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Osteoarthritis: genetic factors, animal models, mechanisms, and therapies

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1. ABSTRACT

Osteoarthritis (OA) is the most common form of joint disease. OA frequently affects knees, hips, hands, and the spine. It is characterized by the progressive destruction of articular cartilage and subchondral bone accompanied by low-grade inflammation that together result in pain and deformity. Recent studies have shed light on the nature of OA genetic susceptibility and confirmed a number of candidate genes involved in the destruction of the synovium, articular cartilage, and subchondral bone in OA pathogenesis. During the progression of OA, there are several cellular changes in joints, including an increase in the number of activated osteoclasts and macrophages and an infiltration of the synovium by activated T-cells and B-cells. Pro-inflammatory mediators (*e.g.* interleukin IL-1, IL-1beta, IL-6, IL-17, and IL-18, and Tumor necrosis actor-alpha), proteinases (*e.g.* matrix metalloproteinase 9 and cathepsin K), and regulators of cartilage and bone formation (*e.g.* BMPs) have been shown to have important roles in OA progression at the molecular level. Studies have suggested that OA shares several common characteristics with rheumatoid arthritis (RA). To systematically understand OA, this review summarizes OA disease genes, mouse models of human disease experimental mouse models, mechanisms of OA pathogenesis, and current OA therapies.

2. INTRODUCTION

Epidemiologic data shows that OA affects people in many countries, including 27 million adults in the United States (approximately 10% of the population)(1), and 3 million individuals in Australia (15% of the population)(2). There are multiple risk factors for OA, such as old age, genetic predisposition, sex, trauma, repetitive stress, obesity, inflammation, lifestyle issues, and comorbidities(3). Muscle weakness and afferent sensory dysfunction are considered predictors of OA onset and progression(4). Recently, Hypoxia-inducible factor-2alpha (HIF-2alpha, encoded by EPAS1) was reported to be the most potent transactivator of COL10A1, and a functional single nucleotide polymorphism (SNP) in the human EPAS1 gene was associated with OA. Others such as COL2A1, COL11A1, and AGC1 are related to OA in both humans and genetically-modified animal models. However, there is still long way to go to confirm these mutant genes in OA pathogenesis. Spontaneous models have been used less in recent years because they have been investigated for long periods of time. Currently, the common techniques for model creation are anterior cruciate ligament transaction (ACLT) and enzymatic alteration such as intra-articular injection with papain, trypsin, or collagenase. Genetically modified models such as Cre-Gdf5/Bmpr1a^{floxP} mice, Gt(ROSA)26Sor$^{tm1(Smo/YFP)Am}$-transgenic mice have also been utilized for the study of OA mechanisms. Chondrocytes, osteoclasts, synovial lining cells, and many cytokines and growth factors participate in OA development. MMPs, IL, TNF, Cathepsin K, IGF, TGF, FGF, VEGF, RANKL, etc. BMP-2, 4, 7 and their downstream genes play different roles in OA occurrence and development, especially in disparate components of joints. Although Non-steroidal anti-inflammatory drugs (NSAIDs), glucosamine and chondroitin, are still widely used in clinics, the use of traditional Chinese medicine and acupuncture are becoming popular in OA patients. This review is focused on the genetic background, model systems, cellular and molecular mechanisms, and therapeutic strategies for OA.

3. GENETIC FACTORS

Several studies have demonstrated that some individuals are genetically susceptible to OA. The genes that facilitate this vulnerability are involved in chondroplasia (cartilage development). Below, we demonstrate that the OA mutant genes developed in animal models are similar to those found in humans.

3.1. Cartilage ECM structural genes

In order to establish the genetic basis for OA, the initial studies focused on cartilage extracellular matrix (ECM) structural genes, such as *COL2A1*(12q13.11) that encodes alpha-1 polypeptide chain of type II collagen. Five studies identified five patients and families with the same cysteine for arginine substitution at position alpha-1-519 of the pro-alpha-1(II) chain who showed joint degeneration similar to early-onset OA. Moreover, some have evidence of mild chondrodysplasia; however, other individuals in these studies did not display any symptoms (5,6). Recently, Hypoxia-inducible factor-2alpha (HIF-2alpha, encoded by EPAS1) has been reported to be the most potent transactivator of COL10A1, and a functional single nucleotide polymorphism (SNP) in the human EPAS1 gene was associated with knee OA in a Japanese population (7).

