CSF-1 Receptor Signaling in Myeloid Cells

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The CSF-1 receptor (CSF-1R) is activated by the homodimeric growth factors colony-stimulating factor-1 (CSF-1) and interleukin-34 (IL-34). It plays important roles in development and in innate immunity by regulating the development of most tissue macrophages and osteoclasts, of Langerhans cells of the skin, of Paneth cells of the small intestine, and of brain microglia. It also regulates the differentiation of neural progenitor cells and controls functions of oocytes and trophoblastic cells in the female reproductive tract. Owing to this broad tissue expression pattern, it plays a central role in neoplastic, inflammatory, and neurological diseases. In this review we summarize the evolution, structure, and regulation of expression of the CSF-1R gene. We discuss the structures of CSF-1, IL-34, and the CSF-1R and the mechanism of ligand binding to and activation of the receptor. We further describe the pathways regulating macrophage survival, proliferation, differentiation, and chemotaxis downstream from the CSF-1R.

The glycoprotein, colony-stimulating factor-1 (CSF-1), also known as macrophage-CSF (M-CSF), was the first of the CSFs to be purified (Stanley and Heard 1977) and was shown to stimulate the formation of colonies of macrophages (Stanley et al. 1978). This led to the identification (Guilbert and Stanley 1980) and purification (Yeung et al. 1987) of the CSF-1 receptor (CSF-1R) and the demonstration that it possessed intrinsic tyrosine kinase activity (Yeung et al. 1987). It was subsequently shown to be identical to the *c-fms* proto-oncoprotein (Sherr et al. 1985) previously studied by Sherr and colleagues (Rettenmier et al. 1985). The *c-fms* cDNA was cloned and shown to encode a typical class III receptor tyrosine kinase (RTK) (Coussens et al. 1986).

The CSF-1R plays a central role in many diseases. Dominant inactivating mutations in the CSF-1R lead to adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (Rademakers et al. 2011; Nicholson et al. 2013). Inappropriate expression of the CSF-1R contributes to the development of leukemias and lymphomas, and autocrine and paracrine regulation of the CSF-1R enhances the progression and metastasis of solid tumors (reviewed in Pollard 2009; Chitu and Stanley 2014). In addition, regulation through the CSF-1R contributes to chronic inflammatory diseases (reviewed in Chitu and Stanley 2006; Chitu et al. 2012). This review focuses on the CSF-1R regulation and signaling in cells of the myeloid lineage.

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THE CSF-1R AND LIGANDS

The CSF-1R and Its Oncogenic Derivatives

The CSF-1R belongs to the platelet-derived growth factor (PDGF) family. Similar to other family members, it possesses a highly glycosylated extracellular region comprised of five immunoglobulin domains (D1–D5, 498 amino acids), a transmembrane domain (21 amino acids), and an intracellular domain comprised of a juxtamembrane domain (JMD) (36 amino acids) and an intracellular tyrosine kinase domain (398 amino acids) that is interrupted by a kinase insert domain (73 amino acids) (Fig. 1A) (Cousens et al. 1986; Rothwell and Rohrschneider 1987; Hampe et al. 1989).

Comparison of the sequences of cat *c-fms* and a *v-fms* retroviral oncogene derived from it revealed that a carboxy-terminal truncation, together with two point mutations (L301S and A374S) in the extracellular D4 domain, subsequently shown to contain the dimerization in-

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Figure 1. Structure of the CSF-1R and regulation of *Csf1r* gene expression. (A) Structures of CSF-1R and oncogenic derivatives. (Left) The *c-fms* proto-oncogene, (middle) the *v-fms* oncogene, encoded by the Susan McDonough strain of feline sarcoma virus (SM-FeSV), and (right) the CSF-1R–RBL6 oncogenic fusion protein. Ovals D1–D5 represent the five extracellular Ig-like domains of CSF-1R. The ligand-binding domains are gray. The blue dots in D4 represent the ionic pairs that have been implicated in receptor homotypic contacts. The intracellular domain is shown as the juxtamembrane domain (JMD, orange), kinase N lobe (ATP, dark blue), kinase insert (KI, green), kinase C lobe (Kin, light blue), activation loop (AL, purple), and carboxy-terminal tail (black). All amino acid substitutions in *v-fms* are shown as annotated red dots and the carboxy-terminal amino acid sequence that is unrelated to *c-fms* is red (Woolford et al. 1988). (B) Evolution of closely related type III RTK genes by gene and genome duplications (based on data from Braasch et al. 2006). (C) (Top) Exon-intron structure of mouse *Csf1r* gene and (bottom) expanded promoter structure and transcription factor (TF) binding sites (based on data from Bonifer and Hume 2008; Ovchinnikov et al. 2010). (D) Regulation of *Csf1r* expression in hematopoiesis (based on data from Bonifer and Hume 2008). The silenced state levels for each parameter were measured in T cells and fibroblasts that do not express the CSF-1R. Mo, monocyte; Mφ, macrophage.

terface (Elegheert et al. 2011; Ma et al. 2012), are critical changes required for the full transforming activity of the oncogene (Fig. 1A) (Woolford et al. 1988). Another oncogenic derivative is the product of a t(3;5)(p21;q33) translocation, RBM6-CSF-1R, a constitutively activated CSF-1R fusion protein comprised of the amino-terminal 36 amino acids of RNA-binding motif 6 (RBM6), joined to the carboxy-terminal 399 amino acids of the CSF-1R, which leads to an acute megakaryoblastic leukemia (Fig. 1A).

