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CARTILAGE

The role of AGEs in pathogenesis of cartilage destruction in osteoarthritis

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Osteoarthritis (OA) is a degenerative disease resulting from progressive joint destruction caused by many factors. Its pathogenesis is complex and has not been elucidated to date. Advanced glycation end products (AGEs) are a series of irreversible and stable macromolecular complexes formed by reducing sugar with protein, lipid, and nucleic acid through a non-enzymatic glycosylation reaction (Maillard reaction). They are an important indicator of the degree of ageing. Currently, it is considered that AGEs accumulation in vivo is a molecular basis of age-induced OA, and AGEs production and accumulation in vivo is one of the important reasons for the induction and acceleration of the pathological changes of OA. In recent years, it has been found that AGEs are involved in a variety of pathological processes of OA, including extracellular matrix degradation, chondrocyte apoptosis, and autophagy. Clearly, AGEs play an important role in regulating the expression of OA-related genes and maintaining the chondrocyte phenotype and the stability of the intra-articular environment. This article reviews the latest research results of AGEs in a variety of pathological processes of OA, to provide a new direction for the study of OA pathogenesis and a new target for prevention and treatment.

Cite this article: *Bone Joint Res* 2022;11(5):292–300.

Keywords: Osteoarthritis, Advanced glycation end products, Cartilage extracellular matrix, Chondrocyte apoptosis, Chondrocyte autophagy

Article focus

- Advanced glycation end products (AGEs) can cause a variety of pathological changes in osteoarthritis (OA), including degradation of the extracellular matrix, inhibition of autophagy of chondrocytes, and promotion of apoptosis of chondrocytes.
- The detailed mechanism underlying the roles of AGEs in the development of OA has yet to be elucidated.

Key messages

- The production of AGEs can be blocked in vivo, and AGEs metabolism can be promoted in many ways.
- AGEs, via the receptor for advanced glycation end products (RAGE) receptor, stimulate a series of pathological reactions such as inflammation, autophagy, apoptosis, and matrix degradation through complex signal transduction mechanisms in cells. In addition, AGEs cross-link to articular cartilage collagen, thus damaging the structure and function of the cartilage matrix.

Strengths and limitations

- This article introduces the generation and metabolism of AGEs in the human body, and discusses the possible pathway mechanism and preventive treatment methods of AGEs in cartilage destruction of OA.
- This article focuses on cartilage destruction in OA, and other pathological processes in OA (e.g. synovitis, subchondral bone pathology, vascular invasion) have not been explored.

Introduction

Osteoarthritis (OA) is the most common chronic and progressive degenerative joint disease, mainly characterized by progressive joint destruction.[1,2] Currently, the World Health Organization lists OA, cardiovascular

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doi: 10.1302/2046-3758.115.BJR-2021-0334.R1

Bone Joint Res 2022;11(5):292–300.

