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REVIEW

Macrophage colony stimulating factor: Not just for macrophages anymore! A gateway into complex biologies☆

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Abstract

Macrophage colony stimulating factor (M-CSF, also called colony stimulating factor-1) has traditionally been viewed as a growth/differentiation factor for monocytes, macrophages, and some female-specific tumors. As a result of alternative mRNA splicing and post-translational processing, several forms of M-CSF protein are produced: a secreted glycoprotein, a longer secreted form containing proteoglycan, and a short membrane-bound isoform. These different forms of M-CSF all initiate cell signaling in cells bearing the M-CSF receptor, called c-fms. Here we review the biology of M-CSF, which has important roles in bone physiology, the intestinal tract, cancer metastases to the bone, macrophage-mediated tumor cell killing and tumor immunity. Although this review concentrates mostly on the membrane form of human M-CSF (mM-CSF), the biology of the soluble forms and the M-CSF receptor will also be discussed for comparative purposes. The mechanisms of

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the biological effects of the membrane-bound M-CSF reveal that this cytokine is unexpectedly involved in many complex molecular events. Recent experiments suggest that a tumor vaccine based on membrane-bound M-CSF-transduced tumor cells, combined with anti-angiogenic therapy, should be evaluated further for use in clinical trials.

Contents

1. Introduction

The colony stimulating factors (CSF) were initially described in the late 1960s and early 1970s as glycoproteins that induced the clonal growth of various hematopoietic lineages from the bone marrow [1]. A variety of these factors were named for their utilitarian functions: M-CSF stimulated macrophages, G-CSF stimulated granulocytes, GM-CSF stimulated both granulocytes and macrophages, while multi-CSF induced the growth of all hematopoietic different cell types. Richard Stanley and his colleagues first identified the undefined M-CSF, purified to homogeneity, and named it colony stimulating factor-1 (CSF-1) [2–5] to reflect a better characterization of this protein. Initially, the human form of M-CSF was isolated from urine. Later it was discovered that a variety of cell types produce this growth factor, simplifying its characterization. For this review we will use the functional name M-CSF. There have been several excellent general reviews previously written about this cytokine [6–10].

Recombinant M-CSF (called Lanimostim/MacroTac) is used clinically in bone marrow transplantation patients [11,12], whose innate immune system has not been fully restored, and consequently suffer from recurrent fungal and bacterial infections due to the lack of myeloid cells. M-CSF stimulates the growth of mononuclear phagocytes from the hematopoietic stem cells, producing more precursor monocytes and macrophages. Infused M-CSF also activates these monocytoid cells to become better phagocytic cells, thereby clearing the microbes by directly engulfing the pathogens. One major toxicity that limits the therapeutic use of this cytokine is thrombocytopenia [13]. This should not be surprising that the M-CSF-activated monocytes/macrophages phagocytosized the platelets, which have the same approximate size as the microbes. The M-CSF-induced thrombocytopenia is reversible, following cessation of the treatment.

M-CSF primarily stimulates the growth of macrophages and resident macrophages of local tissue (Kupffer cells in liver, microglial cells in bone, mesangial cells in the kidney, osteoclasts in bone, etc). M-CSF helps generate two subsets of dendritic cells. In the skin, the Langerhans cells are stimulated [14,15], while in the blood and lymph nodes, plasmacytoid dendritic cells [16] are produced. M-CSF is normally found in detectable levels (2.4 ng/ml or 120 units/ml) in the serum of healthy individuals [17]. M-CSF expression is elevated during pregnancy, up to 400 units/ml, from 9 to 33 weeks of gestation [18]. Low M-CSF levels were associated with spontaneous abortions [19], while elevated M-CSF serum levels were linked with a pathology of the mother called pre-eclampsia [20]. This linkage with pregnancy ultimately proved to be a particularly useful in the fertile area of M-CSF research over the last 22 years. M-CSF plays important roles in many gynecological aspects such as egg follicle development, breast stimulation in preparation for lactation, fetal and placental growth. Since these topics have been covered elsewhere [21–30], we will not review it here.

M-CSF is speculated to be a useful biomarker for a number of cancers (reviewed by Khatma, [31]), including pancreatic [32], colorectal [33,34], breast [35,36], and ovarian cancers [37,38]. In acute rejection of kidney transplant patients [39], circulating M-CSF levels correlated with poor prognosis. It is not yet clear whether the high levels of M-CSF are the cause or the effect of these diseases.