CSF-1R Expression

The CSF-1R is expressed at low levels on hematopoietic stem cells (HSCs) (Sarrazin et al. 2009; Mossadegh-Keller et al. 2013), at higher levels on monocytes and tissue macrophages (Guilbert and Stanley 1980; Byrne et al. 1981), osteoclasts, myeloid dendritic cells (MacDonald et al. 2005), microglia (Nandi et al. 2012), and Paneth cells (Huynh et al. 2009) and controls the development of these cell types. It is also expressed on oocytes and preimplantation embryos, decidual and trophoblastic cells (reviewed in Pollard and Stanley 1996), neural progenitor cells and other neuronal cells (Wang et al. 1999a; Nandi et al. 2012; Luo et al. 2013), renal proximal tubule epithelial cells, and colonic epithelial cells (reviewed in Chitu and Stanley 2014). The broad pattern of expression of CSF-1R is consistent with its pleiotropic actions in embryonic development, adult physiology, innate immunity, inflammation, tissue repair, and in the tumor microenvironment (reviewed in Chitu and Stanley 2014).

The CSF-1R Ligands CSF-1 and IL-34

The known ligands for the CSF-1R are CSF-1 and IL-34 (Lin et al. 2008). Both in vitro and when expressed in vivo under the control of the CSF-1 promoter, the biological activities of homodimeric glycoprotein interleukin-34 (IL-34) resemble those of the secreted glycoprotein isoform of CSF-1 (Wei et al. 2010). Although there are significant differences in their signaling through the CSF-1R (Chihara et al. 2010), it is primarily the differential expression of IL-34 and

CSF-1 (Wei et al. 2010; Greter et al. 2012; Nandi et al. 2012; Wang et al. 2012) that results in their differential spatiotemporal regulation through the CSF-1R in vivo (Wei et al. 2010; Nandi et al. 2012). The transmembrane and proteoglycan CSF-1 isoforms act locally (Wiktor-Jedrzejczak et al. 1991; Sundquist et al. 1995; Van Nguyen and Pollard 2002; Dai et al. 2004; Nandi et al. 2006). However, circulating CSF-1 (Stanley 1979; Janowska-Wieczorek et al. 1991) shows humoral regulation (Cecchini et al. 1994; Pollard and Stanley 1996; Dai et al. 2004). In contrast, IL-34 is not detectable in the circulation of healthy individuals (Hwang et al. 2012; Tian et al. 2013) and thus IL-34 actions are likely to be restricted to the local microenvironments in which they are expressed. Through their different spatiotemporal expression, the two ligands play complementary roles in regulating the development, maintenance, and activity of specific macrophage populations, Langerhans cells, neuronal progenitors (Wei et al. 2010; Greter et al. 2012; Nandi et al. 2012; Wang et al. 2012), as well as osteoclasts (Dai et al. 2002) and Paneth cells (Huynh et al. 2009) and the regulation of cells of the female reproductive tract (Wei et al. 2010). Because all of the CSF-1 deficiency phenotypes are also shared with CSF-1R-deficient mice (Dai et al. 2002), the CSF-1R appears to be the only receptor for CSF-1, whereas IL-34 has recently been shown to act via an additional receptor, receptor-type protein tyrosine phosphatase- ζ (PTP- ζ) (Nandi et al. 2013).

THE CSF-1R GENE—EVOLUTION, STRUCTURE, AND REGULATION

CSF-1R Gene Evolution

The ancestral PDGF/VEGF-related RTKIII family expanded substantially during vertebrate evolution by gene and genome duplications (Rousset et al. 1995; Gu and Gu 2003; Leveugle et al. 2004; Braasch et al. 2006). In zebrafish, *kit* and *csf1r* play critical roles in the development of different neural crest-derived pigment cell types—*kit* for melanocytes (Parichy et al. 1999) and *csf1r* for xanthophores (Parichy et al. 2000; Parichy and Turner 2003)—and it

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is likely that the gene duplications were driven by selection for pigment cell innovations important for speciation (Fig. 1B) (Braasch et al. 2006; Salzburger et al. 2006).

CSF-1R Gene Structure and Regulation in Myeloid Cells

The *Csf1r* gene is located on human chromosome 5 (5q32) and in a syntenic region on mouse chromosome 18 (18D) (Le Beau et al. 1986; Hoggan et al. 1988; Bonifer and Hume 2008), juxtaposed head-to-tail as the 3' neighbor of the PDGFR- β gene (Yarden et al. 1986; Roberts et al. 1988). Both *Csf1r* genes have 21 introns and 22 exons (Hampe et al. 1989; reviewed in Sherr 1990). The human intron 1 is ~26 kb and transcription is initiated upstream of exon 1 in trophoblasts and immediately upstream of exon 2 in macrophages (Visvader and Verma 1989; Roberts et al. 1992). Regulation of *Csf1r* expression has been most studied in mouse, in which intron 1 is only 102 bp and trophoblast and macrophage transcripts are, respectively, initiated 500 bp–300 bp and within 300 bp upstream of the start codon in exon 2 (Sasmono et al. 2003). There are two separate promoter regions: the trophoblast/osteoclast (T/OC) promoter that drives expression in trophoblasts and osteoclasts and contains regulatory elements that increase expression during macrophage differentiation (Bonifer and Hume 2008; Ovchinnikov et al. 2010), and the more proximal macrophage *Csf1r* promoter (M) (Fig. 1C). Maximal CSF-1R expression in differentiated monocytes/macrophages requires a highly conserved 330 bp sequence enhancer element located in the 3' end of intron 2, known as Fms-intronic regulatory element (FIRE), which also has reverse promoter activity (Himes et al. 2001; Sasmono et al. 2003; Laslo et al. 2006; Sauter et al. 2013). FIRE encodes an antisense CSF-1R transcript that may contribute to its ability to overcome repression by uncharacterized repressive elements within intron 2 (Bonifer and Hume 2008; Sauter et al. 2013). None of the *Csf1r* promoters has a TATA box, and transcription initiates at multiple sites for each. For macrophage expression, it is hypothesized that two TATA-as-

sociated factors, Ewing sarcoma (EWS) and FUS/TLS, which bind a loose repeat of CAG or CAA immediately adjacent to the dominant start site cluster, substitute for TATA-binding protein (Krysinska et al. 2007; Bonifer and Hume 2008). Transcription factors regulating *Csf1r* expression that bind sites within the T/OC, M, and FIRE regulatory regions are shown in Figure 1C.