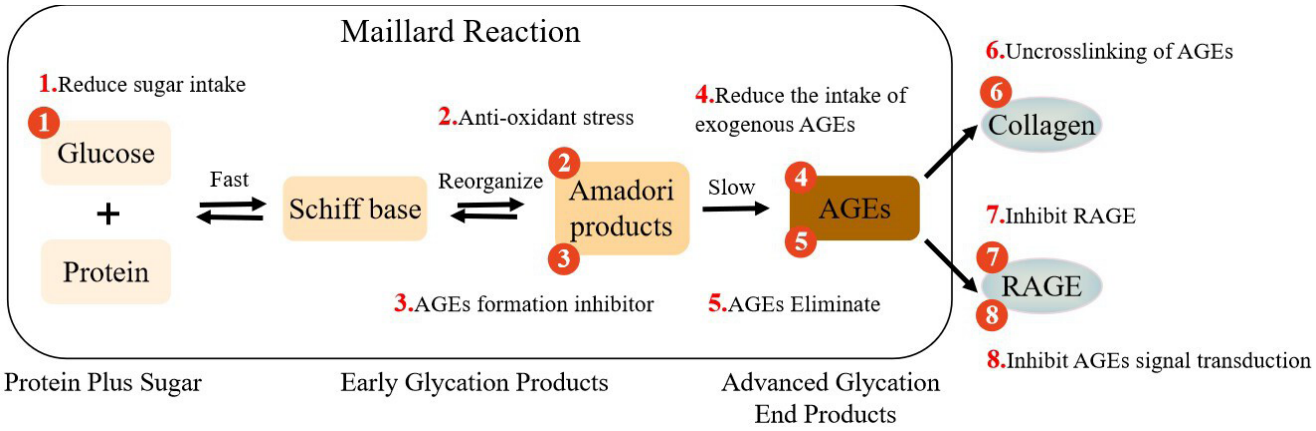

Fig. 1

The process of advanced glycation end products (AGEs) generation, cross-linking with collagen (COL), and interaction with receptor for advanced glycation end products (RAGE). The numbers indicate eight strategies for intervention against AGEs. (1) Control of sugar intake, stabilization of blood sugar, and decreasing accumulation of AGEs. (2) Use of antioxidants to reduce oxidative stress and inhibit the last step of the Maillard reaction. (3) Use of AGEs to form inhibitors to decrease the production of AGEs. (4) Consumption of a low-AGEs diet to decrease the intake of exogenous AGEs. (5) Use of soluble forms of AGEs receptors or AGEs lysozyme to eliminate AGEs. (6) Use of medications (such as ALT-711) to break AGEs cross-links. (7) Inhibition of the AGEs receptor RAGE to prevent downstream signalling pathways from functioning. (8) Inhibition of AGEs signal transduction to block activated intracellular pathways.

disease, and cancer as the three major diseases threatening human health, and the overall incidence of OA is increasing annually.[3] OA not only seriously affects the quality of life of patients, but also places a heavy burden on the social economy and medical care system. Existing OA treatment methods can only alleviate the clinical symptoms, but cannot delay or completely stop the progressive development of OA, with the effective treatment of late OA being joint arthroplasty.[4] The OA prevalence rate is increasing, becoming an ever more serious social and public health problem.[5]

AGEs and OA. The pathogenic factors of OA are very complex. According to one view, OA is a mismatch disease caused by the human body's inability to adapt to a rapidly changing new environment.[6] The joint tissue degeneration caused by human genetic and environmental mismatch is not only affected by immutable age factors, but is also related to many variable factors, including exercise, obesity, metabolism, and diet among others.[7-10] The mechanisms and inter-relationships of these related factors are unclear. With increasing age, the OA incidence increases, and the disease continues to worsen, while excessive exercise and being overweight or obese can lead to excessive mechanical stress load of the joints, which can lead to OA.[11]

Currently, it is considered that the accumulation of advanced glycation end products (AGEs) in vivo is a molecular basis of age-induced OA, and AGEs production and accumulation in vivo is one of the important factors for causing and accelerating the pathological changes of OA.[12-16] The mechanism is related to the direct action of its cross-linking with protein and the indirect action caused by its receptor (receptor for advanced glycation end products (RAGE)) binding, thereby activating a series of intracellular signal transduction pathways.[17-21] AGEs formation inhibitors (e.g. aminoguanidine) and AGEs cross-linking inhibitors (e.g. ALT-711) can delay and improve the pathological changes of OA, but cannot completely prevent OA progression.[20,22] Since AGEs are difficult to decompose and metabolize in vivo, the continuous activation of intracellular signalling pathways induced by the ongoing presence of AGEs may be an important reason for the continuous progression of OA. This article mainly reviews the role of AGEs in OA occurrence and development, aiming to provide a new target and direction for OA treatment.

Formation and cross-linking of AGEs. AGEs are a series of irreversible stable macromolecular complexes formed by reducing sugar with protein, lipid, and nucleic acid through a series of non-enzymatic glycosylation reactions (Maillard reaction). They are an important indicator of the degree of ageing.[23] An unstable compound, the Schiff base, is formed in the early stage of the Maillard reaction, which is the result of the condensation between the electrophilic carbonyl group of the reducing sugar and the free amino group (normally lysine or arginine). The rearrangement of Schiff bases will form a relatively stable ketoamine (Amadori products).[24] Amadori products can also irreversibly form very stable AGEs by participating in oxidation, dehydration, or polymerization (Figure 1).[24] AGEs form covalent bonds with free amino groups on adjacent proteins, thus yielding a cross-linked AGEs structure. Within tissues, glycation results in the formation of protein aggregates, owing to bonds created through three distinct mechanisms: 1) the formation of covalent bonds between glycation end products; 2) the oxidation of sulphur groups (sulfhydryl groups) into disulfide bridges; and 3) the formation of new reactive groups within proteins. Chemical bridges formed by AGEs also result in the reticulation of proteins and their cross-linking (assembly), a phenomenon that occurs within the extracellular matrix (ECM) and greatly

