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Advances in kinase inhibition: treating rheumatic diseases and beyond

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Abstract

Purpose of review—Kinases inhibitors are now used for the treatment of autoimmune diseases. Here are reviewed the most recent findings related to their mechanism of action and some of the newest molecules and targets which are being investigated for autoimmune and inflammatory disorders.

Recent findings—Similarly to p38 inhibitors, Syk inhibitors have not fulfilled the expectations of researchers and clinicians and will likely not be used therapeutically in autoimmunity. BTK inhibitors remain in the preclinical phase. Studies on the mechanism of action of successful Jak inhibitors have revealed that besides T and B cells, bone cells such as osteoclasts and innate immunity cells such as dendritic cells are positively affected. More specific, novel Jak inhibitors are now in clinical trials and newer Jak inhibitors are being developed. Other kinases are emerging from basic studies as potentially druggable and will surely be investigated.

Summary—First generation pan-Jak inhibitors can be useful for a wide variety of pathologies. They act on innate immune cells and can promote tolerance. More specific inhibitors will soon be available and these may be used in a disease-specific manner.

Keywords

Kinase; Jak; Cytokines; Therapy

Introduction

Despite the success of biologics and the effectiveness of disease-modifying anti-rheumatic drugs (DMARDs), the number of patients with autoimmune disorders in need of an effective treatment remains high.

Autoimmune and inflammatory disorders are pathologies in which cytokines such as interferons (IFNs) and interleukins (IL) perpetuate disease. Not surprisingly, effective treatment is achieved by interfering with cytokines' actions. Success, however, has been attained not in the cytoplasm but rather at the membrane (1-3). Cytokine-blocking agents, known as biologics, have revolutionized the treatment of rheumatoid arthritis (RA) and various autoimmune pathologies.

Interfering with the enzymatic activity of cytoplasmic proteins for therapeutic purposes is not a new concept. Among the best known enzymatic reactions, reversible protein phosphorylation is a well-understood event by which signals, originated at the cellular membrane, are relayed to the nucleus culminating in gene expression and cellular functions (4). Cytokines, rely on intracellular (i.e., cytoplasmic) signaling networks to drive cellular fate decisions, ranging from proliferation to differentiation to death (3).

Lately, a new class of orally available drugs targeting intracytoplasmic kinases has successfully entered the clinical arena. The Janus Kinase (Jak) inhibitor, tofacitinib (formerly CP-690,550) has been approved in the USA and in many other countries for the treatment of RA. Other Jak inhibitors like ruxolitinib (approved for myeloproliferative diseases) and baricitinib are in advanced clinical development (2). Furthermore, several other kinases inhibitors are in various stages of development for the treatment of autoimmune and inflammatory pathologies. Here, with the exclusion of protein kinase C inhibitors, which will not be covered because of space limitation, I will focus on ATP-competitive kinase inhibitors. I will highlight some of the latest findings about currently available inhibitor's mechanism of action as well as some of the drugs developed in the last past few months. I will also review some the molecules that have recently attracted interest as possible new targets for therapy in rheumatic diseases.

Targeting the signal

The cytosolic substrates of pro-inflammatory cytokines are ideal targets for the development of small-molecule inhibitors that will modulate cellular responses (Figure 1). Nonetheless, because of the complexity and the intricacies of signaling networks, targeting such substrates is not an easy feat. Kinases act as a rather simple, almost digital, switch and have, therefore, been viewed as ideal targets. Although, achieving sufficient specificity with an ATP competitor was seen as an insurmountable task, successful, orally available kinase inhibitors have been generated. The availability of such compounds has made a significant impact in the treatment of several malignancies. Molecules such as imatinib, the progenitor of all current kinase inhibitors, compete with the ATP-binding site, blocking phosphorylation of the enzyme's substrate (5). The entire downstream signaling cascade is, therefore, halted and cellular responses prevented. With this success in mind, molecules were developed to inhibit kinases involved in the signaling cascades originating from specific immune receptors.