CSF-1R expression is low on HSC (Sarrazin et al. 2009), increases by ~10-fold on macrophage progenitors (colony-forming unit-macrophage, CFU-M) and is further increased gradually as CFU-M differentiate (monoblast → promonocyte → monocyte → macrophage) (Fig. 1D) (Tushinski et al. 1982; Bartelmez and Stanley 1985; Bartelmez et al. 1989). Low, HSC-equivalent levels of expression of *Csf1r* mRNA are found on common myeloid (CMP) and common lymphoid (CLP) progenitor cells (Tagoh et al. 2002, 2004). During CMP differentiation to macrophages, up-regulation of the CSF-1R occurs in two stages. The first stage involves transcription factor assembly (PU.1, Runx1, and C/EBP binding) and chromatin remodeling at the macrophage promoter (Walsh et al. 2002; Krysinska et al. 2007). The second stage involves factor assembly and chromatin remodeling at FIRE (Laslo et al. 2006). This two-step mechanism ensures that high levels of CSF-1R are only expressed in the more differentiated cells that respond to CSF-1 alone and not in multipotent cells that express lower levels and require synergistic growth factors, such as IL-3 or SCF (Bartelmez et al. 1989; Williams et al. 1992). In contrast, during B lymphocyte development from CLP, PAX5 acts as a repressor, silencing the *Csf1r* gene by binding directly to a site overlapping the main *Csf1r* transcriptional start sites recognized by EWS and Fus/TLS (Fig. 1D) (Tagoh et al. 2006; Bonifer and Hume 2008).

STRUCTURE OF CSF-1R AND LIGANDS

CSF-1 and IL-34

The CSF-1R is the only RTK activated by two ligands of unrelated sequence, CSF-1 and IL-34. CSF-1 differs from IL-34 in that, owing to alter-

native splicing and differential proteolysis of a longer precursor in the secretory vesicle, it is expressed in three functionally separable isoforms: a secreted glycoprotein, a secreted chondroitin sulfate proteoglycan, and a membrane-spanning, cell-surface glycoprotein (Rettenmier et al. 1987; Price et al. 1992; Suzu et al. 1992; Dai et al. 2004; Nandi et al. 2006). All three isoforms are dimeric and contain the same amino-terminal 150 amino acids of CSF-1 required for biological activity, but have distinct, yet overlapping activities (Dai et al. 2004; Nandi et al. 2006;

Chitu and Stanley 2014) determined by the remaining carboxy-terminal sequence. In contrast, IL-34 is synthesized as a secreted glycoprotein possessing one biologically active isoform of lower activity in which the codon encoding Glu81 has been spliced out (Lin et al. 2008; Wei et al. 2010).

Despite sharing low sequence similarity, the biologically active regions of IL-34 and CSF-1 have similar four helical bundle (cytokine) folds (Fig. 2A). Both are head-to-head dimers, IL-34 noncovalently associated, whereas CSF-1 is

Figure 2. Structure of CSF-1, IL-34, and CSF-1R ligand–receptor complexes. (A) Topological diagrams of monomeric (*left*) and ribbon representations of dimeric CSF-1 (*top*) and IL-34 (*bottom*) (based on data from Pandit et al. 1992; Liu et al. 2012; Ma et al. 2012). Gray lines in topological diagrams represent intramolecular disulfide bridges; dotted gray line in CSF-1 indicates position of the intermolecular disulfide bond. (B) Structure of CSF-1R ectodomain complex with IL-34 and CSF-1 (based on data from Felix et al. 2013). (C) Model of early events in CSF-1R activation (based on data from Verstraete and Savvides 2012). Gold spheres, phosphotyrosines (P), gray spheres, ubiquitination (Ub). Note that phosphorylation of CSF-1R tyrosine residue 559 and intracellular domain ubiquitination are important for full receptor activation and tyrosine phosphorylation.

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linked through interchain disulfide bonds (Pandit et al. 1992; Liu et al. 2012; Ma et al. 2012). The *N*-linked oligosaccharides are critical for the stability of IL-34, but not of CSF-1 (Liu et al. 2012).

CSF-1/CSF-1R AND IL-34/CSF-1R COMPLEX STRUCTURES

Studies of the interaction of ^{125}I -CSF-1 with macrophages, together with cross-linking studies showed the existence of a single class of high-affinity binding sites through which all of the biological effects of CSF-1 were mediated (Guilbert and Stanley 1980, 1986; Morgan and Stanley 1984; Guilbert et al. 1986). Cell-based studies indicated that the unliganded CSF-1R may undergo rapid dimer-monomer transitions (Li and Stanley 1991), that the CSF-1-binding site was contained in CSF-1R domains D1–D3 (Wang et al. 1993), and that D4 was involved in ligand-induced oligomerization (Carlberg and Rohrschneider 1994). Structural studies, using a combination of electron microscopy and small-angle X-ray scattering, provided evidence for CSF-1R predimerization (Elegheert et al. 2011). Binding of CSF-1 to the CSF-1R is exclusively via the D2 and D3 domains, the D4 domains mediating CSF-1R homotypic interactions, via a broad interaction interface, whereas the D1 and D5 domains point away from the complex (Fig. 2B) (Chen et al. 2008; Elegheert et al. 2011; Ma et al. 2012; Felix et al. 2013). D4 shares a dimerization domain sequence fingerprint that has been identified in other closely related RTK III receptors, Kit and PDGFR (Yuzawa et al. 2007; Yang et al. 2008), and the presence of domains D4 and D5 in the CSF-1:CSF-1R_{D1–D5} significantly decreases the K_d of interaction (Chen et al. 2008; Elegheert et al. 2011; Ma et al. 2012) owing to CSF-1R homotypic interactions. However, the K_d for the CSF-1:CSF-1R_{D1–D5} interaction at 37°C (~ 20 nM, human and mouse [Elegheert et al. 2011]) was still higher than the dissociation constants reported for the binding of mouse (0.4 nM [Guilbert and Stanley 1986]) or human (0.1 nM [Roussel et al. 1988]) CSF-1 to their cognate receptors on cells, suggesting a significant contribution

of the transmembrane domain and spatial confinement of the membrane to affinity (Fig. 2C).

