Role of peroxisome proliferator-activated receptors in osteoarthritis (Review)

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Abstract. Osteoarthritis (OA) is the most common form of arthritis, for which treatment options are not always satisfactory, since complete cure for OA is not yet possible. A better understanding of OA pathogenesis is thus important. The peroxisome proliferator-activated receptor (PPAR) plays a major regulatory role in lipid metabolism and energy homeostasis. This review article aimed to discuss the biological function of PPARs, and their role in regulating OA progression, as well as the therapeutic aspect of PPARs in OA. Studies indicate that PPARs regulate articular cartilage homeostasis through the modulation of various signaling pathways, and reduce the inflammatory responses in human OA cartilage. Furthermore, the deficiency of PPARs in the articular cartilage might be responsible for the acceleration of severe OA by increasing catabolic activity and suppression of chondroprotection. Therapeutic applications of PPAR-agonists can thus reduce the development of cartilage lesions by inhibiting the synthesis of various catabolic and inflammatory factors involved in the pathogenesis of OA. PPARs are thus important proteins in OA regulation, which may have significant importance in OA therapeutics.

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Contents

1. Introduction

Osteoarthritis (OA) is the most common form of arthritis. OA is mainly characterized by the loss of structure in the articular cartilage, remodeling of the subchondral bone and osteophyte formation (1,2). According to a review in 2017, OA has been reported to affect 240 million individuals worldwide (3). The etiology of OA is multifarious, including age, sex, genetic, mechanical stress on the joint, and loss of functional integrity of cellular organelles (4,5). Treatment options of OA have expanded and their availability has greatly been improved. However, these treatments are not always satisfactory, since a complete cure for OA is not yet possible (6,7). Therefore, there is a large demand for alternative therapeutics for OA. A better understanding of the underlying mechanisms of OA pathogenesis may facilitate the discover of more crucial targets, and may reduce the effect the devastating symptoms of OA (8,9).

Currently, the role of proteins associated with lipid metabolism have been identified in health and disease. Among these proteins, peroxisome proliferator-activated receptor (PPAR) has been reported to be involved in reducing inflammatory responses in human OA cartilage (10-12). PPAR is a ligand-activated transcription factor and a member of the nuclear receptor superfamily. It is originally identified to play a key role in lipid homeostasis. There are three isotypes of PPAR: α, γ and β/δ (13,14). PPARα is present in a wide range of cells including endothelial cells, hepatocytes, myocardiocytes

and chondrocytes, and exerts anti-inflammatory effects on various tissues (15,16). PPARγ has potent anti-inflammatory properties and regulates energy storage (17,18). PPARδ is the most widely expressed in whole body tissues, and regulates energy expenditure in cells (19,20).

The present review discusses the association between PPAR and OA, as well as evaluating the protective effects of PPAR on the prevention of OA.

2. Basic structure and function of PPARs

PPARs were originally identified in *Xenopus* frogs by Isseman and Green in 1990 (21). PPARs are similar to steroid or thyroid hormone receptor, and contain four major functional domains: N-terminal ligand-independent transactivation domain; DNA binding domain; co-factor docking domain; and C-terminal ligand-dependent transactivation domain. All isotypes of PPAR share a high degree of structural homology, particularly in the DNA-binding domain and ligand- and cofactor-binding domain (22,23). Fig. 1 represents the schematic representation of the basic mechanism of PPARs.

PPARs heterodimerize with the retinoid X receptor (RXR) and bind to specific regions on the DNA termed peroxisome proliferators response elements (PPREs). The DNA consensus sequence of PPRE is 5'-AGGTCANAGGTCA-3', which occurs in the promoter region of target genes. The function of PPAR/RXR heterodimers is modified by a number of coregulator complexes, which leads to transactivation and transrepression of various genes, for example, cytokine genes or glucocorticoid response element-driven genes (24-26). When activated by a ligand, the PPAR/RXR heterodimer is associated with coactivator protein complexes (such as cAMP response element-binding protein, PPARs coactivators, cAMP response element-binding protein binding protein, and steroid receptor coactivator-1), and the rate of is transcription of target genes is increased (27,28). In the absence of ligands, the PPAR/RXR heterodimer is associated with corepressor complexes (such as nuclear receptor co-repressor, and silencing mediator of retinoid acid and thyroid hormone receptor) and represses gene transcription by chromatin remodeling (27,29). It was reported that activated PPAR/RXR heterodimer may also repress target gene transcription through DNA-independent protein-protein interactions with other transcription factors or coactivators (30,31).

