Biomedicine & Pharmacotherapy 103 (2018) 662–679

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Recent advances in colony stimulating factor-1 receptor/c-FMS as an emerging target for various therapeutic implications

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ARTICLE INFO

Keywords:
CSF-1R/c-FMS
CSF-1
IL-34
CSF-1R inhibitors
Inflammatory disorders
Cancer
Clinical c-FMS inhibitors

ABSTRACT

Colony stimulating factor-1 (CSF-1) is one of the most common proinflammatory cytokine responsible for various inflammatory disorders. It has a remarkable role in the development and progression of osteoarthritis, cancer and other autoimmune disease conditions. The CSF-1 acts by binding to the receptor, called colony stimulating factor-1 receptor (CSF-1R) also known as c-FMS resulting in the cascade of signalling pathway causing cell proliferation and differentiation. Interleukin-34 (IL-34), recently identified as another ligand for CSF-IR, is a cytokine protein. Both, CSF-1 and IL-34, although two distinct cytokines, follow the similar signalling pathway on binding to the same receptor, CSF-1R. Like CSF-1, IL-34 promotes the differentiation and survival of monocyte, macrophages and osteoclasts. This CSF-1R/c-FMS is over expressed in many cancers and on tumour associated macrophages, consequently, have been exploited as a drug target for promising treatment for cancer and inflammatory diseases. Some CSF-1R/c-FMS inhibitors such as ABT-869, Imatinib, AG013736, JNJ-40346527, PLX3397, DCC-3014 and Ki20227 have been successfully used in these disease conditions. Many c-FMS inhibitors have been the candidates of clinical trials, but suffer from some side effects like cardiotoxicity, vomiting, swollen eyes, diarrhoea, etc. If selectivity of cFMS inhibition is achieved successfully, side effects can be overruled and this approach may become a novel therapy for treatment of various therapeutic interventions. Thus, successful targeting of c-FMS may result in multifunctional therapy. With this background of information, the present review focuses on the recent developments in the area of CSF-1R/c-FMS inhibitors with emphasis on crystal structure, mechanism of action and various therapeutic implications in which c-FMS plays a pivotal role. The review on structure activity relationship of various compounds acting as the inhibitors of c-FMS which gives the selection criteria for the development of novel molecules is also being presented.

1. Introduction

Various researches have been made in the field of the treatment of cancer and inflammatory diseases. Different mechanisms are involved in the progression of cellular damage that gives an idea about new drug targets. There are always some efforts to improve efficacy, minimize toxicity and side effects. One well known target is pro-inflammatory cytokine: colony stimulating factor-1 (CSF-1). It comes under the category of colony stimulating factors. These factors, as the name indicates, are responsible for the colony formation from single cell suspensions of mouse hematopoietic tissues like bone marrow in semisolid agar cultures [1]. Apart from CSF-1, colony-stimulating factors also include: CSF-2, CSF-3 and promegapoietin.

Colony-stimulating factor-1 (CSF-1), also called macrophage colony stimulating factor (MCSF), interact with transmembrane receptor, colony-stimulating factor-1 receptor (CSF-1R; c-FMS) leads to the differentiation and proliferation of cells of monocyte/macrophage lineage. c-FMS, along with FLT-3, PDGFR and KIT, listed under the category of receptor tyrosine kinase type III. Interleukin 34 (IL-34), recently recognized as another ligand for CSF-1R, is a cytokines identified as a protein present in various species. The percentage identitiy of human IL-34 varies in different species i.e. 99.6% with chimpanzee, 72% with rat and 71% with mouse [2]. Both, CSF-1 and IL-34 share same receptor and have the same role as that of CSF-1 i.e. differentiation, proliferation and survival of mononuclear phagocyte lineage cells such as monocyte, macrophages and osteoclasts [3]. As compared to CSF-1, IL-34 causes more stronger and rapid phosphorylation of CSF-1R [4].

On the cellular level, a better understanding can be obtained from

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https://doi.org/10.1016/j.biopha.2018.04.046
Received 4 February 2018; Received in revised form 6 April 2018; Accepted 6 April 2018

2.7 Å resolution crystal structures of cFMS. The active and inactive state of a protein tyrosine kinase is regulated by an initial phosphorylation event occurring on conserved tyrosine residue located within the cytoplasmic domain [5]. IL-34 and CSF-1 set up similar extracellular assemblies with CSF-1R for its activation at the cleft between D2 and D3. However, IL-34 binds to CSF-1R more tightly at D1-D2 domains as compared to CSF-1 [6]. N-glycosylated secreted proteins are same but ribbon representations of the cytokine structure of cytokines are different in both cases [6,7]

Tumour associated macrophages (TAM) are involved in tumour progression. Macrophage-colony stimulating factor (CSF-1) signalling through its receptor, CSF-1R promotes the differentiation of myeloid progenitors in heterogenous populations of monocytes, macrophages, dendritic cells and bone resorbing osteoclasts involved in cancer, infectious and chronic inflammatory disease. Overproduction of macrophages in synovial fluid of joints causes osteoarthritis and inhibition of this pathway leads to the reduction in the level of TAM [8]. The discovery of the progenitors of inflammation has sparked a great deal of interest in the field of drug discovery. In addition, macrophage numbers present within target tissues have been strongly correlated with disease severity in cancer and chronic inflammatory disease. Inhibition of c-FMS signalling leads to a reduction in the level of TAM and helps in treatment of various disease conditions associated with macrophages and monocytes, e.g., breast cancer [9], rheumatoid arthritis [10], immune nephritis [11], bone osteolysis [12], atherosclerosis [13], Crohn's disease [14], and renal allograft rejection [15] etc.