Consistent with the cross-competition of CSF-1 and IL-34 for binding to the CSF-1R (Chihara et al. 2010; Wei et al. 2010), both ligands bind to a concave surface formed by the CSF-1R D2 and D3 domains (Fig. 2B) (Chen et al. 2008; Elegheert et al. 2011; Liu et al. 2012; Ma et al. 2012; Felix et al. 2013). Despite their similarities, the IL-34:CSF-1R complex differs from the CSF-1:CSF-1R complex because: (1) there is a $\sim 20^\circ$ rotation difference of their D3 domains when their D2 domains are superimposed, resulting in an elongated pose that differs from the kinked configuration of the CSF-1R:CSF-1 complex; (2) CSF-1 is clamped deeper by the CSF-1R D2–D3 junction than IL-34, so that overlapping, yet different CSF-1R segments are used by each ligand; (3) to compensate for loss of some D2 interactions, IL-34 adopts amino-terminal and carboxy-terminal extensions to contact D3 (Liu et al. 2012; Ma et al. 2012); and (4) the apparent rigidity of the IL-34 structure (Liu et al. 2012; Ma et al. 2012) differs from the more plastic CSF-1 structure, which undergoes local structural rearrangements for receptor binding (Chen et al. 2008).

Studies of mouse IL-34:CSF-1R interactions indicate that the interactions of IL-34 with D2 and D3 are not functionally equivalent. Mutation of individual hydrophilic residues involved in IL-34 interactions with CSF-1R D2 failed to affect IL-34 biological activity, whereas mutations of residues interacting with D3 substantially reduced IL-34 activity suggesting that charge interactions with D2 may capture IL-34 for subsequent interaction with D3 (Liu et al. 2012). Despite the differences between the IL-34:CSF-1R and CSF-1:CSF-1R complexes, the distance between the two D3–D4 junctions important for critical homotypic D4 interactions (Elegheert et al. 2011; Felix et al. 2013) is equivalent (62 Å and 60 Å, respectively) (Ma et al. 2012).

CSF-1R Kinase Structure and Activation

The structure of the inactive human CSF-1R kinase domain is two-lobed, similar to those

of cKIT and FLT3 RTK IIIs (Schubert et al. 2007; Walter et al. 2007). The N lobe comprises a five-stranded, antiparallel β sheet ($\beta 1$ – $\beta 5$) and a single α helix (αC), and is joined to the carboxy-terminal lobe by the kinase insert domain and a hinge region. The C lobe has seven α helices and two β strands. ATP binding, in a deep cleft between the N and C lobes, involves the N lobe and hinge regions, which also provide some catalytic residues. The C lobe mediates substrate binding and catalysis. In its inactive conformation, the CSF-1R kinase domain activation loop (AL) is folded back onto the ATP-binding cleft, with the sole AL tyrosine 809 acting as a pseudosubstrate, blocking substrate binding. Also, Asp-796 of the invariant DFG motif, necessary for Mg^{2+} coordination of ATP, is in a “DFG-out” conformation, owing to its displacement from the active site. The activation of CSF-1R therefore requires flipping of the DFG motif to a “DFG-in” conformation and reorganization of the AL. Interestingly, in other receptor kinases, this can involve phosphorylation of the AL tyrosine, but the data do not support a role for AL tyrosine phosphorylation in the early activation of the CSF-1R (Yu et al. 2012), or of cKIT (DiNitto et al. 2010). In the inactive CSF-1R kinase, the JMD (Q542–K574, between the transmembrane domain and the N lobe), mediates a critical autoinhibitory mechanism by blocking αC , preventing the AL from adopting an active conformation and restricting interlobe plasticity (Walter et al. 2007). Inhibition is relieved by phosphorylation of Tyr-561 (Tyr-559 in mouse). This tyrosine, the first residue to be phosphorylated in response to ligand binding, acts as a switch that is off in the absence of ligand and turned on by phosphorylation in response to ligand (Rohde et al. 2004; Yu et al. 2008; Xiong et al. 2011; Yu et al. 2012). Although the structure of the activated CSF-1R kinase domain has not been reported, the changes that take place on activation can be visualized by superimposing the AL of activated cKIT onto inactive CSF-1R structure (Schubert et al. 2007; Chitu and Stanley 2014). A schematic of ligand-induced CSF-1R activation is shown in Figure 2C.

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Early Events and Role of CSF-1R Tyrosine Phosphorylation

As undifferentiated progenitor cells are rare, CSF-1R signaling has been primarily studied in macrophages (Yu et al. 2008), osteoclasts (Faccio et al. 2007), or in transduced myeloid progenitor cell lines that normally do not express the receptor (Bourette et al. 1995; Csar et al. 2001). The approaches taken have been proteomic (identifying and analyzing the function of proteins tyrosine phosphorylated or activated in the response) (Yeung and Stanley 2003) and genetic (analysis of the effects of CSF-1R mutations) (Yu et al. 2012). CSF-1R signaling in all lineages has recently been reviewed in detail elsewhere (Chitu and Stanley 2014).

