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Review

Renin-angiotensin system in osteoarthritis: A new potential therapy

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ABSTRACT

Osteoarthritis (OA) is one of the most common chronic joint diseases. However, the mechanism remains unclear. The traditional renin-angiotensin system (RAS) is an important system for regulating homeostasis and controlling balance. In recent years, RAS-related components have played an important role in the occurrence of OA. The purpose of this review is to summarize the research results of RAS-related components that are associated with OA. This study systematically searched e-medical databases such as PubMed, Embase, Medline, and Web of Science. The search targets included English publications describing the effects of RAS-related components in OA, including the role of renin, angiotensin-converting enzyme (ACE), Angiotensin II (Ang II), and angiotensin receptor (ATR). Additionally, this study summarizes the potential pathways for RAS-related components to intervene in OA. This study found that RAS-related components including renin, ACE, Ang II, AT1R and AT2R are involved in inflammation and chondrocyte hypertrophy in OA. RAS is involved in signaling pathways including the NF-κB, JNK, VEGFR/Tie-2, and the Axna2/Axna2R axis ones, which may be potential targets for the treatment of OA. Although there are few studies on RAS in the field of OA, the pathogenic effect of RAS-related components is still an important topic in OA treatment, and great progress may be made in this aspect in future studies.

1. Introduction

Osteoarthritis (OA) is one of the most common chronic joint diseases and can lead to joint pain, stiffness, deformity, and narrowed joint space, seriously affecting the quality of life of patients [1–3]. OA can occur and develop in any joint, most commonly in the knee, hip, hand facet, and foot areas [4–6]. The risk of OA is determined by a number of specific risk factors and local factors that can contribute to the susceptibility of the joint to injury, through direct damage to the joint tissue or by damage to the repair process in the affected joint tissue [3]. The main pathological feature of OA is due the progressive degeneration of articular cartilage, which is primarily caused by the death of chondrocytes and the loss of extracellular matrix [7,8].

The components of the renin-angiotensin system (RAS), such as renin [9,10], angiotensin-converting enzyme (ACE) [11–13], angiotensin II (Ang II) [14,15] and angiotensin receptor (ATR) [16,17], play important roles in regulating blood pressure [9,10,13,16–18]. In recent years, studies have shown that major components of RAS, including ACE, AT1R, and AT2R, are expressed in synovial tissue in humans and animals and participate in the pathogenesis of OA and rheumatoid arthritis (RA); their expression levels are related to the degree of inflammation and the severity of arthritis [19–22]. Therapeutic inhibition of AT1R or ACE can improve clinical symptoms by reducing the yield of inflammatory factors [23–27], delaying the development of OA. Therefore, this study summarizes the relationship between RAS and OA susceptibility, depicted in Fig. 1, and provides a theoretical basis for further exploration of OA pathogenesis and early prevention.

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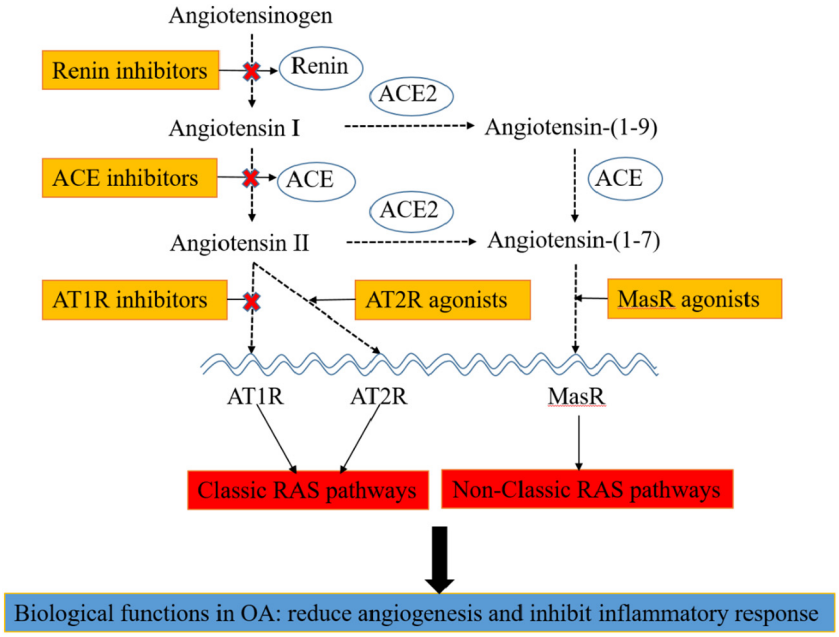