Mutations in different cartilage collagen genes are also associated with OA. For example, mutations in *COL11A1*(1p21.1) and *COL11A2*(6p21.32), encode type XI collagen, cause symptoms such as mild spondyloepiphyseal dysplasia and Stickler Syndrome, a disease characterized by sensorineural hearing loss, caused by a splice donor site mutation resulting in "in-frame" exon skipping(8). A mutation in *AGC1*(15q26.1) that encodes aggrecan protein is associated with severe, premature OA along with spondyloepiphyseal dysplasia(9). The D14 polymorphism with 14 D residues of *ASPN*, an extracellular matrix protein, belongs to the SLRP family, and was identified as the risk allele of OA and lumbar disc degeneration. The function of this gene is to inhibit *in vitro* chondrogenesis and expression of Col2a1 and Agc1 through inhibition of TGF-beta signaling(10,13).

COMP (19p13.11) encodes cartilage oligomeric matrix protein, non-collagenous components, and expresses the phenotype of multiple epiphyseal dysplasia with OA symptoms(14). Matrilin-3, another non-collagenous cartilage extracellular matrix protein, encoded by *MATN3*(2p24.1), is found to cosegregate with OA of the hands. The missense mutation frequency is slightly greater than 2% in patients in the Icelandic population(15). *FRZB* (2q32.1), which encodes both the chondrogenic regulator secreted frizzled-related protein 3, and *CILP* (15q22.31) that codes for a cartilage intermediate-layer protein, has also been reported to be associated with OA in females (16,17).

3.2. Bone mass related genes

OA pathology involves subchondral sclerosis and increased bone density; therefore, attention has also been devoted to genes that encode for proteins influencing bone density. For example, *VDR* (12p13.11) encodes the vitamin D receptor. *CALM1,2* encodes calmodulins, *KL* encodes an enzyme with a key role in calcium and phosphate homeostasis, *CALCA* encodes calcitonin. In turn, *ESR1* (6q25.1) encodes the oestrogen receptor alpha, *BMP2* (20p12.3), *BMP5* (6p12.1), that then encodes bone morphogenetic protein and *OPG* (8q24.12). These latter proteins encode osteoprotegerin. Leptin is a peptide hormone playing a role in bone metabolism. Haplotypes in *LEP*, a gene encoding leptin is related to OA in Chinese patients. This cascade demonstrates the relatively pronounced association with OA (17-29). However, the effect of these gene mutations on disease occurrence might be moderate for the complex pathogenesis in OA.

3.3. Inflammation related genes

Inflammatory cytokines, which are synthesized not only in synovial cells but also in articular cartilage chondrocytes, play an important role in OA. Polymorphism within the IL-1 cluster gene (2q13) and variation in *IL1R1*(2q12-q13*)* and *IL4R* (16p12. 1) are considered OA

