ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

Advances inprogrammed cell death in temporomandibular joint osteoarthritis

Peng Yu[1,2], Yinghao Jing[1,2], Zhongcheng Gong[1,2,*]

[1]Oncological Department of Oral and Maxillofacial Surgery, the First Affiliated Hospital of Xinjiang Medical University, School/Hospital of Stomatology Xinjiang Medical University, Urumqi, 830054, Xinjiang Uygur Autonomous Region, China
[2]Stomatological Research Institute of Xinjiang Uygur Autonomous Region, Urumqi, 830054, Xinjiang Uygur Autonomous Region, China
**Corresponding author: gump0904@aliyun.com*

Abstract: *Temporomandibular joint osteoarthritis (TMJOA) is a clinically common chronic degenerative disease of the TMJ. The degeneration of articular cartilage is a sort of typical pathological characteristics; and chondrocytes' death is the kernel event in cartilaginous degeneration. Programmed cell death (PCD) has become a academic hotspot in the development of TMJ OA. Based on the concept, aetiology, morphological feature, pathogenesis of five well-known PCD including apoptosis, autophagy, pyroptosis, necroptosis and ferroptosis, as well as their recent research progresses on cartilage degeneration, this narrative review was designed and performed.*

Keywords: *Apoptosis; Autophagy; Pyroptosis; Necroptosis; Ferroptosis; Osteoarthritis; Chondrocyte*

1. Introduction

Osteoarthritis (OA) is a disease that can cause severe pain and dysfunction in any joint, including the temporomandibular joint (TMJ)[1]. Cartilage degeneration is the main pathological change in temporomandibular joint osteoarthritis (TMJ OA), and chondrocytes are the only cell type present in cartilage tissue[2] . Therefore, a basic hypothesis was formed that chondrocyte death is the central event in the overall cartilage degeneration process. Programmed cell death (PCD) is a form of cell death that can be regulated and is involved in the development of OA[3] . As a research hotspot, the purpose of this paper is to provide new inspiration and ideas for future basic research on cartilage degeneration in TMJOA based on the research progress of programmed cell death in OA cartilage degeneration.

2. Apoptosis

2.1 Apoptosis overview

Kerr et al [4]formally and systematically defined apoptosis in 1972 as an active, physiological process of cell death that can be induced by cells under certain physiological or pathological conditions. The main morphological features include cell volume reduction, loss of mitochondrial membrane potential, nucleus fixation, and apoptotic vesicle formation, but the cell membrane remains relatively intact and does not activate the inflammatory response[5]. Depending on the conditions, the mechanism of apoptosis is divided into two pathways: endogenous and exogenous [6]. Exogenous apoptosis is mainly mediated by members of the tumor necrosis factor (TNF) family, which form death-inducing signaling complexes on the cell membrane and cause apoptosis [7]. Endogenous apoptosis is caused by changes in the intracellular environment such as endoplasmic reticulum stress and reactive oxygen species aggregation, which cause incomplete mitochondrial membranes, mitochondrial rupture, apoptotic vesicle formation, and consequently apoptosis[6].

2.2 Effect of chondrocyte apoptosis on cartilage degeneration in OA

Chao et al [8]found that the progression of OA is closely related to apoptosis of chondrocytes. In the iodoacetic acid-induced TMJOA rat model, an early feature of cartilage degeneration is chondrocyte apoptosis[9]. Cysteine aspartate-proteinase-3 (caspase-3) plays an important role in apoptosis, and when

ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

stimulated exogenously or endogenously, it mediates chondrocyte DNA long chain breaks and apoptosis, affecting the development of OA [10].Mino-Oka et al [11]found that the effect of mechanical stress on condylar cartilage production, such as hypoxia-inducible factor-1α (hypoxia-inducible factor-1α, HIF-1α), elevated protein expression of vascular endothelial growth factor (VEGF) and caspase-3-mediated chondrocyte apoptosis, which in turn caused significant cartilage degeneration. Secondly, in an interleukin-1β (IL-1β)-induced OA model in mice, Aucubin directly protected mouse articular cartilage tissue by inhibiting chondrocyte apoptosis and effectively slowed the progression of OA in mice[12]. Ding et al[13]found that in a lipopolysaccharide (LPS)-induced chondrocyte injury model, miR-93 slowed down the inflammatory response by inhibiting chondrocyte apoptosis, which may be associated with activation of the TLR4/NF-κB signaling pathway.Therefore, chondrocyte apoptosis appears to be a potential target for therapeutic intervention in OA.

