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Commentary

Pleiotropic effect of fibrates on senescence and autophagy in osteoarthritis

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For a long time, research on osteoarthritis (OA) has mainly focused on alterations and treatment of cartilage morphological features, even though it is now widely acknowledged that other tissues such as synovium, subchondral bone, menisci, ligaments, periarticular muscles, and adipose tissue are equally involved in its pathology [1,2]. In particular, the latter takes part in inflammatory processes and imbalanced metabolism, within the joint, by releasing cytokines and adipokines [1]. It is widely known, nowadays that OA is a multifactorial degenerative and severe disease, in which several factors concur to its onset [2]. Only recently, the concept of the metabolic syndrome-associated OA type emerged next to the post-traumatic and age-related ones [1,2]. There is emerging evidence that beyond the role of common systemic pathogenic mechanisms shared by metabolic diseases and OA, such as low-grade inflammation and oxidative stress, the same diseases may induce a local effect on the joints [3]. Proteomic analyses in isolated healthy and osteoarthritic chondrocytes show that some proteins, including peroxisome proliferators-activated receptors (PPAR) and apolipoproteins, are related to lipid metabolism [4]. Peroxisome proliferator-activated receptor α (PPARα), in particular, modulates the uptake and catabolism of fatty acids by upregulation of genes involved in fatty acid transport, binding and activation, and peroxisomal and mitochondrial fatty acid β-oxidation. Moreover, PPARα ligands exert anti-inflammatory effects on various cell types, including macrophages, smooth muscle cells, endothelial cells, lymphocytes, and other cell types. It has been shown that PPARα activation has an anti-inflammatory effect determined by the inhibition of the nuclear translocation of nuclear factor κB (NFκB) by the upregulation of inhibitor κB (IκB) [5]. Pharmacological PPARα agonists, or fibrates, which have long been used for the treatment of dyslipidemia are recently being used in experimental and clinical studies for their anti-inflammatory effects [6]. This pleiotropic effect of fibrates makes them a potential candidate for the treatment of OA. By exerting anti-inflammatory effects, the fibrates decrease cartilage damage and reduce both local (synovial) and systemic inflammation. In addition, they reduce dyslipidemia and vascular pathology. In a recent and interesting study by Nogueira-Recalde and co-authors, published in *EBioMedicine*, the authors evaluate the effect of fibrates on cartilage damage related to the ageing process and autophagy suppression [7]. The latter brings the chondrocytes to express the so-called senescence-associated secretory phenotype (SASP), which in turn triggers a cascade of pathologic events in cartilage, leading to OA onset. The authors chose to use the PPARα agonists by screening compounds that both decrease senescence and increase autophagy in human chondrocytes. They concluded that PPARα activation by fibrates attenuated inflammation, enhanced autophagy flux specifically in senescent chondrocytes, partially reversing the ageing process and preventing cartilage degradation. The positive effects of fibrates on cartilage have been already reported in the literature [8], even though there are some emerging issues regarding the use of these compounds in relation to the specific OA subtype [9]. However, the novelty and the compelling aspect of the study conducted by Nogueira-Recalde and co-authors relies on the fact that the authors took into account the multi-factorial concert concurring in OA development. In particular, the connection highlighted by them regarded several fundamental aspects of OA aetiology, i.e. lipid metabolism dysregulation involved in the inflammation process occurrence mediated by PPAR pathways, ageing-related chondrocyte phenotype alterations and autophagy-related maintenance of chondrocyte homeostasis changes. The authors decided then to use the compounds able to act on different fronts and to exert a pleiotropic effect on the cartilage tissue, demonstrating, that PPARα ligands selectively act as senolytic agents via apoptotic mechanism and reduce the systemic inflammation. Another important aspect of the study is that to open a new horizon for the basic research concerning the clarification of the paramount interplay existing within the PPAR pathways and their contribution to OA development. Without any doubt, further studies in this field are needed to establish the molecular aspects of PPAR pathways in order to identify the new disease-modifying therapeutic agents to be used in clinical practice. Certainly, the use of fibrates needs to be further investigated in vivo and in humans in order to evaluate its effectiveness on the articular cartilage and to verify their pharmacokinetic, pharmacodynamic, metabolic, pathophysiologic and cytotoxicity on muscles [10]. In conclusion, we firmly believe that the present investigative tactic, based on the multi-

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factorial approach to this complex disease is fundamental to reach the new insights that might be easily transduced into successful therapy for the OA.

Declaration of Competing Interests

All authors have no competing interests to declare.

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