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Review

Research progress on osteoarthritis treatment mechanisms

Yun-Tao Gu[a,1], Jian Chen[a,1], Zhu-Long Meng[b], Wan-Yu Ge[c], Yang-Yang Bian[b], Shao-Wen Cheng[b], Chen-Kun Xing[b], Jiang-Ling Yao[a], Jian Fu[a,*], Lei Peng[a,*]

[a] Department of Orthopaedic Surgery, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, 325000, China
[b] Trauma Center, The First Affiliated Hospital of Hainan Medical College, Haikou, Hainan Province 570100, China
[c] Department of Pathology, Anhui Provincial Hospital, Hefei, Anhui Province 230000, China

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ABSTRACT

Osteoarthritis is a common disease and is frequently encountered in the older population; the incidence rises sharply with age. It is estimated that more than 360 million people suffer from OA. However, the pathogenesis of osteoarthritis remains unclear, and we cannot effectively prevent the progression of OA. The aim of this review was to explore the molecular markers and signaling pathways that induce chondrocyte apoptosis in OA. We searched, using the key words osteoarthritis, chondrocyte apoptosis, autophagy, endoplasmic reticulum stress, molecular targets, and biomarkers, in PubMed, Web of Science, and Google Scholar from 1994 to 2017. We also reviewed the signaling pathways and molecular markers associated with chondrocyte apoptosis and approaches aimed at inhibiting the apoptosis-inducing mechanism to at least delay the progression of cartilage degeneration in OA. This article provides an overview of targeted therapies and the related signaling pathways in OA.

Contents

1. Introduction

Osteoarthritis (OA) is a progressive and degenerative joint disease, and represents one of the largest socioeconomic health-care burdens in the world [1]. It involves increasing age, obesity,

* Corresponding authors.
E-mail addresses: fujiangz@126.com (J. Fu), 15607662705@163.com (L. Peng).
[1] Yun Tao-Gu and Jian Chen contributed equally to this work and should be considered as co-first authors.

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articular cartilage, strain, trauma, congenital joint abnormalities, and joint deformities resulting from many factors, such as the degradation of damaged articular cartilage and bony edges in reactive hyperplasia. It is also known as osteoarthritis, degenerative arthritis, elderly arthritis, and hypertrophic arthritis. Clinical manifestations include the slow development of joint pain, tenderness, stiffness, joint swelling, limited mobility, and joint deformities. The diagnosis, treatment, and rehabilitation of children, adolescents, and adults with bone, joint, and connective tissue disorders has attracted the attention of many scientists and clinicians [2]. Over the years, 'conventional' treatments of bone, joint, and connective tissue disorders have involved analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Acetaminophen does relieve OA pain but its anti-inflammatory effect is weak. However, long-term use can cause liver damage. NSAIDs have anti-inflammatory and analgesic characteristics and can reduce joint pain and improve joint mobility. NSAIDs, such as ibuprofen and naproxen, are effective in treating more chronic forms OA pain. However, long-term consumption of NSAIDs can cause stomach issues, cardiovascular problems, and kidney and liver damage. Narcotics and opioids are used to treat more serious OA pain. These strong conventional drugs have a major risk with regard to the development of dependence. Negative effects of narcotics and opioids also include vomiting, sleepiness, and constipation.

Articular cartilage contains chondrocytes, cells that synthesize and degrade the extracellular matrix (ECM), an avascular tissue that includes non-collagenous proteins, type II collagen, large, aggregating proteoglycans, and smaller hydrophilic macromolecules [3]. The major pathogenic events in OA include loss and abnormal remodeling of the cartilage extracellular matrix [4]. Chondrocytes are the only cell type in the articular cartilage; they respond to injury, maintain tissue homeostasis, and perform the cartilage remodeling process that characterizes OA. Apoptosis has been reported as a possible pathway in the pathology of OA and an association has been demonstrated between programmed cell death in chondrocytes and cartilage degradation in OA [5,6]. Furthermore, recent research has suggested that chondrocyte apoptosis is closely associated with cartilage matrix integrity and the development of OA [7] [8]. In contrast to pathological cell death, apoptosis is programmed, orderly, and does not induce inflammation. Apoptosis is a form of programmed cell death that does not release harmful substances into the surrounding area; it involves a pre-determined sequence of events leading to the elimination of old, unhealthy, and unnecessary cells [9]. The important role of apoptotic mechanisms in cartilage degeneration and the involvement of apoptosis in various conditions associated with OA have been investigated [10,11]. Oxidative stress, endoplasmic reticulum stress, and inappropriate mechanical signals can induce apoptosis in chondrocytes. Studies have found that many factors, such as growth factors, inflammatory cytokines, and signaling pathway molecules, are involved in these processes. This review will address growth factors, inflammatory cytokines, signaling pathways, and other issues to provide a theoretical basis for the treatment of OA.