3. Autophagy

3.1 Overview of cell autophagy

"Autophagy" was first introduced by Duve et al [14]in 1963. It is a phenomenon of cellular self-phagocytosis, in which cells under physiological or pathological conditions form autophagosomes (autophagy) by wrapping proteins and organelle degradation products by bilayers of rough endoplasmic reticulum or Golgi apparatus and other sources[15], and then combine with lysosomes to form autophagic lysosomes for digestion and degradation of various enzymes, and their breakdown products can be reused by cells, thus achieving the maintenance of cell The breakdown products can be reused by cells, thus maintaining cellular homeostasis [16]. Autophagy is a self-protective and immunomodulatory mechanism that protects the host cells, but excessive reliance on autophagy can further lead to massive cell death in the host [15]. Autophagy is divided into the following three more common types: macroautophagy, microautophagy, and molecular chaperone-mediated autophagy. Autophagy is a highly complex and dynamic growth and evolutionary process in biological cells, which can be briefly divided into three complex developmental stages: phagocytic vesicle production, autophagic vesicle differentiation, and finally autophagic lysosome formation, and some major morphological features of autophagy can be clearly observed on transmission electron microscopy scans, such as crescent-shaped phagocytic vesicles and autophagic vesicles with an average diameter of 500 nm [17].

3.2 Effect of chondrocyte autophagy on cartilage degeneration in OA

Autophagy-related proteins Beclin1, ULK1 and microtubule associated protein 1 light chain 3 (LC3) were found to be highly expressed in normal articular cartilage, but significantly reduced in articular cartilage and chondrocytes of OA patients [18]. Xue et al [19]also reported for the first time that some inflammatory factors could effectively inhibit the proliferation and reduce the autophagy rate of rat chondrocytes and that the PI3K/AKT/mTOR signaling pathway could promote autophagy in OA rat articular chondrocytes and thus reduce the inflammatory response. Moreover, rapamycin, often used as a receptor agonist for autophagy, can effectively promote autophagy to slow down the progression of OA [20]. In a study by Zhong et al[21]and others, miRNA-335-5p expression was found to be significantly higher in normal chondrocytes than in OA chondrocytes. Similarly, in transfecting human OA chondrocytes with miRNA-335-5p mimics, cell viability and autophagy-related factors were increased as well as inflammatory factor expression was reduced. In conclusion, numerous studies have shown that autophagy dysfunction can lead to OA and that activation of autophagy can alleviate articular cartilage degeneration[22].

4. Pyrotosis

4.1 Overview of cell scorch death

In 2001, Brad Cookson et al [23]named for the first time a cysteinase-1 (caspase-1)-dependent but distinct from apoptosis mode of death as cytosolic scorch death. The morphological changes include the formation of many micropores and vesicles in the cell membrane, accompanied by cell swelling and rupture, as well as the secretion of various cytokines involved in the inflammatory response, which in turn produce pro-inflammatory signals to surrounding cells and cause osmotic lysis of adjacent cells [24]. Cell scorch death is broadly classified into classical and non-classical pathways, mediated by caspase-1 and caspase-4/-5/-11, respectively. In the classical cell scorch pathway, when cells are damaged, NOD-

ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

like receptor (NLR), apoptosis-associated spot-like protein (ASC) and caspase-1 constitute inflammatory vesicles (NLRP1, NLRP3, NLRC4, etc.), and caspase-1 activated by inflammatory vesicles directly shears Gasdermin D (GSDMD), the executive protein of cell scorch death, forming a plasma membrane pore of about 18 nm in size, resulting in massive release of inflammatory factors and damage-associated molecular patterns (DAMPs), increased intracellular membrane osmotic pressure, and cell swelling and rupture death[25]. Unlike the classical pathway, the non-classical pathway does not require inflammatory vesicles but is directly activated by inflammatory factors such as lipopolysaccharide (LPS), and the activated caspase-4/5/11 shear the GSDMD, which after shearing produces the formation of plasma membrane pores, resulting in cell swelling, rupture and death [25].