For the activation of PPARs, a number of natural or synthetic PPAR ligands, named agonists, have been identified. The mostwell-studied natural PPAR ligands include polyunsaturated fatty acids, eicosanoids, endocannabinoids and endogenous specialized pro-resolving mediators. The synthetic PPAR ligands include fibrates and thiazolidinediones (32,33). PPAR antagonists could also be used as an interesting PPAR modulator. Antagonists are compounds that bind to the LBD but interfere with H12 folding, which inhibits the binding of co-activators or subsequent transcriptional activation. Several antagonists have been identified including MK886, GW6471, BADGE, GW9662, PD068235, SR-202, LG100641, indomethacin, GSK0660, SR13904 and NSC636948 (34).

PPARs play a critical role in regulating diverse biological processes such as development, differentiation, inflammation and wound healing. They also may act as lipid sensors and regulators of energy (lipid and carbohydrate) metabolism (28,35). However, PPARs may cause the metabolic energy imbalance in disease conditions such as inflammation, diabetes, obesity, dyslipidemia, neurodegenerative disorder and cancer (20,36,37).

3. Role of PPARs in disease pathogenesis

PPARs play a major regulatory role in lipid metabolism and energy homeostasis by modulating target genes encoding lipid metabolism enzymes or lipid transporters, triggering a conformational change (38,39). Activated PPARs are known to have the protective and detrimental effect against various types of diseases, including diabetes, dyslipidemia, inflammation, pain, obesity, cancer and neurodegenerative disorders (40,41). PPARs play an important role in the immune response by inhibiting the expression of pro-inflammatory genes by peripheral immune cells through trans-repressive mechanisms. Several factors have been involved in regulating inflammatory signaling pathways mediated by different PPARs. During the inflammatory reaction, PPARs promote the inactivation of NF-κB. Activation of all PPARs by different pro-inflammatory factors causes the inhibition of NF-κB activation, which leads to the inhibition of inflammatory reactions. Activated PPARs bind with and thus inactivate p65 NF-κB through the proteolytic degradation of p65 NF-κB, leading to the reduction of the pro-inflammatory response. PPARα and PPARγ can inhibit the acetylation of p65 NF-κB by binding with p300 and inhibits activation of this pro-inflammatory factor. PPARα and PPARγ can also inhibit NF-κB activation by increasing the expression of IκBα and the activity of SIRT1. Activated PPARβ/δ inactivates NF-κB p65 by disrupting the assembly of TAK1, TAB1 and HSP27 into a complex. PPARγ increases the activity of the E3 ubiquitin ligase, which leads to proteolytic degradation of NF-κB (42-44). PPARs also cause the inhibition of inflammatory reactions by inactivating STATs. Activated PPARα disrupts the activity of STAT1 and PPAR-γ blocks the pro-inflammatory action of IFN-γ, as well as increase the expression of the suppressor of cytokine signaling 3, by inhibiting the JAK-STAT pathway (45).

PPARs also inhibit the proliferation of several types of human cancer cell lines (46,47). PPARs control the expression of genes involved in differentiation, and negatively regulates the cell cycle. PPARs have also shown efficacy in neurodegenerative disorders by inhibiting the activation of microglial cells (20,48). Fu *et al* (49) reported that PPARα has a protective role in obesity by initiating the transcription of proteins involved in lipid metabolism and repressing inducible nitric oxide synthase to repress feeding stimulation. Michalik *et al* (50) reported that PPARα plays a role in wound healing by controlling inflammation at the wound site. Lee *et al* (51) demonstrated that activation of PPARα regulated hepatic autophagy by nutrient status. Lee *et al* (52) showed that activation of PPARα synergizes with the glucocorticoid receptor (GR) to promote self-renewal of early committed erythroid progenitors.

