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Back to the Future: Oral targeted therapy for RA and other autoimmune diseases

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Summary

The molecular biology revolution coupled to the development of monoclonal antibody technology enabled remarkable therapeutic progress in rheumatology, comprising an array of highly effective biological agents. With advances in understanding of the molecular nature of immune cell receptors came elucidation of intracellular signaling pathways engaged by these receptors. These discoveries beg the question whether selectively targeting key intracellular molecules with small molecules would add to the rheumatologic armamentarium. In this review, we discuss several strategies that appear to be successful and ponder their implications for the future of immune targeted therapeutics. We focus on kinases inhibitors, primarily those targeting Janus kinase family members, and spleen tyrosine kinase (Syk) given their advanced status in clinical development and application. Thereafter we will summarize other signal targets that might offer promise in future.

Introduction: A Brief History of the Therapy of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a disease manifested by inflammatory synovitis, articular destruction, and wider co-morbidity including effects in the vasculature, bone, lungs and brain. This leads to progressive disability and adverse social cost to individuals and to the wider health care economy. Recent successes have substantially improved outcomes, built on aggressive use of conventional and biologic disease modifying agents, coupled with significant evolution of our therapeutic strategies. However, unmet need remains, manifest mainly in partial, or non-responses - few patients achieve sustained remission.

Pharmaceutical compounds have long formed the core of therapeutics for RA, drawn from a broad range of chemical classes. Emanating from the original discovery of aspirin, the NSAID class has been widely employed underpinned by superb biochemistry culminating in the advent of COX2 selective agents. These agents however do not achieve true disease modification in that symptoms are improved but not the underlying joint destruction. Furthermore long-term use is limited by gastric and renal toxicity. Glucocorticoids represent probably the most remarkable historic advance in the treatment of inflammatory disease. By manipulating the protean effector function of the glucocorticoid receptor these agents achieve potent anti-inflammatory and immune modification function, and are disease modifying in RA. This same ubiquitous receptor biology results in side effects affecting many systems in the body that again limit their long-term use. The mainstay of RA

therapeutics has been conventional disease modifying anti-rheumatic drugs (DMARDs) comprising a group of agents assembled serendipitously from other disciplines e.g. methotrexate, sulphasalazine, hydroxychloroquine, azathioprine. Their precise, `disease relevant' mechanisms of action remain elusive and critically their introduction was not directed by a rationalization of target biology related to RA pathogenesis. Moreover, they do not specifically target immune cells. Similarly, other immunomodulatory drugs have been found empirically often modulating intracellular targets that are typically ubiquitous. Despite the fact that these are not specifically “targeted therapies”, they clearly have efficacy.

The huge advances in molecular biology and biochemistry in the last 20 years has given us a detailed understanding of the structure and function of dozens of key receptors on immune cells. Ranging from the T cell, B cell and Fc receptors to costimulatory molecules, our understanding of the biochemistry of immune cell activation now is vastly more sophisticated. Molecular cloning also revealed a remarkable array of cytokines that control the growth and differentiation of hematopoietic cells and virtually all aspects of immune response development and resolution. Molecular biology tools permitted the production of recombinant cytokines and cytokine receptors. At this same time, monoclonal antibody technology allowed the generation of therapeutic antibodies. This advance facilitated the introduction initially of TNFi agents with significant impact that has been extended to include a range of biologic agents targeting several cytokines and lymphocyte receptors. This begs new critical questions: knowing what we know about immune cell signaling, can we target intracellular pathways used by the key immunoreceptors that trigger inflammatory responses to generate new drugs that work where others do not? Moreover by selecting signal molecules that operate as critical nodes can we achieve a higher magnitude, or more robust duration of response?

Role of kinases in receptor-mediated signaling

Elegant work in multiple systems established that reversible phosphorylation is a major mechanisms used by all cells. The enzymes that mediate this modification are termed phosphotransferases or kinases. Thanks to completion of the human genome, we now know there are a total of 518 kinases in the human “kinome”. Some receptors like the insulin receptor and epidermal growth factor receptor are themselves kinases, whereas other receptors are directly linked to intracellular kinases. Thus many fundamental processes like cell growth and differentiation are regulated by phosphorylation. Many key immune receptors, including those that are responsible for driving inflammation exert their effect through kinases. One might imagine the prospect of developing *specific* kinase inhibitors as therapeutic agents would be chemically challenging, as the structure of the enzymatic region that contains the ATP is remarkably similar between family members. Despite this, and the finding that most successful inhibitors bind this region, we know that kinases are useful targets for the generation of new drugs, with proof of concept provided originally in the oncology field. In fact, existing FDA-approved kinase inhibitors have a range of selectivity; none are completely specific for a single kinase and others are actually rather broad in the range of kinases they inhibit. The elucidation of the mammalian kinome is relevant in this

regard as the targeted deletion of individual kinases in mice has given us insights into which enzymes should be avoided.