2. Endoplasmic reticulum stress (ERS) and autophagy

2.1. ERS and the unfolded protein response (UPR)

Cartilage degeneration develops along with chondrocyte apoptosis [12], regarded as a key factor in the progression of OA [6]. When death stimuli factor activates one of three distinct cell death pathways – the endoplasmic reticulum (ER) stress pathway, the mitochondrial, or the plasma membrane death receptor pathway – apoptosis is triggered [8]. Stress in the ER, generally as part of the cellular stress response, leads to the accumulation of unfolded or misfolded proteins in the ER; this can happen under a variety of circumstances. In eukaryotic cells, the ER is the place where membrane and secreted proteins undergo folding and assembly before delivery to the extracellular milieu or other cellular compartments. The ER protein folding control mechanisms can be disturbed by various factors, such as infection or hypoxia, leading to ER stress [13]. When cells are unable to successfully accommodate the ER stress or to reestablish homeostasis, the levels of chaperones and ER protein-folding enzymes increase, resulting in triggering of the unfolded protein response (UPR), which then activates a series of cell death programs. ER chaperones, such as 78 kDa glucose-regulated protein (Grp78), which degrade misfolded or unfolded proteins via the ubiquitin proteasome system in the cytosol, enhance folding activity in the ER [14]. Excessive ER stress-induced apoptotic events are mediated by transcriptional activation of the gene for C/EBP-homologous protein (Chop) [15], which immediately regulates death effectors, such as Bcl-2 and Bim [15,16]. The pathogenesis of numerous diseases has been related to ER stress and UPR signaling, including diabetes, neurodegeneration, inflammation, and cancer.

The presence of ER stress is first indicated by ER membrane-bound stress-sensor proteins activating transcription factor 6 (ATF6), protein kinase RNA-like ER kinase (PERK), and inositol-requiring enzyme 1 (IRE1) [17]. One of the first responses of the cell to ER stress is activation of the PERK pathway. The PERK pathway is an arm of the UPR that mediates protein translation. Another transcription factor, ATF6, induces pro-apoptotic events as a response to the continued presence of ER stress in the cell, with activation of Chop [18]. It has been shown that ER stress-induced apoptosis, regulated by nitric oxide, was inhibited by Chop knockdown in rat chondrocytes. It has also been demonstrated that 4 weeks after surgery, the progression of cartilage degeneration was markedly less in Chop-knockout mice in a murine OA model, showing that Chop plays an important role in ER stress-induced apoptosis that leads to cartilage degeneration [19,20]. The evolutionarily oldest ER stress pathway is the IRE1 pathway, which has dual pro-apoptotic and pro-survival roles [21]. ATF6 activation is mediated by Site-1 and Site-2 proteases (S1P and S2P), which travel from the ER to the Golgi in stress, and are activated by intramembrane proteolysis [22] [23]. Through studying advanced OA patients, expression levels of Grp78 and Bcl-2-associated athanogene-1 (bag-1), markers of ER stress, were upregulated in articular cartilage, indicating the role of ER stress in the pathogenesis of OA [24]. It is clear that inappropriate induction of ER stress and UPR activation is detrimental to normal chondrogenic differentiation and/or hypertrophic maturation. ER stress-induced genes include X-box binding protein (XBP1S) and IRE1α, which apparently affect ER stress-mediated apoptosis in chondrocytes [25,26]. Recently, studies have shown the potential therapeutic effect of small-molecule stimulation of adaptive ER stress responses in animal models of OA caused by cartilage destruction. Thus, the development of small-molecule targeted therapies in chondrocytes from individual patients will likely be needed. Additionally, there is currently a paucity of data indicating the direct effect of apoptosis inhibition in the treatment of OA.

2.2. Autophagy

Autophagy is a self-degradative process that is used to remove damaged organelles and protein aggregates, and to offer additional energy in response to cell stress. In eukaryotic cells [27], it can be induced by a wide range of stimuli, such as oxygen depletion and metabolic stress. Although autophagy is not a type of cell death, it plays an important role in regulating cell death and cartilage homeostasis [28]. Considering the significant role of autophagy in