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CSF-1—A Mononuclear Phagocyte Lineage-Specific Hemopoietic Growth Factor

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INTRODUCTION

All of the mature blood cell types of the mouse are derived from a single, pluripotent, hemopoietic stem cell [reviewed in 1]. These stem cells represent only a very small fraction (~0.1%) of the cells of the hemopoietic organs (yolk sac, fetal liver, bone marrow, and spleen). However, each stem cell has the potential to give rise to thousands of mature blood cells by a process of proliferation and differentiation. Owing to the relatively short life-span of blood cells, this process must occur continuously in order to maintain mature blood cell levels. A group of circulating hemopoietic growth factors are involved in regulating these events. They include erythropoientin (erythrocytic lineage) and the colony-stimulating factors (granulocytic and mononuclear phagocytic lineages).

The term "colony-stimulating factor" (CSF) embraces the group of growth factors that stimulate hemopoietic precursor cells to form clones containing granulocytes and/or macrophages [2,3]. At least four subclasses of CSF may be discerned by their different physical properties and their preferential stimulation of neutrophil, eosinophil, neutrophil-macrophage, or macrophage colony formation [reviewed in 4]. Two CSFs stimulate the proliferation of mononuclear phagocytes directly—CSF-1 and CSF_{GM}. CSF-1 [5,6] has been clearly discriminated from the other CSFs by its detection in subclass-specific radioimmuno- and radioreceptor assays [4,6–8]. It is lineage-specific, stimulating the survival, proliferation, and differentiation of mononuclear phagocytes and their precursors [4,9,10]. The macrophage growth factor from L-cell-conditioned medium described by Virolainen and Defendi [11] has been shown to be CSF-1 [12]. CSF_{GM} is a glycoprotein of M_r ~23,000 which stimulates the formation of colonies containing both neutrophilic granulocytes and macrophages and the proliferation of primitive precursor cells of the erythroid lineage [13,14]. It is

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significantly less effective than CSF-1 in generating macrophages in bone marrow cultures, and its actions on mononuclear phagocytes are not mediated by the CSF-1 receptor [8]. Studies with CSF_{GM} [reviewed in 4,14] have been limited by an inability to raise antibodies against it and to radioiodinate it with retention of biological activity.

This review summarizes our studies on the characterization and mechanism of action of CSF-1, and reports briefly on recent studies in which the CSF-1 receptor interaction has been used in the identification and assay of new hemopoietic growth factors.

ASSAY, PURIFICATION, AND PROPERTIES OF CSF-1

The bioassay for the CSFs is based on the CSF-dependent stimulation of bone marrow cells to form colonies of granulocytes and/or macrophages in semisolid agar [3] or methyl cellulose [2] culture media. Standardization and quantitation of this colony assay for CSF-1 have been reviewed elsewhere [4]. A limitation of the colony assay is that it cannot be used to specifically assay CSF-1 in preparations that contain the other CSF subclasses. However, measurement of the CSF-1 concentration in such preparations can be determined by CSF-1-specific competitive binding assays that are based on the ability of CSF-1 to compete for the binding of ^{125}I-CSF-1 to either anti-CSF-1 antibody or the CSF-1 receptor. Murine [7] and human [6] CSF-1 radioimmunoassays are relatively species-specific. However, the murine radioreceptor assay [8] can be used to detect either murine or human CSF-1. Both radioimmuno- and radioreceptor assays appear to detect only biologically active CSF-1 [15]. All CSF-1 assays (including the colony assay) can be standardized against stable preparations to which values in units have been ascribed [reviewed in 4]. One unit of pure CSF-1 contains $\sim$6 pg of protein and gives rise to 1–10 colonies per 7.5×10^4 bone marrow cells [5,15].

CSF-1 has been purified from the medium conditioned by serum-free cultures of murine L cells [5,15], human MIA Pa Ca-2 cells [16], and human urine [6]. The L cell CSF-1 has been shown to be pure by comigration of protein and activity during polyacrylamide gel electrophoresis (PAGE) in the presence and absence of sodium dodecyl sulphate (SDS), during isoelectric focusing [5], and during SDS-PAGE following enzymatic removal of $>85\%$ of the CSF-1 carbohydrate moieties [17]. In addition, formation of the purified protein-antibody complex and the neutralization of its biological activity occur at the same concentration of antibody [5]. CSF-1 represents $\sim 0.1\%$ of the total protein of serum-free conditioned medium, which is the most appropriate starting material for its purification. Thus only small amounts of purified material ($\sim$200 μg) may be obtained from large volumes ($\sim$10 liters) of medium. This problem has been a major limiting factor in molecular studies of CSF-1 and its mechanism of action.