Trials and tribulation: from p38 to Syk

The first kinase inhibitors developed specifically for autoimmune diseases therapy blocked the Mitogen Activated Protein Kinase p38, a serine–threonine kinase that regulates pro-inflammatory cytokines *in vivo*. Unfortunately, none of the compounds developed was effective or sufficiently safe to progress beyond phase III studies. Indeed, the failure of p38 inhibitors has been well documented (6).

The Spleen Tyrosine Kinase (Syk) attracted the interest of several pharmaceutical companies. Syk proximity within the signaling cascade to the membrane receptors, as well as its immune cell–specific expression made its inhibition very appealing. The Syk inhibitor,

fostamatinib (R788) was one of the first to be developed (7). Similar to that observed with p38 inhibitors, *in vivo* preclinical and early clinical results with this Syk inhibitor were encouraging but ended because of its side effects and lack of clear efficacy. Prodrug R406, which is metabolized to active fostamatinib, can potentially inhibit Jaks as well. Side effects, such as hypertension, shown by fostamatinib could also be due to off-target effects on vascular endothelial growth factor 2 (8, 9). Although trials evaluating another Syk inhibitor PRT062607 (also known as BIIB057) have been halted, the inhibitor GS-9973 remains in clinical development, albeit for hematologic malignancies only. It is therefore still possible that the side effects of inhibitors like fostamatinib and PRT062607 could be ascribed to a lack of specificity rather than in the target itself.

JAKing up tolerance?

The importance of Jaks in cytokine signaling and biology, and the development of first-generation Jak inhibitors have been covered extensively (2) (10). Almost 20 years after the observation that individuals with *JAK3* mutations suffered from Severe Combined Immunodeficiency and the formulation of the hypothesis that agents capable of inactivating Jak3 could be used as an immunosuppressant (11), such agents are now available. Despite the fact that first-generation Jak inhibitors tofacitinib and ruxolitinib are approved drugs, clear mechanistic data on JAK inhibitor-mediated immunomodulation are incomplete. For instance, how Jak inhibition reduces structural damage to the arthritic joint remains unclear. Effects on T-cell differentiation and cytokine production have been analyzed in details, but do these drugs exhibit tolerogenic effects? Intriguingly, in a rat model of adjuvant-induced arthritis, tofacitinib administration modulates the secretion of Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL). IL-6 and IL-17 secretion rapidly decreases, with plasma concentrations reducing just 4 hours after tofacitinib administration, whereas decreased secretion of RANKL required at least 4 days. Circulating chemokines such as CCL2 and CCL3 were also reduced upon prolonged dosing. The authors observed decreased joint edema, fewer monocytes and macrophages, lessened CD3⁺ T-cell infiltration, and suppressed osteoclast-mediated bone resorption. Tofacitinib may also directly inhibit osteoclasts by acting on IL-15 signaling, which regulates osteoclasts functions (12).

Tofacitinib also modulates innate immunity, possibly via inhibition of IFN- γ and the downstream STAT-1-mediated cascade (13). The effects of the drug on dendritic cells (DC) *in vitro* were recently analyzed to better understand the effects of tofacitinib on the innate immune response. Secretion of pro-inflammatory cytokines from the LPS-stimulated DC was reduced in a dose-dependent manner, but, surprisingly, secretion of anti-inflammatory cytokines Transforming Growth Factor (TGF)- β and IL-10 remained unaffected. Similarly, surface expression of co-stimulatory molecules CD80 and CD86 was reduced whereas HLA-DR expression was unchanged. Decreased expression of co-stimulatory molecules was dependent on type-I IFN signaling and IRF7 expression. Both these events were impaired by tofacitinib. These results support the hypothesis that exposure to tofacitinib pushes DC towards a tolerogenic phenotype. Furthermore, tofacitinib-treated DC expressed significantly higher mRNA amounts of indoleamine 2,3-dioxygenase (IDO)-1 and -2, which code for two enzymes known to reduce T-cell stimulatory capability (14).

