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REVIEW ARTICLE

Osteoarthritis versus psoriasis arthritis: Physiopathology, cellular signaling, and therapeutic strategies

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Abstract Osteoarthritis and psoriasis arthritis are two degenerative forms of arthritis that share similar yet also different manifestations at the histological, cellular, and clinical levels. Rheumatologists have marked them as two entirely distinct arthropathies. Given recent discoveries in disease initiation and progression, potential mechanisms, cellular signaling pathways, and ongoing clinical therapeutics, there are now more opportunities for discovering osteoarthritis drugs. This review summarized the osteoarthritis and psoriasis arthritis signaling pathways, crosstalk between BMP, WNT, TGF-β, VEGF, TLR, and FGF signaling pathways, biomarkers, and anatomical pathologies. Through bench research, we demonstrated that regenerative medicine is a promising alternative for treating osteoarthritis by highlighting significant scientific discoveries on entheses, multiple signaling blockers, and novel molecules such as immunoglobulin new antigen receptors targeted for potential drug evaluation. Furthermore, we offered valuable therapeutic approaches with a multidisciplinary strategy to treat patients with osteoarthritis or psoriasis arthritis in the coming future in the clinic.

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Introduction

Arthritis is a wide term that encompasses more than 100 different joint disorders. The most common form of arthritis is osteoarthritis (OA),[1] a degenerative condition that affects all the tissues in the joints[2] and further causes the breakdown of the articular cartilage,[3] osteophytes, cysts, sclerosis formation, remodeling of subchondral bones, joint space thinning, and inflammation in the synovial membrane, all of which are commonly associated with its progression.[4,5] This pathology is categorized into two forms. The first form is the primary (idiopathic) form whereby the joint is affected by a natural incident that causes degenerative changes in the joint site and eventually affects one (localized) or more joints (generalized).[6] The other form is the secondary form, which is caused by risk factors, including trauma and other diseases, or disorders of metabolism or bones.[7]

Another form of arthritis is psoriatic arthritis (PsA), which is more of chronic autoimmune arthritis than degenerative arthritis and includes enthesitis, dactylitis, axial disease, peripheral arthritis, nail disease, and psoriatic skin. The earliest manifestations of PsA are exhibited as inflammation of enthesis, known as enthesitis. This disease is associated with increased abnormal activity and worsened prognostic outcomes, with severe inflammation of the finger, toe tendons, and joints, known as dactylitis.[8] Axial disease is another manifestation of PsA that reduces spine movement with the involvement of the joints that connect to the spine and pelvis and is characterized by pain and stiffness of the back and buttocks. Peripheral arthritis is a disease that causes swelling and stiffening of the large joints in the arms and legs, including the elbows, wrists, knees, and ankles.[9,10] Nail disease in PsA is caused by the breakage of blood vessels under the nails and is characterized by white, yellow, or brown discoloration or reddish marks. Psoriatic skin is associated with skin lesions and chronic itching in the elbow, knee, scalp, genital areas, and lower back regions.[11]

Currently, there are no effective drugs to treat arthritis, but more evidence has revealed the characteristics, cellular and molecular pathology, and drug efficacy of therapeutics, such as immunoglobulin new antigen receptor (IgNAR), which is a shark antibody that produces a variable new antigen receptor (VNAR).[12] VNAR was demonstrated to be an effective bio-therapeutic agent in animal models of arthritis.[13,14] In this review, we summarized the physiopathology, cellular signaling, and therapeutic strategies in OA versus psoriasis arthritis, and emphasized the importance of a newly discovered and applied IgNAR in the future treatment of arthritis.

Histological features in OA *vs*. PsA

Joints are formed during mesenchymal stem cell differentiation, whereby different specialized cells are created, depending on the environment and stimulation.[15] Those cells include subchondral osteoblasts, osteoclasts, fibroblast synoviocytes, chondrocytes, and synovium macrophages. All these cells release various cytokines in response to changes in the joint that eventually trigger cartilage disintegration.[6] The activation of interleukin (IL)-23 and IL-17 signaling in joints brings about the induction of OA via different effectors, such as RANKL (receptor activator of the nuclear factor-κB ligand)/RANK (receptor activator of NF-κB),[4,16,17] C-reactive protein,[18] IL-1β, bone morphogenetic protein (BMP)-2,[19] vascular endothelial growth factor (VEGF), IL-1β, tumor necrosis factor (TNF)-α, interferon-γ,[20] monocyte chemoattractant protein (MCP)-1, matrix metalloproteinases (MMPs),[21] and ADAMTS (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs)[22,23] (Fig. 1).

Cartilage

Chondrocytes are cartilage-only cells derived from mesenchymal stem cells with extracellular matrix properties.[24] In normal circumstances, articular cartilage maintains characteristic synthesis of essential extracellular matrix molecules, such as proteoglycans that include aggrecan and type II collagen fibers (Col2a1), throughout life. If the process is disrupted, it can lead to an undesirable event, which may lead to the development of OA.[25] OA is initiated from the vascularization and focal calcification of joint cartilage.[24] Factors such as age, the extent of joint injury, obesity, mechanical stress, and pro-inflammatory cytokines can cause chondrocytes to rebuild the articular cartilage, which in turn results in an elevated number of degrading enzymes in the extracellular matrix capable of destroying the collagen matrix and degrading the articular cartilage. Under this condition, chondrocytes undergo hypertrophy and lose the ability to form a new cartilage matrix.[6] Excessive chondrocyte apoptosis and reduced proliferation are frequently observed to be related to cartilage degradation.[26] The loss of Col2a1 was shown to lead to chondrocyte hypertrophy, whereas Col2a1 supplementation reversed chondrocyte hypertrophy.[27] Apoptosis is a natural process of endochondral ossification that accelerates the progress of arthritis when the cartilage is damaged.[28]

Subchondral bone

Osteoblasts, osteoclasts, osteocytes, endothelial cells, and sensory neurons and the changes in the interactions among these cells lead to microstructural and pathological changes of the subchondral bone during the progression of OA. The equilibrium functions of these cells are needed to maintain homeostasis of joint sites. Increasing differentiation and/or activity of osteoclasts give rise to bone resorption.[17,29] Abnormal remodeling leads to the formation of subchondral cysts[6,30] and osteophytes. However, subchondral bone sclerosis may occur late during the progression of the disease.[6] In animal models and OA patients, over-activated bone remodeling at micro-damaged sites was identified in the subchondral bone.[31] Enhancement of osteoclast-mediated bone resorption and osteoblast-mediated bone formation can be two risk factors at different stages of the disease. The increased osteoblast activity is associated with remineralization and osteosclerosis at the last stage of OA[31] (Fig. 1A).