Table 1. Mutant gene locus and its phenotype in OA disease

Locus	Gene	Phenotype	Reference
1	*PTGS2 , PLA2G4A*	Knee OA	17
1p21.1	*COL11A1*	Stickler syndrome (mild spondyloepiphyseal dysplasia, OA, sensorineural hearing loss)	13
1q25	*COX2*	Female OA	22
2p24.1	*MATN3*	Hand OA (CMCL1[1], DIP[2])	20
2q12-q13	*IL1R1*	Hand (DIP)	35,36,39
2q31.1		Hip OA	51
2q32.1	*FRZB*	Female OA	21
3p12.3-p13		Hand (DIP)	20
3p21.31	*TNA*	Female OA	50
3p24.3	*DVWA*	Knee OA	54
4q13.1-q13.2		Female hip OA	52
4q26-q27		Hand (DIP)	37
4q32.1-q32.2		Hand (DIP)	15
6p12.1	*BMP5*	Female OA	20
6p21.32	*COL11A2*	Stickler syndrome	8
6q12.3-q13		Female hip OA	17,48
6p21	*BTNL2*	Knee OA	55
6q25.1	*ESR1*	Female OA	18
7p15-p21		Hand (DIP)	18
7q21.11	*CD36*	Female OA	17
7q22	*GPR22*	Knee OA, hand OA	54
8q		Early-onset OA, Chondrocalcinosis	49
8q24.12	*OPG*	Female OA	21
10q26.2	*ADAM12*	Female OA	17
11q		Female hip OA, knee OA	50
11q13.4-q14.3		Female hip OA	51
12p13.11	*VDR*	OA	17
12q13.11	*COL2A1*	Early-onset OA	5,6
12q24.31	*NCOR2*	Female OA	17
13q22		Hip OA	52
15q22.2-24.2	*SMAD3*	Knee OA, Hip OA	42
15q22.31	*CILP*	Female OA	17
15q26.1	*AGC1*	Spondyloepiphyseal dysplasia (SED)	9
16p12.1	*IL4R*	OA	34
19p13.11	*COMP*	Multiple epiphyseal dysplasia (MED)	14
20p12.3	*BMP2*	OA	19
20q	*GDF5*	Knee OA, Hip OA	27,28
Xp22.2	*SEDL*	Spondyloepiphyseal dysplasia tarda, OA	38,39
Xcen		Hand (DIP)	38,39
	BLP2, CIAS1	OA	37
	RHOB, TXNDC3	OA	37
	ASPN	OA, LDD[3]	10-13
	CALM1,2	Hip OA	23,24
	KL	Knee OA	25
	EDG2	Knee OA	40
	PITX1	Knee OA	43
	ANP32A	Hip OA	45
	HLA-DQB1	Knee OA	55

[1] The first carpometacarpal [2] distal interphalangeal [3] lumbar-disc degeneration

risk factors (30-34). A genome-wide association scan identified that rs4140564 on chromosome 1 mapping 5' to both *PTGS2* and *PLA2G4A* genes, promotes susceptibility to knee OA. Both of these genes are part of the prostaglandin E2(PGE2) synthesis pathway whose role will be mentioned in a subsequent section(35). *COX2* (1q25), which encodes a cyclooxygenase, and *ADAM12* (10q26.2), which encodes a metalloprotease, were reported to be associated with OA prevalence in a cohort of females(17).

3.4. Other loci variants

Allelic imbalances, such as a *cis*-regulated gene expression for *TXNDC3* (encoding for Thioredoxin domain containing 3), *RHOB* (encoding for RHOB, a GTP-binding protein), and *BLP2* (encoding for BBP-like protein 2), or trans-regulated gene expression of *CIAS1* (encoding for Cold auto-inflammatory syndrome 1), showed a statistically significant association with OA(36). However, some investigators confirmed a negative association between *RHOB* and *TXNDC3* genes with OA(37). Literature pertaining to the identification of the gene for the X-linked recessive form (Xp22.2) may explain the different incidence of OA according to sex(38,39). *CD36* (7q21.11)(encoding for a thrombospondin and collagen receptor), *NCOR2* (12q24.31)(encoding for a nuclear receptor co-repressor), *EDG2* (a functional variant of lysophosphatidic acid G-protein-coupled receptor 2 gene), *DIO2* (encoding type II iodothyronine deiodinase), *SMAD3* (functions in TGF-beta signaling), *PITX1* (transcription factor pituitary homeobox1), *ACE* (angiotensin-converting enzyme gene), and *TNA* (3p21.31)(encoding for tetranectin), were involved in OA prevalence and progression in females(17,40-44). The acidic leucine-rich nuclear phosphoprotein 32 family member A gene (*ANP32A*) encodes a tumor suppressor molecule involved in apoptosis and Wnt signaling, which is reported to be associated with hip OA in women(45). Furthermore, several loci are reported in (Table 1). Some

Table 2. Comparison of human genetic mutant and animal genetic modification related to OA

