A Multitude of Kinases—Which are the Best Targets in Treating Rheumatoid Arthritis?

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KEYWORDS

• MAPKs • Tyrosine kinases • IKK • Jak
• Syk • Small-molecule inhibitors

The advent of biologic therapeutics, most notably anti–tumor necrosis factor (TNF) agents, has dramatically improved the treatment of rheumatoid arthritis (RA). Nevertheless, the available biologics rarely result in disease remission and provide clinical benefit only in subsets of RA patients. In addition, biologics can be administered only by injection and are expensive. Alternative therapies for RA are needed, and small-molecule kinase inhibitors may fit the bill. Small molecules have several features that give them the edge over other therapeutics: they are orally bioavailable, cell permeable, and inexpensive to manufacture. Insight into intracellular signaling pathways involved in inflammation and immunity has allowed the rational design of small molecules that can counteract aberrant immune responses. Small molecules can exert potent anti-inflammatory effects by inhibiting kinases, many of which lie at the nexus of multiple proinflammatory pathways. The therapeutic potential of kinase inhibitors is showcased by their success in the treatment of cancer.

Adaptive and innate immune responses are involved in the pathogenesis of RA, a systemic autoimmune disease characterized by destruction of the synovial joints. Initiation of the disease involves systemic dysregulation of T- and B-cell responses, which leads to a breach in self-tolerance and eventually to the mounting of an immune response against the synovial joints. During the chronic inflammatory stage of the

This work was supported by NIH NIAMS R01 AR-054822, an American College of Rheumatology Within-Our-Reach grant, and Veterans Affairs Health Care System funding awarded to W.H.R.
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Rheum Dis Clin N Am 36 (2010) 367–383
doi:10.1016/j.rdc.2010.02.005 **rheumatic.theclinics.com**
0889-857X/10/$ – see front matter

disease, mast cells, macrophages, neutrophils, T cells, and B cells all infiltrate the synovium, where they release proinflammatory cytokines and matrix metalloproteinases (MMPs) that erode the synovial cartilage. Inflammation in the joints also triggers the development of apoptosis-resistant, hyperproliferative, fibroblast-like synoviocytes (FLS), which produce further proinflammatory cytokines. The synovial hyperplasia, in turn, leads to the formation of a destructive pannus that invades surrounding cartilage and bone. Finally, inflammation suppresses the formation of bone-forming osteoblasts and augments the formation of bone-resorbing osteoclasts, leading to the erosion of bone. Several kinases have been shown to play important roles in one or more of these pathogenic processes.This article discusses the therapeutic potential of small molecules targeting specific protein kinases in the treatment of RA and provides an overview of the progress to date. Lipid kinases—in particular, the phosphoinositide-3 kinases (PI3Ks)—are also emerging as attractive drug targets in the treatment of inflammation. The therapeutic potential of blocking PI3Ks in RA has been recently reviewed[1] and is not discussed further.

MITOGEN-ACTIVATED PROTEIN KINASES: ADVANCES AND SETBACKS

Mitogen-activated protein kinase (MAPK) signaling comprises 3 interrelated pathways, each mediated by a distinct MAPK: p38, extracellular signal-regulated kinase (ERK), or c-Jun N-terminal kinase (JNK). These pathways involve the sequential activation of multiple kinases, such that the MAPKs are activated by MAPK kinases (MKKs), which are themselves activated by MAPKK kinases (MKKKs). Thus, the p38 kinases (α, β, γ, and δ) are activated by MKK3 and MKK6, the ERKs (1 and 2) by MAPK-ERK kinase (MEK) 1 and MEK2, and the JNKs (1, 2, and 3) by MKK4 and MKK7.[2] JNK, ERK, and p38 are the terminal kinases of these pathways and serve to regulate an array of cellular responses through the phosphorylation of serine/threonine residues in discrete sets of transcription factors. All 3 of these MAPKs are activated in RA synovium[3] and have been proposed as therapeutic targets in the treatment of RA.

P38

Enthusiasm for inhibitors of p38—until recently heralded as one of the most promising classes of oral therapeutics for RA—has finally subsided. Many p38 inhibitors have been developed and tested in preclinical and clinical studies. Although the preclinical data were encouraging, with p38 inhibition shown to suppress inflammation and joint destruction in many different models of RA,[4] these initial successes did not extend to the treatment of RA. The first generation of small-molecule p38 inhibitors, which targeted all 4 isoforms of p38, failed in clinical trials owing to liver, brain, and skin toxicities. Nevertheless, the discovery that p38α is the important isoform in RA, acting to drive the expression of proinflammatory cytokines and the formation of osteoclasts,[5,6] engendered hope that selective inhibition of p38α would avoid the adverse effects of the pan-38 inhibitors. Unfortunately, p38α-specific inhibitors did not perform much better (**Table 1**). For instance, clinical development of SCIO-323 and AMG-548 was terminated because of skin toxicity and liver toxicity, respectively,[7] and the p38α inhibitors that did advance to phase II clinical trials proved ineffective.[8,9]

The toxicity and the inefficacy of p38 inhibitors are most likely target based, rendering the systemic targeting of p38 unviable. Multiple structurally unrelated p38 inhibitors have been shown to be toxic to the liver and skin and to induce only transient reductions in markers of inflammation.[4,7] The pivotal position of p38α in the regulation of inflammation is thought to underlie these phenomena. Although its proinflammatory