Kinetics of Early Responses in Macrophages

Studies of CSF-1-induced changes in mouse macrophages at 4°C and 37°C have permitted early steps in this process to be resolved. Before CSF-1 addition, CSF-1Rs are clustered, or are undergoing a rapid dimer-monomer transition (Li and Stanley 1991). CSF-1 binding initially leads to rapid dimerization, a first wave of tyrosine phosphorylation of the CSF-1R, and formation of CSF-1R complexes with Grb2/Sos and with SFK, Cbl, the regulatory subunit of PI-3 kinase (PI3K) (p85), Grb2, and other signaling molecules, many of which become tyrosine phosphorylated (Baccarini et al. 1991; Li and Stanley 1991; Li et al. 1991; Kanagasundaram et al. 1996; Wang et al. 1996, 1999b; Husson et al. 1997). The tyrosine phosphorylated proteins, representing 0.02% of the total cellular protein, are mainly in the membrane fraction (Yeung et al. 1998). The CSF-1R/Sos/Grb2 complexes are more transient than those involving the CSF-1R, Cbl, Shc, p85, and Grb2 (Wang et al. 1999b). Sos/Grb2 dissociates from the CSF-1R, which undergoes a second wave of ty-

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rosine phosphorylation with serine phosphorylation, which is temporally associated with the Cbl-dependent CSF-1R ubiquitination and Cbl ubiquitination (Baccarini et al. 1991; Li and Stanley 1991; Wang et al. 1996, 1999b; Lee et al. 1999). There follows internalization of the CSF-1/CSF-1R complex, its entry into multivesicular bodies, and thence into the lysosomal system, in which both ligand (Guilbert and Stanley 1986) and receptor (Lee et al. 1999) are degraded. In contrast, the ubiquitinated Cbl ubiquitin ligase is not degraded, but recovered in deubiquitinated form in the cytosol 3–10 min after stimulation (Wang et al. 1996, 1999b; Lee et al. 1999) (reviewed in Yeung and Stanley 2003). Tyrosine phosphorylation and ubiquitination of the cell-surface CSF-1R dimers are stoichiometric (Li and Stanley 1991; Li et al. 1991; Wang et al. 1999b), although ubiquitination may be asymmetric and restricted to only one monomer of the ubiquitinated CSF-1R dimer (Xiong et al. 2011). Signaling may also occur from internalized receptors (Huynh et al. 2012). Many of the proteins in complexes with the rapidly tyrosine phosphorylated cellular proteins are cytoskeletal proteins (Yeung et al. 1998; Yeung and Stanley 2003) and the short-term responses include extensive cytoskeletal remodeling (Boockock et al. 1989; Pixley et al. 2001; Chitu et al. 2005; Sampaio et al. 2011; Pixley 2012). Increased protein synthesis is detected as early as 15 min following CSF-1R stimulation and plateaus at 2 h (Tushinski and Stanley 1983).

Later responses include increased motility and chemotaxis (Pixley et al. 2001; Chitu et al. 2005; Sampaio et al. 2011; Pixley 2012), altered gene expression leading to the entry of cells into S phase at ~12 h (Tushinski and Stanley 1985), during which time cell-surface CSF-1R levels are down-regulated, but cell-surface CSF-1Rs are turning over rapidly and presumably signaling (Guilbert and Stanley 1986; Yu et al. 2012; reviewed in Sherr 1991; Yeung and Stanley 2003). The expression of CD11b (Yu et al. 2008) and of chemokines, cytokines, and cell-surface markers of M2 polarization state, are also increased (Fleetwood et al. 2007; Foucher et al. 2013).

Role of Individual CSF-1R Intracellular Domain Phosphotyrosines in Regulation of Macrophage Functions

The functions of the eight tyrosines known to be phosphorylated in the activated mouse CSF-1R proto-oncoprotein/oncoprotein have been investigated in macrophages by their mutation to phenylalanine (to establish/investigate necessity) or by adding them back to a receptor backbone in which all eight tyrosines are mutated to phenylalanine (to establish/investigate sufficiency) (Fig. 3A). Add-back of AL Tyr-807, JMD Tyr-559, and JMD Tyr-544 is sufficient to restore full in vitro CSF-1R kinase activity (Yu et al. 2012). AL Tyr-807 alone confers constitutive activation of CSF-1R-regulated proliferation. JMD Tyr-559 is the first tyrosine phosphorylated in response to ligand (Yu et al. 2008; Xiong et al. 2011). Tyr-559 keeps CSF-1R kinase “off” in the absence of ligand and its phosphorylation relieves this autoinhibition, so that Tyr-559 controls CSF-1R responsiveness to ligand (Rohde et al. 2004; Takeshita et al. 2007; Yu et al. 2012). JMD Tyr-544, phosphorylated in the oncogenic receptor (Joos et al. 1996), is required for full kinase activation (Yu et al. 2008). Add-back of all three tyrosines fully restores CSF-1-regulated CSF-1R kinase activation, bulk cellular protein tyrosine phosphorylation, and the proliferative response (Yu et al. 2012). Tyr-559 is both necessary and sufficient for the recruitment of SFK that, in turn, associate with and activate c-Cbl. Cbl activation leads to CSF-1R multiubiquitination, conformational changes, increased phosphorylation, and internalization of receptor–ligand complexes (Baccarini et al. 1991; Rohde et al. 2004; Xiong et al. 2011). Tyr-721 is necessary and sufficient on the YEFY544,559,807AB background, for mediating macrophage chemotaxis to CSF-1 through the PI3K pathway (Sampaio et al. 2011). Mutations of KI tyrosines 706 or 721, or carboxy-terminal Tyr-974, alter morphological responses (Yu et al. 2008). AL Tyr-807 is required for multipotent progenitor cell differentiation to macrophages, which KI tyrosines 697, 706, and 721 augment (Rohrschneider et al. 1997), although Tyr-706 negatively regulates expres-

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Figure 3. CSF-1R signaling in macrophage survival and proliferation. (A) Biological functions regulated by individual CSF-1R tyrosine residues. (B) Protein interactions and signaling events triggered by individual CSF-1R phosphotyrosine residues (based on data from Pixley and Stanley 2004). (C) CSF-1R signaling for macrophage survival. (D) Pathways mediating CSF-1R proliferative responses in macrophages. Arrows indicate activation; black line-capped arrows, inhibition; gray line-capped arrows, late-phase inhibition; round-capped arrows, increased expression or concentration; diamond-capped arrows, dissociation; dotted arrows, partial contribution; gold spheres, phosphotyrosines; and silver spheres, serine/threonine phosphorylation. Numbered gold spheres indicate the mouse CSF-1R tyrosine residues required for activation of specific pathways. Those without numbers indicate that the CSF-1R phosphotyrosyl residue triggering the response is not known.

sion of CD11b in macrophages (Yu et al. 2008). Phosphorylation of individual CSF-1R tyrosines creates docking sites for several signaling molecules (Fig. 3B) (reviewed in Pixley and Stanley 2004).