4.2 Effect of chondrocyte scorch death on OA cartilage degeneration

Cell scorching is closely associated with the development of OA and exacerbates cartilage degeneration[26].Zu et al [27]isolated and cultured human OA chondrocytes in vitro and detected increased levels of NLRP3, IL-1β, IL-18 mRNA and protein expression.Icariside (icariin,ICA) attenuated LPS-induced chondrocyte by inhibiting NLRP3 inflammatory vesicles scorching and cellular inflammation, and it was further confirmed in a rat OA model that icariin (ICA) alleviated OA by inhibiting NLRP3-mediated cellular scorching.Yan et al [28], in their analysis of a mouse model of OA, found that bivalirudin increased the thickness of hyaline cartilage as well as type II collagen expression and decreased matrix metalloproteinase 13 (MMP13), NLRP3, caspase-1, GSDMD, and IL-1β protein expression, suggesting that bivalirudin may slow the progression of OA by inhibiting scorch death. In addition, LIU et al [29]found that low-dose indomethacin and Hedgehog signaling inhibitors synergistically reduced the expression of caspase-1, IL-1β and IL-18 at the mRNA and protein levels after a more in-depth study, while attenuating cartilage damage in a mouse model of OA, suggesting that there may be a causal link between cellular scorch death and cartilage degeneration. The above indicates that cell scorch death does exist in OA chondrocytes, and the inhibition of cell scorch death mechanism may become a new idea for OA treatment.

5. Necroptosis

5.1 Overview of Necroptosis

In the past, most scholars believed that cell necrosis was an active form of cell death, but after 2000, some scholars began to discover a non-cysteine aspartate protease (caspase) mediated by receptor-interacting protein 1 (RIP1), which has the characteristics of necrosis but is regulated by related genes [30]. In 2005, Degterev et al[31]first officially announced the name of this regulated necrosis as programmed necrosis. Morphological manifestations are early disruption of cell membrane integrity, altered osmotic pressure, and disintegration and release of cytosolic contents into the surrounding environment[32]. When programmed necrosis occurs, its cytosolic contents, such as high mobility group box-1 protein (HMGB), tumor necrosis factor-α (TNF-α), etc., can be directly used as damage associated molecular patterns (DAMPs). molecular patterns (DAMPs) are released into the surrounding environment and trigger inflammatory responses in the surrounding tissues [32]. Among them, the TNF-α-mediated programmed necrosis signaling pathway has received the most attention and has been most intensively studied.

5.2 Effect of programmed chondrocyte necrosis on OA cartilage degeneration

Jana Riegger et al[33]found a possible link between cartilage degeneration and programmed necrosis. Zhang et al [34]found that the expression of programmed necrosis-related markers RIP1 and RIP3 were significantly elevated in chondrocytes under sustained mechanical force and could be reversed by programmed necrosis inhibitor (Nec-1). Similarly, protein expression of RIP3 was found to be significantly higher in cartilage of OA patients than in normal cartilage [35]. In China, it has been reported that HMGB1 mRNA and protein expression were also found to be upregulated in articular disc and synovial specimens from TMJ OA patients and in an in vitro model of TMJ OA induced by IL-1β[36][37]. Studies by Japanese scholars further confirmed the presence of large amounts of HMGB1 in the synovial fluid of OA patients and that its histopathological structure was significantly altered by inhibition of HMGB1 in a collagenase-induced OA model in rats[38].In their work, Liang et al [39]intervened in an unstable medial meniscus (DMM) mouse OA model by a programmed necrosis inhibitor (Nec-1). model, showed that Nec-1 alleviated the inflammatory response, downregulated matrix metalloproteinase (MMP)

ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

and HMGB1 protein expression, and significantly reduced OA cartilage destruction. This suggests that programmed necrosis plays an integral role in OA cartilage degeneration and may be a new therapeutic strategy by inhibiting programmed necrosis.