CSF-1 from both human and murine sources is an acidic glycoprotein of M_r $\sim$45,000–$\sim$76,000 [5,6,17]. A schematic representation of the CSF-1 molecule is shown in Figure 1. Reduction, even in the absence of dissociating agents, destroys the biological activity and halves the M_r of all CSF-1 preparations, reflecting the existence of two similar subunits in the molecule. Studies with L cell CSF-1 indicate that these subunits are of similar charge [5]. The nature and extent of CSF-1 glycosylation has been investigated utilizing endoglycosidase treatment. Irrespective of the M_r of the reduced and alkylated CSF-1 (24,000–33,000), exhaustive treatment

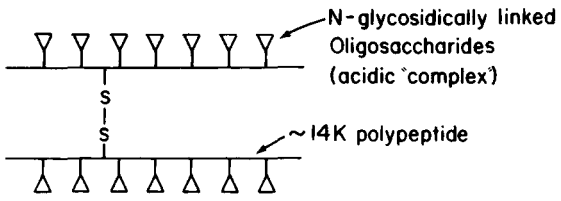

Fig. 1. Provisional structure of murine or human CSF-1 (schematic). The two polypeptide chains are very similar, if not identical. The number of oligosaccharides per molecule is variable and depends on the origin of the preparation. The number of disulfide bonds is unknown.

of reduced and alkylated CSF-1 with endo-β-N-acetylglucosaminidase-D, but not endo-β-N-acetylglucosaminidase-H, gives rise to a molecule of M_r ~ 16,500 of which the polypeptide chain portion accounts for ~ 14,000. Whereas the parent molecule binds concanavalin A, this product does not, indicating that, as intimated from earlier studies [18,19], heterogeneity in the saccharide component could explain the observed variation in M_r of CSF-1 [17]. These results also suggest that the two polypeptide chains in the dimeric CSF-1 molecule are very similar and possibly identical. Because of the specificity of endo-α-N-acetylglucosaminidase-D, it is concluded that the carbohydrate moieties are asparagine-linked, "complex-type" units. Examination of the effects of endo-α-N-acetyl-β-galactosaminidase treatment on the M_r of reduced and alkylated CSF-1 fails to provide evidence of the existence of 0-glycosidically linked oligosaccharides. Treatment of native CSF-1 with endo-β-N-acetylglucosaminidase-D removes carbohydrate almost as efficiently (>85%) as treatment of the reduced and alkylated subunits. Removal does not cause loss of antibody binding, receptor binding, or biological activity [17]. While the carbohydrate moiety does not appear to be necessary for the in vitro biological activity of CSF-1, it may be important for CSF-1 stability [19] and/or the relative resistance of CSF-1 to attack by proteolytic enzymes [20–22].

CELL TYPES EXHIBITING A PROLIFERATIVE RESPONSE TO CSF-1

Stimulation of proliferation by CSF-1 is restricted to cells of the mononuclear phagocytic series whether they be the colony-forming cells of bone marrow or spleen, blood monocytes, or tissue macrophages [reviewed in 4]. The maturation sequence of mononuclear phagocytic cell types and their properties are summarized in Table I. While CSF-1 stimulates the growth of both immature and relatively mature cells of the mononuclear phagocytic series, the immature cells have a higher proliferative capacity and a shorter doubling time than the more mature cells. Mononuclear phagocytes do not become "immortal" (ie, form continuous cell lines) if cultured with CSF-1, but instead have finite capacities for proliferation and eventually give rise to populations of nondividing cells [23]. Mononuclear phagocytes from many different tissues including bone marrow, blood, peritoneal cavity, pulmonary alveoli, and liver are all capable of exhibiting a proliferative response to purified CSF-1 [24]. However, while the proportion of freshly explanted monoblasts, promonocytes, or monocytes that are capable of extensive proliferation is >90%, the proportion of macrophages capable of extensive proliferation varies from ~1% (peritoneal macro-