Fig. 1. Composition of renin-angiotensin system (RAS) and its drug inhibitors and agonists in osteoarthritis (OA).
Abbreviation: X, inhibition; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; MasR, Mas receptor.

2. Potential therapeutic effects of RAS-related component in OA

2.1. Renin inhibitors and OA

Renin is a protease synthesized by juxtaglomerular cells and distal tubules in the kidney, as well as nonrenal tissues such as adipocytes, which catalyzes the production of Ang I from angiotensinogen. Previous studies have found that renin levels are related to the occurrence and development of OA [28,29].

Aliskiren is a nonpeptide renin-blocking agent that can effectively block the production of active renin, thus protecting cartilage tissue from damage [28]. Yan et al. [28] evaluated the effect of aliskiren on osteoclasts in chondrocytes, which interfered with rat OA and significantly reduced the expression of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), Runx2 and type I procollagen n-terminal propeptide. These cartilage-protective properties were accompanied by decreased levels of the RAS components (renin, ACE, and AT1R), suggesting that aliskiren may be a useful potential strategy for the treatment of OA. Tang et al. [29] also found that the RAS components (renin, ACE, AT1R) were significantly increased, however, the AT2R expression was suppressed in OA rats. Cobankara et al. [30] studied the levels of serum ACE and renin in patients with RA and OA, as well as healthy adults. The results showed that there was no significant difference in the average concentration of serum ACE and renin in the three groups. However, the authors found that the levels of ACE and renin in the synovial fluid of RA patients were higher than those of OA patients. Therefore, the authors suggested that local ACE and renin in synovial fluid may lead to arthritis and joint injury.

2.2. ACE inhibitors and OA

ACE, a key enzyme in the RAS, plays an important role in maintaining the stability of the body's internal water, electrolytes, and environment. ACE can catalyze the transformation of Ang I into Ang II, thereby constricting blood vessels, secreting aldosterone and participating in the pathological process of OA [31–33].

Inanir et al. [32] studied the effects of the methylenetetrahydrofolate reductase gene (MTHFR) C677T mutation and the ACE gene insertion/deletion (I/D) mutation on the risk of OA in Turkey. The authors obtained genomic DNA from 421 patients (221 patients with OA and 200 healthy controls), and the ACE gene I/D polymorphism genotype was determined by polymerase chain reaction using I and D allele-specific primers. The results showed that the ACE gene DD genotype and MTHFR gene CC genotype were higher in OA patients than in the normal population and could be used as a genetic marker for osteoarthritis. Qing et al. [33] evaluated the relationship between ACE rs4343 and rs4362 polymorphisms and OA susceptibility. The authors included 109 OA patients and 114 healthy individuals and found that the ACE rs4343 and ACE rs4362 polymorphisms were significantly higher in OA patients than in the normal population. Moreover, the results of haplotype analysis showed a complete linkage disequilibrium in the ACE rs4343 and rs4362 polymorphisms, further confirming that the GT haplotype significantly increased OA susceptibility. Conversely, the AC haplotype is a protective factor for OA occurrence.

Similarly, Tang et al. [29] found that captopril has protective effects on cartilage in a rat OA model, as captopril alleviated chondrocyte hypertrophy and cartilage degradation. Thus, inhibition of ACE targets the local RAS and to at least partially alleviates OA-induced bone and joint damage. In a recent study, Hong et al. [34] studied ACE gene I/D polymorphism in 142 patients with primary OA and 135 healthy volunteers. The author analyzed the correlation between ACE I/D polymorphism and clinical features of OA by using clinical parameters such as onset age, kellgren-lawrence grading, Lequesne functional index. Allele frequency and carrying rate of early-onset OA were significantly higher than that of late-onset OA. The ratio of OA patients with severe radiology and poor function who carried the I allele was higher than those with better radiological and functional OA. However, Shebab et al. [35] found no significant correlation between the ACE gene I/D polymorphism genotype and the control group in OA patients from Kuwait.