Downstream Signaling Pathways in the Macrophage Lineage

Survival

Low CSF-1 concentrations stimulate macrophage survival that is associated with inhibition

of total protein degradation (Tushinski et al. 1982; Tushinski and Stanley 1983). The PI3K/Akt pathway has a central role in CSF-1-mediated macrophage survival (Fig. 3C) (Kelley et al. 1999; Murray et al. 2000; Golden and Insogna 2004; Chang et al. 2009). In macrophages, Akt can be activated directly through the CSF-1R pTyr721/PI3K pathway (Lee and States 2000; Sampaio et al. 2011) and indirectly by ceramide-1-phosphate (C1P) (Gómez-Muñoz et al. 2004, 2005, 2010; Steinbrecher et al. 2004), or the Gab2/PI3K pathway (Lee and States

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2000; Lee et al. 2011; Yu et al. 2012), which is counterbalanced by a CSF-1R pTyr559/Lyn/SHIP-1 pathway (Baran et al. 2003).

PI3K-independent pathways of CSF-1R-mediated survival involve phospholipase C (PLC) (Xu et al. 1993) and Fms-interacting protein (FIMP) (Mancini et al. 2004). PI3K and PLC independently enhance survival by controlling glucose uptake (Chang et al. 2009). CSF-1R-regulated PKC-dependent serine phosphorylation translocates FIMP from the nucleus, where it inhibits CSF-1R-mediated signaling, to the cytosol, thereby enhancing macrophage survival and differentiation (Fig. 3C) (Mancini et al. 2004).

Proliferation

Macrophage proliferation is associated with a CSF-1 dose-dependent increase in protein synthetic rate (Tushinski and Stanley 1983). CSF-1R pTyr-807 signaling activates both the MEK and PI3K pathways that independently contribute to macrophage proliferation (Munugalavada et al. 2005; Yu et al. 2012). A CSF-1R pTyr-559/SFK-dependent pathway also contributes to macrophage proliferation (Takeshita

et al. 2007; Yu et al. 2012). In addition, CSF-1 increases C1P production and C1P stimulates proliferation through activation of PI3K/Akt, JNK, and ERK1/2 pathways (Fig. 3D) (Gangoiti et al. 2008).

Multiple ERKs may be involved in the control of macrophage proliferation, as their involvement has been inferred by MEK inhibition. ERK5 is activated in a SFK-dependent manner by CSF-1 and is necessary for optimal proliferation (Rovida et al. 2008). ERK1/2 phosphorylation may act as a sensor of CSF-1 concentration (Rovida et al. 2002). Via activation of membrane-associated PKC- ϵ , the CSF-1R mediates increases in the expression of dual specificity phosphatase-1 (DUSP-1) that suppresses prolonged Erk1/2 activation, which would lead to cell-cycle arrest (Valledor et al. 1999). In myeloblasts, increased PKC- ζ activity regulates Erk1/2 activation and proliferation in a developmental stage-specific manner (Lee 2011). Overexpression of PKC- ζ in myeloblasts increased the intensity and duration of Erk1/2 phosphorylation and the proliferative response to CSF-1 (Fig. 4B). In contrast, in macrophages, PKC- ζ activates a negative regulatory step upstream of MEK (Fig. 3D) (Lee 2011).

Figure 4. CSF-1R signaling in macrophage differentiation. (*Top*) Morphology of May-Grünwald-Giemsa-stained macrophage precursors. Gray arrows (*middle panel*) indicate that Gab2 significantly contributes to these pathways in monoblasts, but not in pro-monocytes. Symbols are as described in the legend for Figure 3.

The transmembrane adaptor protein DAP12 mediates CSF-1R proliferative signals through a MAPK- and Akt-independent pathway. The cytoplasmic domain of DAP12 contains immunoreceptor tyrosine-based activation motifs (ITAMs), which become phosphorylated in response to CSF-1R activation, recruiting and activating the cytosolic tyrosine kinase Syk, which activates the Pyk2 tyrosine kinase that phosphorylates β -catenin, triggering its nuclear translocation and activation of cell-cycle genes. The response is enhanced by DAP12-independent CSF-1R inhibition of β -catenin degradation (Otero et al. 2009). DAP12 deficiency leads to impaired CSF-1R-mediated proliferation and survival, but does not affect differentiation (Nataf et al. 2005; Otero et al. 2009).

Proline serine threonine phosphatase interacting protein 2 (PSTPIP2) is a membrane-cytoskeletal adaptor highly expressed in myeloid cells (Chitu and Stanley 2007, 2009). PSTPIP2 deficiency increases Erk1/2 phosphorylation and CSF-1-induced myeloid precursor proliferation, whereas overexpression in macrophages inhibits Erk1/2 phosphorylation and growth (Chitu et al. 2009). PSTPIP2 interacts with PEST-family tyrosine phosphatases PTPN12 (Chitu et al. 2012) and PTPN18 (Wu et al. 1998) and, as suggested by studies with PSTPIP1 (Yang and Reinherz 2006), it is possible that PSTPIP2 acts by recruiting PTP-PEST to signaling complexes upstream of Erk1/2 (Fig. 3D).

Differentiation

CSF-1R activation directly induces monocytic cell fate in HSCs through up-regulation of the myeloid transcription factor PU.1 (Mossadegh-Keller et al. 2013). It also instructs granulocyte/macrophage progenitors (GMP) to differentiate into macrophages (Rieger et al. 2009).

