

# CSF-1 — The Swiss Army Cytokine of Innate Immunity

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Today, Dr. Richard Stanley will give the E. Donnell Thomas Lecture summarizing his original and influential work on colony stimulating factor-1 (CSF-1), also known as macrophage colony stimulating factor (M-CSF). Dr. Stanley's seminal research identified and characterized CSF-1, its receptor and signaling pathways, its role in normal macrophage biology, and its role in macrophage development and neoplasia. CSF-1 has a multitude of targets and functions, providing to innate immunity much what the Swiss Army knife does for a camper.

It also happens to be an important tool for neoplastic cells. CSF-1 expression has been correlated with poor prognosis in breast cancer. Dr. Stanley hypothesized that CSF-1 production is a critical component to development of metastatic breast cancer. His work demonstrated that production of CSF-1 by the malignant cells facilitates tumor progression and metastasis through the recruitment and regulation of tumor-associated macrophages. There is a coordinated cytokine dialogue between the neoplastic cells and macrophages initiated by CSF-1. This exchange induces macrophage production of vascular endothelial growth factor, which influences angiogenesis and production of matrix metalloproteinases, which function in tumor invasion.

Recent research by Dr. Stanley in a breast cancer xenograft model demonstrated that anti-CSF-1 antibody could reverse chemoresistance by reducing expression of resistance genes and reduce angiogenesis, macrophage recruitment, and down-regulated expression of matrix metalloproteinases.

Normally, CSF-1 is expressed in three different isoforms, the result of splice variants from a single gene. Both secreted and membrane-stable forms of this molecule can be found. It is produced by a variety of cells, including endothelial cells, fibroblasts, bone marrow stromal cells, osteoblasts, thymic epithelial cells, keratinocytes, astrocytes, myoblasts, and mesothelial cells, to name a few. The implication of this diversity in macromolecular forms is realized in the diverse receptors, cells expressing the receptors, and functions of this cytokine. Thus it could be important in other types of metastatic malignancies in addition to breast cancer.

The high-affinity CSF-1 receptor (CD115) belongs to the class III tyrosine kinase receptor family. Other members of this family include stem cell growth factor receptor (c-kit), Flt3, PDGFR- $\alpha$ , and PDGFR- $\beta$ . The CSF-1R is expressed primarily on cells of the macrophage lineage. More significant is the pervasiveness of CSF-1R<sup>+</sup> cells. Binding of CSF-1 to CSF-1R promotes receptor dimerization and subsequent activation of the tyrosine kinase domain, leading to transphosphorylation. Subsequent steps lead to receptor ubiquitination and eventual receptor internalization and degradation.

CSF-1 is a model pleiotropic molecule, potentially inducing proliferation, differentiation, and survival of CSF-1R<sup>+</sup> cells, depending on cell type and associated signals. Clearly, bone marrow stromal cells provide CSF-1 to cells of the CSF-1R<sup>+</sup> macrophage lineage, critical for hematopoiesis of the monocyte-macrophage lineage. Furthermore, CSF-1 is a key regulator of macrophages.

The clinical relevance of this cytokine and its receptor is potentially far-reaching. CSF-1 plays a major role in immunity against fungal, bacterial, viral, and parasitic infections. The pleiotropic and poly-functional activity of CSF-1 make it an attractive therapeutic target. Animal models and pre-clinical studies will provide important insights into the role of CSF-1 in cancer pathogenesis.