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Review

Tyrosine kinases as targets in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the accumulation and proliferation of inflammatory cells in the synovial (joint) lining, resulting in the formation of pannus tissue, which invades and destroys adjacent cartilage and bone. In RA macrophages, B cells, mast cells, fibroblast-like synoviocytes (FLSs) and $CD4^+$ T lymphocytes become activated and contribute to synovial inflammation and joint destruction. It has been showed that different tyrosine kinases participate in the activation of those cells having important participation in the physiopathology of RA. Therefore, the tyrosine kinases inhibitors could be the next step in the treatment of patients with RA. This review focuses on recent advances on the role of tyrosine kinases and their inhibitors in the physiopathology of RA.

Contents

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5%–1% of the world population. RA is characterized by the accumulation and proliferation of inflammatory cells in the synovial (joint) lining, resulting in the formation of pannus tissue, which invades and destroys adjacent cartilage and bone [1]. Although the aetiology of RA remains unknown, macrophages, B cells, mast cells, fibroblast-like synoviocytes (FLSs) and $CD4^+$ T lymphocytes become activated and contribute to synovial inflammation and joint destruction [2].

In RA: a) macrophages infiltrate the synovium and secrete tumour necrosis factor-alpha (TNF-α) and other proinflammatory cytokines that potentiate inflammation [3,4]; b) mast cell activation through c-Kit (receptor tyrosine kinase critical for mast cell development and activation) results in the release of mediators that contribute to the inflammatory and degradative processes, including histamine, heparin, neutral proteases, and TNF-α [5–10]; c) fibroblasts express PDGFR (platelet-derived growth factor receptor) and proliferate in response to a variety of PDGF ligands. Both PDGFR and its ligands are over expressed in RA synovial tissue, and PDGF (platelet-derived growth factor) is a potent stimulant of synovial hyperplasia [11–13].

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Furthermore, bone and cartilage destruction is one of the most serious complications in RA patients, which can result in progressive morbidity and significant disability. The cells involved in this complication have been extensively studied and although the mechanisms of cartilage destruction in RA were well described, the specific mechanisms responsible for bone erosion in this disease have only recently been studied. The studies of bone erosion in patients with RA and in animal models of inflammatory arthritis such as collagen-induced arthritis (CIA) have provided powerful evidence that bone-resorbing osteoclasts play an important role in the structural joint damage involved in inflammatory arthritis [14]. Osteoclast precursors express receptor activator of NF- κB (RANK) and differentiate osteoclasts in the presence of receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) [15–17]. RA synovial tissues produce M-CSF, RANKL, and various cytokines that could increase osteoclast formation or activity, including interleukin 1-alpha (IL-1α and -beta (IL-1β), TNF-α, IL-6, IL-11, and IL-17 [18–21].

There are evidences that tyrosine kinases inhibitors (TKIs) have the ability of inhibiting mast cell c-Kit, FLS PDGFR, macrophage c-Fms, the phosphorylation of c-*fms*, a receptor M-CSF [22] that is an essential factor for osteoclast formation [23–26], and inhibit TCR-mediated signal transduction, cellular proliferation, cytokine production, and in vivo T cell responses [27]. All these factors have important participation in the physiopathology of RA; therefore the TKIs could be the next step in the treatment of patients with RA. Consistent with these *in vitro* evidences, recent cases reports describe severe RA patients treated with TKIs, who show marked improvement in the joint pain and disease activity [28,29] and animal studies where the TKIs treat, prevent, and inhibit osteoclastogenesis and joint destruction in CIA [30–32].

Tyrosine kinases represent a diverse and rapidly expanding superfamily of proteins, including both transmembrane receptor tyrosine kinases (RTK) and soluble cytoplasmic enzymes also known as nonreceptor tyrosine kinases (NRTK). Tyrosine kinases modulate a wide variety of cellular events, including differentiation, growth, metabolism and apoptosis [33–37]. This is a review about the participation of tyrosine kinases in the physiopathology of RA and the possible therapeutic effects of TKIs. Specifically, this systemic review will cover some concepts about the tyrosine kinases and its inhibitors. Then it is going to be discussed the tyrosine kinases involved in RA such as the PDGFR in fibroblast, the c-kit in mast cells, the c-Fms and VEGFR in macrophage, the c-fms and c-Src in osteoclast, the TCR signaling in T cells and others kinases. Finally, the clinical and animal studies published about TKIs in RA will be discussed.