TABLE I. Properties of Freshly Explanted Cells of the Mononuclear Phagocytic Lineage

	Property			
Cell type	% Cells capable of proliferation	Proliferative capacity of cells capable of proliferation	CSF-1 receptor	Glass adherent cells
CFU-C[a]		+++	+	−
↓				
Monoblast	>90	++	+	+
↓				
Promonocyte	>90	++	+	+
↓				
Monocyte	>90	++	+	+
↓				
Macrophage	1-50[b]	+	+	+

[a]Undifferentiated, nonadherent, colony-forming cell.
[b]Percent varies depending on source—eg, 50% of peritoneal exudate macrophages, 1% of resident peritoneal macrophages.

phages) to ~50% (peritoneal exudate macrophages). As this kind of variation among different macrophage populations is not observed for the CSF-induced release of plasminogen activator [25], proliferative senescence within the mononuclear phagocytic series may not necessarily be associated with a loss of the regulation of other functions by CSF-1.

STIMULATION OF CELL SURVIVAL AND DIFFERENTIATION BY CSF-1

In addition to its effects on proliferation, CSF-1 stimulates the survival and differentiation of mononuclear phagocytes. Bone marrow–derived macrophages, resident peritoneal macrophages, and peritoneal exudate macrophages will die if cultured in the presence of culture medium containing only 15% fetal calf serum [10]. Addition of CSF-1, at concentrations below those stimulating significant cell proliferation (~20 pM), will prevent cell death. The effect of CSF-1 on the differentiation of immature mononuclear phagocytes has been less well studied; nevertheless, it is clear that the nonadherent mononuclear phagocyte precursor cells (CFU-C) of bone marrow rapidly differentiate into adherent, proliferating macrophages if pure CSF-1 alone is added to serum-containing culture medium (Tushinski and Bartelmez, unpublished observations).

CSF-1 RECEPTORS AND THE NATURE AND DISTRIBUTION OF CSF-1 BINDING CELLS

Detailed analysis of the binding and uptake of a growth factor is important for the identification of the cells with which it interacts directly and for the elucidation of the biochemical mechanisms underlying its effects on target cells. CSF-1 can be radiolabeled with ^{125}I to high specific radioactivity (300,000 cpm/ng) without loss of biological or antibody binding activity [5,15]. Initial studies of the binding and uptake of murine ^{125}I-CSF-1 have been carried out on murine peritoneal exudate macrophages, 50% of which are capable of extensive proliferation in the presence of CSF-1

and >95% of which were shown to bind ^{125}I-CSF-1 specifically [26]. The binding (at 4°C) of ^{125}I-murine CSF-1 to these macrophages is of high affinity ($K_d \leqslant 10^{-13}$ M, Table II) and not competed for by other known CSF subclasses, growth factors, or hormones [26]. A variety of approaches, including thick-section light autoradiography, temperature jump, and pH 4 dissociation experiments, indicate that ^{125}I-CSF-1 binds a cell surface receptor at 4°C (Guilbert et al, in preparation).

The interaction of ^{125}I-CSF-1 with peritoneal exudate macrohages at 37°C is complex. ^{125}I-CSF-1 is destroyed by macrophages at 37°C by a process involving CSF-1 receptor-mediated internalization, significant intracellular accumulation, and subsequent intralysosomal degradation [17] (Guilbert et al, in preparation). The relationship between CSF-1 degradation and the proliferative response of cells is not clear at the present time.

Studies of the distribution, frequency, and morphology of murine binding cells [26,27] indicate that binding is restricted to cells of the mononuclear phagocytic system, and that the CSF-1 receptor is an excellent marker of mononuclear phagocytic cells, irrespective of their tissue of origin or state of differentiation (Table III). Furthermore, the occurrence of the receptor on continuous murine cell lines is restricted to macrophage or myelomonocytic cell lines [26].

TABLE II. Parameters of Murine ^{125}I-CSF-1 Binding to Murine Peritoneal Exudate Macrophages at 4°C, pH 7.35

Parameter	Value
On-rate constant (k_{on})	$\sim 10^8$ M^{-1} min^{-1}
Off-rate constant (k_{off})	$\leqslant 10^{-5}$ min^{-1}[a]
Dissociation constant (k_{off})/(k_{on})	$\leqslant 10^{-13}$ M

All data derived from kinetic analyses. Equilibrium methods could not be used owing to instability of the empty receptor sites relative to the occupied receptor sites [15].
[a]Possibly irreversible.