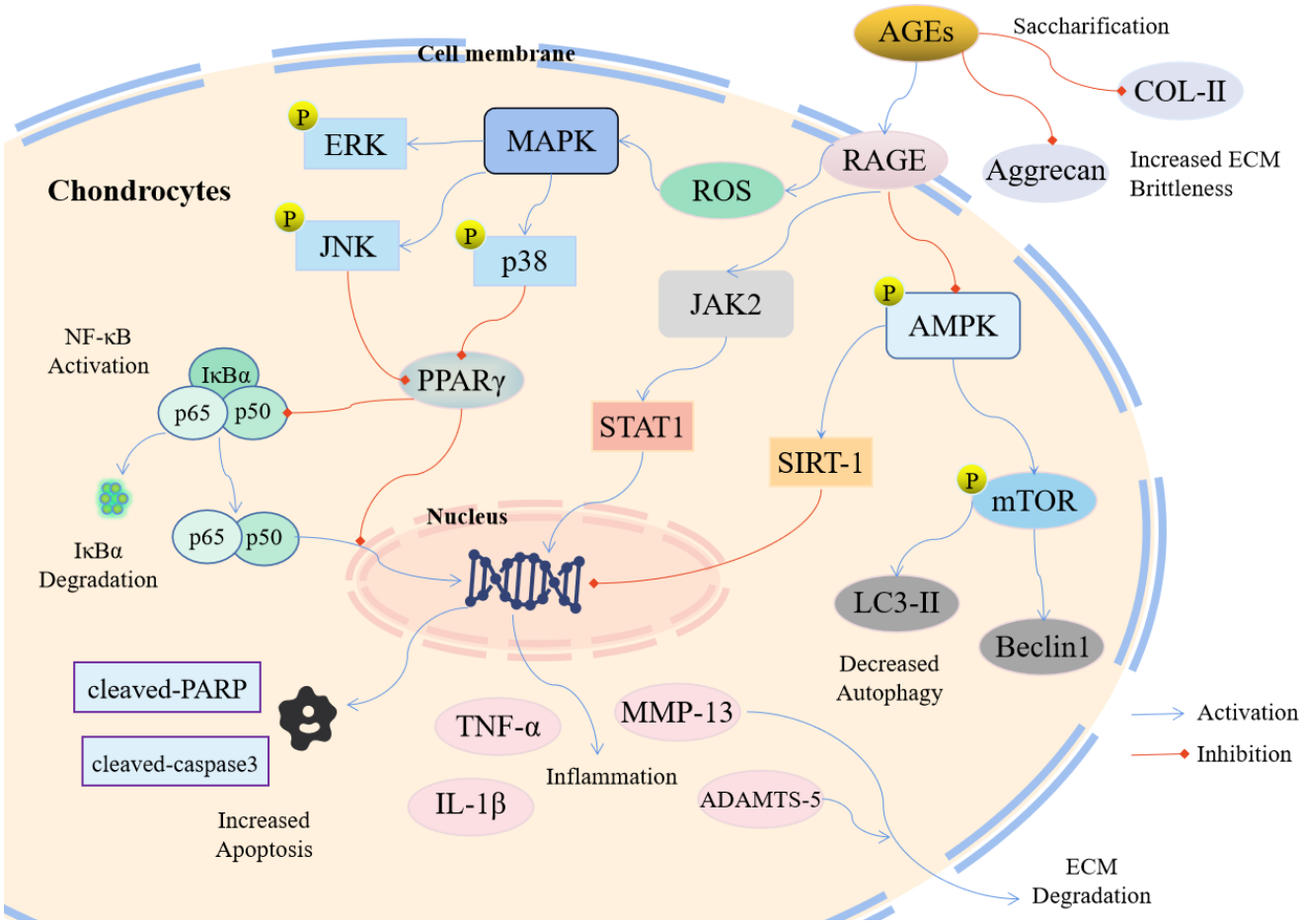

Fig. 2

Molecular schematic diagram of the involvement of advanced glycation end products (AGEs) in the pathogenesis of osteoarthritis (OA). Extracellular matrix (ECM) degradation, chondrocyte apoptosis, and autophagy play important roles in the occurrence and development of OA. Red arrows indicate inhibition, and blue arrows indicate activation. ADAMTS, A Disintegrin and Metalloproteinase with Thrombospondin motifs; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; COL-II, type II collagen; ERK, extracellular regulated protein kinases; IκBα, inhibitor of NF-κB; IL-1β, interleukin-1β; JAK2, janus kinase 2; JNK, c-Jun N-terminal kinase; LC3-II, light chain 3B; MAPK, mitogen-activated protein kinase; MMP-13, matrix metalloproteinase 13; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; p38, p38 mitogen-activated protein kinase; PARP, poly ADP-ribose polymerase; PPARγ, peroxisome proliferator-activated receptor γ; RAGE, receptor for AGEs; ROS, reactive oxygen species; SIRT-1, sirtuin 1; STAT1, signal transducer and activator of transcription 1; TNF-α, tumour necrosis factor α.