Human genetic target	Animal genetic target
COL2A1	COL2A1-(Dmm/+)
COL11A1	COL11A1-(Cho/+)
COL11A2	COL9A1-/-
AGC1	AGC-(Cmd/+)
ASPN(SLRP family)	BGN, FM (SLRP family)
COMP	Integrin-alpha-1 mutant
MATN3	
FRZB	
CILP	
VDR	
ESR1	
BMP2	Cre-Gdf5/Bmpr1a^{floxP}
BMP5	
OPG	
IL1R1	TNF transgenic mice
IL4R	
PTGS2 , PLA2G4A(PGE2)	
COX2	
ADAM12	ADAMTS5(-/-), MT-1-MMP-deficient
BLP2, CIAS1	
RHOB, TXNDC3	
CD36	
NCOR2	
SEDL	
SMAD3	SMAD3(-/-)
GDF5	GDF5 deficient mice

chromosomes were frequently positive such as chromosome 2, 6, and 16. Animal models have been used to study the mechanisms of OA more fully in relation to human genetic mutations.

4. ANIMAL MODELS

Animal models include genetically modified and experimentally induced models that mimic OA pathogenetic mechanisms.

4.1. Genetically modified models

4.1.1. Factitious models

Many studies have exploited the availability of knockout or transgenic mouse models to address the roles of certain molecules in OA pathogenesis. It has been revealed that polymorphisms or mutations in genes encoding extracellular matrix genes and signaling molecules are associated with OA susceptibility (11,56). Thus, the loss or mutation of a single gene in a mouse model, such as Collagen IX (57,58), Col2a1, Col11a1, aggrecan, MT-1-MMP(59), alpha-1 integrin subunit (60), and ADAMTS5 (61) may lead to cartilage degeneration similar to that in OA patients. More specifically, the disruption of chondrocytes results in the interruption of the formation and remodeling of the cartilage matrix, such as the production of proteoglycans and aggrecan (62,63).

SLRPs are extracellular molecules that bind to TGF-betas, collagens, and other molecules. *In vitro*, SLRPs were shown to regulate collagen fibrillogenesis. Biglycan (BGN) and fibromodulin (FM) were two of the most prominent and widely expressed SLRPs. Cre-loxP sites flank the gene encoding BMP receptor type 1a (Bmpr1a). A promoter of the gene encoding growth differentiation factor 5 (Gdf5) is used to deplete this BMP receptor and direct cre-recombinase expression. Thus, Cre-Gdf5/Bmpr1a^{floxP} mice are conditional knockout mice that are unable to produce BMP receptor type 1a selectively in developing joints(64). The BGN-deficient, FM-deficient, and BGN/FM double knockout, Cre-Gdf5/Bmpr1a^{floxP} mice develop earlier and more severe osteoarthritis (61-67). Ptch1$^{+/-}$, Col2A1-Gli2, COL2-rtTA-Cre, Gt(ROSA)26Sor$^{tm1(Smo/YFP)Am}$-transgenic mice were also chosen for the development of OA. Among these, the Col2A1-Gli2-transgenic mouse overexpressed the hedgehog (Hh)-activated transcription factor Gli2 under Col2A1 regulatory elements in chondrocytes. The Gt(ROSA)26Sor$^{tm1(Smo/YFP)Am}$-transgenic mouse expresses the constitutively active W539L point mutation of the SMO homolog protein (SmoM2) by Cre-mediated recombination. SmoM2 was expressed in chondrocytes when this mutant mouse was crossed with COL2-rtTA-Cre mice under doxycycline administration (68). Other mutant mice such as TNF transgenic mice develop a severe destructive arthritis, osteophyte, and subchondral bone stiffness. The relationship of human genetic mutations and animal genetic modification is documented in (Table 2).

4.1.2. Spontaneous models

Spontaneous models refer to certain breeds of animals that are genetically predisposed to OA and can develop symptoms at a relatively young age. In the laboratory, these models include rhesus macaques, dogs, guinea pigs, and mice. In some views, these models could be seen as genetic mutant species with unclear backgrounds.