Ruxolitinib also affects DC biology. Drug treatment not only inhibited monocyte differentiation to DC but it also impaired DC activation and cytokine production, especially that of IL-12, in response to Toll-Like Receptor stimulation. DC-mediated T-cell responses were also reduced when ruxolitinib was administered *in vivo* where DC displayed reduced migratory capacity. Intriguingly, *in vitro* treatment of human DC with TG101348, an inhibitor that exhibits more specificity toward Jak2, also inhibited DC activation and functions in a dose-dependent manner (15). Altogether, these two studies suggest that Jak2, which is also inhibited by tofacitinib, plays a major role in DC-dependent innate immunity. Notably, DC-dependent Th17 differentiation and autoimmune inflammation is dependent on p38 (16).

Tyk2, a member of the Jak family, is involved in the signaling cascade of IL-12, IL-23, type-I IFN as well as IL-6 and IL-10, and its activity is also relevant for innate immune responses. Tyk2 deficiency in human results in hyper-IgE syndrome, absence of IL-12 and IL-23 responses, and defects in IFNs, IL-6, and IL-10 functions. Recently, the contribution of Tyk2 to various cytokines was dissected using a series of inhibitors with varying degree of specificity for Tyk2 and other Jaks (17). The authors noted that Tyk2 enzymatic activity is critical for IL-12 and IL-23 signaling but less so for type-I IFN and other cytokines and that a Jak1-specific compound better inhibited IL-6 and IL-10 signaling. We can speculate that a specific Tyk2 inhibitor would have less broad immunosuppression and, therefore, could be safely used for diseases such as psoriasis or inflammatory bowel disease for which inhibition of IL-12 and IL-23 is proving quite successful (18, 19).

The Jak1/Jak2 inhibitor GLPG0634 shows promising therapeutic potential for rheumatologic diseases. Similar to tofacitinib (13), this drug inhibits the differentiation of Th1, Th2, and Th17 cells. *In vivo* oral dosing resulted in reduced IFN-dependent gene expression and, in a rat model of CIA, swelling, bone erosion, cartilage degradation and circulating levels of inflammatory cytokines were reduced to the levels comparable to what was achieved with etanercept (20). Whether this compound affects the innate immune response in a manner like the above-mentioned drugs do remains to be seen, but a reduction of two interferon-induced genes like Mx1 and Mx2 seems to suggest it does.

It is not surprising that these drugs could be useful beyond rheumatic diseases. In fact, tofacitinib can reverse the pathological manifestations observed in a gluten-free mouse model of celiac disease. Transgenic mice overexpressing human IL-15 under the control of an intestinal enterocyte-specific promoter develop an immune-mediated inflammatory disorder with intestinal infiltration by CD8⁺, NKGD2⁺ T cells and develop IL-15-dependent, inflammation-mediated intestinal villi atrophy. Notably, after 42 days of treatment with tofacitinib, the population of IL-15-dependent pathogenic CD8⁺ cells in the intestinal tissues and in the circulation is reduced. Moreover, tofacitinib administration resulted in diminished splenomegaly and absence of macroscopic or microscopic signs of intestinal inflammation. Importantly, 10 weeks after stopping the treatment, the number of pathogenic T cells increased, again suggesting that celiac patients would require long-term therapy with Jak inhibitors (21).

Selectivity: just around the corner?

Second-generation Jak inhibitors are being developed to be more specific with potentially less side effects and will likely be used for specific diseases. Some molecules like VX-509 (Jak3 specific), GSK2586184 (GLPG0778; Jak1 specific), pacritinib (SB1518; Jak2 specific), AC430 (Jak2 specific), PF-04965842 (Jak1 specific) are already in various phases of clinical studies for diseases ranging from RA to lupus to psoriasis and myelofibrosis. Several other “third-generation” lead compounds, with increased specificity, have been recently reported. Pyrrolabisamides, cyclopyrrolopyrazines, and tricyclic core structures are being investigated for Jak3-specific inhibition. Cyclopropylamides have been modified to generate Tyk2-specific molecules whereas pyridopyrimidine derivatives are being evaluated as Jak1/Jak2 inhibitors (22-29).