increases structural rigidity.[25] The glycosylated collagen is further cross-linked, damaging the structure and function of cartilage matrix, and the hardness and brittleness of articular cartilage are subsequently increased accordingly, such that articular cartilage will be damaged even in the normal physiological weightbearing range.[26] The Maillard reaction occurs very slowly in normal subjects, and frequently occurs on proteins with a long half-life, including collagen and crystallin, among others.[25] Under normal circumstances, a very small number of AGEs will be produced in the human body, but when the human body is in the state of ageing, inflammation, hyperglycaemia, or oxidative stress, the glycosylation rate is notably accelerated. Once excessive AGEs accumulation occurs, it will lead to many pathological changes in the human body. Following AGEs production, they will accumulate in various tissues, including articular cartilage, in the ageing body. Some studies have shown that AGEs are involved in the occurrence and development of various chronic degenerative diseases, including OA,[17,18] diabetes,[27] neurological diseases,[28] cardiovascular diseases,[29,30] and some types of cancer.[31,32]

Metabolism of AGEs. AGEs are mainly metabolized by the kidney. The free AGEs and AGEs peptides are filtered through the glomeruli, some are reabsorbed by the proximal tubules, and the rest are excreted in the urine. Studies have shown that with regard to dietary AGEs renal clearance, only 30% of the AGEs intake was eliminated in patients with normal renal function within 48 hours, which was reduced to less than 5% in patients with diabetic nephropathy.[33] The residual AGEs in the body bind to protein and deposit in various tissues, affecting tissue function, and can no longer be excreted from the body. When AGEs are excessively deposited in the body, the effective balance mechanism between AGEs accumulation (endogenous production and exogenous intake) and the

AGEs detoxification system will be disrupted, resulting in a further decrease in the AGEs clearance rate, leading to a vicious circle.[34,35]

AGEs receptors. There are two routes for AGEs to exert their effect in the human body: one is to directly modify proteins, thereby changing their structure and causing a direct pathological effect; and the other is to bind to its receptor, RAGE, causing an indirect pathological effect through receptor mediation. Currently, it is considered that the most important cause of disease reaction is by AGEs exerting their effect by combining with RAGE (Figure 2). RAGE is a multi-ligand receptor, which is a member of the immunoglobulin superfamily. Its gene is located on chromosome 6.[36] The ligand binding domain of RAGE can recognize a variety of molecules, including AGEs, S100 protein, high-mobility group box-1 protein, and amyloid β-protein.[37] RAGE is a 35 kDa transmembrane protein of 394 amino acids, of which 19 form a transmembrane domain and 43 form a C-terminal tail, which participates in communication with transduction mediators.[38] The role of AGEs in inflammation is played by activating RAGE. The activation of RAGE induces a cascade of inflammation, upregulates RAGE expression through a positive feedback loop, and promotes inflammation and tissue damage.[39] Studies have shown that in RAGE-deficient mice, immune cell recruitment is inhibited and the inflammatory response is substantially reduced.[38] Another class of AGEs cell surface receptors (AGE receptor 1 (AGE-R1), AGE-R2, and AGE-R3) have the opposite functions to RAGE. Some studies have shown that these receptors are involved in AGEs endocytosis and clearance.[40,41] AGE-R1 can reduce intracellular oxidative stress, and its expression is reduced in many chronic and age-related diseases.[41]

AGEs deposition in articular cartilage. The AGEs level in articular cartilage is higher than that in other bodily tissues, and most AGEs are located in the articular surface cartilage, which is highly correlated with OA severity.[42,43] Age-related increases in cartilage AGEs levels may be at least partly responsible for the age-related decline in the synthetic capacity of cartilage; the concentration of non-specific glycation products increases in OA with age. Studies have shown that, compared with other tissues of the body, articular cartilage contains higher levels of pentosidine (a major form of AGEs); the level of pentosidine increases 50-fold from the ages of 20 to 80 years.[42,44–46] Detailed studies on cartilage collagen have shown that all characteristic products of AGEs (pentosidine, Nε-(carboxymethyl)lysine (CML), and Nε-(carboxyethyl) lysine (CEL)) are deposited in cartilage collagen.[42,47] Although pentosidine is also deposited in proteoglycan, it is deposited primarily in the articular cartilage collagen in older people, thus potentially explaining why the collagen conversion rate is markedly lower than that of proteoglycan.[48]

Destruction of articular cartilage by AGEs

AGEs regulate ECM degradation. The occurrence of OA mainly manifests in the changes of articular cartilage. There are no nerves or blood vessels in articular cartilage, and it is mainly composed of ECM and chondrocytes, while type II collagen (Col-II), aggrecan, hyaluronic acid, and chondroitin sulfate constitute the ECM.[49-51] The main indicator for OA is ECM degradation. When OA occurs in the joint, the expression and content of matrix metalloproteinases (MMPs) and A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) increase,[26,52] which accelerates cartilage stroma degradation, and the proteolytic metabolism of Col-II and aggrecan is enhanced, which leads to ECM destruction and articular cartilage degeneration.