The Rhesus monkey model is described to be particularly suitable for studying changes in cartilage collagen because the animal's long life span allows for the development of osteoarthritis over time. Morphological studies demonstrate that in these monkeys, as in humans, the disease is characterized by persistence of the chondrocyte density typified by an increase in (Ca) calcium, (P) phosphorus, (Mg) magnesium, (S) sulfur, (K)

potassium, glycosaminoglycan (GAG) and collagen(69) in the cartilage of young animals(70). An epidemiological study showed increased incidence of OA disease with aging, and in females with increased parity. Therefore, these models are ideal because of the high prevalence rate, available age matched controls, and joints large enough for radiological and morphological studies. However, the drawbacks of using these big animals are their relatively long lifespan, uncontrolled environmental factors, ethic concerns, and the limitation of financial funding.

Immunologic reactivity has been observed with anti-type I, II collagen antibodies existing in sera and synovial fluids of dogs(71). Moreover, the changes in proteoglycan levels in the cartilage of the canine model were very similar to those observed for human OA cartilage(72). However, compared to human OA in the early phase of the disease, dogs display more serious changes in synovitis and joint capsule fibrosis.

Degenerative arthritis has been extensively studied in guinea pigs. The OA observed in this model has been found to have similar histologic, radiologic, and biochemical changes as those observed in human OA, such as breakdown of cartilage aggrecans(73), meniscal ossification(74), chondrocyte ATP depletion(75), and subchondral bone remodeling(76). Moreover, findings indicate that body mass in guinea pigs is an important predisposing factor for the development of spontaneous OA of the knee. There are several disadvantages pertaining to the guinea pig model. Some researchers observed the effect of matrix metalloproteinase inhibitors and ascorbic acid on OA from this spontaneous model (77-80). Also, OA progresses slowly in the guinea pig, which is not cost effective. Both of these reasons limit application and advancement of this particular model.

Recently, attention has been focused on small animals such as mice of STR/ORT, C57Bl/6, and BALB/c strains(81,82). Mice are utilized to examine cartilage degeneration(83), including loss of glycosaminoglycans in cartilage matrix, and type II collagen degradation(84), disturbed protein transport and sugar synthesis in chondrocytes, and irregularity of the free margin of the anterior segment of the meniscus. Nevertheless, cruciate ligament collagen metabolism is upregulated in this model(85). Additionally, it was observed that a horizontal cleft developed along the tidemark and eburnation of the subchondral bone(86). Moreover, the mice model also lacks morphological changes, such as fibrillation of the cartilage matrix, chondrocyte clustering, osteophyte formation or inflammation, possibly because of the animal's small joints and poor reparative ability. Smaller joints also instigate many other problems for investigators.

4.2. Experimentally induced models

Experimentally induced models evolved due to the demands of the research field. Previous reviews separated these models into monoarticular and polyarticular OA. However, monoarticular OA does not exist, because bilateral joints systemically or biomechanically interact, resulting in the bilateral articular OA.

4.2.1. Biomechanical factors

Biomechanical models of arthroses are of three types: surgical (intra-articular and extra-articular), immobilized, and overload.

Intra-articular surgical models usually induce instability of the joint. The original joint disease models developed historically were induced by patella dislocation(87) and patellectomies(88). However, these models showed severe erosive and proliferative lesions of the joint. As a result, less severe injury and more gradual degenerative progression were required for OA model creation. The Hulth-Telhag model is the classical OA model made by transecting the anterior and posterior cruciate ligaments and removing the meniscus. Degradation of type II collagen was seen as early as 3 weeks in this rabbit model(89). Recently, the popular surgical models are the anterior cruciate ligament transaction (ACLT) and the partial meniscectomy model(90,91). The combination of patella removal with ACLT could accelerate the occurrence of OA to approximately two weeks after the surgery, and further advance its development(92). Other methods such as tibial osteotomy(93), below-knee amputation, femur valgus osteotomy(94), or pelvic osteotomy(95), could also lead to degenerative arthritis. In these surgically-induced animal models, joint inflammation and repair were produced primarily in cartilage and synovium. One interesting surgical variant is the groove model made by Marijinissen. This model induces cartilage degeneration by one-time trauma (with features of OA at 10 weeks after induction), without causing synovial inflammation characteristic of the original model. This method increases the sensitivity of detecting defects of therapy aimed at cartilage protection and repair(96,97).

