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Editorial

Does signaling pathway inhibition hold therapeutic promise for osteoarthritis?

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Osteoarthritis was long viewed as a degenerative joint disease characterized by gradual cartilage attrition. Mechanical factors were very often incriminated and patient management limited to pain control. Subsequently, osteoarthritis was defined as a family of diseases involving all the articular and periarticular tissues, including the muscles and tendons [1]. The role for synovitis and subchondral-bone sclerosis has been firmly established. Research focused on the joint tissues and documented changes in the metabolic activity and phenotype of chondrocytes, synoviocytes, and subchondral-bone osteoblasts. Several signaling pathways have been incriminated in these changes. Examples include the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, whose activation by numerous cytokines (e.g., IL-1) and growth factors upregulates the expression of many genes involved in connective tissue inflammation and breakdown; and the NF-κB/HIF-2α pathway, which plays a role in endochondral ossification. Activation of the κB/HIF-2α pathway by mechanical factors or proinflammatory cytokines stimulates production by the chondrocytes of osteogenic factors, matrix metalloproteinase (MMP)-13, and collagen type X [2]. Another relevant pathway is JAKs/STATs, which ensures rapid signal transduction between membrane receptors and target genes. Janus kinases (JAKs) are involved in activating phosphorylation via the transcription factors signal transducers and activators of transcription (STATs), which migrate to the nucleus, where they bind to DNA sequences within target gene promoters. The JAKs/STATs pathway is activated by numerous cytokines such as IL-6. JAKs/STATs activation induces the expression of genes encoding proinflammatory cytokines and MMPs directly involved in cartilage breakdown and synovial membrane inflammation [3]. Activation of the Insulin/IGF-1/Pl3k/Akt/forkhead-box class O (FoxO) pathway is related to chondrocyte aging. FoxO factors play a central role in cell resistance to oxidative stress [4] and their inhibition results in decreased antioxidant production. The Wnt pathway is also a focus of active research. Its role is complex. Wnt pathway activation and inhibition induce osteoarthritis in experimental animals [5]. These pathways constitute potential treatment targets.

More recently, osteoarthritis has been described as a metabolic disease, based on evidence of a correlation between clinical hand osteoarthritis severity and obesity [6]. Obesity does not increase the mechanical loads on the hands, and a systemic effect of obesity on hand osteoarthritis has therefore been suggested [7]. Adipose tissue releases proinflammatory cytokines (e.g., tumor necrosis factor-α, IL-6) and adipokines (e.g., leptin, adiponectin, and visfatin), which exert deleterious effects on joint tissues (Fig. 1) [8]. Studies of patients with obesity have shown associations linking osteoarthritis to the metabolic syndrome and its components (hypertension, dyslipidemia, and type 2 diabetes). Furthermore, associations have been reported between knee osteoarthritis and metabolic syndrome components such as type 2 diabetes and hypertension, independently from the presence of obesity or other known risk factors for osteoarthritis [9]. Finally, the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and hyperglycemia increases the risk of knee osteoarthritis development and progression [10]. The link between metabolic syndrome and osteoarthritis may be chronic low-grade systemic inflammation characterized by elevated circulating levels of reactive oxygen species, oxidized low-density lipoproteins (LDLs), lipid mediators, or adipokines.

These recent data have changed the manner in which both patients and healthcare professionals view osteoarthritis. Clinicians and researchers are now seeking to classify patients with osteoarthritis based on the disease phenotype. Potential categories include metabolic osteoarthritis, early genetic osteoarthritis, age-related osteoarthritis, and posttraumatic osteoarthritis. Phenotype-based classification will result in management strategies tailored to the disease characteristics, thereby increasing the response rates to each treatment.

The therapeutic objective in patients with osteoarthritis is to control the symptoms via a combination of pharmacological and nonpharmacological treatments [11]. The main nonpharmacological treatments are weight loss and physical exercise designed to maintain muscle function and to decrease body fat. Nonsteroidal anti-inflammatory drugs and paracetamol are the most widely used drugs but carry a high risk of severe side effects that limits their use in patients with osteoarthritis and comorbidities.

In contrast to patients with rheumatoid arthritis (RA), those with osteoarthritis have not yet benefited from treatment breakthroughs capable of significantly slowing disease progression.