6. Ferroptosis

6.1 Overview of Ferroptosis

In 2003, Dolma et al[40], in a joint study on the mechanism of RAS oncogene-mutated human foreskin fibroblast death induced by the small molecule Erastin, discovered a novel cell death mode that could not be reversed by the use of various cell death inhibitors such as apoptosis, necrosis, autophagy, and pyroptosis, but could be effectively reversed by treatment with the antioxidant vitamin E and iron chelator (desferrioxamine). In 2012, Dixon et al[41]first formally introduced this new form of programmed cell death, named " Ferroptosis", which is morphologically and biochemically different from other forms of programmed cell death. Morphological aspects show a gradual rupture of the cell membrane, a decrease in the size of mitochondria, an increase in the relative density of mitochondrial membranes, and a decrease or even disappearance of mitochondrial cristae, but the nucleus is basically normal in size[42]. Biochemical features include elevated lipid peroxidation, accumulation of iron and reactive oxygen species (ROS), depletion of intracellular glutathione (GSH), and inactivation of glutathione peroxidase 4 (GPX4)[43]. The mechanisms of iron death regulation are complex and involve mainly iron metabolism, lipid peroxidation metabolism and imbalance of antioxidant system. GPX4 has been shown to be a key regulator of iron death, and inhibition of GPX4 induced Ferroptosis in a mouse tumor model[44]. The results of Doll et al[45]suggested that long-chain esteryl coenzyme A synthetase 4 (ACSL4) is a key substance in triggering iron death-related mechanisms when GPX4 is inactivated.Chang et al[46]found that the oncogene p53 promoted iron death by suppressing the expression of solute carrier family 7member 11 (SLC7A11).

6.2 Effect of chondrocyte Ferroptosis on OA cartilage degeneration

Up to now, the study of Ferroptosis in OA is at an early stage, and in TMJ OA is at a blank stage. However, there are some common features between the two, such as abnormal iron metabolism, lipid peroxidation and mitochondrial dysfunction. The lack of mechanisms to promote normal iron excretion in the body and the lack of effective blood circulation in articular cartilage also predispose iron ions to accumulate in cartilage for a long period of time, thus creating an iron overload environment[47]. As early as 2005, studies began to initially demonstrate that the concentration of iron in the synovial fluid of OA patients was much higher than that of rheumatoid arthritis patients and healthy subjects[48].In 2021, Yao et al[49]also found for the first time that chondrocytes could undergo iron death in a state of inflammation or iron overload, and that the iron death inducer Erastin selectively upregulated the protein expression of chondrocyte MMP13 and inhibited the protein expression of chondrocyte The results were reversed by ferroptosis inhibitor (Ferrostain-1), and similarly, intra-articular injection of ferroptosis inhibitor (Ferrostain-1) in its rat OA model slowed cartilage degradation and increased protein expression of collagen II and GPX4, demonstrating that chondrocyte ferroptosis promotes the development of OA. In addition, it has been found that D-mannose slows the progression of OA by reducing the sensitivity of chondrocytes to ferroptosis[50]. It can be expected that as iron death in OA becomes more comprehensively studied, the use of ferroptosis for OA may become a new means of treatmen.