Large data are reported in literature about the inhibitors including 3, 4, 6-substituted 2-quinolones, 2-(α-methylbenzylamino) pyrazines, arylamide, anilinoquinolines, pyrido [2,3-d]pyrimidin-5-one, 4-arylamido 3-methyl isoxazole, pyrazolylamine, bisamides, benzothiazole [16]. According to the data of 2017, various CSF-1R inhibitors are in clinical trial include: Pexidartinib, PLX7486, ARRY-382, JNJ 40346527, BLZ945, Emactuzumab, AMG820, IMC-CS4, MCS110 etc. [17]. Recently rational recombination therapies are developed involving the fusion of CSF-1R inhibitors and chemotherapies, irradiation, anti-angiogenic therapy, cancer immunotherapy using an immunodeficient mouse model. The CSF-1 receptor is successful in regulating various substrates, its inhibition will lead to inhibition of various disease conditions such as rheumatoid arthritis, immune nephritis and breast cancer. It may be one approach for multitargeting. There are functional similarities between IL-34 and CSF-1 but different signalling patterns. IL-34 found to be master regulator of various diseases such as autoimmune disease, infections, inflammation and cancer [18]. Both, CSF and IL-34 binds to the extracellular segment of CSF-1R, eliciting dimerization and intracellular autophosphorylation of CSF-1R and thereby, initiating intracellular signalling. They regulate the migration, proliferation, function and survival of macrophages linked with a wide range of pathologies including cancer, inflammation, autoimmune and infectious diseases. At the cellular level, the signal transduction through CSF-1/c-FMS needed to be strictly controlled because any modification will leads to various disease conditions as shown in Fig. 1.

2. Crystal structure of c-FMS and binding pattern of CSF-1 and IL-34

c-FMS is a 972 amino acids polypeptides containing transmembrane glycoprotein [19]. It contains all the necessary domains required for tyrosine kinase activity, i.e. 512 amino acid N-terminal extracellular segment, hydrophobic 25 amino acid membrane spanning region, a 435 amino acid intracellular domain. Various protein tyrosine kinases contain 60–100 residues with different sequence [20]. The overall structure of c-FMS-PTK, c-KIT [21] and FLT-3 [22] closely resemble with each other i.e a typical bi-lobal PTK folds and JM (Juxtamembrane domain) domain PTK domain contains two lobes: N and C-terminal lobe. The N-terminal lobe of cFMS-PTK contains- five stranded antiparallel β-sheet (β1-β5) and a single α-helix. C-terminal lobe containsseven α-helices (αD, αE, αEF, αF-αI) and two β strands (β6 and β7) and activation loop located between β7 and αEF (residues 796–825). (Fig. 2.1 A) [23].

Its auto-inhibited structure contain N-terminus packed between residues of the glycine-rich loop, the activation loop and the αC helix. Both its N and C termini wrapping around the αC helix and the JM domain adopts a twisted hairpin conformation (Fig. 2.1B). The

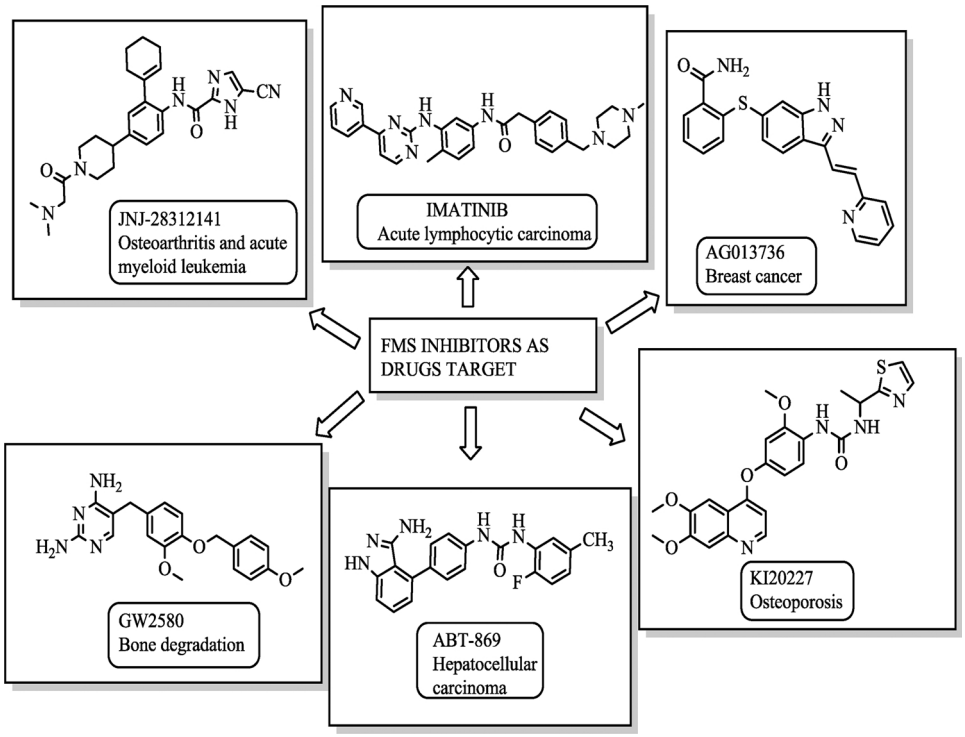

Fig. 1. Various disease conditions where cFMS can be a possible target.