While the potential range of kinases that could be targeted in rheumatic disease is large, the first successful candidates appear to be those that are downstream of cytokine, antigen, and Fc receptors.

Targetting Type I/II cytokine receptors: Efficacy of Janus kinase inhibitors in autoimmune disease

Cytokines that bind type I and type II cytokine receptors comprise a range of factors including: interleukins, interferons, and colony stimulating factors, as well as hormone-like cytokines (erythropoietin, prolactin, growth hormone and leptin). These receptors all exert their effect through the activation of Janus kinases or Jaks. The intracellular domains of these various receptors selective bind to the different Jaks, Tyk2, Jak1, Jak2 and Jak3, in various combinations (Figures 1,2). Jak1 and Jak2 are broadly employed by many different cytokines whereas Jak3 has more limited function, associating with the common gamma chain, γc. The essential function of Jaks in cytokine signaling is demonstrated by very clear genetic data [1]. Loss of function mutations of *JAK3* and *TYK2* profoundly inhibit immune responses in both mouse and humans. Loss of function mutations of *JAK1* and *JAK2* have not been identified in humans; however, these kinase have profound effects as evidenced by knockout mice. Germline deletion is lethal and signaling by multiple cytokines is abrogated.

The first selective Janus kinase (Jak) inhibitor (jakinib) to be tested in humans was tofacitinib (formerly designated CP-690,550). Tofacitinib inhibits Jak3 and Jak1 and to a lesser extent Jak2 [2]. It has little effect on Tyk2, and has little activity on kinases other than Jaks [3]. Tofacitinib was found to effective in a variety of pre-clinical models ranging from transplant to arthritis models [2,4]. Its efficacy in human disease has been investigated in multiple clinical trials in rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis and renal transplantation [5–10]. In RA treatment in particular, tofacitinib exhibits comparable efficacy to adalimumab and methotrexate [11]. Of particular importance, tofacitinib was found to be effective in patients who had failed multiple biologics. There is evidence to suggest that tofacitinib therapy prevents structural damage; however, this work will need to be confirmed and in particular the optimal dose for this outcome needs to be established. Based on these findings, this drug has been recommended for approval for the treatment moderate to severe RA who have failed other disease modifying drugs. Encouraging early efficacy is emerging in psoriasis and in ulcerative colitis indicating broader disease applicability of this mechanism-based kinase inhibition approach.

Although one might have assumed, based on mouse knockout data that targeting Jak2 would be problematic, the discovery that gain-of-function *JAK2* mutations underlie the myeloproliferative disorders provided a rationale for purposefully targeting this kinase [12]. One such inhibitor, ruxolitinib (INCB18424), a Jak1/2 inhibitor, is efficacious in this setting, but has also been studied in RA [13,14]. Similarly, baracitinib (INCB28050) is also a Jak1/Jak2 inhibitor and it too showed efficacy in a Phase II trial in RA. Extended studies are ongoing.

Mechanism of Action of First-Generation Jakinibs

A variety of cytokines that signal by Type I/II cytokine receptors play pivotal roles in the immunopathogenesis of RA and other autoimmune diseases. As a potent inhibitor of Jak3, tofacitinib very effectively blocks signaling by common γc cytokines: IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 [1]. To a lesser extent tofacitinib blocks Jak2 and therefore blocks IL-12 and IL-23 (as well as common β chain-using cytokines, IL-3, IL-5, GM-CSF). As a result, tofacitinib has potent effects on lymphocytes. It blocks differentiation of Th1 and Th2 cells and interferes with the generation of pathogenic Th17 cells [2]. Tofacitinib appears to have little effect on lymphocyte numbers in humans; however, NK cells and $CD8^+$ T cells declined in nonhuman primates [15,16]. It remains to be determined whether alterations in NK cell number will be an issue in humans treated with tofacitinib. It will also be important to formally define the functional impact of tofacitinib on lymphocyte subsets in patients to characterize more precisely the relevant mode of action in RA – this in turn will optimize the appropriate choice of next-generation jakinib selectivity.