Studies with multipotent precursor cell lines (Fig. 4A) indicate that CSF-1R Tyr-807 and Tyr-721 promote macrophage differentiation via the PLC- γ 2 pathway (Bourette et al. 1997). Tyr-807 is also required for the tyrosine phosphorylation of p46/52 Shc (Csar et al. 2001) and the tyrosine phosphorylation, activa-

tion, and membrane translocation of PKC- δ leading to increased expression of PKA-related protein kinase (Pkare), all of which contribute to monocytic differentiation (Junttila et al. 2003).

The Erk1/2 pathway has a central role in CSF-1R-regulated myeloid differentiation. CSF-1 induces early (peaking at ~ 5 min) and persistent (starting at 1 h) waves of MEK/Erk1/2 phosphorylation. However, only the late wave, which is independent of Grb2/Sos assembly or PI 3-kinase activity, is required for macrophage differentiation (Gobert Gosse et al. 2005). Mona, an adaptor protein that increases late Erk1/2 phosphorylation (Bourgin et al. 2002) and Gab3 are coinduced during monocytic differentiation in a CSF-1R Tyr-807-dependent manner (Fig. 4A). Mona interacts with Gab3 and with the CSF-1R pTyr-697 site. This site is also important for Gab3 tyrosine phosphorylation, induction of Mona expression, and macrophage differentiation (Bourgin et al. 2002). Gab proteins interact with Shp2 and mediate Erk1/2 activation downstream from growth factor receptors (Nishida et al. 1999; Meng et al. 2005; Lee et al. 2011). The Gab3/Mona complex, but not Mona alone, enhances macrophage differentiation in cell cultures (Bourgin et al. 2000; Wolf et al. 2002). However, as macrophage development is normal in Gab3-deficient mice (Seiffert et al. 2003) it appears that CSF-1R/Mona/Gab3/Erk1/2 pathway is not essential for steady-state macrophage development in vivo.

CSF-1R also induces the expression/activation of several other regulators of multipotent progenitor proliferation/differentiation (Fig. 4A). These include DUSP5, a negative-feedback regulator of Erk1/2, which inhibits macrophage differentiation and favors granulocytic differentiation (Grasset et al. 2010), interferon-inducible gene 204 (Ifi204), which suppresses proliferation and favors differentiation (Dauffy et al. 2006), and the adaptor proteins suppressor of cytokine signaling 1 (Socs1) and SKAP55-related (SKAP55R). Socs1 associates with CSF-1R pTyr-697 and pTyr721 binding sites to inhibit proliferation by an unknown mechanism (Bourette et al. 2001). CSF-1 induces SKAP55R

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tyrosine phosphorylation and actin association. SKAP55R overexpression decreases CSF-1R-induced proliferation, but does not affect differentiation (Bourette et al. 2005).

Studies with myeloblasts/monoblasts/promonocytes (Fig. 4B) confirm the central role of the Erk1/2 pathway in CSF-1-induced differentiation (Wilson et al. 2005). In myeloblasts, a CSF-1R pTyr-559/SFK pathway initiates the activation of STAT3 (Marks et al. 1999) and Erk1/2 and the inactivation of PP2A, which plays a significant role in enhancing Erk1/2-mediated macrophage differentiation (McMahon et al. 2001). In multipotent cells, via a SFK-independent pathway, Gab2 becomes tyrosine phosphorylated, associating with signaling molecules, including Grb2, Shp2, and p85, to activate Erk1/2 and differentiation (Liu et al. 2001). T-cell protein-tyrosine phosphatase (Tcptp) dephosphorylates the activated CSF-1R, negatively regulating differentiation by suppressing both CSF-1R association with the Grb2/Gab2/Shp2 complex and activation of Erk1/2 (Simoncic et al. 2006). Gab2 deficiency in mice leads to a decreased frequency and proliferation of CFU-M, which retain the capacity to differentiate to macrophages (Lee et al. 2011). Studies with Gab2 mutants unable to interact with Shp2 or PI3K show that both interactions are required for restoration of CFU-M frequency and proliferation. As constitutively active Akt only rescues CFU-M size, but not frequency, the Gab2/PI3K/Akt axis predominantly promotes the proliferation of committed macrophage progenitors. Gab2 is required for Akt activation only in monoblasts and regulates Erk1/2 activity in a developmental stage-specific manner, increasing activation in monoblasts and promonocytes and decreasing activation in macrophages (Lee et al. 2011).

In primary human monocytes (Fig. 4C), CSF-1 triggers a cyclic activation of the PI3K and Erk1/2 pathways that is correlated with successive rounds of CSF-1R Tyr-723 phosphorylation and dephosphorylation. Successive waves of Akt activation, increasing in amplitude and duration, are required for caspase activation, which, via cleavage of nucleophosmin, enhances macrophage differentiation (Jacquel et al.

2009) toward a trophic, M2-like phenotype (Guery et al. 2011). Erk1/2 was activated with coordinated kinetics, but was not essential for nucleophosmin cleavage, and its role remains to be defined. In contrast, the SFKs, Hck, and, to a lesser extent, Lyn, but not Fyn or Src, mediated nucleophosmin cleavage downstream from CSF-1R (Jacquel et al. 2009).

Chemotaxis

CSF-1 triggers a rapid membrane ruffling response followed by cell spreading and polarization (Boockock et al. 1989; Webb et al. 1996; Chitu et al. 2005), processes involving a dynamic reorganization of the actin cytoskeleton (reviewed in Park et al. 2011; Pixley 2012) and focal adhesions (Fig. 5) (Pixley et al. 2001; Sampaio et al. 2011). CSF-1 stimulates a biphasic actin polymerization response that initially peaks at 30 sec of stimulation and is followed by a longer-lasting wave, peaking at 5–6 min (Sampaio et al. 2011; Ishihara et al. 2012). The small GTPases, Cdc42, Rac, and Rho and their downstream effectors, Wiskott-Aldrich syndrome protein (WASP) and WASP-family verprolin homologous 2 (WAVE 2) actin nucleators, regulate actin polymerization and CSF-1R-induced chemotaxis (Kheir et al. 2005; Ridley 2008; Cammer et al. 2009; Dovas et al. 2009; Ishihara et al. 2012).