Synovium

The synovium prevents friction between articulating bones in the joint cavity.[32] The two major cellular components of

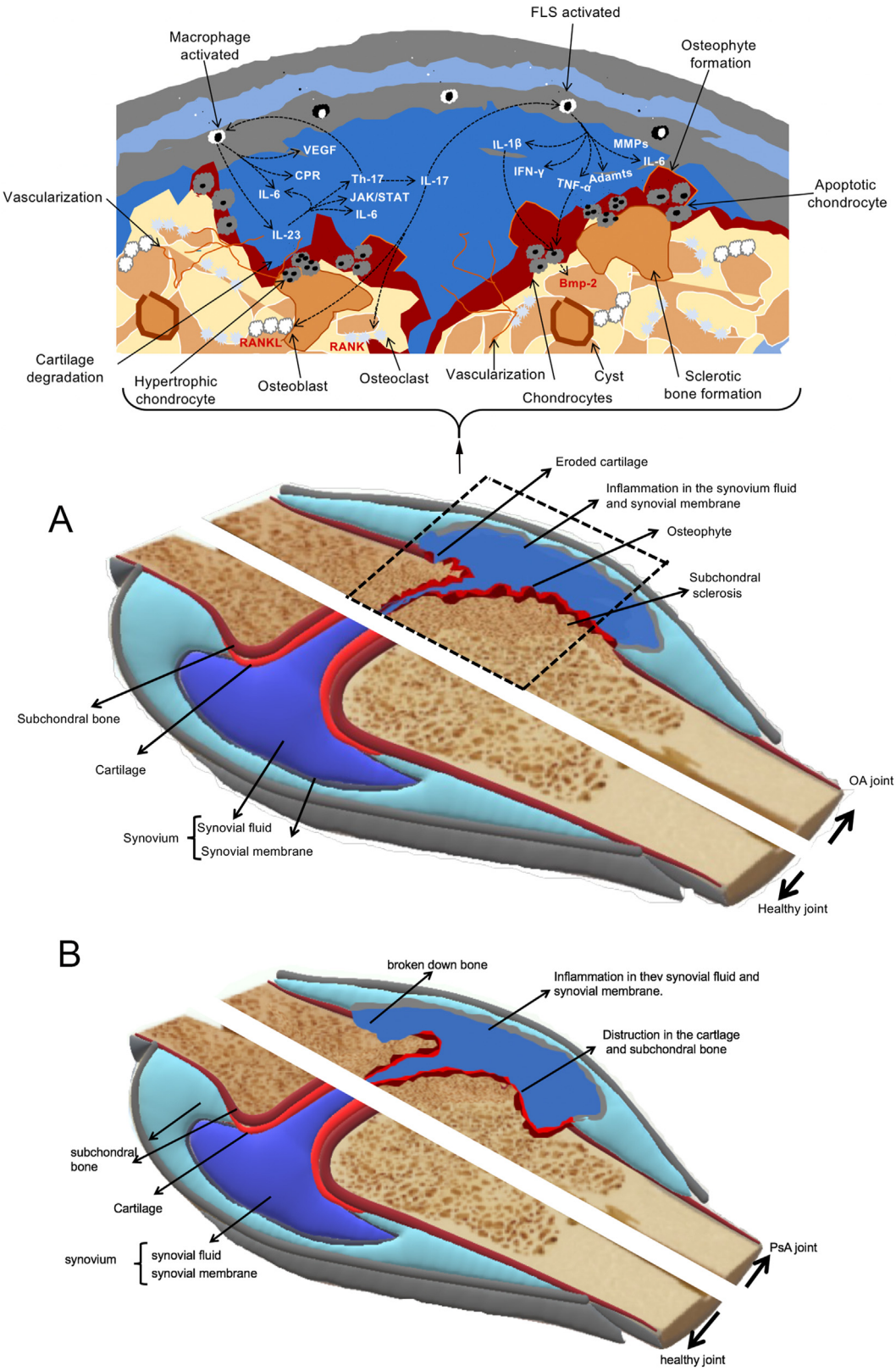

Figure 1 The appearance of healthy, osteoarthritic, and psoriatic arthritic joints. **(A)** Osteoarthritic joints with cellular changes in different cells and the release of cytokines. The activation of IL-23 and IL-17 signaling in joints induces OA via different effectors, such as RANKL/RANK, C-reactive protein, IL-1β, BMP2, VEGF, IL-1β, TNF-α, IFN-γ, MCP-1, MMPs, and ADAMTS. **(B)** Psoriatic arthritis joints and anatomical pathology.

the synovium are macrophage-like and fibroblast-like synoviocytes.[33] The fibroblast-like synoviocytes are presumably responsible for producing hyaluronan and lubricin molecules that prevent synovial fluid from leaving the joint capsule. Synovial macrophages are usually dormant,[6] but once activated, they are responsible for the elimination of excess materials and pathogens from the joint, the secretion of enzymes, cytokines, and chemokines for triggering the inflammatory response, and cartilage degeneration.[32] The hyaluronic acid found in the synovial fluid balances its production and degradation during the entire lifetime.[7] This results in a less lubricated and viscous synovial fluid in due course with a reduced ability for filtration and shock absorbance, and finally breaks down the coating over the surface of the joint to leave the cartilage exposed to mechanical stresses and inflammatory damages. Eventually, the synovial membrane proliferates and becomes inflamed, and the cartilage is gradually destroyed[32] (Fig. 1A).

Anatomical pathology in OA *vs*. PsA

PsA is a chronic, autoimmune form of arthritis that causes joint inflammation, while OA is considered a degenerative joint disease. The conjoining pathological processes between them are described, whereby the two initiators of both these diseases are signals such as hyaluronic acid fragments, fibronectin, and necrotic fragments that damage the tissue.[1] The starting point of OA and PsA might be at the same anatomical region (enthesis).[8] The presence of structural entheseal lesions along with low cortical bone mineral density at entheseal segments is associated with a higher risk of developing PsA in patients.[34] Enthesitis-related bone edema in PsA is common in OA as well.[35] A male patient was reported with enthesis in knee OA.[36,37] Magnetic resonance imaging during early OA has confirmed several different anatomical abnormalities within damaged joints; therefore, OA is defined as idiopathic with an enthesis-associated micro-anatomical basis[8,38] (Fig. 1B).

OA patients manifest similar inflammatory symptoms as PsA patients, such as enteropathies, tendinopathies, and joint swelling. Patients with PsA show clinical symptoms that are more indicative of changes in joint and cartilage destruction. Therefore, there is a specific overlapping pattern between these two disease entities.[39] Differentiating OA from PsA is difficult due to the shared abnormalities in entheses and ligaments. Even synovitis assessment through gadolinium-diethylenetriamine pentaacetic acid revealed the similarities between them. Magnetic resonance imaging results showed the dissimilarities between PsA and rheumatoid arthritis, as well as the differences between rheumatoid arthritis and OA, but it was difficult to distinguish the differences between PsA and OA as they share the same micro-anatomical basis.[8]

Erosive hand osteoarthritis is considered an uncommon variant of OA and is indicated by inflammation, proximal interphalangeal joints, hyaline articular cartilage degeneration, subchondral bone remodeling, and osteophyte formation, which leads to dysfunction of the joint. It has similar morphological features as the form of PsA occurring in the nails, such as erosions, joint space narrowing, and subchondral sclerosis.[40] One significant challenge in diagnosis is distinguishing psoriatic arthritis distal interphalangeal joints from erosive hand osteoarthritis, and this is because both diseases preferentially affect distal interphalangeal joints with similar clinical features.[40] Additionally, severe inflammation of the joint caused by the swelling of fingers and toes (dactylitis) in PsA is common[9,10] (Fig. 1B).