Finally, tofacitinib blocks Jak1, which in addition to being vital for γc cytokines, is also critical for gp130-using cytokines and interferons. The former are especially relevant to RA, as IL-6 is an important gp130-using using cytokine. Consequently, tofacitinib can block innate immune responses. In model systems, tofacitinib blocked the production of pro-inflammatory cytokines, macrophage activation and attenuates TNF responses [2]. Tofacitinib also blocks the effect of type I interferons and IL-6 on synovial fibroblasts, inhibiting chemokine expression [17]. In an arthritis model, tofacitinib reduced RANKL production, and by this means limited structural damage [18]

Because ruxolitinib and baricitinib inhibit Jak1 and Jak2, they block the same cytokines as tofacitinib. That is, deletion of *JAK3* (or *Jak3* in the mouse) blocks lymphocyte development because of its requisite role in common gamma chain cytokine signaling [19–22]. However, gene targeting of *Jak1* also results in a SCID phenotype [23]. It too is required for signaling by common gamma chain cytokines insofar as it is an obligate partner for Jak3 in these receptors. From this perspective, the expectation would be that these drugs might have very similar overall mechanisms of action, in terms of the cytokines that are blocked; however, the extent and duration of inhibition likely differs.

Side effects of jakinibs

The most common, important side effect of jakinibs is infection. These include upper respiratory and other infections, but also opportunistic infections including *M. tuberculosis* and Herpes zoster. Patients treated with jakinibs can also develop anemia, leukopenia and thrombocytopenia, this likely due to interference with signaling by erythropoietin and other colony-stimulating factors, which rely on Jak 2 for their action. An unexpected side effect is hyperlipidemia, perhaps reflecting direct effects on cholesterol metabolism which is itself dysregulated in the context of chronic inflammatory diseases However, use of other immune modulators are also associated with altered lipids, e.g. tocilizumab; it is likely that this reflects the evolutionary integration of metabolic and immune regulatory function.

The future of jakinibs in treating autoimmune disease

We are obviously just in the beginning of the use of jakinibs in the treatment of RA and IBD. Biologics have raised the bar in the treatment of autoimmune disease given that they are effective and safe. Since tofacitinib is now, and should other jakinibs be, approved for these indications, it will be of interest to see how clinicians deploy these agents. The fact that they are oral agents is likely to be seen as advantageous In addition, since a not insubstantial proportion of patients do not respond to biologics, this is a likely setting in which jakinibs will be used. Earlier intervention in the RA treatment paradigm may emerge with increasing safety datasets emerging. The question also arises whether jakinibs will be useful in other clinical settings. Clinical trials in other arthritides are underway. Preclinical data suggest that jakinibs may be useful in systemic lupus erythematosus; certainly their ability to block the action of type I interferons makes them potentially attractive [24–26]. As prototypic Th2-mediated diseases, severe asthma and allergies are likely another setting where jakinibs, especially topical formulations, may be of use. Their potential utility has already been established in preclinical models [27]. An obvious further question is to what extent jakinibs will be generally useful as steroid-sparing or steroid-replacing agents across an even wider range of inflammatory diseases.

The present jakinibs are relatively nonselective and so, the development of more selective second generation agents is underway. VX-509 is a newer Jakinib, which is reportedly more specific for Jak3; it too showed efficacy in RA a Phase IIa study [28]. Of interest, a reportedly selective Jak1 inhibitor, GLPG0634, has also showed efficacy in a Phase II trial. It will be of great interest to assess the relative merits of inhibiting the various Jaks in different clinical settings, particularly in balancing safety and efficacy. However, while one might assume that more selectivity would be better, this assumption is not always borne out. Consider the experience with NSAIDS and selective Cox2 inhibitors.

Targeting B cell and Fc Receptors: Syk and Btk inhibitors

A number of key immunologic receptors including the T cell receptor (TCR), B cell receptor (BCR) and Fc receptors (FcRs) are structurally related. These receptors are complexes comprised of ligand binding subunits associated with signaling subunits. They are referred to as multi-chain immune recognition receptors, a family that includes the TCR, BCR and FcRs, but many other important receptors as well. Importantly, all these receptors are linked to protein tyrosine kinases and tyrosine phosphorylation of the receptor itself is the first step in receptor-mediated signaling (Figure 3) [29–33]. This is mediated by Src family protein tyrosine kinases. Phosphorylation of a given receptor on on critical tyrosine residues (referred to as immunoreceptor tyrosine based activation motifs orITAMs) leads to the recruitment of Syk and/or Zap-70; by virtue of their tandem src homology (SH) 2 domains. Subsequently, another class of tyrosine kinases are activated, the plextrin-homology domain containing kinases. Btk is one such kinase. Although clinically useful Syk and Btk inhibitors have been developed, no Src family inhibitors have emerged as successful drugs in the clinic as yet.