2.3. Ang II inhibitors and OA

Ang II is a biologically active octapeptide produced by ACE-mediated Ang I cleavage that not only regulates blood pressure and humoral homeostasis but also contributes to different inflammatory responses

[36,37]. By binding to two different angiotensin receptors on the cell surface, mainly AT1 and AT2 receptors, Ang II regulates cell proliferation and apoptosis [36]. Pattacini et al. [37] assessed Ang II treatment of fibroblasts in patients with OA synovial cell apoptosis and found that Ang II may be involved with important mediators that amplify fibroblast-like synoviocytes (FLS) by activating the AT1R-NF-κB pathway and blocking the caspase cascade, reducing the ability of these cells to undergo apoptosis.

Ang II can also stimulate the production of several kinds of growth factors, such as platelet-derived growth factor [38], insulin-like growth factor 1 [39] and vascular endothelial growth factor (VEGF) [40]. Previous studies have reported that activation of the local RAS stimulates the expression of osteoclast-generating cytokines in osteoblasts [41]. In addition, Ang II reduces osteocalcin mRNA expression and reduces alkaline phosphatase activity through the AT1R [42]. Therefore, it may be reasonable to attribute the cartilage-protective benefits of RAS inhibition primarily to reduced Ang II levels and reduced downstream signaling in OA. Additionally, Yan et al. [28] showed that the mRNA expression of matrix metalloproteinase-9 (MMP-9), CAII and TNF-α increased significantly and Runx2 expression decreased significantly in OA rats compared with that in the sham group. The levels of TNF-α increased and Runx2 decreased after aliskiren treatment, while MMP-9 and CAII remained unchanged. The results suggest that aliskerin may attenuate cartilage damage by inhibiting the production of renin.

2.4. AT1R inhibitors and OA

It is known that there are two major receptors for angiotensin, AT1R and AT2R [43]. The AT1 receptor subtype is a G protein-coupled receptor that signals through phospholipase-C and calcium [2]. Among them, AT1R seems to be the most sensitive to Ang II, while AT2R is the most susceptible to Ang III [44]. However, previous studies have found that both Ang-(1–7) and Ang II can act as ligands for AT2R [45].

In a variety of tissues and organs, Ang II regulates cell growth and apoptosis through both AT1R and AT2R in both autocrine and paracrine manners, where AT1R mediates most of the function of Ang II, promoting tumor growth and tumor angiogenesis [46,47]. Locally produced Ang II from synovial tissue acts on the synovial AT1R to regulate synovial perfusion and growth; specific AT1R antagonists may help elucidate the role of angiotensin in arthritis. In addition, the AT1R has been shown to be involved in the synovial microvasculature and synovial matrix of RA synovial membranes [48]. Yan et al. [28] found that OA rats treated with aliskiren reduced expression of AT1R, inhibited the local RAS, and inhibited cartilage destruction. Tang et al. [29] also found similar results. In rat tibia articular cartilage, expression of RAS components, including AT1R mRNA and protein, was increased in the OA group, but after captopril treatment, RAS activation was inhibited in OA rats, delaying the development of OA.

2.5. AT2R agonists and OA

The human AT2R receptor is a G protein-coupled receptor with 7 transmembrane hydrophobic regions, and studies on the signal transduction mechanism of the AT2 receptor are still unclear. Moreover, the physiological action produced by the binding of Ang II to the AT2R receptor is opposite that of the effect mediated by binding to the AT1R and is mutually antagonistic [45,46].