MMPs are a group of proteolytic enzymes that contain active Zn^{2+} and consequently are called metalloproteinases. They are divided into many groups according to the structure of the catalytic region. MMP-1, MMP-8, and MMP-13 are also known as collagenases. MMP-13 can specifically cleave the triple helix structure of collagen and is the strongest enzyme in Col-II cleavage.[53,54] It has been recognized to play an important role in cartilage destruction and can degrade Col-I, Col-II, and aggrecan. Col-II degradation, as the proteolytic substrate of MMP-13, will destroy the arched fibre structure of cartilage, while its degradation of aggrecan makes chondrocytes inelastic, thus exposing these cells originally embedded in ECM to attack by MMPs and inflammatory factors, resulting in cartilage destruction.[55] Yang et al[55] found that AGEs treatment of rabbit chondrocytes for 48 hours increased tumour necrosis factor-α (TNF-α) and MMP-13 expression. Pretreatment with RAGE antagonist anti-RAGE or mitogen-activated protein kinase (MAPK) inhibitor greatly inhibited TNF-α and MMP-13 expression. The authors also hypothesized that AGEs induced increased TNF-α and MMP-13 expression in chondrocytes through the AGEs/RAGE/MAPK indirect pathway. TNF-α is a pleiotropic cytokine that can regulate cell inflammatory response, proliferation and differentiation, and immune response. It can promote the synthesis of nitric oxide, prostaglandin E2 (PGE2), and MMPs in chondrocytes, affect chondrocyte gene expression, and reduce Col-II and aggrecan synthesis and promote their decomposition, resulting in ECM degradation.

Ma et al[21] confirmed the hypothesis of Yang et al[55] that interleukin-1 (IL-1), TNF-α, and MMP13 expression is increased and peroxisome proliferator-activated receptor γ (PPARγ) expression is decreased in AGEs-treated primary human chondrocytes. These effects can be reversed by RAGE antagonists, P38 MAPK-specific inhibitors, c-Jun N-terminal kinase (JNK)-selective inhibitors, and PPARγ agonists. RAGE activation by AGEs triggers a series of downstream signal transduction pathways, including the activation of MAPK JNK/p38, downregulation of PPARγ, and upregulation of nuclear factor-κB (NF-κB), resulting in increased TNF-α and MMP13 expression and ECM degradation.[21] PPAR is a ligand-activated transcription factor, which is a member of the nuclear hormone receptor superfamily. It has three forms: PPARα, PPARβ, and PPARγ. Of these, PPARγ is the most expressed in chondrocytes

and participates in the inflammatory response of chondrocytes and ECM catabolism.[17-19] In the rabbit OA model induced by AGEs, enhancement of PPARγ activity has a substantial inhibitory effect on rabbit articular cartilage degeneration.[56] Huang et al[18] found that AGEs can induce increased IL-1β and TNF-α in chondrocytes by reducing adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) activity and downregulating sirtuin 1 (SIRT-1) expression. Activating PPARγ can reverse this process, and activation of the PPARγ/AMPK/SIRT-1 pathway can alleviate the inflammatory state induced by AGEs. PPARγ activation can also upregulate NF-κB inhibitor protein (IκB) expression and inhibit the binding of NF-κB transcription factors to NF-κB p65, resulting in a decrease in NF-κB activity and the expression of downstream inflammatory factors. Mahali and Manna[57] found that AGEs could downregulate PPARγ expression and induce NF-κB activation. These results showed that there was a negative correlation between PPARγ expression and the NF-κB activation level. Lin et al[58] confirmed that PPARγ agonists can reverse the increased MMP expression induced by TNF-α in synovial cells, whereby the PPARγ agonists can inhibit NF-κB activation. Chen et al,[20] after incubating primary human chondrocytes with PPARγ agonists for two hours, could detect IκBα in the cytoplasm and NF-κB p65 in the nuclei of chondrocytes. These results showed that PPARγ agonists could inhibit the increased IκBα expression and the decreased NF-κB p65 expression induced by AGEs in human chondrocytes. This suggests that PPARγ agonists inhibit IL-1, MMP-13, and TNF-α expression induced by AGEs by activating NF-κB. A large number of studies have shown that NF-κB plays a key role in OA occurrence and development.[14,16,59] The NF-κB family consists of p50/p105, p52, Rel, p65 (RelA), and RelB. When these proteins are dimerized, they can produce functional NF-κB, with the p50-p65 dimer in particular being common. Following binding to IκB, NF-κB p65 is inactivated, and multiple stimuli will lead to the dissociation of NF-κB p65 and IκB, thus activating the NF-κB pathway to induce the expression of various "injury response genes".[60] Activated NF-κB can induce the release of cellular inflammatory factors (IL-1, TNF-α, etc), trigger the inflammatory response of the body, and promote MMP expression. These cellular inflammatory factors and enzymes can further activate NF-κB, thus creating a vicious circle to destroy articular cartilage.[61,62]