7. Summary and Outlook

In addition to the above, there are various cell death modes, such as Paraptosis, Methuosis, Oncosis, Anoikis, and Cuprotosis. In addition, there are multiple signaling pathways in OA cartilage degeneration, such as Notch[51]and Wnt/β-catenin[52]involved in apoptosis, NF-κB[53]involved in focal death, and PI3K/AKT [54]involved in autophagy. The research progress of programmed cell death in TMJ OA is a new clinical hotspot, but also faces great challenges. For example, it is sometimes difficult to effectively identify the regulatory roles of various types of cell death modalities at different times in the development of TMJ OA. Whether there is an interconnection between different forms of cell death. In this article, we would like to summarize the sources, concepts and mechanisms of programmed cell death, including apoptosis, autophagy, programmed necrosis, scorch death and iron death, and some of the current research progress in TMJ OA, hoping to lay the foundation for future research on the role of cell death in TMJ OA, and to promote the development of new therapeutic targets, thus providing valuable clues

ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

for the development of related molecular targets. We hope to provide valuable clues and tools for drug development.

References

[1] Wang X D, Zhang J N, Gan Y H, et al. Current understanding of pathogenesis and treatment of TMJ osteoarthritis [J]. J Dent Res, 2015, 94:666-673.
[2] Scrivani S J, Keith D A, Kaban L B. Temporomandibular disorders [J]. N Engl J Med, 2008, 359:2693-2705.
[3] Yang J, Hu S, Bian Y, et al. Targeting Cell Death: Pyroptosis, Ferroptosis, Apoptosis and Necroptosis in Osteoarthritis [J]. Front Cell Dev Biol, 2021, 9:789948.
[4] Kerr J F, Wyllie A H, Currie A R. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics [J]. Br J Cancer, 1972, 26:239-257.
[5] Zhang Y, Chen X, Gueydan C, et al. Plasma membrane changes during programmed cell deaths [J]. Cell Res, 2018, 28:9-21.doi: 10.1038/cr.2017.133
[6] Kesavardhana S, Malireddi R K S, Kanneganti T D. Caspases in Cell Death, Inflammation, and Pyroptosis [J]. Annu Rev Immunol, 2020, 38:567-595.
[7] Yuan X, Gajan A, Chu Q, et al. Developing TRAIL/TRAIL death receptor-based cancer therapies [J]. Cancer Metastasis Rev, 2018, 37:733-748.
[8] Cheng C, Tian J, Zhang F, et al. WISP1 Protects Against Chondrocyte Senescence and Apoptosis by Regulating αvβ3 and PI3K/Akt Pathway in Osteoarthritis [J]. DNA Cell Biol, 2021, 40:629-637.
[9] Wang X D, Kou X X, He D Q, et al. Progression of cartilage degradation, bone resorption and pain in rat temporomandibular joint osteoarthritis induced by injection of iodoacetate [J]. PLoS One, 2012, 7:e45036.