Syk inhibitors

Syk (spleen tyrosine kinase) and ZAP (zeta associated protein)-70 make up a small structurally distinct kinase family. Both are involved in antigen receptor signaling. ZAP70 functions immediately downstream of the T cell receptor whereas Syk is critical for B cell receptor and Fc receptor signaling in B cells and myeloid cells respectively [34,35]. Patients that lack ZAP70 have a severe combined immunodeficiency characterized by lymphopenia [36]. Despite the obvious importance of Zap70, a selective, clinically useful inhibitor has yet to be developed.

In contrast to ZAP70, Syk is minimally expressed in T cells and its major role is in B cells and myeloid cells. Syk plays an analogous role to Zap70 in B cell receptor signaling, binding the phosphorylated intracellular domains of the B cell antigen receptor [37]. It also plays a similar critical role for Fc receptors [33,38] However, Syk plays other functions including roles in intergrin signaling. Indicative of its protean functions, Syk-deficient mice die in the perinatal period with fatal hemorrhage due to abnormal blood vessel and lymphatic formation [39,40]. Nonetheless, mice transplanted with Syk-deficient bone marrow are resistant to models of rheumatoid arthritis and asthma suggesting that this kinase could be a useful therapeutic target. Preclinical studies of one Syk inhibitor, fostamatinib (R788), showed efficacy in preclinical arthritis models [41]. This inhibitor has gone on to clinical trials in patients with RA [42,43]. Phase II trials in people with moderate to severe RA yielded mixed results - patients with inadequate prior response to methotrexate exhibited satisfactory responses whereas those previously treated with TNF inhibitors did not apparently benefit. Trial design issues beset the latter study and the results of larger phase III studies are now awaited to properly define the potential of this inhibitor and indeed the syk pathway in the RA therapeutic armamentarium.

Given the breadth of actions of Syk in B cells, myeloid and other cells, defining the precise mechanism of action a Syk inhibitor such as fostamatinib in RA is challenging. The drug certainly interferes with B cell activation and in fact, it has been reported that short-term use of fostamatinib impairs B lymphocyte development at the transitional stage without affecting mature B cell populations [44]. It is likely though, that in addition to effects on B cells, important aspects of the drug efficacy relate to effects on myeloid and other cells, particularly mast cells and neutrophils, and perhaps also osteoclasts.

Side effects of fostamatinib include neutropenia, transaminitis and hypertension. The mechanism underlying hypertension is somewhat elusive at present; however, given the broad roles of Syk and its role in vascular development, it is possible that the this side effect of fostamatinib may be related to Syk inhibition and not a peculiarity of this particular drug. It should also be pointed out that fostamatinib might inhibit kinases other than Syk itself – it has for example been suggested that hypertension may reflect effects on VEGF receptor function Indeed, now that it is relatively straightforward to survey the effect of any given drug on the kinome, it is a fair expectation for rheumatologists to know what spectrum of kinases is being inhibited. As with jakinibs, it is not obvious that greater selectivity is necessarily advantageous; indeed, there are circumstances in which a broader spectrum inhibitor might be beneficial.

Phase III studies for fostamatinib in RA are currently underway. Given the importance of Syk for B cells and Fc receptor signaling, a likely further setting in which to use a Syk inhibitor would be SLE. In fact, fostamatinib has shown efficacy in mouse models of SLE [45,46]. The other obvious setting is which Syk inhibitors may very well have utility is in B cell malignancies [47].

Btk inhibitors

After activation of Src family kinases and Syk or Zap-70, a third, structurally distinct class of tyrosine kinases, known as the plextrin homology (PH) domain-containing kinases, are recruited to the antigen receptor signaling complex [48]. This family, also referred to as the Tec family of kinases includes Itk, Rlk, Btk, Bmx and Tec. The best-explored member is Btk - Bruton's or X-linked agammaglobulinemia (XLA) is due to mutations of eponymous kinase Bruton's tyrosine kinase or Btk. Mutations of *Btk* (or *BTK*) in mice and humans abrogates B cell development resulting in a lack of mature B cells [49,50]. Btk is critical for signal transduction downstream of the B cell receptor but also play a role in Toll like receptor and Fc-receptor signaling in myeloid cells. Btk deficient DC's have impaired secretion of inflammatory cytokines and Btk mast cells have impaired degranulation in response to Fc-receptor activation. By contrast, T cells are unaffected and Btk deficient patients can live essentially normal lives providing they receive regular transfusions of immunoglobulin. This can be explained by the fact that other PH-domain kinases including Tec, Itk and Rlk are expressed in T cells and mice lacking combinations of the three have T cells varying degrees of impaired function.