2. Tyrosine kinases and tyrosine kinases inhibitors

Tyrosine kinases modulate a wide variety of cellular events, including differentiation, growth, metabolism and apoptosis [33–37]. The human genome encodes for almost 600 proteins kinases. Approximately 100–200 protein kinases are present in each cell, located upstream and downstream of epidemiologically relevant oncogenes or tumour suppressor genes [38]. Tyrosine kinases represent a diverse and rapidly expanding superfamily of proteins, including both transmembrane receptor tyrosine kinases (RTK) and soluble cytoplasmic enzymes also known as nonreceptor tyrosine kinases (NRTK). Common features of all tyrosine kinases include a separate domain for substrate binding, ATP binding, and catalysis [39]. The latter domain promotes the transfer of the terminal phosphoryl group from ATP to a tyrosine amino group acceptor in a substrate.

Phosphorylation of tyrosine residues in target proteins is essential for maintaining cellular homeostasis, yet this post-translational modification also provides the means by which a number of cellular oncogenes deregulate various signalling pathways and induce transformation [35]. Activation of the tyrosine kinases domain of either class of tyrosine kinases enzymes results in interaction of the protein with other signal transducing molecules and propagation of the signal along a specific signal transduction pathway (Fig. 1) [33–37,40–44]. Activation of transmembrane tyrosine kinases is typically initiated by binding a ligand (e.g., hormone or growth factor) to a specific site within the extracellular domain of the receptor. Upon ligand-binding, these receptors commonly undergo dimerization, resulting in autophosphorylation of tyrosine residues within the cytoplasmic domain [45,46]. These phosphorylation events activate the kinase, thereby increasing its intrinsic tyrosine kinases activity, and produce new binding sites for intracellular adapter molecules that bring signal transduction molecules into close proximity. Receptors that lack tyrosine kinases activity but harbor sites for tyrosine phosphorylation (often catalyzed by the soluble cytoplasmic tyrosine kinases enzymes) activate identical or similar

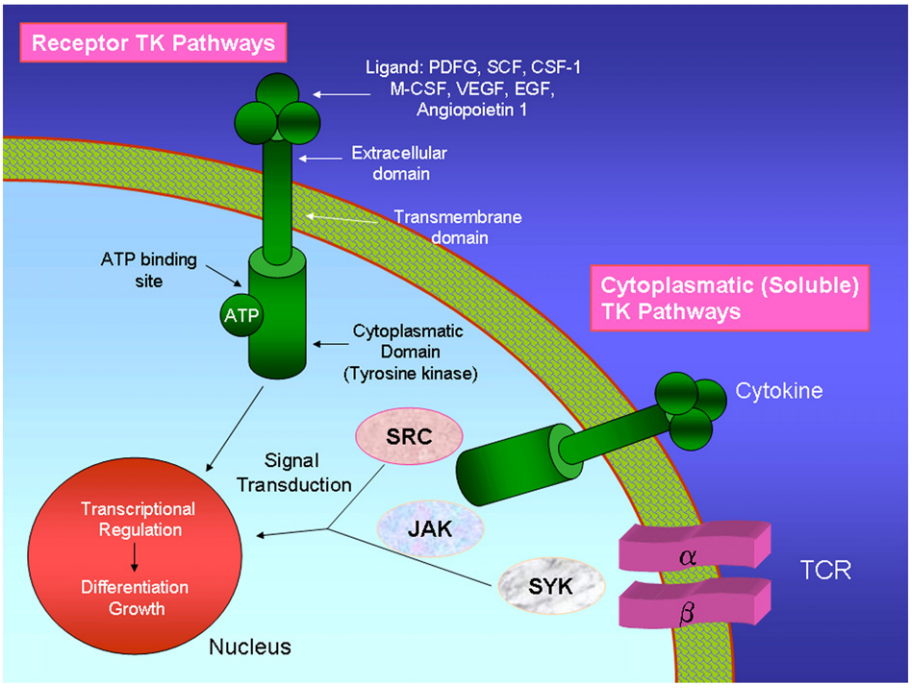

Fig. 1. Schematic representations of the different tyrosine kinases (TK) signaling pathways involved in RA.