The ADAMTS family is a family of zinc-dependent proteases integrated in the ECM or dissociated in the plasma. It can regulate cell adhesion and migration by degrading or remodelling the ECM. It is widely expressed in a variety of tissues and organs of the human body. Some studies have found that ADAMTS-4 and ADAMTS-5 are the main enzymes to degrade aggrecan.[63] ADAMTS-4 and ADAMTS-5 are expressed in articular cartilage of both normal subjects and OA patients. In the early stage of OA, the balance between ADAMTS and tissue inhibitor of metalloproteinase-3 is lost, and ADAMTS-4 and ADAMTS-5 production is increased, which leads to aggrecan breakdown.[64] Other studies have found that the activity of ADAMTS-5 is approximately 1,000 times that of ADAMTS-4. In mouse OA, ADAMTS-5 is the main enzyme that decomposes aggrecan, whereas in ADAMTS-5-knockout mice, OA occurrence and development are effectively inhibited.[65]

AGEs regulate chondrocyte apoptosis. Apoptosis is an orderly death of cell autonomy controlled by genes, and it is a regulatory pathway involving specific intracellular signal pathways and gene sets. The imbalance of apoptosis will lead to the occurrence and development of cancer, developmental abnormalities, and degenerative diseases.[66] In the process of apoptosis, cells also display some morphological characteristics, including chromatin condensation, DNA fragmentation, cell contraction, and plasma membrane bubbling apoptotic body formation among others.[67] Apoptosis plays an important role in maintaining the homeostasis of various tissues in the body and regulating the normal development of embryos. Chondrocyte apoptosis is an important pathological feature of OA. Its initiation includes physical factors, biochemical factors, oxidative stress, and age factors, involving multiple signal transduction pathways, and is closely related to the disease progression. Some studies have shown that chondrocyte apoptosis is positively correlated with the severity of cartilage destruction and ECM depletion in human OA tissue specimens.[68] The signal pathway of chondrocyte apoptosis is very complex, and its upstream pathway is mainly involved in the MAPKs signalling pathway, phosphatidylinositol-3 kinase (PI3K)-protein kinase B (AKT) pathway, JAKs/STAT1 pathway, and NF-κB pathway. The MAPKs pathway includes the extracellular signal-regulated protein kinase (ERK) pathway, JNK pathway, and p38 protein kinase pathway. Among them, the JNK and p38 pathways mainly inhibit cell growth and promote apoptosis, which play an important role in OA occurrence and development.[69] Zhang et al[19] found that after mouse chondrocytes were treated with AGEs, the apoptosis rate and the expression of MMP13 and apoptosis markers (cleaved-poly ADP-ribose polymerase (PARP) and cleaved-caspase-3) increased. AGEs could induce the phosphorylation of the p38, JNK, and ERK proteins and lead to cytoplasmic IκBα degradation and nuclear p65 transport. After 30 minutes of incubation with p38 inhibitor, JNK inhibitor, or NF-κB inhibitor, the apoptosis rate and the expression of MMP-13 and apoptosis marker proteins (cleaved-PARP and cleaved-caspase-3) induced by AGEs were notably decreased. It was confirmed that AGEs can phosphorylate MAPKs and activate the degradation of cytoplasmic IκBα and the transport of nuclear p65, thus increasing the apoptosis rate of chondrocytes and the expression of MMP-13 and apoptosis marker proteins (cleaved-PARP and cleaved-caspase-3).[19]