The robust and discrete genetic phenotype associated with BTK-deficiency, make it a logical pharmacological target. The Btk inhibitor PCI-32765 has efficacy in animal models of arthritis and as expected, acting on multiple effector cells [51,52]. This drug is currently in Phase II clinical trials for the treatment of B cell lymphomas including myeloma and chronic lymphocytic leukemia; however, given the success of B cell-directed therapy in RA, targeting Btk in RA would seem logical. Whether the absence of T cell mediated effects will diminish its potential for beneficial effects in RA is currently unclear.

Targeting Downsteam Kinases

After activation of the kinases proximal to antigen and Fc receptors, other critical kinases are also activated. These include members of the protein kinase C (PKC) family, mitogen-activated protein kinase (MAPK) family, the lipid kinases phosphoinositide 3-kinase, protein kinase B (PKB also known as AKT) and mammalian Target of Rapamycin (mTor) (Figure 3).

Protein kinase C family

One of the first defined antigen receptor-controlled signal transduction pathways was phospholipase C γ-mediated hydrolysis of phosphoinositide (4,5) bisphosphate. This results in the production of inositol polyphosphates and diacylglycerol, which regulate intracellular calcium levels and activate a number of diacylglycerol-activated serine kinases respectively [37,53–55]. Prominent among the diacylglycerol activated kinases are the members

of the protein kinase C family. One effector component of PKC in lymphocytes concerns activation of the NF-κB pathway [56]. In T cells PKCθ seems to be the main isoform responsible for NF-kB activation [57]. The PKC inhibitor sotrastaurin, AEB071, which blocks α, β, and θ isoforms, is currently undergoing clinical trials in psoriasis and renal transplantation [57–59]. On the basis of this mode of action it is reasonable to think that this drug may have efficacy in other autoimmune diseases.

PI-3K/PKB/mTor

Cytokines, antigen receptors, costimulator molecules and chemokines all can induce tyrosine phosphorylation of substrates, which activate another kinase, phosphatidylinositol 3-kinase (PI-3K). This enzyme generates the active lipids phosphatidylinositol $(3,4)P_2$ and $PI(3,4,5)P_3$, which activate protein kinase B (PKB, also called Akt) [60–62]. This in turn activates another kinase, PDK1. This pathway is important for the uptake of nutrients and the regulated metabolism of glycolysis [63–65]. The PI3K/ PKB signalling pathway has functions far beyond its roles in immune cells and is activated in human tumors [66,67]. This has made it a prime target for the development of small molecule inhibitors for the treatment of cancer; it remains to be seen is such drugs have a useful immunosuppressive function within an acceptable safety window.

Another kinase downstream of PI3K is the serine/ threonine kinase mammalian target of Rapamycin (mTOR), which regulates protein synthesis in response to cellular nutrient and energy levels [68]. It is activated by cytokines, but also by many other factors; in fact, mTor is conserved from yeast to mammals. At this juncture, it may seem odd to purposefully target a kinase that is ubiquitously expressed in all eukaryotes; however, rapamycin was generated and developed empirically in 1975, long before the elucidation of immune cell signaling pathways. As the name suggests, mTOR is inhibited by the macrolide, rapamycin, now licensed for the treatment of graft rejection as sirolimus. Sirolimus does not inhibit mTOR by direct binding to the ATP binding pocket, like the other inhibitors discussed thus far. Rather, it acts indirectly, associating with FK506 binding protein 12 (FKBP12). In view of the ubiquitous expression of mTOR and its role in protein translation, it is not surprising that sirolimus would be associated with varied side effects; these include hyperlipidemia, hypertrigliceridemia, myelosuppression and delayed wound healing [69]. Sirolimus has less renal toxicity than calcineurin inhibitors making it an attractive agent in allograft prophylaxis. There are currently three rapamycin derivatives undergoing clinical trials namely temsirolimus, everolimus and AP23573 [70].