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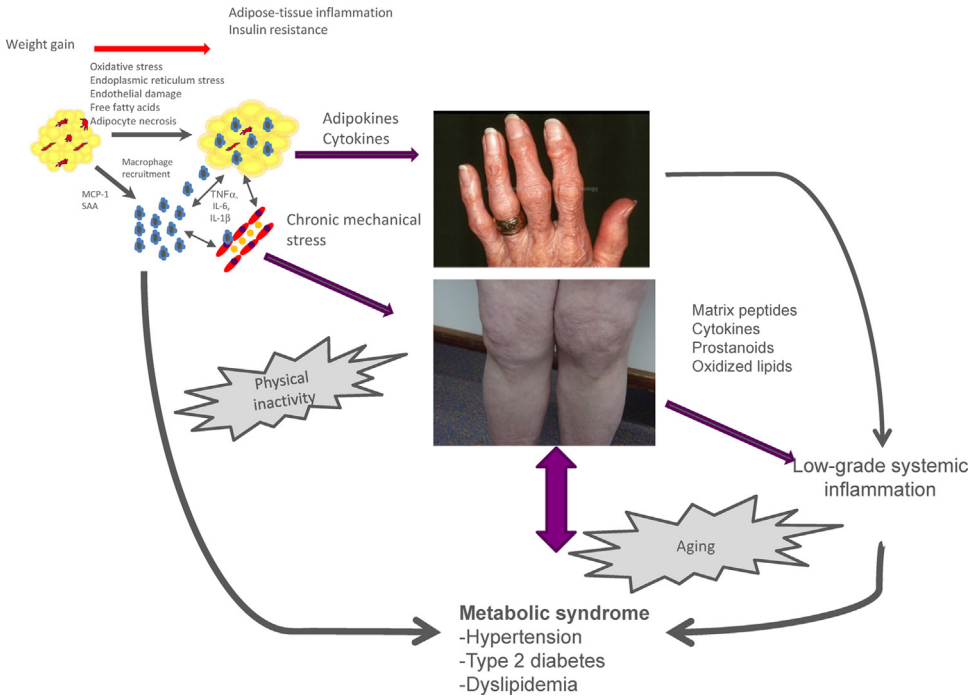

Fig. 1. Pathophysiology of osteoarthritis (OA) associated with obesity. MCP-1: monocyte chemotactic protein-1; SAA: serum amyloid A; IL-1β: interleukin-1 beta; TNF-α: tumor necrosis factor alpha; IL-6: interleukin-6. Since a relationship was demonstrated between hand osteoathritis and obesity, obesity-related OA is considered as a metabolic diseases involving systemic between the two conditions through the release of proinflammatory cytokines but also adipokines likes leptin, adiponect ot visfatin which can directly activate chondrocytes like mechanical stress or proinflammatory cytokines. Obesity also promotes a number of co-morbidities, including the metabolic syndrome, which may increase the risk of OA. Finally, OA, particularly age-related OA, is associated to chronic low-grade inflammation through the mediator released by joint tissues but also by other ageing tissue.

Biotherapies targeting IL-1 or TNF have shown little efficacy in patients with hand or knee osteoarthritis [12]. In addition, the severe side effects of these targeted treatments limit the acceptability of their long-term use, as they are disproportionate with the severity of osteoarthritis. Nevertheless, patients with osteoarthritis may benefit from therapeutic advances achieved in RA, notably from the development of small molecules that specifically inhibit the JAKs. An example is CP-690,550 (tofacitinib). JAK/STAT pathway inhibition is now a treatment target not only in RA, but also in osteoarthritis. Tofacitinib inhibits the activity of JAKs 1, 2, and 3, exhibiting greater affinity for JAK3 than for JAKs 1 and 2. Tofacitinib has been evaluated in six phase II studies and six phase III studies including about 5000 patients with RA [3]. The results showed significant decreases in symptoms and disease activity, even in patients having failed prior biotherapies [13]. The incidence of side effects (infections and gastric perforation) was similar to that seen with biotherapies [14]. To our knowledge, tofacitinib has not yet been evaluated in patients with osteoarthritis. Nevertheless, the results of trials in RA suggest that tofacitinib may eventually become the first specific signaling pathway inhibitor for evaluation in patients with osteoarthritis. Finally, the recently identified Runx1 inhibitor TD-198946 prevents the development of cartilage damage in mice with osteoarthritis induced by surgical meniscectomy and section of the median knee ligament [15].

Signaling pathways hold promise as treatment targets in osteoarthritis, as their inhibition or activation regulates the expression of a set of target genes directly involved in joint tissue metabolic dysfunctions. Nevertheless, the first clinical trials in RA have shown that specific regulation of the JAK/STAT pathway induces numerous side effects. Thus, safety concerns may limit the use of specific inhibitors or activators of signaling pathways in osteoarthritis. The risk/benefit ratio must remain at the center of treatment decisions, as osteoarthritis is a slowly progressive and moderately severe disease that is associated with multiple comorbidities.

Disclosure of interest

YH is the founder and a shareholder of Artialis SA and Synolyne Pharma, two spin-off of the University of Liège. He has received consulting fees from Tilman SA and the Laboratoires Expanscience. He has also received speaker fees from IBSA and BioIberica.

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