## Phylogeny

CSF1R is classified in the tyrosine kinase (TK) group and is a member of the platelet-derived growth factor receptor (PDGFR) family, as established by Manning et al., 2002 (achkova2016roleofthe pages 5-6, el‐gamal2013fmskinaseinhibitors pages 1-3, el‐gamal2013fmskinaseinhibitors pages 23-26, mun2020themcsfreceptor pages 2-3, rojo2017transcriptionalmechanismsthat pages 15-16, ross2006m‐csfc‐fmsand pages 7-7). It also belongs to the type III receptor tyrosine kinase family, which includes c-kit, Flt-3, PDGFRα, and PDGFRβ (achkova2016roleofthe pages 1-3, hume2012therapeuticapplicationsof pages 1-2). The CSF1R protein is highly conserved between humans and mice, and its expression is controlled by the Fms-intronic regulatory element (FIRE), which is functionally conserved across amniotes (mun2020themcsfreceptor pages 2-3, rojo2017transcriptionalmechanismsthat pages 1-2). Receptor–ligand interactions have evolved independently, with conservation across species including birds and fishes (rojo2017transcriptionalmechanismsthat pages 2-3).

## Reaction Catalyzed

ATP + a [protein]-L-tyrosine = ADP + a [protein]-L-tyrosine phosphate (achkova2016roleofthe pages 5-6, el‐gamal2013fmskinaseinhibitors pages 23-26, rojo2017transcriptionalmechanismsthat pages 15-16).

## Cofactor Requirements

The kinase activity of CSF1R requires divalent metal cations, specifically Mg²⁺ and/or Mn²⁺, as essential cofactors to coordinate ATP in the active site and facilitate phosphate transfer (achkova2016roleofthe pages 1-3, achkova2016roleofthe pages 5-6, el‐gamal2013fmskinaseinhibitors pages 1-3, mun2020themcsfreceptor pages 2-3, rojo2017transcriptionalmechanismsthat pages 15-16). ATP acts as the phosphate donor substrate and is not considered a cofactor (achkova2016roleofthe pages 5-6, el‐gamal2013fmskinaseinhibitors pages 1-3, rojo2017transcriptionalmechanismsthat pages 15-16).

## Substrate Specificity

I cannot answer.

## Structure

CSF1R is an integral transmembrane glycoprotein composed of an extracellular domain (ECD), a single transmembrane helix, and an intracellular cytoplasmic domain (achkova2016roleofthe pages 1-3, mun2020themcsfreceptor pages 2-3). The ECD contains five immunoglobulin (Ig)-like domains (D1-D5); domains D1-D3 mediate ligand recognition, while D4-D5 stabilize the ligand-receptor complex (el‐gamal2013fmskinaseinhibitors pages 1-3, rojo2017transcriptionalmechanismsthat pages 2-3). The intracellular region contains a juxtamembrane domain (JMD, residues 538–581), a split tyrosine kinase domain separated by a kinase insert domain (KID, residues 680-751), and a carboxyterminal tail (el‐gamal2013fmskinaseinhibitors pages 10-12, mun2020themcsfreceptor pages 2-3, rojo2017transcriptionalmechanismsthat pages 2-3).

The kinase domain has a two-lobe structure connected by a hinge region (el‐gamal2013fmskinaseinhibitors pages 7-10). The 2.7 Å crystal structure of the autoinhibited human c-Fms kinase domain has been resolved (PDB ID: 2OGV), as has the structure of macrophage colony stimulating factor bound to Fms (PDB ID: 3EJJ) (rojo2017transcriptionalmechanismsthat pages 15-16). Key regulatory features include the activation loop (residues 796–825), which starts with a conserved DFG motif (Asp796-Phe797-Gly798) and switches between active (DFG-in) and inactive (DFG-out) conformations (el‐gamal2013fmskinaseinhibitors pages 7-10, el‐gamal2013fmskinaseinhibitors pages 10-12). In the inactive state, the JMD has an autoinhibitory role, binding near the ATP-binding pocket and locking the activation loop in an inactive conformation (el‐gamal2013fmskinaseinhibitors pages 10-12).

## Regulation

CSF1R activation is initiated by binding of its ligands, CSF-1 or IL-34, which induces receptor dimerization and autophosphorylation on multiple tyrosine residues (achkova2016roleofthe pages 1-3, hume2012therapeuticapplicationsof pages 1-2). In its inactive state, the receptor is an autoinhibited monomer; ligand binding causes a conformational shift in the juxtamembrane domain (JMD) that relieves this autoinhibition (mun2020themcsfreceptor pages 2-3, rojo2017transcriptionalmechanismsthat pages 2-3).

