Journal of Investigative Surgery

ISSN: 0894-1939 (Print) 1521-0553 (Online) Journal homepage: https://www.tandfonline.com/loi/iivs20

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To cite this article: Paola Castrogiovanni, Silvia Ravalli & Giuseppe Musumeci (2020) Apoptosis and Autophagy in the Pathogenesis of Osteoarthritis, Journal of Investigative Surgery, 33:9, 874-875, DOI: 10.1080/08941939.2019.1576811

To link to this article: https://doi.org/10.1080/08941939.2019.1576811

Published online: 24 Mar 2019.

Journal of Investigative Surgery, 33: 874–875, 2020

ISSN: 0894-1939 print / 1521-0553 online
DOI: 10.1080/08941939.2019.1576811

COMMENTARY

Apoptosis and Autophagy in the Pathogenesis of Osteoarthritis

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Osteoarthritis (OA) is a degenerative disease in which a low-grade inflammation in cartilage and synovium occurs, causing a deterioration of cartilage and the consequent joint disability. OA is a multifactorial disease depending on genetic and/or epigenetic factors, such as sex, age, cellular senescence, and lifestyle. Several and different molecular pathways are involved in the pathogenesis of OA, and an extensive scientific literature exists concerning this issue in order to achieve possible preventive and/or therapeutic treatments for OA patients [1]. Molecules involved in the cartilage degeneration are numerous and acting through pathways often shared with other molecular signals. Nowadays, research is addressed to investigate the biomarkers involved in the onset and pathogenesis of OA, developing new diagnostic and prognostic assays of this disease. Scientific data suggest a crucial role for death/survival of chondrocyte, in fact, apoptotic cell death has been highlighted in human osteoarthritic tissue specimens, also associated with extracellular matrix degradation and calcification which severity has been positively correlated with apoptosis [2]. Apoptosis is a highly regulated and controlled "programmed cell death," conferring advantages during the lifecycle of organisms. It can be activated through two alternative pathways, death receptor-mediated and mitochondria-dependent, leading to the activation of caspases responsible for the deterioration of tissues [2, 3]. Among the biomarkers of OA, for example, nitric oxide plays an evident role in chondrocyte apoptosis [4]. Nitric oxide operates through the mitochondria-dependent pathway and it increases the synthesis of pro-inflammatory cytokines involved in the degeneration of the extracellular matrix of cartilage [5]. Even if nitric oxide alone does not induce apoptotic cell death in chondrocytes, scientific data report that it can cause cell death and induce the tumor suppressor protein p53 via p38 mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB) [6]. In contrast to apoptosis, autophagy is a self-degradative process involved in response to cell stress, for balancing sources of energy. Autophagy is important for cartilage homeostasis as it promotes cell survival by adapting cells to stress conditions. Moreover, autophagy has also been considered as a nonapoptotic cell death program [7] and it shares some characteristics with apoptosis such as the absence of inflammation during the death process and ATP consumption [7]. Recent data support the idea that autophagy could occur in combination with apoptosis in OA [7]. In particular, it seems that in early stages of OA, autophagy could be activated as an adaptive response that avoids cell death, whereas, in late stages of OA, it could be conjunctly activated with apoptosis as an alternative pathway to cellular death [8]. Identification of biomarkers of chondrocyte death (apoptosis and/or autophagy) may help the development of novel therapies that could reduce the speed of the degenerative processes in OA. Rapamycin is an autophagy activator and it has an inhibitory effect on inflammation. Moreover, autophagy can remove debris from catabolic disorders and delay the degeneration of cartilage caused by inflammation [9]. Data from the current literature show that, in human chondrocytes, rapamycin activates autophagy preventing the development of OA in vitro, while the systemic and/or intra-articular injection of rapamycin reduces the severity of experimental OA in vivo [10].

In a recent and interesting research, published in *Journal of Investigative Surgery*, authors investigated

Received 26 January 2019; accepted 28 January 2019.
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the effect of rapamycin, at 20 nM noncytotoxic concentration, in human chondroblasts cell culture and in an OA mouse model and related mechanism using several molecular tests and histological evaluation [9]. These data demonstrated that rapamycin at 20 nM concentration does not impair cell viability. Moreover, rapamycin in the in vivo experiments induces autophagy that shows the ability to clear catabolic genes, instead, in the in vitro experiments, in which the autophagy pathway was silenced by ATG5 siRNA, rapamycin inhibits catabolic genes and inflammation [9]. The relation between autophagy activated by rapamycin and the NF-κB signaling pathway has been confirmed, demonstrating that rapamycin may inhibit the activation of the NF-κB signaling pathway. The authors conclude that rapamycin can inhibit the overexpression of inflammatory catabolic genes by activating autophagy, and may suppress the NF-κB signaling pathway in chondrocytes to break the positive feedback loop with inflammatory factors and reduce the rate and level of inflammation progression. These findings add evidence to screening of the target clinical therapy for OA and explore individualized treatment for OA patients in clinical practice [9]. This article is a testimony of the efforts that the scientific community did, to help better understanding, the molecular mechanisms and therapeutic interventions to reduce the progression of the OA disease.

We take this opportunity, with this commentary, to thank all scientists who give a valid contribution to improve the effects of this debilitating disease for OA patients.

DECLARATION OF INTEREST

The authors report no conflict of interest.

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