The downstream pathways of chondrocyte apoptosis mainly include the death receptor pathway, mitochondrial pathway, and endoplasmic reticulum stress (ERS)-responsive apoptosis pathway. When chondrocytes were stimulated by an apoptosis signal, the mitochondrial

outer membrane potential (Δψm) decreased, the outer membrane ruptured, and cytochrome C and apoptosis inducing factor (AIF) were released into the cytoplasm, thus promoting chondrocyte apoptosis.[70] OA chondrocytes displayed mitochondrial dysfunction, and the activity of the electron transport chain was lower than that of normal cells. The pathways that may affect cartilage degradation include chondrocyte inflammation and matrix decomposition, cartilage calcification, increased chondrocyte apoptosis, and the limited ability to repair DNA damage, which is also an important cause of chondrocyte apoptosis in OA.[71,72] Yang et al[73] analyzed the effects of AGEs on mitochondrial stability and caspase activation in rabbit chondrocytes. The results showed that after AGEs treatment, the rabbit chondrocyte Δψm decreased and its adenosine triphosphate (ATP) production decreased. Cytochrome C is released from mitochondria to the cytoplasm to activate caspase-3, thereby upregulating B cell lymphoma/leukemia-2 (Bcl-2) and Bcl-2-associated X protein (BAX) expression, which eventually leads to apoptosis. Zhang et al[74] also found that AGEs can induce the production of reactive oxygen species (ROS) and increase the content of carboxyl groups in ATDC5 cells. ROS can oxidize amino acid residues on proteins to form protein carbonyl groups and cause cell damage.[75] The experimental results showed that AGEs could also decrease the Δψm and increase nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX-4) expression, cytochrome C translocation from mitochondria to the cytoplasm, and activate caspase-3, thereby upregulating Bax and Bcl-2 expression, causing cell apoptosis.[74] It has been reported that AGEs can induce ERS. The most important change in ERS is that the increase of intracellular Ca^{2+} leads to elevated mitochondrial Ca^{2+}. The increase of mitochondrial Ca^{2+} can disrupt the electron transport chain and increase the presence of ROS, which leads to apoptosis and the production of MMPs.[76,77] Yamabe et al[77] found that AGEs could increase X-box binding protein 1 (XBP1) expression, and induce chondrocyte apoptosis in mice in vivo and in vitro. XBP1 is a key regulator of ERS and is widely used as a marker for ERS,[78] while C/EBP homologous protein (CHOP) is an important apoptosis-inducing factor during ERS.[79] These results show that AGEs deposition in cells caused AGEs to modify the proteins related to the endoplasmic reticulum unfolded protein response, and induce chondrocyte apoptosis through ERS to participate in OA occurrence and development.

AGEs regulate chondrocyte autophagy. Autophagy is a unique life phenomenon in eukaryotic cells and a highly conservative internal regulatory mechanism of the body. It plays a vital role in regulating energy and nutrition and maintaining energy metabolism in the body.[80,81] Autophagy can transport damaged organelles and intracellular macromolecules to lysosomes for degradation and reuse, which is the basic component of intracellular homeostasis.[82] With increasing age, the basic autophagy activity of cells decreases with the reduction in clearance efficiency, resulting in an increase in the aggregation of various macromolecular proteins, which eventually leads to cell degeneration, functional defects, and even apoptosis. In the process of apoptosis, the activity of intracellular autophagy decreases greatly. Autophagy can inhibit the initiation of apoptosis and protect cells. In recent years, the inhibition of chondrocyte apoptosis by autophagy has attracted wide attention.[83] Studies, such as the one by Feng et al,[84] have found that the expression of key autophagy-related proteins is markedly decreased in OA cartilage. In a study of primary human chondrocytes, autophagy was found to inhibit caspase-9 and MMP-13 expression, thus inhibiting chondrocyte apoptosis and ECM degradation to reduce the risk for OA.[84] Other studies, such as the one by Vasheghani et al,[85] have found that ROS expression was greatly decreased during autophagy, indicating that autophagy plays an important role in the protection of cells during oxidative stress.[85] Wang et al[17] found that stimulating human primary chondrocytes with AGEs increased the mammalian target of rapamycin (mTOR) phosphorylation level and inhibited microtubule-associated protein light chain 3B (LC3-II) expression, resulting in decreased autophagy activity. Following chondrocyte pretreatment with PPARγ agonist, it was found that the agonist increased LC3-II expression and inhibited mTOR phosphorylation. These results suggest that AGEs may affect the autophagy activity of cartilage through PPARγ regulation of the mTOR pathway. LC3 is frequently used as a marker to evaluate the degree of autophagy, which increases with the increase of autophagy membrane. In the process of autophagy, the pro-LC3 synthesized in the early stage of autophagy related gene 4 (Atg4) cleavage exposes the C-terminal glycine to form cytoplasmic-soluble LC3-I. Following induction of autophagy, LC3-I is coupled with the substrate phosphatidylethanolamine (PE) on the surface of the autophagy membrane under the combined action of E1-like ligase Atg7, E2-like ligase Atg3, and E3-like ligase Atg5-Atg12-Atg16L complex to form membrane-bound LC3-II, and bind to autophagy vesicles.[86] Therefore, the amount of LC3-II is related to the degree of autophagy body formation, and the ratio of LC3-II/LC3-I is normally used to evaluate the level of autophagy.[87] Huang et al[88] verified this in rat chondrocytes. AGEs can inhibit LC3-II and Beclin 1 expression, decrease the autophagy activity, and increase MMP-3 and MMP-13 expression and even apoptosis. Pretreatment with an autophagy inducer can reverse this effect and alleviate OA occurrence and development.