Biomarkers in OA *vs*. PsA

Biomarkers serve as measurable parameters that can indicate the normality and pathogenicity of biological processes in PsA and OA patients.[41] The evaluated biomarkers (IL-18, IL-20, IL-6, MMP1, MMP3, cartilage oligomeric matrix protein (COMP), proteoglycan aggrecan, and human cartilage glycoprotein-39) were elevated in OA and PsA patients compared to the controls.[39,41] The serum concentrations of IL-18 and IL-20 were statistically significantly higher in the sera of OA patients than in the control group. IL-20, COMP, MMP-3, and human cartilage glycoprotein-39 may be diagnostic markers of knee OA.[42] IL-6 was found to have a higher level of expression in PsA patients, suggesting its use as a clinical biomarker[43] (Fig. 1).

Among the OA and PsA patients, the serum levels of proteoglycan aggrecan in OA patients were statistically significantly higher than those in PsA patients. Furthermore, proteoglycan aggrecan and COMP showed a significant difference between OA and PsA patients (odds ratio: 0.995 and 1.003, respectively). COMP was elevated in PsA[44,45] and OA patients,[46] and serum COMP is used as a biomarker in OA disease for early cartilage lesions of the knee.[47] In addition, clusterin is an ATP-independent holdase chaperone that prevents proteotoxicity from protein aggregation. The secreted form of clusterin can be measured in synovial and systemic fluids and may have translational potential as a biomarker for early repair responses in OA.[48] Resistin has shown associations with inflammatory and catabolic factors in OA joints,[49] with high levels in PsA patient serum as well.[50] High concentrations of DKK1 were detected in both OA and PsA.[8] Chemokine (C-X-C motif) ligand 10 was identified as a predictive biomarker in PsA patients with psoriasis, and its level was reduced after the development of PsA. It may have an important etiological role in PsA, and it is a candidate biomarker for distinguishing PsA patients from healthy individuals and patients with OA.[51] MCP-1 was found to be elevated in the serum of both OA and PsA patients but was independently associated with PsA versus OA patients[52] (Table 1).

Table 1 Potential biomarkers in OA and PsA patients.

OA	PsA	Reference
IL-18, IL-20	IL-6	43
Proteoglycan aggrecan		44,45
Cartilage oligomeric matrix protein	Cartilage oligomeric matrix protein	47
Clusterin		48
	Chemokine (C-X-C motif) ligand 10	51
Extracellular vesicles		56

Serum collagen levels are dysregulated in PsA patients compared to healthy controls and therefore could serve as a potential biomarker.[53] Circulating extracellular vesicle microRNA levels are altered in PsA patients. For example, there were significantly lower levels of plasma extracellular vesicle let-7b-5p and miR-30e-5p in PsA patients than in healthy controls, suggesting a potential biomarker for arthritis in psoriasis patients.[54] Increasing evidence demonstrated that extracellular vesicles can be used for the diagnosis and treatment of OA.[55] A comprehensive cartilage proteome profile revealed a reduction of serpinA5 in locally damaged cartilage and sera of OA patients compared with the control group, suggesting that serpinA5 can serve as a potentially valuable OA biomarker.[56] Since the use of new technology such as single-cell sequencing, more biomarkers can be precisely targeted in the clinic for an earlier diagnosis and better treatment of OA and PsA.

Inflammatory responses in OA *vs*. PsA

Inflammatory responses occur following changes in the joints. Several different cells and cytokines play essential roles in mediating the inflammatory responses in OA and PsA patients. Macrophages and dendritic cells release IL-23 during chronic inflammation.[4,57,58] The serum levels of IL-17a and IL-23 were increased in OA patients.[59] In PsA patients, a higher concentration of IL-23 and IL-17 triggered dactylitis and enthesitis.[60] IL-23 poses a risk factor to the joints[4,17] in PsA patients,[61] and IL-23 plays an important role in excessive bone resorption[62] and promotes osteoclast formation[62] and osteoclast differentiation *in vitro*[63] (Fig. 2). Additionally, keratinocytes, neutrophils, Th17 cells, γδT cells, and osteoclasts are stimulated by IL-23 [61]. Dendritic cells also produce IL-12 and are associated with PsA pathogenesis.[64] The involvement of STAT3 is suggested because Th17 cells produce IL-17 in a STAT3-dependent manner that eventually induces bone remodeling of osteoblasts in PsA patients.[60,65] In one study, patients with higher levels of IL-17 complained of painful knee joints.[4] IL-17a stimulates mesenchymal stem cell differentiation[15] and influences the production of MMPs.[4,66] The synovial fibroblasts in PsA patients expressed higher levels of IL-17a that induced the up-regulation of *IL6*, *CXCL8*, and *MMPs*.[67] In PsA lesions, IL-17a and IL-17e are involved in neutrophil accumulation. IL-17a together with other Th17 cytokines can further up-regulate the production of other chemokines that are implicated in psoriasis pathogenesis.[68]

In OA progression, Th17 cells, natural killer cells, mast cells, neutrophils, and innate lymphoid cells[5,6] are potential IL-17a producers.[15] Fibroblast-like synoviocytes are stimulated by IL-17, which produce granulocyte-macrophage colony-stimulating factor effector that stimulates monocytes and induces inflammatory effectors, such as IL-1, IL-6, and TNF.[69] IL-6 is a chief stimulator of C-reactive protein production,[18] which induces an inflammatory