4. PPARs in OA

Mitochondrial dysfunction plays an important role in the initiation and progression of cartilage degeneration in OA by impairing chondrocyte growth, increasing chondrocyte oxidative stress and enhancing inflammatory responses (53,54). PPARs have been implicated in regulating articular cartilage homeostasis through

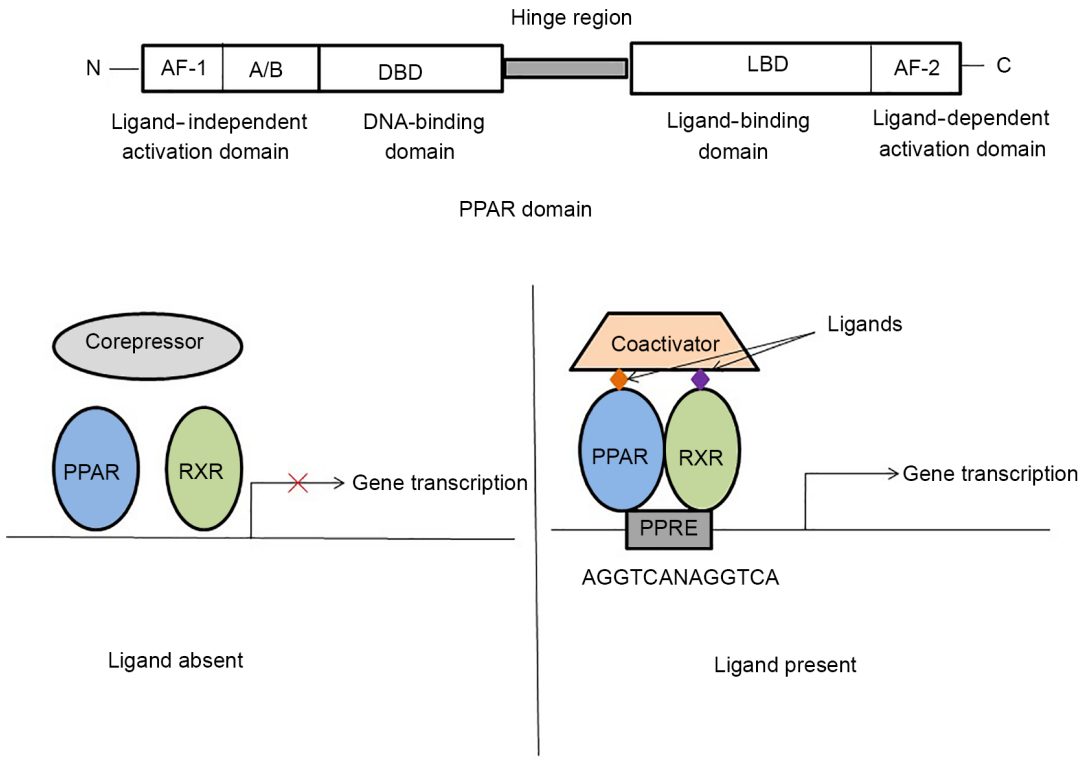

Figure 1. Basic mechanism of PPARs. PPARs heterodimerize with RXR and bind to PPREs. When activated by a ligand, the PPAR/RXR heterodimer is associated with coactivator protein complexes and the rate of transcription of target genes is increased. In the absence of ligands, the PPAR/RXR heterodimer is associated with corepressor complexes and gene transcription is repressed by chromatin remodeling. PPARs, peroxisome proliferator-activated receptors; RXR, retinoid X receptor; PPREs, peroxisome proliferators response elements.