Extra-articular procedures which include ovariectomy(98), myomectomy(99) and tendonotomy(100) could also produce progressive OA. Ovariectomized models are useful for studying the effect of estrin and estrin-like substances on OA in postmenopausal women(98).

Immobilization models of OA were made in forced fixed position including flexed, intermediate, and extending posture. It was found that in both early and advanced OA, the synthesis rate of glycosaminoglycans and collagen increased, especially after half to one month, but the collagen content did not change(101). Moreover, a non-specific inflammatory cell response was rapidly induced in the synovial tissue in three days by abrasion(102). In the immobilization and subsequent remobilization experiment, plasma hyaluronate was maximally regulated shortly (45min) after splint removal(103). These studies elucidate the significance of joint motion.

Overload models include compression induction either without surgery or with excessive exercise. In the past, these models were combined with other methods to accelerate and aggravate the degenerative process(104,105). To initiate OA-like changes in an *in vitro* single-impact load model, a simple drop-tower device was

used. This model would be valuable for understanding the early molecular pathways involved in the process(106,107).

4.2.2. Structural factor

In experimental structural OA models, tissue composition of one or more structural components of joints is degraded(105). Traditionally, structural OA models have been classified into groups (*e.g.* physical, chemical, and enzymatic) based on the selectivity of their action on target tissues or tissue components, such as collagen, proteoglycan, chondrocytes, or synoviocytes. Endocrine manipulation such as intra-articular corticosteroid administration, a high fat diet, or oral administration of quinolone analogues can promote the development of OA from a systemic view. These animal models help us to investigate the mechanisms of OA, especially at the cellular and molecular levels.

In physical alteration models, freezing, electrolysis, or ionizing radiation of articular cartilage may cause lesions in an anatomically discrete manner(108). Micromechanical models of surgical trauma induced by incision, shaving, abrasion or contusion perpetuate similar results(109-111). These models are useful to investigate the replication and matrix regeneration of chondrocytes. For example, defects that penetrate the subchondral bone could induce chondrocyte regeneration from reparative fibrocartilageinous calluses growing toward the marrow, while lesions that do not invade into subchondral bone usually fail to show this regeneration(112).

Chemical alteration refers to intra-articular administration of chemical agents such as heat, fixatives, protein denaturants, acids, alkalis, or ionic solutions to degrade the matrix and the superficial articular cartilage(105). Saline injection spawned synovial inflammation.

Currently, the most common technique used to generate models is enzymatic alterations. These models are created by proteolysis induced by the enzymes papain, trypsin, hyaluronidase, and collagenase(82). This model has been used to investigate broken collagen framework, synovial inflammation, cartilage proteoglycan depletion, chondrocyte necrosis, and ligament matrix injury and subsequently regeneration. Furthermore, intra-articular injection of cytotoxic drugs, including thiotepa, nitrogen mustard, colchicines, osmic acid, or iodoacetate directly damage articular cells. Indirect agents such as vitamin A and Filipin stimulate chondrocytes to produce and secrete matrix proteolytic enzymes by labializing cells and lysosome membranes(113). Sometimes, it's hard to differentiate between biochemical agents and chemical agents. Croton oil, carrageenin, zymosan, and dextran sulphate have been used to induce degenerative arthritis. However, changes in these models are complex. For instance, specific biological mediators such as IL-1/OSM, TNF, and TGF-beta2 may be intra-articularly injected. IL-1 has a more direct inhibitory effect on proteoglycan synthesis, which is mediated by metalloproteinases(114). Ectogenous TGF-beta2 induces synovial fluid, synovial cells hyperplasia, cartilage edema, and proteoglycan degradation. Moreover, synovitis observation requires the application of magnesium tetrasilicate, or talcum powder, via intra-articular injection. These models provide an opportunity to study the effect of endogenous factors on the progression of OA.