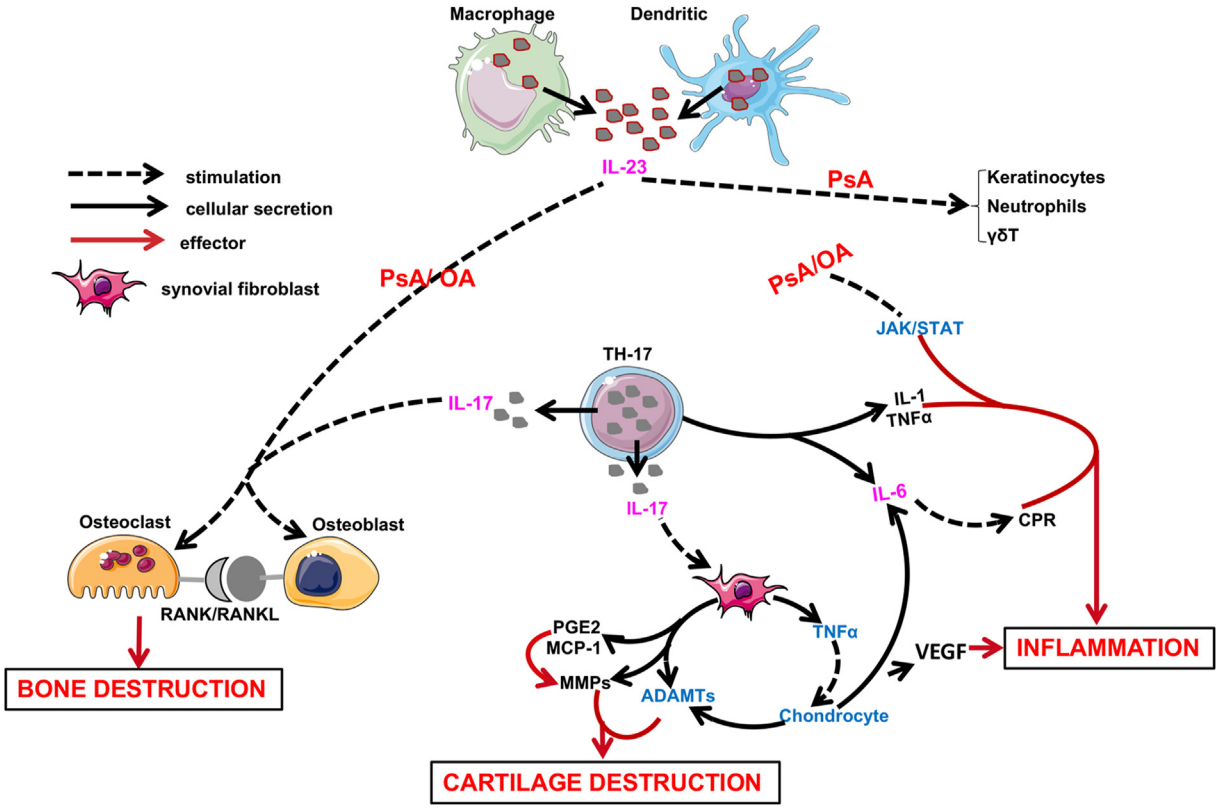

Figure 2 Inflammatory response of IL-23 and IL-17 in OA and PsA. IL-23, produced by dendritic cells and macrophages, interacts with IL-23 receptors on target cells, including Th-17 cells, keratinocytes, neutrophils, gamma delta (γδT) cells, osteoblasts, and osteoclasts. This interaction induces the production of different effector molecules that trigger cartilage and bone degradation together with an inflammatory response that induces the progression of PsA and OA.

response and plays a significant role in OA development.[70] The high level of IL-17 is consistent with a high degradation of cartilage.[4] Fibroblast-like synoviocytes stimulated by IL-1β produce more MCP1 chemokines,[20] as OA patients showed a high level of *MCP1* in the synovial fluid.[71] Notably, the binding of MCP1 to membrane receptors of chondrocytes induces the production of MMPs, which damage the articular cartilage[21] and induce the production of ADAMTS,[22] which degrade COMP, an important regulator of cartilage extracellular matrix assembly and a potential biomarker of cartilage degradation[23] (Fig. 2).

Prostaglandin E2 is one of the main catabolic factors involved in OA, through a process in which metalloproteinase is crucial for cartilage degradation.[72] Its elevated levels have been reported in synovial fluid in OA patients.[73] Synovial fluid and serum levels of VEGF were higher in OA patients.[18] VEGF promotes angiogenesis and contributes to synovial membrane inflammation.[74] VEGF, TNF-α, and IL-6 were observed in synovial fluid.[2] Increasing levels of IL-17a and IL-23 give rise to the up-regulation of cytokines, such as IL-6, IL-8, MMPs, and RANK, which caused PsA to progress through the induction of bone resorption, osteoclastogenesis, bone matrix structure changes, swelling of the joint, skin changes, and nail deformities.[60] IL-23 directly induced RANKL expression in synovial fibroblasts and up-regulated the expression of *RANK*/*RANKL* in osteoclast precursors.[75,76] IL-17a stimulated by IL-23 promoted RANKL production in osteoblasts and up-regulated *RANK* in osteoclast precursors, which gave rise to the progression of OA[17] (Fig. 2).

Cellular signaling pathways in the progression of OA and PsA

TLR signaling

Toll-like receptors (TLRs) are an essential element of the self-sustaining inflammatory loop, responsible for the chronic and destructive progression of OA and PsA.[41] TLR2 was significantly up-regulated on monocytes in both active and inactive PsA patients. TLR4 was similarly expressed in PsA patients.[77] The stimulation of TLR4 by lipopolysaccharide induces the release of critical pro-inflammatory cytokines that are necessary to activate potent immune responses in the MyD88-dependent, MyD88-independent, and TRIF-mediated pathways.[78] The MyD88-dependent pathway begins with the MyD88 and TIRAP adaptor. TIRAP-MyD88 regulates early NF-κB activation and production of pro-inflammatory cytokines.[79] A genome-wide meta-analysis from 5065 PsA patients and 21,286 healthy controls identified the key pathways that differentiated PsA, including NF-κB signaling,[80] suggesting a strong association of NF-κB signaling with PsA pathology.

The NF-κB response includes the expression of inflammatory mediators, such as inducible nitric oxide-synthase and cyclooxygenase type-2.[81] Inducible nitric oxide-synthase catalyzes the nitric oxide response, which stimulates the secretion of MMPs and represses collagen II and proteoglycan synthesis, resulting in extracellular matrix degradation in an OA model.[82] Prostaglandin E2 is a mediator of inflammation produced from lipopolysaccharide-induced endogenous arachidonic acid by cyclooxygenase type-2, and it is associated with cartilage degradation due to the stimulation of MMPs and ADAMTS5 secretion in joint chondrocytes.[83] Lipopolysaccharide is a potent inducer of osteoclastogenesis.[4] It was found to be reduced in the absence of IL-23 in *vivo* studies.[17] The p38 MAPK and NF-κB pathways stimulated the expression of MMP13 and VEGF, which led to an increase in *S100A12* expression in cartilage and eventually contributed to OA progression.[84] TLR2 and NF-κB-dependent signaling increased *MMP13* and *ADAMTS5* expression and decreased *Col2A1* and *aggrecan* expression in chondrocytes.[84] The catabolic responses of the cartilage are caused by the signaling of TLR-2/NF-κB involved in the MyD88-dependent pathway.[85] ADAMTS4, ADAMTS5, MMPs, nitric oxide, cathepsin K, IL-6, and IL-8 are catabolic factors in human chondrocytes,[84] which globally result in a net loss of cartilage.

Wnt signaling

The Wnt signaling pathway is required for the healthy maintenance of the joints.[25] However, Wnt signaling contributes to the destruction of the articular cartilage[25,86] by increasing chondrocyte hypertrophy and expression of cartilage-degrading MMPs that lead to increased catabolic activity in chondrocytes.[86,87] Wnt16-deficient mice reduced the expression of lubricin, which is a chondroprotective agent that protects chondrocytes against mechanical damage.[87] The deletion of frizzled-related receptors in an OA mouse model increased articular cartilage loss and altered MMP3 activity.[88] Mice with a frizzled receptor deficiency exhibited an increase in cartilage damage, which was associated with the activation of Wnt signaling and the expression of destructive tissue enzymes. The excessive Wnt activation increased susceptibility to OA in humans and mice.[25]