Conclusions and future prospects

The pathogenesis of OA is complex, and ageing is the most important factor in its pathogenesis. With increasing age, the most obvious change in the body is the production and deposition of AGEs. Once AGEs bind to proteins, they are difficult to remove, such that the deposition of AGEs depends on the rate of protein degradation in the body.

There is no effective mechanism for scavenging AGEs in the human body, and the renewal rate of chondrocytes is very slow; thus, AGEs are readily deposited in articular chondrocytes, which results in persistent AGEs damage to these cells.[89] Some studies have confirmed that AGEs can increase collagen glycosylation of articular cartilage and decrease aggrecan synthesis in the ECM, which leads to the increase of ECM brittleness, and the ability to resist pressure and shear force is substantially decreased.[59] In addition, AGEs bind to their receptor RAGE and mediate complex intracellular signal transduction mechanisms (p38 mitogen-activated protein kinase (p38 MAPK), stress-activated protein kinase (SAPK)/JNK, MAPKs, NF-κB, JAK/STAT, AMPK/SIRT-1) to produce a series of pathological reactions, including inflammation, autophagy, apoptosis, and ECM reduction, and promote OA occurrence and development. It has been confirmed that AGEs can induce increased ROS production by activating RAGE, activate the NF-κB pathway through the MAPK pathway, stimulate TNF-α, MMP-13, and IL-1β expression in chondrocytes, leading to ECM degradation,[20,21] and promote chondrocyte apoptosis.[19] A high AGEs concentration can activate the AKT/mTOR pathway in chondrocytes and reduce the occurrence of autophagy in these cells.[17]

Since AGEs are one of the factors in OA pathogenesis, we can reduce the intake of exogenous AGEs and the production of endogenous AGEs to inhibit the occurrence and development of OA. Food is one of the main sources of exogenous AGEs. Research on different diet plans aims to determine the content of AGEs in different foods. In addition, high molecular weight AGEs that are bound to proteins from foreign substances can be detected.[90,91] Combining the correct choice of food and cooking methods together with physical exercise can avoid the harmful effects of a high-AGEs diet on the body.[33,92] Studies on endogenous AGEs have shown that substances such as aminoguanidine, pyridoxamine, and monomer amino acids (such as lysine and arginine) can effectively inhibit AGEs formation, AGEs-induced protein cross-linking, and tissue collagen accumulation and hardening.[93] In articular cartilage, monomer amino acids can inhibit AGEs formation, thus preventing reticular collagen sclerosis.[94] Other studies have shown that the PPARγ agonist pioglitazone[17-19] and G-protein coupled receptor[95,96] can reduce AGEs-induced chondrocyte inflammation, apoptosis, and ECM catabolism by inhibiting the NF-κB pathway. The specific mechanism and function of AGEs related to OA need further research and investigation to determine the function and specific action sites of AGEs and intervene there to reduce AGEs intake and production from both exogenous and endogenous sources. Additionally, chondrocytes in vitro, OA animal models, and OA patients should be investigated to further discover and verify the effects of AGEs on the pathogenesis and pathological changes of OA, which lays the foundation for OA diagnosis, prognosis, prevention, and treatment.

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Funding statement:

- The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: grants from the National Nature Science Foundation of China (NO.82072977), Research Project of Hunan Health Commission (NO.B2019162), Nature Science Foundation of Hunan (NO.2019JJ50861), and Hunan Provincial Innovation Foundation for Postgraduate (NO.CX20200548).

ICMJE COI statement:

- The authors declare that they have no conflict of interest.

Acknowledgements:

- We thank the Second Xiangya Hospital of Central South University for their support.

Open access funding

- The authors report that they received open access funding for their manuscript from The Second Xiangya Hospital of Central South University.