Autophosphorylation is a key regulatory mechanism, creating docking sites for SH2 domain-containing proteins (el‐gamal2013fmskinaseinhibitors pages 1-3). Key autophosphorylation sites include Y544, Y559 (Y561 in UniProt numbering), Y697, Y706, Y721 (Y723 in UniProt numbering), Y807, and Y974 (achkova2016roleofthe pages 6-6, mun2020themcsfreceptor pages 3-5, rojo2017transcriptionalmechanismsthat pages 2-3). Phosphorylation of Y561 (mouse Tyr559) in the JMD is essential for full activation and recruits Src family kinases and the E3 ubiquitin ligase c-Cbl (rojo2017transcriptionalmechanismsthat pages 2-3). Phosphorylation of Y723 (corresponding to mouse Tyr721) is critical for binding of PI 3’-kinase SH2 domains, initiating PI3K/Akt signaling, while Y697 phosphorylation activates the MAPK pathway (achkova2016roleofthe pages 6-6, rojo2017transcriptionalmechanismsthat pages 2-3). Phosphorylation of Tyr807 in the activation loop is critical for kinase activation (el‐gamal2013fmskinaseinhibitors pages 10-12).

Negative regulation occurs via multiubiquitination mediated by c-Cbl, which targets the receptor for internalization and degradation, thereby attenuating the signal (el‐gamal2013fmskinaseinhibitors pages 1-3, mun2020themcsfreceptor pages 3-5, rojo2017transcriptionalmechanismsthat pages 2-3).

## Function

CSF1R is primarily expressed on cells of the myeloid lineage, including monocytes, macrophages, dendritic cells, microglia, osteoclasts, and Langerhans cells (el‐gamal2013fmskinaseinhibitors pages 1-3, mun2020themcsfreceptor pages 1-2). Its ligands are CSF-1 and IL-34 (achkova2016roleofthe pages 1-3). Upon activation, CSF1R recruits signaling partners including Src family kinases, the p85 subunit of PI3K, PLCγ2, Grb2, Shc, and Sos1 (achkova2016roleofthe pages 1-3, rojo2017transcriptionalmechanismsthat pages 15-16). This initiates downstream signaling cascades including the PI3K/Akt, ERK1/2, Raf, and MAP kinase pathways (achkova2016roleofthe pages 1-3).

CSF1R signaling is essential for the survival, proliferation, differentiation, and motility of mononuclear phagocytes (achkova2016roleofthe pages 1-3, mun2020themcsfreceptor pages 1-2). It is a key regulator of osteoclast proliferation and differentiation and is required for normal bone development (mun2020themcsfreceptor pages 1-2). In cancer, CSF1R signaling promotes tumor cell survival and invasion, and it shapes an immunosuppressive tumor microenvironment by recruiting and reprogramming tumor-associated macrophages (TAMs) (achkova2016roleofthe pages 1-3, el‐gamal2013fmskinaseinhibitors pages 1-3).

## Inhibitors

Inhibitors targeting CSF1R include monoclonal antibodies and small-molecule tyrosine kinase inhibitors (hume2012therapeuticapplicationsof pages 1-2, ries2015csf1csf1rtargetingagents pages 2-3). Small-molecule inhibitors include pexidartinib (PLX3397), which is FDA-approved for tenosynovial giant cell tumors, as well as GW2580, imatinib, dasatinib, sunitinib, Ki20227, linifanib, axitinib, and CEP-701 (el‐gamal2013fmskinaseinhibitors pages 23-26, mashkani2010colonystimulatingfactor1 pages 7-8, unknownauthors2023challengesandprospects pages 1-2).

## Other Comments

CSF1R is encoded by the c-fms proto-oncogene (achkova2016roleofthe pages 1-3). Overexpression and dysregulation of the CSF-1/CSF1R axis are documented in cancers including breast, prostate, ovarian, colorectal, and classical Hodgkin’s lymphoma, where it often correlates with poor prognosis (achkova2016roleofthe pages 1-3, unknownauthors2023challengesandprospects pages 1-2). The pathway is also implicated in inflammatory diseases such as rheumatoid arthritis and Crohn’s disease, and in bone osteolysis (el‐gamal2013fmskinaseinhibitors pages 1-3).

Mutations in CSF1R are linked to distinct human diseases. Monoallelic mutations cause adult-onset leukodystrophy with axonal spheroids and pigmented glia (ALSP), whereas biallelic mutations lead to skeletal disorders like osteosclerosis (mun2020themcsfreceptor pages 1-2). Loss-of-function mutations in animal models cause osteopetrosis, severe deficiencies in macrophage populations, growth retardation, and infertility (hume2012therapeuticapplicationsof pages 1-2).

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