The stabilized fusion of β-catenin protein in mice is resistant to phosphorylation by GSK-3β in articular chondrocytes, causing a significant increase in the expression of chondrocyte marker genes, including *aggrecan*, *MMP9*, *MMP13*, *Alp*, and *Col10a*, and up-regulated expression of *Bmp2*, which led to excessive hypertrophy in articular cartilage.[88] Overexpressed inhibitor of β-catenin and T cell factor[89] prevented the binding of β-catenin to T cell factor-1 [3] in articular chondrocytes and increased cell apoptosis and articular cartilage destruction.[89] The progression in OA was due to high levels of Wnt5a in articular cartilage.[90] Wnt5a up-regulation in OA induced type II collagen degradation.[86] Wnt1-inducible-signaling pathway protein 1[87,91] was implicated in chondrocyte hypertrophy, osteophyte formation, and subchondral bone sclerosis.[86] It induces MMP3, MMP13, and ADAMTS4/5, which can cause articular cartilage damage.[92] The serum level of Dkk1 was also found to be abnormally elevated in PsA patients. The elevation of Dkk1 might be involved in the mechanism of bone erosion in PsA patients.[93] A recent genome-wide meta-analysis confirmed that the Wnt signaling pathway is highly associated with PsA development.[80]

TGF-β signaling

TGF-β signaling shows dual roles. High levels of TGF-β activation or lower but long-lasting TGF-β activation led to

osteophyte formation. The inhibition of endogenous TGF-β enhanced proteoglycan loss in OA animals.[94] Knockout of *TβRII* in mesenchymal stem cells (Nestin^{+}) in subchondral bone suppressed mesenchymal cell clusters and reduced subchondral angiogenesis, calcification, and cartilage damage. Active TGF-β was detected in the synovial fluid of OA patients.[3] Inhibition of TGF-β activity in the subchondral bone attenuated articular cartilage degeneration and suppressed subchondral bone remodeling in the OA mouse model. Cellular *SMAD3* knockout mice showed abnormal hypertrophic chondrocytes, articular cartilage, and joint destruction, similar to human OA, through the induction of collagen II expression and repression of Runt-related transcription factor 2 (RUNX2)-inducible MMP13 expression. SMAD3 was found to form a complex with RUNX2 during chondrocyte differentiation and eventually inhibited RUNX2 via a mechanism independent of PTHrP. Furthermore, ALK5/SMAD1/5/8 cascade activation led to OA progression, while ALK5/SMAD2/3 cascade activation improved cartilage protection and inhibited chondrocyte hypertrophy.[95]

BMP signaling

BMP signaling transduces extracellular stimuli through non-canonical Smad-independent (*e.g.*, p38 MAPK, JNK, and Erk1/2) and canonical Smad-dependent pathways (ligands, receptors, and Smads). Overexpression of BMPs leads to hypertrophy, differentiation of chondrocytes, and the formation of osteophytes, while BMP inhibitors reversed the formation of osteophytes in OA.[96] BMPs can trigger *SOX9* (sex-determining region Y box 9) and *RUNX2* expression, which contributes to cartilage damage. The intra-articular injection of noggin protein (a BMP2 inhibitor) reduced the expression of *IL1β* and *BMP2*, which prevented cartilage degeneration and OA development.[97] *BMP2* was up-regulated in chondrocytes and cartilage along with the severity of OA.[97] Multiple intra-articular injections of BMP2 induced significant osteophyte formation in knee joints with decreased cartilage degradation and the extent of subchondral structure remodeling.[97] Therefore, BMP2 has a dual role of anabolic and catabolic effects that cause cartilage damage.

FGF signaling

Fibroblast growth factor (FGF) signaling is initiated following extracellular stimuli in which the FGF ligand binds to its receptor to phosphorylate tyrosine residues on the receptor, which then recruits other proteins in the cytoplasm. MAP kinase effectors include JNK, ERK, and p38 mitogen-activated kinase that facilitate the activation of RAS/MAP kinase and PI3K/AKT pathways.[98] FGF2 has been identified as an anabolic mediator because Fgf2 ablation increased the susceptibility to OA development in mice.[99] *Fgf2* deletion in mice produced a more severe OA phenotype.[100]

Adapted recombinant adeno-associated virus expressing FGF2 significantly decreased type I collagen expression within cartilaginous repair tissue.[101] Treatment of normal chondrocytes with FGF23 resulted in increased *RUNX2* expression, whereas it did not affect *SOX9* expression, suggesting convincing associations among RUNX2, SOX9, and FGF23 in osteoarthritic chondrocytes.[102] FGF1 induction was observed in the articular cartilage in a rat OA model.[103] FGF receptor antagonists AZD4547 and NVP-BGJ398 down-regulated the expression of *MMP1* and *MMP13*, and up-regulated *aggrecan* and *collagen II*, both in the absence and presence of exogenous FGF2. FGF2 induced catabolic effects in human OA cartilage. Moreover, FGF receptor antagonists showed promising beneficial effects on balancing both catabolic and anabolic factors within OA cartilage.[104] In human articular chondrocytes, FGF2 stimulation enhanced chondrocyte proliferation through the up-regulation of *ADAMTS5* and *MMP13*, which was successfully rescued by an FGFR1 inhibitor.[105]

VEGF signaling

Higher VEGF serum concentrations were found in OA patients.[106] Articular cartilage degeneration, angiogenesis, and inflammation are well-known features of OA.[107] The VEGF-A/VEGFR2 signaling pathway correlated with the degree of OA.[108] At the early stages of cartilage degeneration, VEGF-A was up-regulated in the cartilage tissues.[109] In OA chondrocytes, the addition of recombinant VEGF contributed to the production of MMP1 and MMP3, but not in normal chondrocytes.[110] Targeting the inhibition of VEGF has been shown to be a promising approach for treating OA, such as antcin K, which markedly suppressed VEGF expression in human synovial fibroblasts to treat OA.[111] As a selective HDAC6 inhibitor, ricolinostat (ACY-1215) has demonstrated chondroprotective effects in OA. The level of HDAC6 was elevated in human OA osteoblasts *in vitro*. Higher expression of HDAC6 in osteoblasts contributed to OA progression, and therefore HDAC6 inhibitor is a potential therapeutic target for treating OA.[112] Similarly, VEGF also plays a role in the pathogenesis of PsA.[113] PsA synovial fibroblasts secreted factors that differentially regulated endothelial cell function, and secreted soluble mediators in the PsA joint microenvironment that induced a more pro-angiogenic phenotype.[114] VEGF levels were regarded as a possible indicator of active psoriasis arthritis[115] (Fig. 3).