5. MECHANISMS

5.1. Cellular changes

Damage resulting from OA can be observed in the three components that constitute a joint: articular cartilage, subchondral bone, and/or synovium. The degree of pathological changes in OA is determined by the aforementioned factors(115).

Articular cartilage is unvascularized, aneural, and full of ECM, which is mainly composed of water, type II collagen, and proteoglycan aggrecan(116). Other components have been identified in the matrix, such as type IX and XI collagen, cartilage oligomeric matrix protein, matrilin-3, decorin, biglycan, and fibromodulin(117). Chondrocytes are another important component of cartilage. Chondrocytes are encapsulated within a lacuna, which hinders their ability to migrate to the site of injury. Thus, chondrocytes do not have the capacity for renewal, proliferation, or repair(118). In normal cartilage, there are four zones of chondrocytes: resting cells orientating within the collagen fibers in the superficial zone, large and randomly distributed cells in the middle zone, columns of chondrocytes in the deep zone, and hypertrophic cells in the calcified zone(116).

The pathological changes of OA in articular cartilage are less anabolic and more catabolic, such as the loss of ECM and cell apoptosis. Cartilage matrix degradation products like type II collagen, proteoglycans, and fibronectin seemed to aggravate cartilage destruction with the fibrils at the articular surface(119). When OA occurs and proceeds, the regular cellular populations change into one of three types. The first type of cellular population is singular and clustered. The second type is elongated and secretory like fibro-chondrocytes or other dedifferentiated phenotypes, which express several proteins such as biglycan, decorin, perlecan, and type I and X collagen to form repaired fibrocartilage(120,121). The last type is irregularly shaped cells such as those that undergo pyknosis. The thinning of the soft articular surface accompanied with the thickening of the hypertrophy chondrocytes layer lead to upward shift of the tidemark between articular and calcified cartilage(122). Neovascularisation was found to break the tidemark through microcracks and fissures that occur in the cartilage, which seems to produce mesenchymal stem cells (MSCs) or bone progenitor cells like the second type of cells previously mentioned(123). Features of OA in the subchondral bone are fibrillation, sclerosis, even collapse, together with bone cysts, thickened cortical plate, extensive remodeled trabeculae and osteophyte formation surrounding articular margins(115,124,125). Increase in subchondral bone stiffness are considered as an adaptation to changes in the biomechanics of the joint, but it simultaneously limits the strain in the articular cartilage(122).

Osteoclasts also play a crucial role in the process of OA. In OA-like lesions in the mandibular condyle of rat, osteoclastogeneis occurred by increased osteoclast numbers and proportion of surface area in the subchondral bone regions(126). The subchondral bone plate could be thinning 4 weeks after instability-, collagenase-induced OA, with osteoclasts observed underneath it(127).

There are three types of synovial lining cells within the superior and middle layers: macrophages, fibroblasts, and undifferentiated precursors. The deep layer includes adipose, fibrous, and areolar tissue. Synovial fluid is produced by fibroblasts in the synovium, and is considered an ultrafiltrate of plasma because of the presence of hyaluronate and lubricin(128). In the normal state, nutrients in the synovial fluid and cellular repair components are diffused within the cartilage. In OA, synovial fibers thicken and more pro-inflammatory mediators arise in the synovial liquid. There is also evidence that activated T-cells, B-cells, and macrophages infiltrate the synovium in OA (129). However, mature and activated osteoclasts could not found in the OA synovium(130).

Thus, OA is distinguished by the following features: thin, fibrillated articular cartilage, reduced joint space, thickened capsule, and angiogenesis with possible innervation, synovitis, subchondral bone sclerosis, and osteophytes at joint margins (131).

5.2. Molecular changes

Many cytokines and growth factors, some of which participate in cartilage development, are produced by the synovial fibroblasts, chondrocytes, osteoblasts and osteoclasts in OA.