Terenzi et al. [49] confirmed the presence of AT2R in human synovial tissue and cultured human FLS. In particular, AT2R expression was also observed in the synovial lining and lining of patients with RA and OA. Furthermore, there was a difference in the expression of AT2R between RA and OA synovia. In fact, all RA synovial specimens showed that AT2R immunostaining was stronger than that in OA patients' synovial lining and synovial cells. Consistent with these results, a large body of evidence supports the notion that AT2R is only sparsely expressed in healthy tissues in adults, whereas receptor expression is strongly upregulated in the case of tissue damage [50]. The tissue protective properties of AT2R under different conditions, including stroke [51,52], myocardial infarction [53,54], atherosclerosis [55,56] and OA [19,27], have been demonstrated in various in vivo studies using selective receptor agonists and antagonists.

Terenzi et al. [49] used the selective agonist CGP42112A to activate AT2R on RA-FLS, which significantly downregulated the expression of IL-1β and IL-6, while the opposite effect was observed when AT2R was silenced in cells. In addition, treatment of RA-FLS with an AT2R agonist significantly reduced the DNA-binding activity of NF-κB p65, which is recognized as a transcriptional activator of proinflammatory factor genes such as IL-1β and IL-6. In contrast, Tang et al. [29] found that RAS components such as renin, ACE and AT1R were significantly increased in OA rats, but AT2R was reduced in the proximal tibia. Interestingly, the expression of renin, ACE and Ang II was significantly reduced in captopril-treated OA rats compared to untreated OA rats, while a decrease was observed in expression of the AT1R receptor. These results may indicate that Ang II signaling through its receptors AT1R and AT2R plays a key role in the pathological changes of articular cartilage in OA. However, it is worth noting that AT1R and AT2R may have opposite effects. The results from Tang et al. [29] showed that, compared with the sham operation group, the OA group had increased AT1R mRNA and protein expression, while AT2R mRNA and protein expression in the proximal tibia of OA rats decreased. Further, AT2R expression increased and AT1R expression decreased in the proximal tibial end of the OA group treated with captopril, compared with the OA group.

3. Potential therapeutic relationship between RAS-related components and inflammatory response in OA

In most previous studies, Ang II was thought to produce a potent release of proinflammatory mediators by acting on AT1R. During the inflammatory response, a locally high concentration of Ang II increases vascular permeability by stimulating the production of prostaglandins and VEGF, thereby triggering an inflammatory response, such as the production of monocyte chemoattractant protein type 1 (MCP-1), TNF-α, IL-6, and IL-8 [57,58].

Previous studies have shown that AT1R and ACE inhibitors and AT2R agonists have protective effects in OA. For example, in an animal model of acute and chronic arthritis, it has been shown that the ACE inhibitor has significant antiinflammatory properties and inhibits the severity of collagen-induced arthritis [59,60]. Martin et al. [61] evaluated the clinical efficacy of the ACE inhibitor captopril in the treatment of RA for 15 active RA patients. Ten of the 15 RA patients had improved clinical symptoms, including joint pain and decreased joint swelling, accompanied by a decrease in levels of the inflammatory factor C-reactive protein (CRP) at 24 and 48 weeks. In another randomized, double-blind study, Bird et al. [62] studied the use of the ACE inhibitor ramipril for 8 weeks and found that inhibition of ACE significantly improved endothelial function and decreased plasma TNF-α concentrations, but inflammatory parameters such as erythrocyte sedimentation rate (ESR), CRP, IL-1, and IL-6 levels were not affected. In addition, Silveira et al. [63] found that Ang II-induced AT1R and ACE expression levels were significantly enhanced in OA rats. However, the use of losartan reduced signs of local inflammation, including symptoms of pain and edema, and improved histological joint changes in osteoarthritic rats. Wang et al. [64] recently reported that the therapeutic effect of losartan on adjuvant-induced OA rats may be related to upregulation of AT2R and downregulation of AT1R. Intraarticular injection of rats with the AT2R agonist CGP42112 significantly reduced the severity of arthritis. This study suggests that upregulation of AT2R may be another mechanism by which plays a therapeutic role in osteoarthritic rats.