Signaling crosstalk

Wnt and TGF-β/BMP signaling interactions

BMP2 induces Wnt/β-catenin signaling activation through low-density lipoprotein-related receptor 5 and contributes to chondrocyte hypertrophy and cartilage degradation in OA.[116] In OA chondrocytes, TGF-β signaling via cellular Smad2/3 complex was shown to be skewed by Wnt signaling using Wnt3a, which eventually led to chondrocyte hypertrophy. Additionally, *in vivo* overexpression of the canonical *Wnt8a* decreased Smad2/3 phosphorylation and increased Smad1/5/8 phosphorylation.[95] However, in *Smad3*$^{-/-}$ chondrocytes, TGF-β treatment resulted in the absence of β-catenin.[117] Both Smad3 and Smad4 were required for interaction with β-catenin and protected β-catenin from ubiquitin-proteasome-dependent degradation.[118] Cellular communication network factor 4 is known

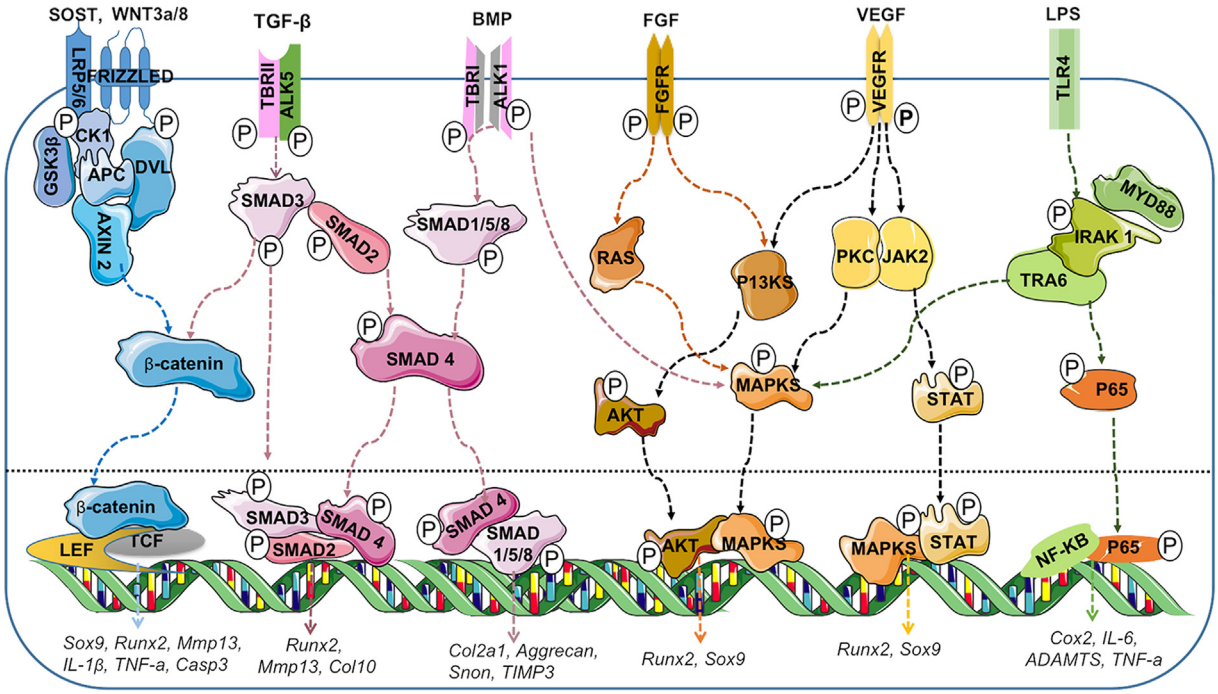

Figure 3 Signaling pathways with crosstalk play pivotal roles in the progression of OA and PsA. Signaling crosstalk shows a potential gene regulatory network for targeting gene expression to regulate OA and PsA development.

as a WISP1 (WNT1 inducible signaling pathway protein 1) downstream target of β-catenin.[119] Its gene knockout mice exhibited down-regulation of the chondrocyte marker genes and altered the activity of TGF-β signaling, suggesting that it is important for cartilage repair *in vivo* through the interplay with TGF-β signaling[120] (Fig. 3).

VEGF, Hippo, and WNT signaling crosstalk

The VEGF signaling pathway is a primary factor of angiogenesis initiation, which is regulated by Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ).[121] Blocking YAP is a possible therapy for preventing cartilage disintegration in OA. YAP activation by Wnt5a and Wnt5b via the Wnt signaling pathway targets genes such as *SOX9*, enhancing the proliferation and migration of chondrocytes. Wnt and Hedgehog signaling crosstalk is involved in cartilage degeneration through the induction of *ADAMTS4* and *MMP13* expression.[87] Cartilage degradation can be regulated by the inhibition of Hippo-YAP/TAZ and NF-κB signaling,[122] in which STAT3 accelerates the progression of OA through the NF-κB signaling pathway by expressing a series of genes, leading to joint destruction and the occurrence of OA symptoms[123] (Fig. 3).

TLR, NF-κB, and mTOR signaling interplay

The TLR4 inhibitor TAK-242 slightly inhibits the mobilization of NF-κB into the nucleus and is used for the treatment of TLR4-mediated inflammatory responses.[124] Activation of PI3K/Akt can be used as an anti-osteoarthritic by blocking TLR4,[125] and vertical inhibition of PI3K/Akt/mTOR signaling plays an important role in OA treatment.[126] Blocking NF-κB signaling via the regulation of PI3K/Akt signaling has demonstrated protection against OA pathogenesis.[127] Furthermore, sitagliptin and tofacitinib significantly decreased inflammatory parameters, including the JAK/STAT and TLR4/NF-κB pathways, offering synergistic anti-inflammatory effects and more protective function in an OA model[128] (Fig. 3).

Therapeutic strategies in OA *vs.* PsA

Ongoing therapy for PsA

The focus on novel therapies targeting IL-17 and IL-23 pathways improved clinical outcomes in PsA pathogenesis.[30] Therapies for inflammatory joints such as conventional disease-modifying anti-rheumatic drugs (csDMARDs) reduce the progression of joint damage and reduce the immune responses in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. A biological DMARD that targets the IL-23 and IL-17 pathways was suggested as a PsA therapy. Additionally, tsDMARD and apremilast are used against the synthesis of multiple pro-inflammatory cytokines and anti-inflammatory molecules, such as the agents targeting IL-17, IL-23, and JAK inhibitors. Different JAK inhibitors have been investigated in clinical trials[129] and produced superior outcomes for safely treating psoriatic arthritis.[130] Guselkumab, a monoclonal antibody that selectively blocks the p19 subunit of IL-23, was found to be an effective drug for PsA patients in clinical practice.[131] Bimekizumab is a dual IL-17 A and IL-17 F inhibitor for the treatment of psoriasis arthritis with no unexpected adverse events identified.[132] Ixekizumab produced a higher efficacy than adalimumab in the simultaneous achievement of

Table 2 Biological DMARDs target the IL-23 and IL-17 signaling pathways.

DMARD	Target	Treatment and effects	Reference
Ustekinumab	p40	Enthesitis and dactylitis	45,65,76,96,134
Guselkumab	p19	Active PsA (enthesitis and dactylitis)	9,45,96,135
Risankizumab	p19	PSA treatment	45
Ixekizumab	IL-17a	Enthesitis and dactylitis	30,96,134
Brodalumab	IL-17a	Efficacy in patients with PsA	45
Bimekizumab	IL-17a; IL-17 F	Joint improvement, positive response to treatment	45,30,60
Secukinumab	IL-17a	Enthesitis and dactylitis	9,134,45,96
Tofacitinib	JAK	Moderate-to-severe PsA	134,45

Table 3 Pain relief medication for OA.

Medications	Treatment and Effects	Reference
Duloxetine	Anti-depressant, effective for knee OA	139
Acetaminophen (paracetamol)	Mild-to-moderate OA of the hip or knee	138,140
naproxen (diclofenac)	Chronic arthritis	37,141,142
Herbal therapy: arnica, capsaicin, and comfrey	OA with no serious side effects	143
Intra-articular glucocorticoids: hydrocortisone and triamcinolone	A lesser risk of severe local adverse reactions in knee OA with short-term improvement	144
Mesenchymal stem cell therapy	Knee OA	145–148

targets in PsA patients,[133] suggesting a novel therapeutic strategy in the clinic (Table 2).

