## Phylogeny

CSF1R is a member of the tyrosine kinase (TK) group, specifically within the platelet-derived growth factor receptor (PDGFR) / type III receptor tyrosine kinase family that also comprises c-Kit, Flt-3, PDGFRα and PDGFRβ (Achkova & Maher, 2016; Hume & MacDonald, 2012). The protein is highly conserved between human and mouse, and its expression is driven by the functionally conserved Fms-intronic regulatory element (FIRE) across amniotes (Mun et al., 2020; Rojo et al., 2017). Receptor–ligand pairs have co-evolved but retain cross-species conservation extending to birds and fishes (Rojo et al., 2017).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine phosphate (Achkova & Maher, 2016; El-Gamal et al., 2013; Rojo et al., 2017).

## Cofactor Requirements

Catalytic activity requires divalent metal ions, Mg²⁺ and/or Mn²⁺, which coordinate ATP in the active site (Achkova & Maher, 2016; El-Gamal et al., 2013; Mun et al., 2020).

## Substrate Specificity

No experimentally defined peptide or protein substrate motif is provided in the cited sources.

## Structure

CSF1R is an integral membrane glycoprotein consisting of:  
• Extracellular domain with five Ig-like subdomains (D1–D5); D1–D3 mediate ligand binding, D4–D5 stabilize the complex (El-Gamal et al., 2013; Rojo et al., 2017).  
• Single-pass transmembrane helix.  
• Cytoplasmic region comprising a juxtamembrane domain (residues 538–581), a split kinase domain interrupted by a kinase insert (residues 680–751) and a C-terminal tail (El-Gamal et al., 2013; Mun et al., 2020).

The kinase domain adopts the canonical two-lobe architecture joined by a hinge (El-Gamal et al., 2013). Crystal structures include the autoinhibited kinase domain (PDB 2OGV) and macrophage colony-stimulating factor bound to the receptor (PDB 3EJJ) (Rojo et al., 2017). The activation loop (residues 796–825) starts with the conserved DFG motif that toggles between DFG-in and DFG-out states; in the inactive conformation, the juxtamembrane segment occupies the ATP pocket to lock the activation loop (El-Gamal et al., 2013).

## Regulation

Ligand binding (CSF-1 or IL-34) induces receptor dimerization, conformational change in the juxtamembrane domain, and trans-autophosphorylation (Achkova & Maher, 2016; Mun et al., 2020). Key autophosphorylation sites include Y544, Y559 (UniProt Y561), Y697, Y706, Y721 (UniProt Y723), Y807 and Y974 (Achkova & Maher, 2016; Rojo et al., 2017).  
• Y561 phosphorylation recruits Src family kinases and the E3 ligase c-Cbl.  
• Y723 creates a PI3K docking site; Y697 links to MAPK signalling.  
• Y807 within the activation loop is essential for full catalytic activation (El-Gamal et al., 2013).

Negative regulation is mediated by c-Cbl-dependent multi-ubiquitination, promoting internalization and degradation (El-Gamal et al., 2013; Mun et al., 2020).

## Function

Expression: predominantly on myeloid-lineage cells—monocytes, macrophages, dendritic cells, microglia, osteoclasts, Langerhans cells (El-Gamal et al., 2013; Mun et al., 2020).  
Ligands: CSF-1 and IL-34 (Achkova & Maher, 2016).  
Downstream partners: Src family kinases, PI3K-p85, PLCγ2, Grb2, Shc, Sos1 (Achkova & Maher, 2016; Rojo et al., 2017).  
Pathways: PI3K/Akt, ERK1/2, Raf, MAPK cascades.

Physiological roles include survival, proliferation, differentiation and motility of mononuclear phagocytes; regulation of osteoclast development and normal bone homeostasis (Achkova & Maher, 2016; Mun et al., 2020). In cancer, CSF1R signalling supports tumour cell survival/invasion and conditions an immunosuppressive tumour microenvironment via tumour-associated macrophages (Achkova & Maher, 2016; El-Gamal et al., 2013).

## Inhibitors

Therapeutic agents encompass monoclonal antibodies and small-molecule kinase inhibitors such as pexidartinib (PLX3397; FDA-approved), GW2580, imatinib, dasatinib, sunitinib, Ki20227, linifanib, axitinib and CEP-701 (El-Gamal et al., 2013; Mashkani et al., 2010; Ries et al., 2015).

## Other Comments

CSF1R is encoded by the c-fms proto-oncogene. Over-activation of the CSF-1/CSF1R axis is documented in breast, prostate, ovarian, colorectal cancer and classical Hodgkin lymphoma, generally correlating with poor prognosis (Achkova & Maher, 2016). The pathway is also implicated in rheumatoid arthritis, Crohn’s disease and bone osteolysis (El-Gamal et al., 2013).  
Human disease mutations: monoallelic variants cause adult-onset leuko­dystrophy with axonal spheroids and pigmented glia; biallelic variants produce skeletal disorders such as osteosclerosis (Mun et al., 2020). Loss-of-function in animal models leads to osteopetrosis, macrophage deficiency, growth retardation and infertility (Hume & MacDonald, 2012).

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