Although there are some pharmacological similarities between ACE,

AT1R and AT2R, important pharmacological differences may have clinical implications. The ACE inhibitor acts by inhibiting the catalysis of inactive Ang I to active Ang II, resulting in a decrease in Ang II levels. It may be more effective to choose to block AT1R-mediated Ang II signaling more selectively than to block ACE. One study found that RA patients treated with the AT1R antagonist losartan were associated with a significant reduction in CRP and ESR [65]. Previous studies suggest that when AT1R is inhibited, the increased Ang II levels may potentially lead to the activation of AT2R. Considering that AT1R and AT2R have opposite effects, continued AT2R activation may induce antiinflammatory mechanisms that provide potential complementary therapeutic benefits [66]. Therefore, AT2R agonists can also be considered a new drug that can be used to treat inflammatory and immune diseases.

4. Potential mechanisms of RAS-related components involved in OA signaling pathways

4.1. Related studies on the NF-κB signaling pathway

NF-κB signaling is involved in a wide range of biological processes, including cell proliferation, differentiation, apoptosis, senescence, inflammation, and immune response [67–69]. NF-κB signaling is widely involved in the pathophysiology of OA through various actions and is activated in OA chondrocytes during aging and inflammation [70].

In addition to its catabolism in chondrocytes, the RAS system also plays an important regulatory role in the development of arthritis through the NF-κB signaling pathway. Pattacini et al. [37] evaluated the effect of Ang II treatment on apoptosis of FLS in patients with OA and RA. The results suggest that Ang II may be involved in the important mediators of FLS growth and reduce their ability to undergo apoptosis by activating NF-κB and blocking the caspase cascade. Scott et al. [71] demonstrated that the expression of angiopoietin-I is regulated by TNF-α, which is mainly induced by the activation of NF-κB in RA synovial fibroblasts. This study also suggested that the involvement of NF-κB may be related to the treatment of angiogenesis in chronic inflammation. Meanwhile, Terenzi et al. [49] also confirmed that AT2R agonist treatment of RA-FLS significantly reduced the DNA-binding activity of NF-κB p65 and inhibited degeneration in OA.

4.2. Related studies on the c-Jun N-terminal kinase (JNK) signaling pathway

The JNK signaling pathway is an important signaling pathway downstream of transforming growth factor β1 (TGF-β1) [72]. The JNK signaling pathway can efficiently and specifically deliver multiple stimulatory signals in response to extracellular inflammatory responses [73,74]. Ang I was hydrolyzed by ACE to the 8 amino acid peptide Ang II, and then Ang II can be hydrolyzed by ACE2 to the 7 amino acid peptide Ang - (1–7). Finally, Ang-(1–7) can be produced in both the circulation and tissues and mediates biological benefits by activating the specific G-protein-coupled receptor MasR [75,76]. Studies have shown that non-canonical RAS consisting of the Ang-(1–7)-Mas receptor axis is generally opposite to stimulated Ang II-AT1R. At the same time, Ang I is directly cleaved into Ang-(1–7) by endopeptidases such as neprilysin, thimet oligopeptidase and prolyl oligopeptidase [75]. Thus, ACE inhibitors can potentially increase the circulating levels of Ang-(1–7) in both clinical and experimental studies [75,76].

Recent studies have shown that Ang-(1–7) can inhibit angiogenesis and reduce VEGF [77] and tumor metastasis [78]. Recent studies have confirmed that Ang-(1–7) has antiinflammatory properties. Jiang et al. [74] found that lipopolysaccharides (LPSs) significantly increased the expression of the proinflammatory cytokines TNF-α and IL-6 in macrophages, while Ang-(1–7) inhibited the production of these LPS-stimulated inflammatory cytokines in a dose-dependent manner, suggesting that Ang-(1–7) has antiinflammatory properties in LPS-induced macrophages. Additionally, the authors studied the role of the JNK signaling pathway, and the results show that Ang-(1–7) inhibits TLR4-dependnent stimulation of JNK/FOX01and abolishes TLR4 expression, which may provide a potential mechanism for its anti-inflammatory effects for chronic inflammatory diseases.