The first wave of actin polymerization is initiated by the Cdc42- and CSF-1R pTyr-721/PI3K p110 δ -dependent activation of WASP (Papakonstanti et al. 2008; Cammer et al. 2009; Sampaio et al. 2011; Mouchemore et al. 2013). CSF-1R also induces SFK-dependent tyrosine phosphorylation of WASP Tyr-291, which, although not necessary for WASP activation (Cammer et al. 2009), is necessary for macrophage chemotaxis to CSF-1 (Dovas et al. 2009). PSTPIP2 is tyrosine phosphorylated within 30 sec and inhibits actin polymerization and the ruffling response (Chitu et al. 2005). By competing with other F-BAR family proteins for phosphatidylinositol 4,5-bisphosphate (PIP2)-rich membrane-binding sites and recruiting PTPN12 to those sites, PSTPIP2 may mediate the local dephosphorylation and par-

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Figure 5. CSF-1R signaling in macrophage migration and chemotaxis. (*Top panels*) Scanning electron microscopic images of macrophages stimulated with CSF-1 for the indicated times. The dotted gray arrow indicates a hypothetical mechanism. Symbols are as described in the legend for Figure 3.

tial inactivation of WASP (Cote et al. 2002; Tsujita et al. 2013).

The second wave of actin polymerization leading to membrane ruffling involves Rac1/IRSp53 activation of the WAVE2/Abi complex (Kheir et al. 2005; Abou-Kheir et al. 2008) and is pTyr-721/PI3K independent (Sampaio et al. 2011). CSF-1R-regulated membrane ruffling also requires PLD2 lipase and Rac2 GEF activities (Mahankali et al. 2011a,b). Rac2 initially increases, but subsequently inhibits PLD2 activity, by preventing PLD interaction with PIP2 at the plasma membrane, thus leading to cell immobilization (Peng et al. 2011). Although the above studies in macrophage cell lines indicate that Rac1 and Rac2 are required for chemotaxis (Allen et al. 1998; Abou-Kheir et al. 2008), the findings are in conflict with those in primary macrophages, in which absence of Rac1, Rac2, or both, did not affect CSF-1-induced chemotaxis (Wells et al. 2004; Wheeler et al. 2006). An

additional conflict relates to the mechanism of Rac1 activation by CSF-1R. Although studies in SHIP^{-/-} macrophages implicate Vav proteins (Vedham et al. 2005), studies in single or triple-deficient Vav1/2/3^{-/-} primary macrophages indicate that they are not required (Wells et al. 2005; Bhavsar et al. 2009). In contrast, the PI3K/Akt pathway plays a central role in CSF-1R-induced chemotaxis (Sampaio et al. 2011), via phosphorylation of PKC- ζ and LIMK/Co-filin (Zhang et al. 2009). Two adaptor proteins, Lnk and STAP-2, suppress Akt activation and inhibit CSF-1-induced macrophage migration (Ikeda et al. 2007; Gueller et al. 2010). The CSF-1R pTyr-721/PI3K pathway also regulates cell adhesion by controlling paxillin phosphorylation (Owen et al. 2007; Sampaio et al. 2011) and PTP- ϕ expression (Pixley et al. 2001; Sampaio et al. 2011).

During cell migration, the formation of adhesion structures is locally disrupted by inhibi-

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tory proteins (e.g., PTP- ϕ), and actomyosin-dependent contractility is necessary for retracting the trailing edge. S100A4 is a Ca^{2+} and myosin IIA-binding protein that inhibits actomyosin assembly downstream from the CSF-1R (Li et al. 2003, 2010). S100A4 deficiency leads to a defective CSF-1 chemotactic response, owing to reduced persistence and size of membrane protrusions associated with persistent and enhanced actomyosin-IIA assembly and hyperphosphorylation and mislocalization of paxillin (Li et al. 2010). The small GTPase Rho is required for CSF-1-mediated macrophage chemotaxis (Jones et al. 1998) and promotes tail retraction by controlling myosin activity (Hanley et al. 2010). In macrophages stimulated with CSF-1, Rho undergoes cycles of activation and deactivation. Although the mechanism of activation is unclear, RhoA deactivation is mediated by the CSF-1R/PI3K p110 δ /p190RhoGAP axis (Papakonstanti et al. 2007).

PERSPECTIVE

CSF-1R signaling promotes myeloid differentiation, monocytic commitment, and the survival, proliferation, and chemotaxis of macrophages by regulating the tyrosine phosphorylation, activation, or expression of multiple proteins. Several of these proteins (e.g., Gab2, PKC- ζ) regulate downstream signaling pathways in a developmental stage-specific manner. Some conflicting results, in primary macrophages compared with macrophage cell lines, may result from the utilization of different effector isoforms by the activated CSF-1R (Papakonstanti et al. 2007). Thus caution should be taken in extrapolating results to different developmental stages, or types of macrophages. The existence of a new CSF-1R ligand, IL-34, that also interacts with PTP- ζ , which is coexpressed with the CSF-1R in several cell types, including HSC (Sarrazin et al. 2009; Himburg et al. 2012) and neural progenitors (von Holst et al. 2006; Nandi et al. 2013), may provide additional mechanisms for fine-tuning CSF-1R signaling in development, immunity, and disease. The discovery that Epstein–Barr virus encodes BamHI-A rightward frame-1 (BARF1), a secret-

ed hexameric protein that binds the CSF-1 dimer interface with picomolar affinity and conformationally renders the cytokine unable to interact with the CSF-1R (Strockbine et al. 1998; Elegheert et al. 2012; Shim et al. 2012), explains how Epstein–Barr virus eludes the immune response and offers a starting point for therapeutic targeting of both CSF-1 and BARF1.

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