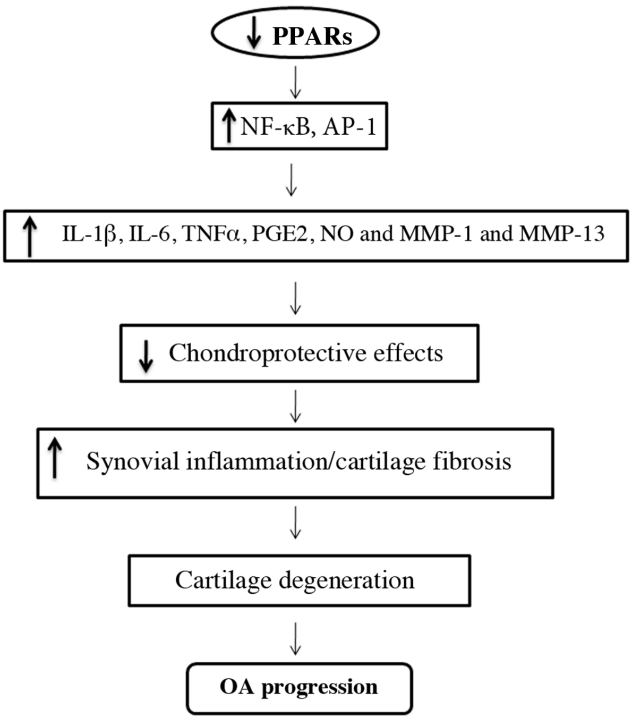

Figure 2. Mechanism of action of reduced level of PPARs in the progression of OA. The loss of PPARs can enhance the synthesis of various catabolic and inflammatory factors and reduces chondroprotective effects. Suppression of chondroprotection results in increased synovial inflammation and cartilage fibrosis, which could be a contributing factor in cartilage destruction and the progression of OA. PPARs, peroxisome proliferator-activated receptors; OA, osteoarthritis; IL, interleukin; TNF, tumor necrosis factor; PGE2, prostaglandin E2; NO, nitric oxide; MMP, matrix metalloprotease.

the modulation of various signaling pathway. The reduction of PPARα may promote inflammatory and destructive responses in OA cartilage. Loss of PPARα increases the expression of MMP1 and MMP13, as well as enhances the production of triglycerides and cholesterol levels in plasma, and thereby induces cartilage degradation in OA. PPARδ can act as a promoter of cartilage degeneration in O (55). Ratneswaran *et al* (56) reported that PPARδ activation by GW501516 (a selective PPARδ agonist) resulted in enhanced expression of several proteases in chondrocytes, increased aggrecan degradation and glycosaminoglycan release; whereas cartilage-specific PPARδ-knockout mice showed strong protection from cartilage degeneration in a mouse model of posttraumatic OA.

The deficiency of PPARγ in the articular cartilage may be responsible for the acceleration of severe OA by increasing catabolic activity and the suppression of chondroprotection (Fig. 2) (57,58). Wang *et al* (59) reported that PPAR-γ coactivator (PGC)-1α is the master regulator of mitochondrial biogenesis that critically mediates anti-catabolic activity in chondrocytes. Mitochondrial biogenesis has been impaired in human OA chondrocytes that promote chondrocyte pro-catabolic responses. PPARγ was also reported as a master adipogenic regulator that may influence the deposition of fat in both skeletal muscle and connective tissues. Deposition of fat is a strong risk factor for OA in the knee. The major adipose tissue in knee joint is infrapatellar fat pad (IPFP) that can produce inflammatory cytokines and adipokines. Consequently, PPARγmay associate with the pathological changes of IPFP in OA by triggering adipogenesis, via the activation of different signaling pathways (60-63). It is also reported that loss of PPARγ can enhance

Table I. Therapeutic agents targeting PPARs for the treatment of OA.

Authors	Isotype of PPAR	Therapeutic agents	Experimental sample	Effects	(Refs)
Clockaerts *et al*, 2011	PPARα	Wy-14643 (PPARα agonist)	Human OA cartilage	Anti-inflammatory and anti-destructive effects.	(55)
François *et al*, 2006	PPARα	Clofibrate (PPARα agonist)	Rabbit articular chondrocytes	Counteracts IL-1β-induced MMP-1, MMP-3 and MMP-13 production.	(15)
Vasheghani *et al*, 2015	PPARγ	PPARγ expression vector	Cartilage-specific PPARγ KO mice	Reduces mTOR expression, increases expression of autophagy markers and suppresses the expression of OA inflammatory/ catabolic factors.	(58)
Monemdjou *et al*, 2012	PPARγ	PPARγ agonist	Cartilage-specific PPARγ KO mice	Decreases cartilage degradation, synovial inflammation, cartilage fibrosis and decreases expression of catabolic factors.	(12)
Fahmi *et al*, 2011	PPARγ	PPARγ agonist	OA animal model	Inhibits inflammation and decreases synthesis of cartilage degradation products.	(65)
Ratneswaran *et al*, 2015	PPARδ	PPARδ inhibitor	PPARδ-KO mice	Decreases cartilage degeneration.	(56)
Qu *et al*, 2017	PPARγ	Mangiferin	Human OA chondrocytes	Inhibits IL-1β-induced inflammatory response.	(71)
Wang *et al*, 2018	PPARγ	Antarctic krill oil	OA mice	Improves articular cartilage degeneration via activating chondrocyte autophagy and inhibiting apoptosis.	(72)
Wang *et al*, 2019	PPARγ	Galectin-3	Human OA chondrocytes	Increases anti-inflammatory and antiapoptotic effect.	(73)
Jingbo *et al*, 2015	PPARγ	Betulinic acid	Human OA chondrocytes	Inhibits IL-1β-induced inflammation.	(74)
Kang *et al*, 2017	PPARγ	Oleanolic acid	db/db mice	Prevents high-glucose-induced cartilage degeneration, inhibits apoptosis and decreases SOD2 protein degradation.	(75)