TABLE III. Distribution and Frequency of ^{125}I-CSF-1 Binding Cells in Murine Tissues

Cell type	Percent labeled cells	Average number of ^{125}I-CSF-1 molecules/labeled cell
Bone marrow	4.3	5,600
Spleen	2.4	9,600
Blood mononuclear	7.5	3,000
Peritoneal exudate	ND (98.0)	ND (73,000)
Peritoneal	17.0 (95.0)	10,000 (24,000)
Alveolar	11.8	16,000
Lymph node	0.4	8,000
Blood granulocyte	0	0
Thymus	0	0

Data obtained from autoradiographs and cell binding experiments on freshly explanted cells [27]. ND, not done. Figures in parentheses are from the adherent fractions of these cell populations that were cultured for 24 hr in the absence of CSF-1 prior to binding [15,26]. With the exception of the alveolar cells, the proportion of labeled cells in the cell population was not significantly different from the reported proportion of mononuclear phagocytes. In the case of the alveolar cells, the proportion of labeled cells was significantly lower than the reported proportion of mononuclear phagocytes, and macrophages could be seen that did not have grains associated with them.

MECHANISM OF CSF-1 ACTION

In order to study the cell biological and molecular aspects of the mechanism of CSF-1 action, it is desirable to work with homogeneous populations of target cells. The more immature cells of the mononuclear phagocytic series represent a very small proportion of the cells in the tissues in which they occur (bone marrow, spleen, blood; Table III). As it is difficult to purify large numbers of these cells, their effectiveness as a target cell population is limited. On the other hand, the more mature cells (macrophages) are easily isolated as relatively pure populations but exhibit heterogeneity in their proliferative responses (Table I) and are contaminated with CSF-1-producing cells of fibroblastoid morphology. The latter problems, however, can be overcome by culturing mouse bone marrow cells in the presence of CSF-1-containing preparations for 3 days and selecting from the nonadherent (or undifferentiated; Table I) fraction those cells that become adherent—ie, differentiate, during a subsequent 2-day culture period. These selected cells, termed "bone marrow-derived macrophages" (BMM) because of their macrophage morphology, represent a homogeneous population that responds to CSF-1 by extensive proliferation and >95% of which binds ^{125}I-CSF-1 [10].

The effects of CSF-1 on BMM morphology have been studied at the light-microscopic level. Relative to nonproliferating BMM, proliferating BMM are much enlarged and have a "foamy" appearance owing to the presence of numerous phase-lucent vacuoles. As these vacuoles do not stain with Oil Red O and do not possess cytochemically demonstrable acid phosphatase activity, they are probably pinocytic in origin. Proliferating cells also exhibit increased membrane ruffling and possess larger numbers of filopodia than do nonproliferating cells [10]. These latter changes appear within minutes after CSF-1 addition to nonproliferating cells (Tushinski et al, in preparation). The relationship between CSF-1-induced vacuolation, the intralysosomal destruction of CSF-1, and the proliferative response to CSF-1 is currently being studied in BMM populations.

Studies on the requirement of CSF-1 for BMM proliferation indicate that its presence during the G_1 phase of the cell cycle is both necessary and sufficient for entry of BMM into S phase and their progression through G_2 and M (Tushinski et al, in preparation). Removal of CSF-1 from exponentially growing BMM cultured in 15% fetal calf serum–containing medium decreases the rate of DNA synthesis by more than 100-fold. Addition of CSF-1 to these cells causes them to resume DNA synthesis within 10–12 hr, but has more immediate effects on protein metabolism. Within 2 hr after CSF-1 addition, the BMM protein synthetic rate is maximally stimulated and this, together with the CSF-1-induced decrease in the rate of intracellular protein degradation, leads to an accumulation of total cell protein, which is apparent in as little as 2 hr after stimulation. The increased protein synthetic rate is a linear function of the CSF-1 concentration, whereas the inhibition of protein degradative rate is an exponential function of the CSF-1 concentration, and inhibition of the protein degradative rate may be an integral part of the mechanism by which CSF-1 induces BMM survival [40]. Current studies of the mechanism of CSF-1 action on BMM are directed toward the analysis of very rapid events, including ion transport and protein phosphorylation, which may be induced by the growth factor.