Mitogen activated protein kinase (MAPK) family

The MAPK family constitutes a complex phospho-relay system of signal transduction, composed of three sequentially activated kinases that are themselves modulated by phosphorylation [71,72]. The top level of kinases is termed MAPK kinase kinases (MAPKKK or MKKK), the middle level MAPK kinases (MAPKK or MKK) and the lowest tier consists of the MAPKs. Like the mTor pathway, MAPKs are also conserved within eukaryotes. Three main MAPK cascades in mammalian cells include the ERK1,2 cascade, the JNK1/2 cascade and the p38 MAPK cascade. They are all activated in lymphocytes and antigen presenting cells downstream of ligand binding to antigen receptors, co-stimulatory and

adhesion molecules or cytokine receptors. Their differential function allows for fine tuning of cell responses to exogenous stress, cytokine and other immune receptor stimuli.

The ERK1,2 cascade is ubiquitous in mammalian cells and is generally considered to be one the main effector pathways regulated by the GTPase p21ras and the MKKK Raf. This pathway is activated in immune cells but is also activated in cancer. The mixed kinase inhibitor, Sorafenib is able to inhibit many kinases including Raf and is FDA approved in the treatment of liver and renal cell cancer [73]. Sorafenib is relatively well tolerated despite its ability to inhibit numerous kinases. Its role as an immunosuppressant has not been explored although its use is associated with the development of posterior encephalopathy syndrome [74], a side effect typically associated with the use of calcineurin inhibitors and other immunosuppressant drugs [75]. Other Raf inhibitors are under development. In addition, selective inhibitors of ERK are being developed: FR180204 has been shown to inhibit the development of CIA in mice and is being considered as an agent in the treatment of RA [76].

JNKs are activated by multiple receptors including the TCR, costimulatory molecules and the TNF receptor. Mouse CD4 T cells deficient in JNK1 or 2 have impaired Th1 polarization [77–79]. In CD8+ T cells the JNK proteins have contrasting roles: *Jnk1*-deficient CD8 T cells have impaired proliferation and cytokine production, whereas *Jnk2*-deficient CD8+ T cells have elevated cytokine expression [80,81]. Importantly, this pathway is important in TNF and IL-1 signaling [82–84] A number of small molecule inhibitors of Jun Kinases have been identified and are currently being investigated in animal models of autoimmune and inflammatory disease [85].

The third limb of the MAPK superfamily is the p38 MAPK cascade, which was identified as part of a drug screen specifically intended to find inhibitors of TNF-mediated inflammatory responses [86]. Although many p38 inhibitors have been reported, their development into therapeutic drugs has been frustrated by either unacceptable toxicity (AMG 548, BIRB 796) or poor efficacy (SCIO-469, VX-702) [87]. Nonetheless, work continues in this area continues [88]. While in principle, p38 inhibitors would be expected to be excellent anti-inflammatory drugs, the future of this approach is uncertain [89].

Conclusions

There is no question that effectiveness of biological therapies has been remarkable. However, it is also clear that there are now some new kids on the block to consider. Oral targeted therapies appear to be a reality, with the recent licensing of the first arrival, but rheumatologists will need to consider how they will use these agents in their practice. They will have to be develop an understanding of how these drugs are working, of how selective these agents are and whether selectivity is beneficial or not. With hundreds of potential kinases to target, this is field that is likely to expand considerably; rheumatologists are going to have to dust off their biochemistry texts! In the field of kinase inhibitors, much activity comes from oncology. There is a sense in which we are going back to the future since rheumatologists have a long history of borrowing drugs from oncologists. One might imagine, a range of such agents will have utility in autoimmune disease. The good news is

that its an exciting time – on top of very effective biologic agents, it appears that a number of highly effective oral drugs are on the horizon.

Acknowledgments

Nil

Biographies

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KEY POINTS

1. Biological therapies have revolutionized the therapy of rheumatoid arthritis; still, not all patients achieve remission and many exhibit partial responses
2. Advances in understanding signal transduction by key immunologic receptors offers numerous opportunities for devising new, oral targeted therapies
3. More than 60 cytokines signal by the Jak-Stat pathway and genetic evidence has established the criticality of these factors in cytokine signaling.
4. Janus kinase (Jak) inhibitors (Jakinibs) have now been approved for the treatment of rheumatoid arthritis and other diseases
5. A variety of other Jakinibs are being developed and tested in a range of autoimmune diseases
6. Spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase (Btk) are critical kinases downstream of key immunological receptors and inhibitors are being tested in rheumatoid arthritis and other diseases.
7. The human kinome comprises 518 kinases, so there is no shortage of potential new targets.