PPARs, peroxisome proliferator-activated receptors; OA, osteoarthritis; KO, knockout; IL, interleukin; MMP, matrix metalloprotease; SOD, superoxide dismutase.

the synthesis of various catabolic and inflammatory factors, including inflammatory cytokines such as interleukin (IL)-1b, IL-6, tumor necrosis factor-α, prostaglandin E2, nitric oxide (NO) and matrix metalloproteinases (MMPs) involved in the pathogenesis of OA (64,65). Moreover, loss of PPARγ reduces chondroprotective effects, anti-inflammatory and anti-fibrogenic effects, resulting in increased synovial inflammation (accumulation of macrophages) and increased synovial and cartilage fibrosis; this could be a contributing factor resulting in cartilage destruction and the progression of OA (57,66).

5. Therapeutic aspect of PPARs in OA

As we have already discussed that OA is a progressive degenerative joint disorder and the most common form of arthritis, it has become a socioeconomic and clinical concern. Traditional OA treatments are still unsatisfactory to stimulate the regeneration of cartilage. PPARs play a critical role in regulating cartilage health, and the lack of PPARs leads to the degeneration of cartilage in OA (12,67,68). Several studies have found that PPARs may be a therapeutic target to counteract the degradative mechanisms associated with OA (Table I) (12,15,55,56,58,65,69-73). These studies have showed that PPAR agonists can reduce the development of cartilage lesions by inhibiting the synthesis of various catabolic and inflammatory factors involved in the pathogenesis of OA (74,75).

Clockaerts *et al* (55) hypothesized that PPARα activation leads to anti-inflammatory and anti-destructive effects in human OA cartilage. Cartilage explants obtained from patients with OA were cultured and Wy-14643 (a potent and selective PPARα agonist) was added to the cultures. It was found that the addition of PPARα agonist Wy-14643 inhibited the inflammatory and destructive responses in human OA cartilage explants

by decreasing the mRNA expression of MMP1, MMP3 and MMP13 in cartilage explants, as well as decreasing the secretion of inflammatory marker NO in the culture medium of cartilage explants (55). François *et al* (15) demonstrated that the addition of clofibrate (another PPARα agonist) counteracts IL-1β induced MMP1, MMP3 and MMP13 production in rabbit articular chondrocytes. Vasheghani *et al* (58) investigated the role of PPARγ in maintaining cartilage homeostasis and the specific *in vivo* role in OA pathophysiology. Inducible cartilage-specific PPARγ knockout (KO) mice were subjected to the de-stabilization of medial meniscus (DMM) model of OA. It was found that PPARγ KO mice exhibit increased cartilage degradation, chondrocyte apoptosis and the overproduction of OA inflammatory/catabolic factors through aberrant mTOR signaling and the suppression of key autophagy markers in the articular cartilage (58). Furthermore, *in vitro* rescue experiments using PPARγ expression vector and *in vivo* studies using PPARγ-mTOR double KO mice showed reversed phenotypes of PPARγ KO mice chondrocytes by reducing mTOR expression, increasing expression of autophagy markers and suppressing the expression of OA inflammatory/catabolic factors (58). Monemdjou *et al* (12) also reported that activation of PPARγ by its agonists can decrease the development of cartilage lesions in OA animal models. Cartilage-specific PPARγ knockout (KO) mice were generated using the Cre-lox system, which exhibited reduced cartilage degradation, synovial inflammation, cartilage fibrosis and decreased expression of catabolic factors (12). Fahmi *et al* (65) also indicated that agonists of PPARγ decreased the development and progression of cartilage lesions in OA animal models by inhibiting inflammation and reducing the synthesis of cartilage degradation products.

