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Syk kinase as a treatment target for therapy in autoimmune diseases

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Treatment of rheumatoid arthritis (RA) has been revolutionized by the introduction of targeted biologic treatments in the last few years [1]. These medications not only convincingly block inflammation but also protect the patients for bone-erosions, the main reason for disability in RA. Although these are highly effective drugs, they are nevertheless associated with significant side effects, such as reactivation of tuberculosis and other latent infections. Since most of these medications are injectable, they are also associated with significant discomfort and cost. Studies such as the one reported in this issue of Clinical Immunology by Pine et al. [2] are therefore important as we explore new therapeutic approaches with less side effects and less cost.

The authors use a new compound that can be given intravenously and orally (as a prodrug) that can block the activation of the spleen tyrosine kinase (Syk). This protein kinase associates with a variety of receptors on the surface of different cells of the immune system [3]. More recently it has also been shown to play a role in non-immune cells, such as the osteoclasts [4] as well as in breast cancer [5;6]. The binding of a receptor (such as the Fc receptor) and its ligand leads to the phosphorylation of a specialized protein motif called immunoreceptor tyrosine activating motif (ITAM) by the Src-family kinases (Fig. 1). These ITAM are situated on the intracytoplasmic domain of protein chains that are part of the receptor complex. This in turn leads to recruitment and activation of Syk and its association with the phosphorylated ITAM via its Src homology-2 domain (SH2). The activated Syk enzyme phosphorylates (activates) adaptor proteins such as SLP-76 family which lead to the activation of various genes and cytoskeletal rearrangement [3;7]. This pathway is shared by a variety of cells of the myeloid and lymphoid lineage making Syk a central control molecule of diverse cell responses to external stimuli.

An expanding list of immune but also non-immune cells depends on Syk for the intracytoplasmic propagation of signaling (Fig. 2). Syk was found initially to associate with the gamma chain of the high affinity receptor for the IgE (FcεRIγ) in mast cells [8]. The same gamma chain though is expressed in a variety of myeloid (including osteoclasts) and lymphoid cells (reviewed in [7]). In these cells the gamma chain associates with different receptors such as the FcγR, the alphaVbeta3 integrin and the T cell receptor. Upon engagement of these

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receptors with their ligands, Syk is activated orchestrating such diverse cellular processes as phagocytosis (in macrophages), bone resorption (in osteoclasts), or cytokine production (in T cells and monocytes). This makes Syk a therapeutic target for an array of inflammatory diseases.

In RA, inhibition of Syk may prevent bone erosions by dampening inflammation and decrease in the production of cytokines such as IL-1 and TNF- α , decreased effector T cell function or by directly inhibiting bone resorption by osteoclasts. The study presented in this issue provides significant insight into the effect of Syk signaling inhibition in collagen induced arthritis, a well studied animal model of RA. The authors show convincingly that Syk inhibition shortly after disease onset abrogates joint inflammation and bone erosions. Although the authors propose that interrupted osteoclastic signaling may account for the decreased erosions observed in the model, the exact mechanism is still unclear. Further confocal microscopic analysis of the joint specimens for expression of Syk may provide more definite answer as to the cells that mainly express Syk in collagen induced arthritis and RA and pave the way for even cell-specific Syk inhibition.

A different paradigm exists in SLE where the Fc γ -Syk associates with the T cell receptor (TCR) *in lieu* of the ζ chain-Zap70 [9]. This substitution is responsible at least in part for the overactive T cell phenotype observed in SLE and therefore Syk inhibition may lead to normalization of T cell function with lower calcium flux and more balanced gene expression. On the other hand R406, as shown in this study, may hamper immune-complex clearance by the monocyte-macrophage system which in the case of SLE may lead to further immune-complex deposition in the kidneys and greater availability of apoptotic nuclear material, the main source of autoantigens.

Another category of diseases that may benefit from Syk inhibition is the allergic diseases. Syk is the main molecule that transduces the signal generated by the engagement of Fc ϵ RI on mast cells by IgE. Inhibition of Syk will prevent mast cell degranulation and attenuation of symptoms in diseases such as asthma and allergic rhinitis [10].

The caveat with Syk inhibition as therapeutic modality is that Syk is important for key physiologic processes of the immune system. The reticulo-endothelial system depends on Syk for the correct recognition via the FcR and phagocytosis of foreign particles that are opsonized by immunoglobulin and/or complement [3]. Syk is also involved in B cell signaling through the B cell receptor and its inhibition may alter humoral immune responses as well [11].

Aberrant or upregulated expression of kinases is a key feature of many diseases and has therefore received great attention in manufacturing targeted therapies. Imatinib, a specific tyrosine kinase inhibitor has shown great results in the treatment of leukemia [12]. Similarly, Syk would be an attractive therapeutic target in a variety of conditions. A major challenge (as with most drugs) will be to inhibit Syk activity enough to stop pathologic processes (such as excessive osteoclast activity and inflammatory cytokine production in RA) without disrupting necessary cell functions (such as normal bone turnover or immune surveillance against tumors and infections).

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Figure 1. The role of Syk in immune cell signaling

Immunoreceptors (e.g. Fc receptor, FcR) are complexes of specialized molecules that are responsible for both the recognition of appropriate ligands and transduction of the signaling to the cytoplasm. Upon engagement of an immunoreceptor with its ligand (e.g. the FcR with IgG), members of the Src family of kinases phosphorylate distinct intracytoplasmic domains called ITAM (Immunoreceptor Tyrosine Activating Motifs). These ITAM reside on the intracytoplasmic molecular component of the receptor (in the case of Fc receptor, the FcR γ chain). Subsequently, the kinase Syk interacts with the ITAM and becomes activated. The activated Syk phosphorylates in turn adaptor proteins such as SLP-76 leading eventually to transcription factor activation, gene transcription and cytoskeletal rearrangement.

Figure 2. The role of Syk in different cells

A. Macrophages recognize opsonized foreign (and self) antigens via the FcγR. This leads by activation of Syk to the phagocytosis of the foreign material.

B. Effector CD4+ T cells upregulate Syk that associates with the T cell receptor (TCR)/CD3 complex via the Fcγ chain. Once the TCR binds to the MHC-Antigen complex on the antigen presenting cells (APC), Syk is activated which in turn leads to the production and secretion of an array of inflammatory cytokines.

C. Mast cells bear the FcεR on their surface that associates with the Fcγ chain and therefore Syk. Once the allergen-IgE complex binds to the FcεR, Syk is activated leading eventually to the secretion of stored histamine from the mast cells and the initiation of the allergic reaction.