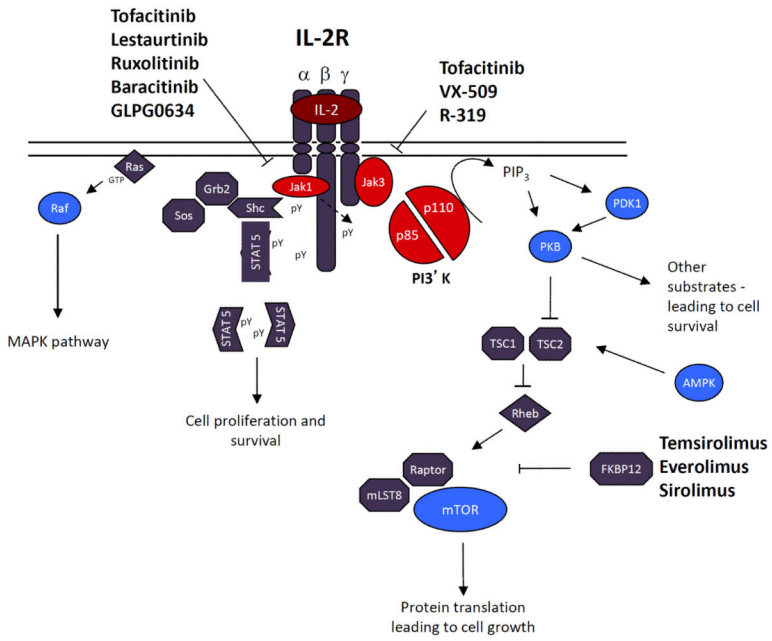

Figure 1. The role of Janus kinases (Jaks) in signaling by Type I/II cytokine receptors

Cytokines are structurally diverse and bind to structurally distinct receptors. One major class of cytokines are those that bind receptors belonging to the Type I/II family. These include many, but not all interleukins, interferons, colony and stimulating factors, as well as growth hormone, prolactin, and erythropoietin. Of note, IL-1, IL-17 and TNF do not signal by the Jak-Stat pathway. Shown here are the signal transduction pathways stemming from the IL-2 receptor in T cells culminating in the activation of the of signal transducer and activator of transcription 5, MAPK, and mTOR serine/ threonine kinase. The Raf-Ras-MAPK pathway is linked to cytokine receptors like the IL-2 receptor by adapter molecules such as SHC, Grb2 and SOS. IL-2 and other cytokines also activate PDK1 and PKB (Akt) leading to activation of mTor. In this regard, it is useful to note that although the term Jak-Stat pathway is frequently used, other pathways are also activated. As best we can tell, these pathways are also dependent upon Jaks; although, this is an area that deserves further research. Tyrosine kinases are indicated in red and serine threonine kinases are indicated in blue. The effect of various jakinibs is depicted. mTor inhibitors are also shown.

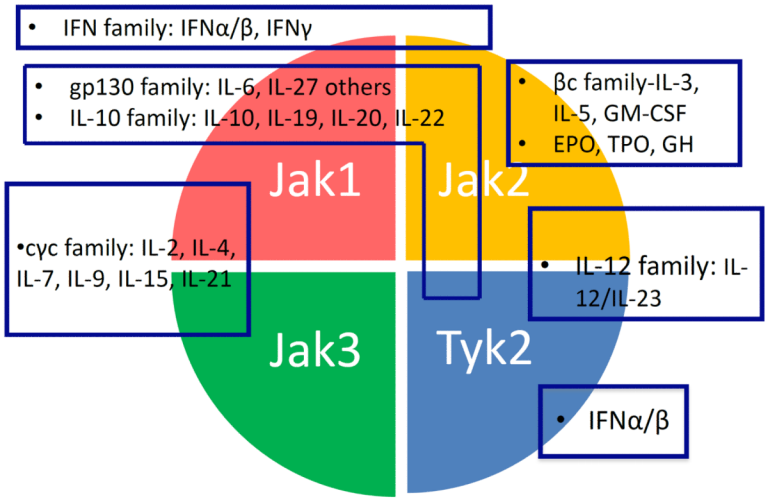

Figure 2. Usage of different Jaks by various cytokines

In considering the mechanism of action of different jakinibs it is useful to keep in mind the dependence of different cytokines on the various Jaks. Jak3 has the most selective function. As best we can tell, it associates uniquely with the common γ chain, γc. This cytokine receptor subunit is used by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. Inhibition of Jak3 therefore blocks signaling by these cytokines. Common γ chain cytokines also utilize Jak1, so agents that block Jak1 will also block IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. In contrast to Jak3, Jak1 is used by a number of other cytokine those that use gp130 (IL-6 and related cytokines), interferons, and IL-10-family cytokines. Like Jak1, Jak2 is important for signaling by an array of cytokines including IFNγ, IL-6, and other cytokines. Jak2 is important for signal by IL-3, IL-5 and GM-CSF. It is especially critical for erythropoietin (EPO), thrombopoietin (TPO), and growth hormone (GH). Thus, inhibitors that block Jak1 and Jak2 interfere with signaling by many proinflammatory cytokines, but also interfere with EPO signaling and thus can cause anemia. Tyk2 also contributes to IL-6 and IL-10 signaling and is especially important for the actions of IFNα/β. At present, there are no Tyk2 inhibitors in clinical use.