Yamagishi et al. [27] evaluated whether RAS could aggravate mechanical load-induced knee OA in mice to determine whether the mechanical load of articular chondrocytes could transmit intracellular signals through AT1R in chondrocytes. The researchers found that the expression levels of AT1R, COLX and MMP-13 in chondrocytes of OA mice were significantly higher than those of the control group. Yamagishi et al. [27] confirmed that the phosphorylation of JNK could be increased by Ang II in cartilage cells, and the AT1R inhibitor (Olmesartan) reversed the phosphorylation of JNK and delayed the progression of OA in rats. These results suggest that AT1R may promote the OA inflammatory response through JNK and accelerate the progression of OA.

4.3. Related studies on the VEGFR/Tie-2 signaling pathway

VEGF is a key regulator of angiogenesis, and the VEGF family consists of VEGF-A (commonly known as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F and placental growth factor (PlGF), which act on cells by binding to the appropriate receptors [79,80].

Endothelial cell tyrosine kinase (Tie kinase) is a coreceptor of angiopoietin, a tyrosine kinase receptor that is specifically expressed in endothelial cells and certain hematopoietic progenitors and plays an important role in vascular development. In joints affected by inflammation, inflammatory cytokines maintain the inflammatory process and have a significant effect on angiogenesis, resulting in the proliferation of synovial membranes and vasospasm [79]. There is evidence that angiopoietin 1 and angiopoietin 2 and their tyrosine kinase receptors Tie1 and Tie2 are critical in vascular development [80]. In addition, previous studies have confirmed that angiopoietin 1, angiopoietin 2, Tie1 and Tie2 are upregulated in RA synovial tissues, as well as angiogenic effects of the angiotensin/Tie2 signaling pathway-mediated TNF-α and IL-6 in arthritis [81,82].

Previous studies have reported the role of inflammatory mediators in the expression of VEGF in OA synovial fibroblasts and in angiogenesis, and the increased expression levels of these proangiogenic factors and VEGF are positively correlated with the severity of OA [83]. Meanwhile, Chen et al. reported that TGF-β1 treatment of human chondrocytes in OA significantly upregulated genes involved in chondrocyte hypertrophy and vascular development in culture [84]. Vignola et al. [85] also found that serum VEGF concentrations in patients with juvenile idiopathic arthritis were significantly higher in synovial fluid than in normal controls. Therefore, the role of angiogenesis seems to be crucial in the pathogenesis of arthritis. Jiang et al. [86] assessed VEGF and angiopoietin 2 in RA synovial tissue and found that VEGF increased angiopoietin 2 secretion through HUVEC and RA synovial tissue and that exogenous angiopoietin 2 promoted HUVEC migration, adhesion, and angiogenesis. Blocking the angiopoietin/Tie2 pathway with an endothelial cell tyrosine kinase (Tie2 kinase) receptor antibody inhibited the proangiogenic effects of exogenous Ang2 and VEGF in HUVECs.

4.4. Related studies on the Axna2/Axna2R axis signaling pathway

Annexin a2 (Axna2) is a pleiotropic calcium- and anionic phospholipid-binding protein and is a member of the multigene annexin family. In autoimmune diseases, including systemic lupus erythematosus and lupus nephritis, Axna2 can bind to its autoantibodies and induce inflammatory changes [87]. Axna2 is not only involved in inflammation and the immune response but also plays an important role in metastasis and malignant tumor erosion, especially in angiogenesis [88,89]. Therefore, Axna2 may be involved in the pathogenesis

of arthritis.

Yi et al. [88] found that the expression of Axna2 and Annexin a2 receptors (Axna2R) in RA patients was upregulated compared with that in healthy patients and OA patients. Collagen-induced arthritis in mice showed significantly increased joint swelling inflammation and neovascularization with exogenously added Axna2. In vitro mechanism studies by Yi et al. [90] have shown that the Axna2/Axna2R axis promotes the proliferation of vascular endothelial cells and upregulates the expression of MMPs, VEGF and angiopoietin 2 through the HH signaling pathway, leading to increased angiogenesis and promoting the role of angiogenesis in RA. The above results indicate that the role of Axna2 is instructive for understanding the development of arthritis. The overexpression of Axna2 can promote the development of arthritis, and the inhibition of Axna2 may provide new potential measures to reduce angiogenesis with arthritis treatment.