Ongoing therapy for OA

Fascinum, a human monoclonal antibody against nerve growth factor, has been shown to alleviate pain in OA patients and is in a phase III trial for assessing its efficacy and safety. Tanezumab is a monoclonal neutralizing antibody that blocks nerve growth factor[136] and is an effective treatment for arthritis pain.[137] The FDA fast-tracked tanezumab development due to a step-change improvement in pain relief. However, it eventually did not reach statistical significance compared to the placebo at 16 weeks. Currently, when the OA disease is severe, the only option is performing surgery to replace the damaged joint.[136,138] However, during the initial stage of the disease, exercise is usually recommended, as well as various medications for pain relief[136] (Table 3).

The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs) are agents that inhibit the conversion of OA development.[149] DMOADs can slow OA progression and restore joint structure and function.[138] DMOADs must fully penetrate the targeted sites.[150] However, DMOADs have not yet proven efficacious in a clinical trial.[7] The use of DMOADs in the form of inferior alveolar injection was suggested as a possible treatment option.[4] Another study suggested the development of drug delivery systems for targeted therapy of OA,[150,151] so that when drugs are injected directly into intra-articular joint space, they are rapidly cleared; however, they provided only short-term benefits, and multiple and higher doses were needed to balance the lost particles, which may further cause undesirable toxicity.[150] Selumetinib is a non-ATP-competitive mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2) inhibitor. Selumetinib promoted cartilage matrix synthesis, inhibited matrix decomposition, and exerted a protective function in chondrocytes, suggesting that selumetinib is a potential therapeutic agent for OA[152] (Table 4).

Emerging discovery of a shark antibody to treat OA *vs.* PsA

Immunoglobulin new antigen receptor (IgNAR) is a shark antibody that produces a VNAR antibody. Shark species that produce this antibody in an immunized and a non-immunized form are the banded wobbegong (*Orectolobus maculatus*), spiny (*Squalus acanthias*), bamboo (*Chiloscyllium plagiosum*), and nurse sharks (*Ginglymostoma cirratum*).[12] This antibody is suggested to be an effective treatment for arthritis[13,14] and other diseases.[153,154] The nature of this antibody suggests potential for biological therapy. This antibody has the smallest (12 kDa) antigen-binding variable domain known in vertebrates,[155] and a high thermostability and physicochemical stability. Engineering this antibody as a VNAR-Fc molecule is a next-generation therapeutic method that may overcome the limitations of classical monoclonal antibodies, such as complex structure, large size, and limited tissue penetration. VNARs provide a novel drug modality and may support the development of new therapy alternatives.[156]

VNAR neutralization of various cytokines in arthritis

Several cytokines are involved in arthritis diseases.[20,113,157,158] The therapeutic potential of VNARs may be in neutralizing various cytokines.[159,160] TNF-α plays a

Table 4 Various DMOADs in clinic use for OA.

Target	Therapeutic agent	Reference
Cartilage regeneration	OP-1, sprifermin, platelet-rich plasma, mesenchymal stem cells, TPX-100, SYSADOA, gene therapy, senolytic, and fisetin agents	[7,138]
Cartilage breakdown inhibition	Wnt, ADAMTS, cathepsin K inhibition, MMPs, and osteogenic protein 1	[7,138]
Subchondral bone remodeling	Bisphosphonates, strontium ranelate, calcitonin, cathepsin K inhibition, parathyroid hormone, TGF-β inhibition, TPX-100, anti-resorption, and vitamin D	[138]
Subchondral angiogenesis inhibition	Subchondral angiogenesis inhibition (bevacizumab, halofuginone), and nerve growth factor inhibition	[7]
Synovial inflammation inhibition	Arachidonic acid pathway inhibition, nitric oxide inhibition, SYSADOA, platelet-rich plasma, hyaluronic acid, oxygen-ozone, gevokizumab, lutikizumab, anakinra, canakinumab, diacerein, tocilizumab, XT-150 adalimumab, etanercept, and infliximab	[7]

vital role in rheumatoid arthritis and PsA pathology.[161] Recombinant human cytokine TNF-α (rhTNF-α) was identified *in vitro* (VNAR) and in immunized *Heterodontus francisci* shark species. VNARs inhibited pro-inflammatory cytokine overproduction, suggesting VNARs to be a potential immunotherapeutic drug.[160] VNARs against the recombinant human VEGF165 (rhVEGF165) generated by an immunized *Heterodontus francisci* shark showed positive results in treating vascular eye diseases.[162] VNARs from synthetic libraries against VEGF inhibited angiogenesis *in vitro*.[159] The cytokine interferon expressed in various tumor cells stimulated programmed death-ligand 1 (PD-L1 or CD274); during the testing of a semi-synthetic shark VNAR phage library against anti-PD-L1 single domain antibodies, interferon was not up-regulated in cultured CAR(B2) T cells.[153] Autoimmune uveitis was treated using anti-TNF-α VNAR S17 as effectively as corticosteroids by balancing TNF/IL-10 and attenuating the serum concentration of IL-6 [161].

Humanized VNARs

Variable domains of the IgNAR antibody are easily produced as recombinant proteins, designated as sdAbs.[163] VNARs can be reformatted by transplanting into other domains and therefore forming structural motifs without losing their parental efficiency.[12] This antibody is suggested to be an effective treatment for arthritis.[13,14] The effective application of VNARs in arthritis was reported in animal models. The average *in vivo* arthritis inhibition and histopathology percentage levels were 88% and 86%, respectively.[13] Fused VNARs retained antibody-dependent cell-mediated cytotoxicity.[50] An anti-TNF-α VNAR-human TNF-α complex has been constructed which interacted with two adjacent TNF-α promoters.[13,14] It was evaluated to be an effective target for treating arthritis[13] (Fig. 4).

The shark VNAR domain was observed by crystallization data of its framework regions, which is similar to human immunoglobulin variable domains.[164–166] The fusion was intended to lower the differences between the natural IgG and bispecific antibody format. The humanizing process was reported to be effective in minimizing the undesired immunogenicity of VNARs by replacing amino acid residues in the framework of the VH domain.[167] The binding ability of the parent antibody was retained by reducing single-chain Fv fragments using an engineering process for full-length mAbs,[168,169] thus leading to low immunogenicity,[170,171] and eventually avoiding unfavorable outcomes of anti-drug antibodies.[167] The study converted individual VNARs into VNAR-Fc fusions. VNARs were humanized by converting more than half of their complementarity-determining regions to those of a human germline Vk1 sequence, DPK9,[164] and eventually, the specificity and affinity of the antigen binding of the parental VNAR were retained.[164] The anti-drug antibodies were detected in preclinical *in vivo* efficacy testing using non-immunoglobulin VNAR fusion anti-hTNF-α biologics (Quad-X™ and D1-NDure™-C4) and Humira®, a brand of adalimumab, and low immunogenicity of the VNAR was exhibited.[172] E06 VNAR also showed low immunogenicity compared to the positive controls.[166]