Because of the limited amount of pure CSF-1 available for whole animal work, almost all studies of the mechanism of CSF-1 action have been carried out in vitro.

However, measurement of CSF levels and colony-forming cells in a variety of experimental and clinical situations is consistent with an involvement of the CSFs as a group in the physiological regulation of granulocyte and macrophage production [reviewed in 28]. Other in vitro studies indicate that CSF-1 stimulates the release of plasminogen activator [25,29], prostaglandins [30], and interleukin-1 [31] by macrophages. It is apparent from these observations and from its separate effects on cell morphology, protein synthetic, and protein degradative rates, that CSF-1 regulates a pleiotropic response by mononuclear phagocytes.

GROWTH FACTORS STIMULATING MONONUCLEAR PHAGOCYTE PROGENITOR CELL PRODUCTION

It is clear that CSF-1 plays an important role in the generation of mononuclear phagocytes from CFU-C and in the regulation of the activities of mononuclear phagocytes in general. However, the question remains as to how the CFU-C themselves are derived from pluripotent, hemopoietic stem cells and whether hemopoietic growth factors are involved in that process. Bradley and colleagues [32,33] have developed an assay for a precursor cell of the CFU-C. They have termed this precursor the high-proliferative potential colony-forming cell (HPP-CFC). HPP-CFCs share many properties with hemopoietic stem cells and can be stimulated to form much larger colonies of macrophages than those formed by CFU-C in the presence of CSF-1. Formation of these larger colonies requires the presence of both CSF-1 and a factor which synergizes with CSF-1 [34] (Bartelmez et al, unpublished observations). In order to investigate the roles of the synergistic factor and other hemopoietic growth factors that might regulate the generation of CFU-C, we have developed assays which detect factors that stimulate an increase in the numbers of nonadherent ^{125}I-CSF-1 binding cells during short-term culture. Two growth factors have been resolved. Both increase the number of CSF-1-binding, nonadherent cells—one in the absence of CSF-1, while the other requires CSF-1 for its action. These factors (M_r ~30,000 and M_r ~20,000, respectively) act on more immature cells than those that respond to CSF-1 alone and appear to be distinct from CSF_{GM}. Current studies in this area are directed toward the purification and characterization of these new hemopoietic growth factors and analysis of their effects on the generation of precursor cells for other hemopoietic cell lineages.

SUMMARY AND CONCLUSIONS

CSF-1 is the only mononuclear phagocyte lineage-specific growth factor described to date. Despite its unusually high degree of glycosylation, it appears that a completely deglycosylated form might still retain in vitro biological activity. This conclusion raises the question of the function of the CSF-1 oligosaccharides. Since CSF-1 acts on macrophages that release proteases [35–37] and which are found with CSF-1 in areas of local inflammation, its substantial glycosylation may provide protection from extracellular degradation. It is interesting to note that without its carbohydrate, CSF-1 shares structure-activity relationships with the biologically ac-

tive subunit of nerve growth factor (β-NGF). β-NGF is a dimer composed of two noncovalently associated polypeptide chains of M_r ~14,000 with identical or completely overlapping sequences [38]. Determination of the amino acid sequence of the CSF-1 polypeptide chain(s) will resolve the question of whether CSF-1 is related to β-NGF, which belongs to the family of insulin-related growth factors [39].

As in the case of other growth factors and the polypeptide hormones, the biological effects of CSF-1 are mediated by a specific cell-surface receptor. These effects include the stimulation of target cell survival, proliferation, and differentiation as well as other morphological and functional changes. Studies on the mechanism(s) by which the CSF-1 receptor system leads to the pleiotropic effects of CSF-1 on mononuclear phagocytes will be facilitated by the recent development of methods for obtaining homogeneous populations of target cells (BMM). However, the restricted occurrence of the CSF-1 receptor among cells of the mononuclear phagocytic series makes it an excellent marker of this lineage, and has already led to the delineation of two new growth factors that may be involved in directing hemopoietic cell proliferation and differentiation at the level of the hemopoietic stem cell. These latter studies may help elucidate the basic mechanisms by which several growth factors interact in the generation of mature cells from immature precursor cells in proliferating tissues.

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