New kids on the block

The success of Jak inhibitors has paved the way for the development of more kinases inhibitors. Several druggable targets have been proposed for autoimmune disorders and a few are being actively investigated (Figure 1). Below are some of the newest and most intriguing molecules currently being developed or considered for as targets.

Inhibitors of Bruton's Tyrosine Kinase (BTK) are being developed mostly for the treatment of B- or T-cell leukemias and lymphomas. However, in a mouse model of collagen-induced arthritis (CIA), ibrutinib (PCI-32765), an irreversible inhibitor of BTK and of IL-2-inducible T-cell kinase (ITK), and another BTK inhibitor, CGI1746, are efficacious in ameliorating the disease. Decreased pro-inflammatory cytokine secretion and attenuated collagen-specific antibodies production resulted. Furthermore, significant reductions synovitis, bone destruction, and pannus formation were observed. Similar results were also obtained for GDC-0834 as well as PCI-45292, in a rat model of CIA (30-32). None of these molecules has yet been used in clinical studies for autoimmune disorders.

Rho-associated kinase (ROCK) 1 and 2 are two serine-threonine kinases that are activated by the small GTPase Rho. The Rho-ROCK cascade regulates cellular functions ranging from cell adhesion and motility to cytoskeleton rearrangement. In Th17 cells, ROCK2 phosphorylates IRF4 (33) and regulates the production of IL-4, IL-21, as well as immunoglobulin isotype-switching and differentiation of mature B cells. Furthermore, ROCK2 haploinsufficiency impairs Th17 differentiation. Inhibition of ROCK2 activity by the pan-ROCK inhibitor, fasudil, resulted in improvement of the disease in various preclinical models of lupus (33, 34). Another compound, which might be a specific ROCK2 inhibitor, KD-025 (also known as SLx-2119), has recently been proposed to inhibit IL-17, IL-21, and IL-22 expression and Th17 differentiation by inhibiting Interferon regulatory factor (IRF) 4, STAT-3, and RAR-related orphan receptor (ROR) γ t expression. This new compound is being investigated in lupus, psoriasis, and non-alcoholic steatohepatitis.

Two serine-threonine kinases have very recently surfaced as possibly important mediators of inflammation. Recent publications have revealed the functions of cyclin-dependent kinase 8 (CDK8) and receptor interacting protein-1 (RIP1).

CDK8 is a member of a protein complex that includes cyclin C, MED12, and MED13, which associates with the Mediator complex, which ultimately regulates RNA polymerase II-dependent transcription. So far, few CDK8 targets have been identified, but all of them are chromatin-associated proteins. STATs belong to this list of CDK8 targets. CDK8 phosphorylates a serine residue in the STATs' C-terminal transactivation domain (TAD) (35-39). This event occurs when STAT1 (or STAT3) is bound to a promoter (40). In the case of STAT1, S727 phosphorylation by CDK8 is required for IFN- γ -inducible antiviral responses and is dependent on an IFN- γ -driven signaling cascade (41). Molecules capable of interfering with CDK8 enzymatic activity might disrupt the self-reinforcing inflammatory pathways involving IFN- γ . Notably, two pan-CDK inhibitors, roscovitine and kenpaullone, ameliorate the diseases in a murine model of experimental autoimmune encephalomyelitis, a Th-17-driven pathology. In this case, the two drugs acted by restoring IL-2 production when TFG- β was present, ultimately enhancing T-regulatory cell activity (42).

RIP1, a death domain-containing protein, is a critical regulator of inflammation and cell death. RIP1 binds the intracellular domain of CD95 (FAS) and Tumor Necrosis Factor (TNF) receptor-1 and has both kinase-dependent and -independent activities. The kinase activity of RIP1 is essential for necroptosis, a caspase-independent pathway of programmed cell-death. Recently, it was shown that RIP1's kinase activity is essential for TNF- α production after caspase inhibition (43). Furthermore, RIP1 regulates IL-1 α production, facilitating chronic inflammatory diseases. Notably, this activity is inflammasome- and IL-1 β -independent (44). How RIP1 regulates IL-1 α and TNF- α production is not completely understood, but inhibition of RIP1 activity may, indeed, provide a novel approach to treat chronic autoinflammatory and autoimmune diseases.