These studies demonstrated the promising applications of VNARs in biotherapy. Therefore, blocking disease targets by using VNARs might provide a novel direction for treatment. Various cytokines were neutralized by VNAR treatment.[159,160] Hence, using VNARs is promising due to their improved efficacy over human antibodies, as most of the current clinical therapies have failed to fully meet treatment targets using IgG2. The strength of the VNAR's effect in OA is due to its small size, high-temperature stability, long complementarity-determining region 3 that can target a small epitope, and low immunogenicity after VNAR engineering.[12]

Multi-blocker signaling pathways

Diseases that progress along various paths may remain unresponsive to therapy using a single path,[173] as chondrocyte stimulation depends on the interaction of various signaling molecules.[28] Single-target drugs may not always induce the desired effect on the entire biological system, even if they successfully inhibit or activate a specific target.[174] Design strategies should be directed against multiple targets. It might be overwhelming to deal with all the combined target genes. The most important factor is that we should be precise as to which targets should be combined to design better drugs for specific complex diseases.[174] Therefore, the approach of blocking multiple signaling pathways for OA treatment is preferable, as various signaling pathways play

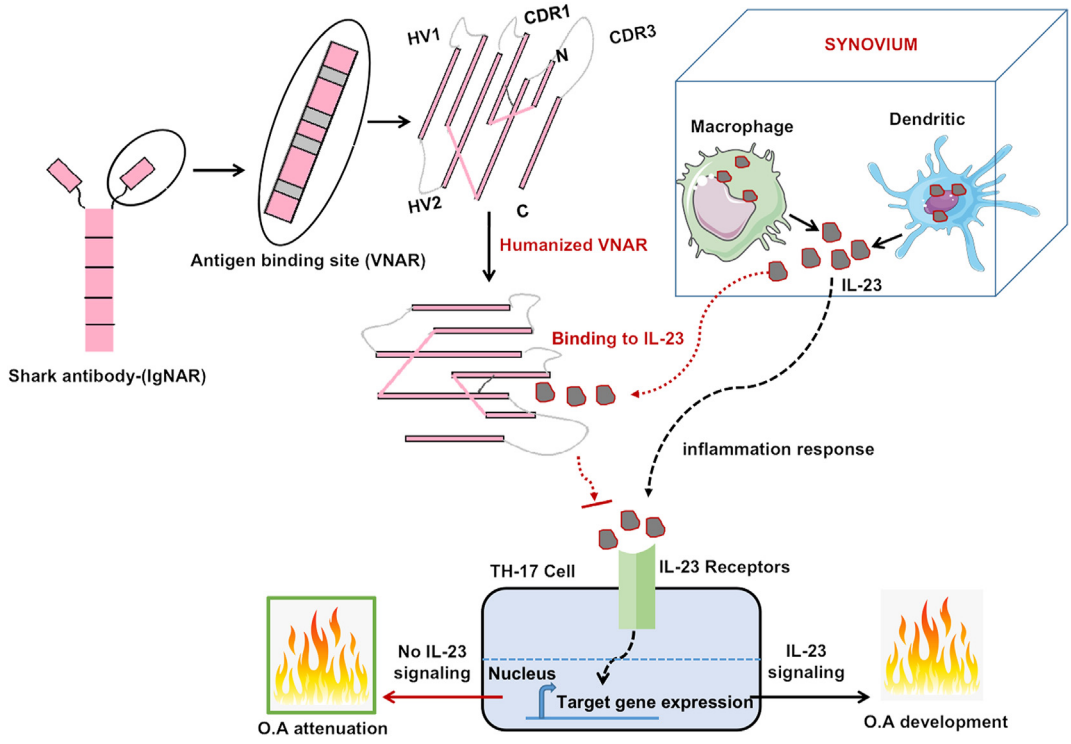

Figure 4 Humanized VNARs in OA attenuation. VNARs specifically responded to antigens such as IL-23 and produced a shark antibody to block the interaction of inflammatory responses during the development of OA symptoms.

a significant role in OA, such as the loss of TET1-mediated 5-hydroxymethylcytosine that protected *Tet1*$^{-/-}$ mice from OA development, including protection from the degeneration of cartilage surfaces and osteophyte formation, by directly preventing the activation of multiple OA pathways.[175]

Novel combination biological therapy is a promising treatment strategy, such as a combination of an IL-23 inhibitor (risankizumab) with a TNF-α inhibitor (golimumab) to treat PsA and produced a significant improvement with no adverse effects.[176] The PD-1/PD-L1 play an essential role in treating cancer conditions and generate promising outcomes in PsA.[177] The antitumor efficacy of JAKi was most effective when combined with SRCi and provided a potential combination strategy for the treatment of advanced ovarian cancer.[178] Connective tissue growth factor is a multifunctional protein in cells. Pamrevlumab is a monoclonal antibody against connective tissue growth factor, which is an FDA-approved drug for treating idiopathic pulmonary fibrosis and Duchenne muscular dystrophy. In a recent study, connective tissue growth factor antibodies were confirmed to serve as a new drug for OA.[179]

Enthesitis treatment target in osteoarthritis

The enthesis is the specific point at which tendons or ligaments attach to bone.[180] This point is where enthesitis (inflammation of enthesis) takes place at the early stage of OA.[8] Determining a microanatomic basis in hand OA at all stages of the disease showed that the ligaments and enthesis are the sites of the earliest stage of pathology.[181] Even at the beginning of knee OA in different animal models, observations within the diseased joint revealed the presence of enthesis and ligament anatomical abnormalities, therefore demonstrating OA to have an enthesis-associated micro-anatomical basis.[8,38] Targeting diseases in their earliest stage is preferable. Regarding enthesitis insights, treatments for OA should consider its strong linkage with enthesitis.

Summary and perspectives

OA and PsA affect the cartilage of the joint in mainly older people with symptoms of discomfort and pain. There are still no drugs to completely alleviate these conditions. Recent highlights refreshed our knowledge of the importance of developing PsA and OA clinical therapies to prevent joint damage caused mainly by OA. These therapies address the starting point of the disease through the mechanisms of various signaling pathways and represent combination methods by also utilizing IgNAR antibodies that can prevent the destruction of cartilage, subchondral bones, and early synovitis. The ultimate purpose is to provide the best possible evidence or scientific discoveries to demonstrate how, when, and where a molecule target works in special cells in clinical disease. However, there are still unsolved problems, such as how the drugs in development can be delivered specifically, effectively, and properly at disease sites. Novel technologies such as single-cell sequencing can also be used to advance the application of precision medicine to treat patients with different conditions in OA and PsA. Taken together, these explorations will be significantly important for translational medicine in the

clinic, and uncovering new targeting molecules should be integrated for consideration as novel therapeutic strategies in treating OA. Understanding the cellular mechanism of OA and PsA pathology will in turn provide a solid basis to utilize specific and efficacious antigens to treat OA disorders in animal models with potential translation into the clinic.

Author contributions

JS, JL, and YH wrote the manuscript. JS, JL, YH, QW, BW, HW, and DW conducted the literature review and revised the manuscript. GC helped in writing and revising the manuscript, and supervised the study.

Conflict of interests

The authors declare no conflict of interests.

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