[10] Hwang H S, Kim H A. Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis [J]. Int J Mol Sci, 2015, 16:26035-26054.
[11] Mino-Oka A, Izawa T, Shinohara T, et al. Roles of hypoxia inducible factor-1α in the temporomandibular joint [J]. Arch Oral Biol, 2017, 73:274-281.
[12] Wang B W, Jiang Y, Yao Z L, et al. Aucubin Protects Chondrocytes Against IL-1β-Induced Apoptosis In Vitro And Inhibits Osteoarthritis In Mice Model [J]. Drug Des Devel Ther, 2019, 13:3529-3538.
[13] Ding Y, Wang L, Zhao Q, et al. MicroRNA-93 inhibits chondrocyte apoptosis and inflammation in osteoarthritis by targeting the TLR4/NF-κB signaling pathway [J]. Int J Mol Med, 2019, 43:779-790.
[14] Duve C D. Structure and Functions of Lysosomes [M]. Funktionelle und Morphologische Organisation der Zelle, 1963.
[15] Liu X, Tang Y, Cui Y, et al. Autophagy is associated with cell fate in the process of macrophage-derived foam cells formation and progress [J]. J Biomed Sci, 2016, 23:57.
[16] Kanayama M, Shinohara M L. Roles of Autophagy and Autophagy-Related Proteins in Antifungal Immunity [J]. Front Immunol, 2016, 7:47.
[17] Kovács A L, Pálfia Z, Réz G, et al. Sequestration revisited: integrating traditional electron microscopy, de novo assembly and new results [J]. Autophagy, 2007, 3:655-662.
[18] Caramés B, Taniguchi N, Otsuki S, et al. Autophagy is a protective mechanism in normal cartilage, and its aging-related loss is linked with cell death and osteoarthritis [J]. Arthritis Rheum, 2010, 62:791-801.
[19] Xue J F, Shi Z M, Zou J, et al. Inhibition of PI3K/AKT/mTOR signaling pathway promotes autophagy of articular chondrocytes and attenuates inflammatory response in rats with osteoarthritis [J]. Biomed Pharmacother, 2017, 89:1252-1261.
[20] Bao J, Chen Z, Xu L, et al. Rapamycin protects chondrocytes against IL-18-induced apoptosis and ameliorates rat osteoarthritis [J]. Aging (Albany NY), 2020, 12:5152-5167.
[21] Zhong G, Long H, Ma S, et al. miRNA-335-5p relieves chondrocyte inflammation by activating autophagy in osteoarthritis [J]. Life Sci, 2019, 226:164-172.
[22] Duan R, Xie H, Liu Z Z. The Role of Autophagy in Osteoarthritis [J]. Frontiers in Cell and Developmental Biology, 2020, 8.
[23] Cookson B T, Brennan M A. Pro-inflammatory programmed cell death [J]. Trends Microbiol, 2001, 9:113-114.
[24] Ball D P, Taabazuing C Y, Griswold A R, et al. Caspase-1 interdomain linker cleavage is required for pyroptosis [J]. Life Sci Alliance, 2020, 3.
[25] Xia X, Wang X, Cheng Z, et al. The role of pyroptosis in cancer: pro-cancer or pro-"host"? [J]. Cell Death Dis, 2019, 10:650.
[26] Man S M, Kanneganti T D. Regulation of inflammasome activation [J]. Immunol Rev, 2015, 265:6-21.
[27] Zu Y, Mu Y, Li Q, et al. Icariin alleviates osteoarthritis by inhibiting NLRP3-mediated pyroptosis