Ratneswaran *et al* (56) reported that PPARδ potentially have opposing roles in OA development, with PPARα and PPARγ acting in a protective manner and PPARδ in a degenerative manner. The role of PPARδ as a promoter of cartilage degeneration was examined in a mouse model of posttraumatic OA and suggested that pharmacologic inhibition of PPARδ is a promising therapeutic strategy for the treatment of OA. They treated mouse chondrocytes and knee explants with a pharmacologic agonist of PPARδ (GW501516) and evaluated that PPARδ activation by GW501516, resulting in increased expression of several proteases in chondrocytes, as well as aggrecan degradation and glycosaminoglycan release in knee joint explants (56). In the *in vivo* study, PPARδ was deleted from the cartilage of mice and found that cartilage-specific PPARδ-KO mice showed strong protection in the DMM model against posttraumatic OA from cartilage degeneration (56).

Several other studies focused on naturally occurring plant products that may activate PPARs and provide a preventive strategy for the treatment of OA. Qu *et al* (71) investigated the role of mangiferin (MFN) in human OA chondrocytes. Cells were treated with various concentrations of MFN and found that MFN inhibited IL-1β-induced inflammatory response in human OA chondrocytes by activating PPARγ (71). Wang *et al* (72) suggested that Antarctic krill oil (AKO) improves articular cartilage degeneration via activating chondrocyte autophagy and inhibiting apoptosis in mice with OA. It was also shown that AKO upregulates PPARγ and reduces mTOR signaling, and thereby maintains cartilage homeostasis in OA model mouse (72). Wang *et al* (73) reported that the downregulation of galectin-3 (Gal-3) protects from lipopolysaccharide-induced chondrocytes injury in OA via the regulation of TLR4 and PPARγ-mediated NF-κB signaling pathway. This indicated that the activation of PPARγ effectively increases anti-inflammatory and antiapoptotic effect in human OA chondrocytes, through the depletion of Gal-3 (73). Jingbo *et al* (74) investigated the protective effect of betulinic acid (BA; a triterpenoid isolated from birch bark) against OA progression. It was suggested that BA inhibited IL-1β-induced inflammation in OA chondrocytes by activating PPARγ (74). Kang *et al* (75) reported that hyperglycemia-induced cartilage degeneration induces OA. It was suggested that oleanolic acid (OLA) prevents high-glucose-induced cartilage degeneration via PPARγ-associated mitochondrial stabilization. It was also reported that OLA treatment inhibited apoptosis and decreased SOD2 protein degradation via PPARγ (75).

6. Future research

OA is the most prevalent chronic human health disorder that is characterized by cartilage degeneration. It is a leading cause of disability, which reduces mobility and increases dependency (76,77). Due to the lack of PPARs playing a critical role in the pathogenesis of OA, the activation of PPARs using PPAR agonists may be interesting therapeutic targets for the prevention of OA progression (78,79). Investigation of novel physiological roles of PPARs and the identification of specific PPAR agonists, which reduce the risk of OA by limiting cartilage degeneration, may provide exciting therapeutic strategies in the future. Moreover, the precise molecular mechanisms through which PPARs exert their actions require clarification. For example, the detailed signal transduction mechanism from ligand binding (PPAR-agonists) to gene transcription should be clarified. In addition, clinical investigations on PPAR activation in patients with OA should be performed for the establishment of this therapeutic approach.

7. Conclusion

OA is a slowly progressive disease that is becoming a worldwide epidemic. Early identification and administration of effective treatment, to inhibit the destructive or inflammatory responses in cartilage, may be the best strategies against OA. A better understanding of the pathogenic mechanisms may provide the knowledge to identify new targets to develop therapeutic drugs for OA. PPARs are affected in OA and targeting PPARs might be an innovative approach for the treatment of OA. The use of selective targets of PPARs may minimize the side effects and might be a promising therapeutic avenue for the treatment of OA. More studies are necessary to identify selective agonists for efficiently targeting PPARs in the prevention and treatment of OA.

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Availability of data and materials

Not applicable.

Authors' contributions

ZD and GH reviewed the design of the review, and drafted and proofread the article. WJ created the figures and revised the article. WX, WL and WZ participated in literature collection, analysis and summary. ZD supervised the project. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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