Overall, CDK8 and RIP1 have emerged as regulators of the production and effects of inflammatory mediators such as IL-1 α , TNF- α , and IFN- γ and appear to be appealing druggable targets.

The lipids connection

The class I phosphoinositide 3-kinases (PI3Ks) are lipid kinases which phosphorylate phosphatidylinositol-(4,5)-phosphate to produce phosphatidylinositol-(3,4,5)-phosphate (PIP3). The intermediate PIP3 is critical for the activation of downstream signaling pathways as it recruits and activates several pleckstrin homology domain-containing proteins. In turn, these proteins are involved in biochemical and biological events ranging from glucose metabolism to differentiation, proliferation and survival of several cell types including immune cells. For this reason molecules in this pathway have been investigated as potential therapeutic targets. Most of the compounds developed so far have been tested in the treatment of malignancies. The pan-PI3K inhibitor buparlisib is in phase III development for breast cancer whereas the PI3K- δ -specific idelalisib is been tested in chronic lymphocytic leukemia, and so are several other new molecules. Given that PI3K- δ and PI3K- γ are preferentially expressed in immune cells, inhibitors capable of interfering with their enzymatic activity have been tested in inflammatory and autoimmunity models. The PI3K- δ -specific compound IC87114 has been shown to reduce cytokine secretion in T cells obtained from patients with allergy as well as arthritis. Notably, administering the drug to

mice resulted in reduced hypersensitivity responses (45). Furthermore, this compound was capable of protecting non-obese diabetic mice, a murine model of type I diabetes, from progressing into a severe diabetic status, reducing inflammatory cell infiltration in the pancreas as well as delaying loss of glucose homeostasis (46). Another molecule, capable of inhibiting both, PI3K- δ and PI3K- γ , IPI-145, has been shown to have therapeutic activities in several mouse models of disease ranging from CIA to SLE models to ovalbumin-induced asthma (47).

Once again, it appears that drugs developed for treating cancer may become useful to the practicing rheumatologist in a not-too-distant future.

Conclusions

Specifically blocking the enzymatic activity of phosphotransferases had been considered, not too long ago, an impossible task. Nonetheless, history has taught us that what may not be druggable today it can become druggable in the future. In fact, 20 years of intense research, albeit with some failures, have brought us orally available kinase inhibitors. Jak inhibitors are here and the practicing rheumatologist uses them!

We are also starting to understand how these drugs work as well as their limitations. The hope is that more selective inhibitors will be disease-specific and have reduced side effects. Moreover, other targets are actively pursued and few intriguing molecules are being considered.

Advances in basic biology research, computational chemistry and increased understanding of the pathophysiology of rheumatic diseases will surely keep pushing us ahead. We cannot predict the future but, if we build on the latest successes, we should be able to help a larger number of patients suffering from autoimmune and inflammatory disorders.

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Key Points

- Despite initial setbacks kinase inhibitors for autoimmune and inflammatory disease therapy are now a reality.
- Appealing targets such as p38 and Syk have not fulfilled their promise whereas Jak inhibitors have demonstrated clinical efficacy with limited side effects.
- We have started to have a better idea of the mechanism of action of currently available Jak inhibitors. By inhibiting multiple Jaks, their activity is not limited to the adaptive immune compartment but they also affect cells involved in the innate immune response such as dendritic cells and other cell types.
- The use of pan-Jak inhibitors may go beyond rheumatic diseases.
- New, more selective, Jak inhibitors are being tested in clinical studies and will soon know their efficacy and safety profile.
- Given the success obtained with the Jak inhibitors, other targets have emerged and are actively being pursued.

Figure 1. Immune receptors signaling pathways involve several kinases

Signaling originated at the cell membrane when ligand interact with receptors travel through the cytoplasm to reach the nucleus and regulate gene expression. Kinases are a key part of the intra-cytoplasmic cascade as they are involved in direct activation of several transcription factors as well as controlling several other biochemical events.