ISSN 2618-1584 Vol. 5, Issue 3: 63-68, DOI: 10.25236/FMSR.2023.050311

[J]. J Orthop Surg Res, 2019, 14:307.
[28] Yan J, Ding D, Feng G, et al. Metformin reduces chondrocyte pyroptosis in an osteoarthritis mouse model by inhibiting NLRP3 inflammasome activation [J]. Exp Ther Med, 2022, 23:222.
[29] Liu Q, Wu Z, Hu D, et al. Low dose of indomethacin and Hedgehog signaling inhibitor administration synergistically attenuates cartilage damage in osteoarthritis by controlling chondrocytes pyroptosis [J]. Gene, 2019, 712:143959.
[30] Holler N, Zaru R, Micheau O, et al. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule [J]. Nat Immunol, 2000, 1:489-495.
[31] Degterev A, Huang Z, Boyce M, et al. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury [J]. Nat Chem Biol, 2005, 1:112-119.
[32] Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation [J]. Nature, 2015, 517:311-320.
[33] Riegger J, Brenner R E. Evidence of necroptosis in osteoarthritic disease: investigation of blunt mechanical impact as possible trigger in regulated necrosis [J]. Cell Death Dis, 2019, 10:683.
[34] Zhang C, Lin S, Li T, et al. Mechanical force-mediated pathological cartilage thinning is regulated by necroptosis and apoptosis [J]. Osteoarthritis Cartilage, 2017, 25:1324-1334.
[35] Jeon J, Noh H J, Lee H, et al. TRIM24-RIP3 axis perturbation accelerates osteoarthritis pathogenesis [J]. Ann Rheum Dis, 2020, 79:1635-1643.
[36] Feng Y, Fang W, Li C, et al. The expression of high-mobility group box protein-1 in temporomandibular joint osteoarthritis with disc perforation [J]. J Oral Pathol Med, 2016, 45:148-152.
[37] Li C, Cai H, Meng Q, et al. IL-1β mediating high mobility group box protein-1 expression in condylar chondrocyte during temporomandibular joint inflammation [J]. J Oral Pathol Med, 2016, 45:539-545.
[38] Hamada T, Torikai M, Kuwazuru A, et al. Extracellular high mobility group box chromosomal protein 1 is a coupling factor for hypoxia and inflammation in arthritis [J]. Arthritis Rheum, 2008, 58:2675-2685.
[39] Liang S, Lv Z T, Zhang J M, et al. Necrostatin-1 Attenuates Trauma-Induced Mouse Osteoarthritis and IL-1β Induced Apoptosis via HMGB1/TLR4/SDF-1 in Primary Mouse Chondrocytes [J]. Front Pharmacol, 2018, 9:1378
[40] Dolma S, Lessnick S L, Hahn W C, et al. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells [J]. Cancer Cell, 2003, 3:285-296.
[41] Regulated by PTHrP treatment [J]. Arch Oral Biol, 2014, 59:1032-1041.
[42] Dixon S J, Lemberg K M, Lamprecht M R, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death [J]. Cell, 2012, 149:1060-1072.
[43] Xie Y, Hou W, Song X, et al. Ferroptosis: process and function [J]. Cell Death Differ, 2016, 23:369-379.
[44] Huang L, McClatchy D B, Maher P, et al. Intracellular amyloid toxicity induces oxytosis/ferroptosis regulated cell death [J]. Cell Death Dis, 2020, 11:828.doi: 10.1038/s41419-020-03020-9
[45] Yang W S, SriRamaratnam R, Welsch M E, et al. Regulation of ferroptotic cancer cell death by GPX4 [J]. Cell, 2014, 156:317-331.
[46] Doll S, Proneth B, Tyurina Y Y, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition [J]. Nat Chem Biol, 2017, 13:91-98.
[47] Chang L C, Chiang S K, Chen S E, et al. Heme oxygenase-1 mediates BAY 11-7085 induced ferroptosis [J]. Cancer Lett, 2018, 416:124-137.
[48] Simão M, Gavaia P J, Camacho A, et al. Intracellular iron uptake is favored in Hfe-KO mouse primary chondrocytes mimicking an osteoarthritis-related phenotype [J]. Biofactors, 2019, 45:583-597.
[49] Yazar M, Sarban S, Kocyigit A, et al. Synovial fluid and plasma selenium, copper, zinc, and iron concentrations in patients with rheumatoid arthritis and osteoarthritis [J]. Biol Trace Elem Res, 2005, 106:123-132.
[50] Yao X, Sun K, Yu S, et al. Chondrocyte ferroptosis contribute to the progression of osteoarthritis [J]. J Orthop Translat, 2021, 27:33-43.
[51] Zhou X, Zheng Y, Sun W, et al. D-mannose alleviates osteoarthritis progression by inhibiting chondrocyte ferroptosis in a HIF-2α-dependent manner [J]. Cell Prolif, 2021, 54:e13134.
[52] Liu Z, Ren Y, Mirando A J, et al. Notch signaling in postnatal joint chondrocytes, but not subchondral osteoblasts, is required for articular cartilage and joint maintenance [J]. Osteoarthritis Cartilage, 2016, 24:740-751.
[53] Ma L, Wu J, Jin Q H. The association between parathyroid hormone 1-34 and the Wnt/β-catenin signaling pathway in a rat model of osteoarthritis [J]. Mol Med Rep, 2017, 16:8799-8807.
[54] Rigoglou S, Papavassiliou A G. The NF-κB signalling pathway in osteoarthritis [J]. Int J Biochem Cell Biol, 2013, 45:2580-2584.
[55] Deng Z, Liu Y, Wang C, et al. Involvement of PI3K/Akt pathway in rat condylar chondrocytes regulated by PTHrP treatment [J]. Arch Oral Biol, 2014, 59:1032-1041.