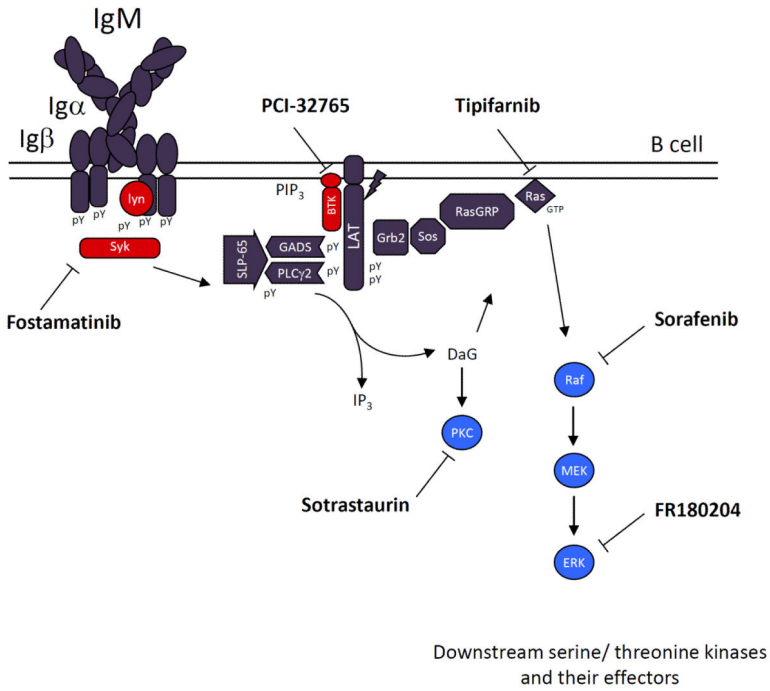

Figure 3. The proximal signalling events in response to the B cell receptor activation

A number of key immune receptors are structurally similar. Such receptors include the B cell receptor, T cell receptor and Fc receptors. These receptors are referred to as multichain immune recognition receptors and are just 3 of many different receptors in this family that trigger activation of immune cells. In the case of the B cell receptor, antigen binding activates Src family kinases such as Lyn, which phosphorylate receptor subunits. This allows the recruitment of Syk and activation of these membrane-proximal tyrosine kinases lead to phosphorylation of adapter molecules including SLP-76, GADS and LAT. This in turn activates Btk, phospholipase Cγ, and Ras. In this manner, second messengers like diacyglycerol and inositol trisphosphate are produced and downstream kinases including PKC, Raf, MEK, and Erk are activated. The actions of various inhibitors are depicted. Tyrosine and lipid kinases are indicated in red, serine/ threonine kinases indicated in blue.

Table 1

Jakinibs in trials for autoimmunity and cancer

Agent	Targeted Jak	Indication	Stage of Development
Tofacitinib	3, 1, 2	RA	FDA approved for RA
		Psoriasis	III
		Ulcerative colitis	III ongoing
		Dry eyes	II
		Renal transplantation	II
		Juvenile Idiopathic Arthritis	I
VX-509	3	RA	II
R-348	3	RA	I
Ruxolitinib	1, 2	MF	FDA approved for MF/PV
		Polycythemia vera	
		Essential thrombocythemia	
		Acute Leukemia, Lymphoma	II
		Multiple Myeloma	I/II
		Prostate Cancer	II
		Breast Cancer	II/terminated
INCB18424 (topical formulation)	1, 2	Psoriasis	II
Baricitinib (LY3009104 or INCB-28050)	1, 2	RA	II
		Psoriasis	IIb
		Diabetic Nephropathy	II
CYT387	1, 2	MF	I/II
GLPG-0634	1, 2, Tyk2	RA	II
SAR302503 (TG101348)	1, 2	MF	I/II
Pacritinib (SB1518)	2	MF	II

Abbreviations: RA: rheumatoid arthritis; IBD: inflammatory bowel disease; MF: myelofibrosis, SLE: systemic lupus erythematosus