R, shares no sequence homology to M-CSF, and is thought to bind a different domain on CSF-1R. (3, 4) Despite these differences, both M-CSF and IL-34 control the differentiation, survival and proliferation of mononuclear phagocytes, including monocytes, macrophages, dendritic cells, Langerhans cells, microglia, and osteoclasts. The differences observed between M-CSF and IL-34 function are thought to be due primarily to differential expression patterns. (5)

Although initially described as a macrophage growth factor, M-CSF expression has since been shown to be critical in numerous pathways. Osteopetrotic (op/op) mutant mice have severe deficiencies in many mononuclear phagocyte populations, including osteoclasts, monocytes, and macrophages, resulting in osteopetrosis and impaired fertility. This deficiency results from a spontaneous null mutation in the CSF-1 gene. (6) Further, humans lacking CSF-1R function develop leukoencephalopathy, and increased CSF-1R signaling is associated with the development and poor prognosis of cancer, highlighting the importance of M-CSF and IL-34 in regulating immune homeostasis. In fact, a variety of inflammatory conditions and malignancies have been correlated to increased levels of M-CSF, including rheumatoid arthritis. (7) Administration of CSF-1 as a therapeutic has been explored and shows promise in promoting tissue repair, and inhibition of CSF-1 or CSF-1R may have applications in cancer treatment. (8)

Homologs of human M-CSF identified by HomoloGene are found in chimpanzees, rhesus macaques, dog, cow, mouse, and rat. (1) Further, avian orthologs for M-CSF, IL-34, and CSF-1R have been found and shown to function in monocytic proliferation. (9) M-CSF also displays some reactivity across species, with human and porcine M-CSF interacting with CSF-1R from human, pig, mouse, dog and cat. Murine M-CSF has some cross-reactivity to both pig and feline CSF-1R. (10, 11) Together, these data suggest evolutionary conservation of M-CSF across vertebrates, emphasizing the importance of M-CSF and the monocytic phagocytes.

M-CSF is well known for its role in the proliferation, differentiation and survival of monocytic phagocytes. However, as an appreciation is gained for the widespread necessity of these cells throughout many organ systems, our understanding of the importance of M-CSF continues to grow. M-CSF regulation is critical to maintaining homeostasis, and dysregulation impacts development, fertility, inflammation, osteoclastogenesis, immunity, and cancer development and progression.

References

1. NCBI. Gene ID:1435, CSF-1 [Homo sapiens]. [Last update: 8 Sept, 2013].
2. L.J. Guilbert and E.R. Stanley, J. Cell Biol. 85, 153 (1980).
3. X. Ma *et al.*, Structure 20, 676 (2012).
4. H. Liu *et al.*, Biochim. Biophys. Acta 1824, 938 (2012).
5. S. Wei *et al.*, J. Leukoc. Biol. 88, 495 (2010).
6. W. Wiktor-Jedrzejczak *et al.*, Proc. Natl. Acad. Sci. USA 87, 4828 (1990).
7. Y. Nakamichi *et al.*, J. Bone Miner. Metab. (2013). [epub ahead of print] PMID: 23740288.
8. D.A. Hume and K.P. MacDonald, Blood 119, 1810 (2012).
9. V. Garceau *et al.*, J. Leukoc. Biol. 87, 753 (2010).
10. D.J. Gow *et al.*, Cytokine 60, 793 (2012).
11. D.J. Gow *et al.*, Cytokine 61, 630 (2013).

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