5. Local RAS activation of cartilage is associated with degradation of cartilage matrix and involvement in the regulation of OA

The pathological changes of OA are mainly chondrocyte hypertrophy, cartilage matrix separation and degradation, cartilage calcification layer thickening, and perivascular bone sclerosis remodeling [91]. Studies have found that the interaction between angiogenesis and the bone-cartilage interface in the bone-cartilage composite unit is associated with OA [92]. This interaction greatly increases the ability of cytokines and inflammatory mediators produced by osteoblasts in the subchondral bone to pass through the calcification layer and the tidal barrier, affecting the normal homeostasis of chondrocytes and matrix metabolism in OA [91–93].

Walsh et al. [93] found that subchondral bone vessels in patients with OA could break through the tidal line into noncalcified cartilage, accompanied by the invasion of sympathetic and sensory nerves, and believed that the vascular density in the bone-cartilage composite unit was positively correlated with the severity of OA. Pan et al. [94] and Hwang et al. [95] found that the rate of luciferin passing through the bone-cartilage interface in OA rats was faster than that in the normal group, and the hydraulic conductivity between bone-cartilage in OA patients was significantly increased. Sanchez et al. [96] showed that coculture of osteoblasts in the subchondral bone in the sclerotic region of OA with chondrocytes can reduce the secretion of proteoglycans and type II collagen and increase the secretion of matrix metalloproteinases. Therefore, the enhancement of vascular formation and interaction in the bone-cartilage composite unit is important for inducing the pathological process of OA.

Kawakami et al. [97] isolated and cultured chondrocytes in patients with OA and confirmed that the chondrocytes partially expressed AT1R and AT2R by RT-PCR and showed increased expression with stimulation of IL-1 in OA pathology. Although the hypothesis that AT2R has an opposite function to AT1R in chondrocyte hypertrophy in most of the studies, the specific mechanism is still controversial [97–99]. Tsukamoto et al. [98] found that by activating the AT2R step in RAS, chondrocyte hypertrophy can be induced, which is characterized by increased expression of type X collagen, MMP-13 and Runt-related transcription factor 2, while AT1R activation suppressed the effect in the cell line ATDC5. On the contrary, Kawahata et al. [99] constructed a mouse rib fracture model and used Ang II as a treatment, and they found that the hypertrophy of chondrocytes increased significantly after the intervention during the healing process of costal cartilage fracture, indicating that Ang II was one of the molecules regulating chondrocyte hypertrophy. After the addition of the AT1R antagonist, the hypertrophy and apoptosis of chondrocytes were inhibited, and the expression levels of the antiapoptotic genes Bcl-2 and Bcl-xl were increased. All of the above studies indicate that the presence of the local RAS is associated with OA, and its key site of activity may become a new target for the prevention and treatment of OA.

6. Future and prospects

In the pathological development mechanism of OA, there are two pathways of Ang II-AT1R and Ang-(1–7)-Mas receptor axis, and Ang-(1–7) has a beneficial effect in addition to the antagonistic effect on Ang II-AT1R pathway. Thus, OA may reflect the deprivation of Ang-(1–7) and enhanced expression or activation of the Ang II-AT1R pathway, particularly since ACE inhibitors and AT1R blockers may increase local Ang-(1–7) tones [75,76]. The current studies have confirmed that the RAS signaling pathway is involved in the occurrence and development of OA and plays an important regulatory role in cartilage degeneration. The persistent changes in the local RAS can lead to sustained cartilage damage, which provides a new way for us to find therapies for OA, for example, potential gene targets for inhibiting Ang II-AT1R and activating Ang- (1–7) MasR axis related signaling pathway, so as to eventually reduce angiogenesis and delay OA. Although there are few studies on RAS in the field of OA, the pathogenic effect of RAS-related components is still an important topic in OA treatment, and great progress may be made in this aspect in future studies.

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Author contributions

BS, YZ and YGW conceived and designed the study. BS and YGW performed study selection, reviewed all potential articles. MYL, YGW, YZ and JFZ extracted data and conducted statistical analysis. YGW, YZ, XXL, MYL and JZ wrote the manuscript. YGW, XXL, JFZ and JZ revised the manuscript. All the authors finally approved the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest.

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