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The role of Syk in osteoarthritis★

Vasileios C. Kytтары

Division of Rheumatology, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Ave, CLS-936, Boston, MA 02215, USA. Fax: +1 617 735 4170.

vkytтары@bidmc.harvard.edu.

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Osteoarthritis (OA) is the most common joint disease affecting in various forms more than 20% of the population above the age of 25 [1]. The medical treatment of OA has largely remained stagnant and mainly aims at alleviating pain associated with the disease. To date no disease modifying drugs have been successfully developed partly because the exact chain of events that initiate the osteoarthritic process, propagate tissue damage, and importantly cause pain and functional limitations are unclear.

From a pathophysiological standpoint, the osteoarthritic joint is characterized by aberrant metabolism in both the bone and cartilage compartments, and oftentimes inflammation especially at the synovial area [2]. The cause of the inflammatory response, and its relative contribution to tissue damage of the osteoarthritic joint is unclear though. Findings from synovial fluid analysis suggest that OA is associated with local innate immune system activation [3]. As part of this system, macrophages but also cells that are not classically thought as immune cells such as chondrocytes release mediators that cause or augment an inflammatory response that further damages the cartilage and its underlying bone.

Inorganic calcium containing crystals, found in damaged joints [4], have been implicated in the activation of the immune system. These crystals include calcium pyrophosphate dehydrate (CPPD) and basic calcium phosphate (BCP). CPPD and BCP are commonly found in osteoarthritic joints but are not necessarily associated with inflammation or found only in joints with osteoarthritis [5]. These crystals turn on the production of cytokines [6], nitric oxide [7] and matrix metalloproteinases [8]. There is some evidence that the mitogen activated kinase (MAPK) and protein kinase C (PKC) pathways mediate BCP effects on articular cells [9], but the exact mechanism that activates cells that come in contact with BCP crystals remains controversial. Calcium containing crystals may be internalized and switch on calcium-dependent signaling pathways or interact with surface receptors and activate the cells to proliferate and produce cytokines.

In this issue of Clinical Immunology Cunningham et al. [10], explored further the role of BCP in inducing inflammatory responses. The authors first show that LPS primed murine macrophages incubated with BCP produce high levels of interleukin (IL)-1 β and IL-18, both important cytokines in propagating joint damaging responses. More importantly, longer incubation of non-primed macrophages with BCP resulted in production of S100A8, a well-

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described damage associated molecule that may further activate the macrophages through Toll like receptors leading to production of IL-1 β . Therefore BCP may cause the production of IL-1 β both directly and indirectly through autocrine effect of S100A8.

The authors sought to further characterize the signaling pathways that lead to the production of pro-inflammatory cytokines by BCP. They found that the spleen tyrosine kinase (Syk) and PI3 kinase are necessary for the induction of IL-1 β following macrophage activation by BCP. Importantly, pharmacologic inhibition of Syk and PI3K resulted in complete abrogation of proinflammatory cytokines by these cells. The chain of events that leads to BCP-induced Syk activation remains obscure. As stated above, the crystals could be endocytosed and activate the kinase in the cytosol, or interact with an unknown receptor on the surface of the cells. Since Syk is a molecule that associates with immunoreceptors, interaction of BCP with an as yet non characterized membrane receptor would be the most likely pathway to lead to Syk activation.

The immunoreceptors that preferentially or promiscuously interact with Syk include among others the B cell receptor, the Fc receptor [11], C-type lectin receptor (reviewed in [12]), and the T cell receptor [13]. Given this wide distribution among immune cells, Syk represents an attractive target for the treatment of various autoimmune and allergic diseases as well as metabolic bone diseases and lymphomas. The oral Syk inhibitor fostamatinib has already shown positive results in two phase II trials in rheumatoid arthritis [14] and is moving forward in a phase III study. Based on the study by Cunningham et al., inhibition of Syk may alter the course of osteoarthritis and calcium crystalline arthropathies. Since osteoarthritis is a complex pathologic process, *in vivo* studies using animal models of OA, will first be needed to test the usefulness of fostamatinib or other Syk inhibitors in treating OA. These studies will also answer several questions regarding the contribution of Syk to OA pathology:

- a. Which cell types express Syk in the osteoarthritic joint?
- b. How is Syk activated by BCP?
- c. Does Syk cause an inflammatory response or is also contributing to osteoclast activation and bone resorption?

Eventually, these studies will set the stage for clinical trials of Syk inhibitors in selected patients with OA, especially patients who have co-existing inflammation and/or deposition of calcium in the joints.

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