Synthesis of catabolic factors, such as matrix metalloproteinases (MMPs), membrane-type I MMP, MMP-1,3,8,9,13,14 and the aggrecanase protein ADAMTS1,4 and 5, is increased (59,74,118,132-135) and synthesis of their inhibitors such as TIMP is decreased by pro- or inflammatory cytokines like interleukin IL-1, IL-6, IL-17 and IL-18, TNF-alpha(136-139), nitric oxide (NO), PGE2, COX-2, and netrins along with their receptors(140). Some chemokines including CC-chemokine ligand-5 (CCL5), IL-8, growth-related oncogene-α (GROα) and monocyte chemotactic protein (MCP-1) are also elevated in OA tissues to induce inducible nitric oxide synthase (iNOS), MMP-1, IL-6 and stimulate proteoglycan depletion(141). However, some of these factors such as MMP-1 also show opposite changes depending upon the severity of OA(142). Recently, it was demonstrated that the signaling pathway of shear-induced IL-6 expression is related to the roles of E prostanoid (EP)2 and EP3 in cAMP/protein kinase A- and PI3-K/Akt-dependent NF-kappaB activation(143). Cathepsin K, TRAP, and osteocalcin mRNA levels were raised in the intertrochanteric region of the proximal femur of OA patient with femoral neck fracture(144). Besides cathepsin K, cathepsin B, L from the chondrocytes play a role in further cartilage destruction with the local fallen pH value of the cartilage(145). Moreover, nuclear factor of activated T cells 2 (nfat2), osteoclast-associated receptor (oscar), and alkaline phosphatase (ALP) mRNA expressions were found to be enhanced in the synovial fluid of OA patient (146).

Anabolic factors such as insulin-like growth factor (IGF-1), TGF-beta, connective tissue growth factor (CTGF), fibroblast growth factors (FGFs), vascular endothelial growth factor (VEGF), OPG/ receptor activator of NF-kappaB ligand (RANKL), and BMPs either decrease or increase proceeding reaction with damaged spatiotemporal variations(147-149). Additionally, some neuropeptides like substance P, corticotropin-releasing factor, urocortin, and vasoactive intestinal peptide may also be involved in OA development(150,151). In RANKL- and TNF-induced OA, increasing NF-kappaB p100 protein and TNF receptor-associated factor 3 (TRAF3) accumulations in osteoclast precursors (OCPs) could limit bone destruction, indicating an anabolic effect for these two proteins(152). Anti-inflammatory cytokines including IL-4,10,13 etc play a role in inhibiting IL-1beta, TNF and proteases, upregulating IL-1Ra and TIMP production(153).

Senescence markers such as senescence-associated enzyme beta-galactosidase (SA-betagal), p53, p21, p16, superoxide dismutase 2 (SOD2), reactive oxygen species (ROS) and telomere shortening are also exhibited in OA(154). However, the function of these factors is complex. For example, a reduction in SOD2 has been reported to be associated with an increase in ROS in the earliest stages of OA, but also with a reduction of collagenase gene expression(153). Moreover, these findings pose difficulties in distinguishing age-related changes from OA.

Nowadays, more and more novel initiators of OA have being found such as transmembrane serine proteinase matriptase in cartilage destruction, which activates selective proMMPs and induces collagenase expression(155). HIF-2alpha, induced by NF-kappaB, is crucial for endochondral ossification(7). Three of the autophagy-related factors, Unc-51-like kinase 1 (ULK1), Beclin1, and microtubule-associated protein 1 light chain 3 (LC3), showed a reduction or loss of expression in the development of OA(156). The cytokine levels in OA have been reviewed in detail (157). These biochemical substances interact and contribute to cellular changes. Several cytokines, such as inflammatory factors(158), and the Wnt signaling pathway(159), have been widely reviewed. Therefore, the focus in this paper is on BMPs, and the molecules mentioned above or in other reviews would be summarized in Figure 1.

5.3. BMPs

BMP-2 is present in chondrocytes during neonatal growth of articular cartilage, but is scarcely expressed in normal adult articular cartilage. However, the BMP gene has been genetically linked to OA.

5.3.1. BMPs and articular cartilage

BMP-2 mRNA and protein were found in both clustering and individual chondrocytes in moderately or severely damaged OA cartilage. In moderately damaged

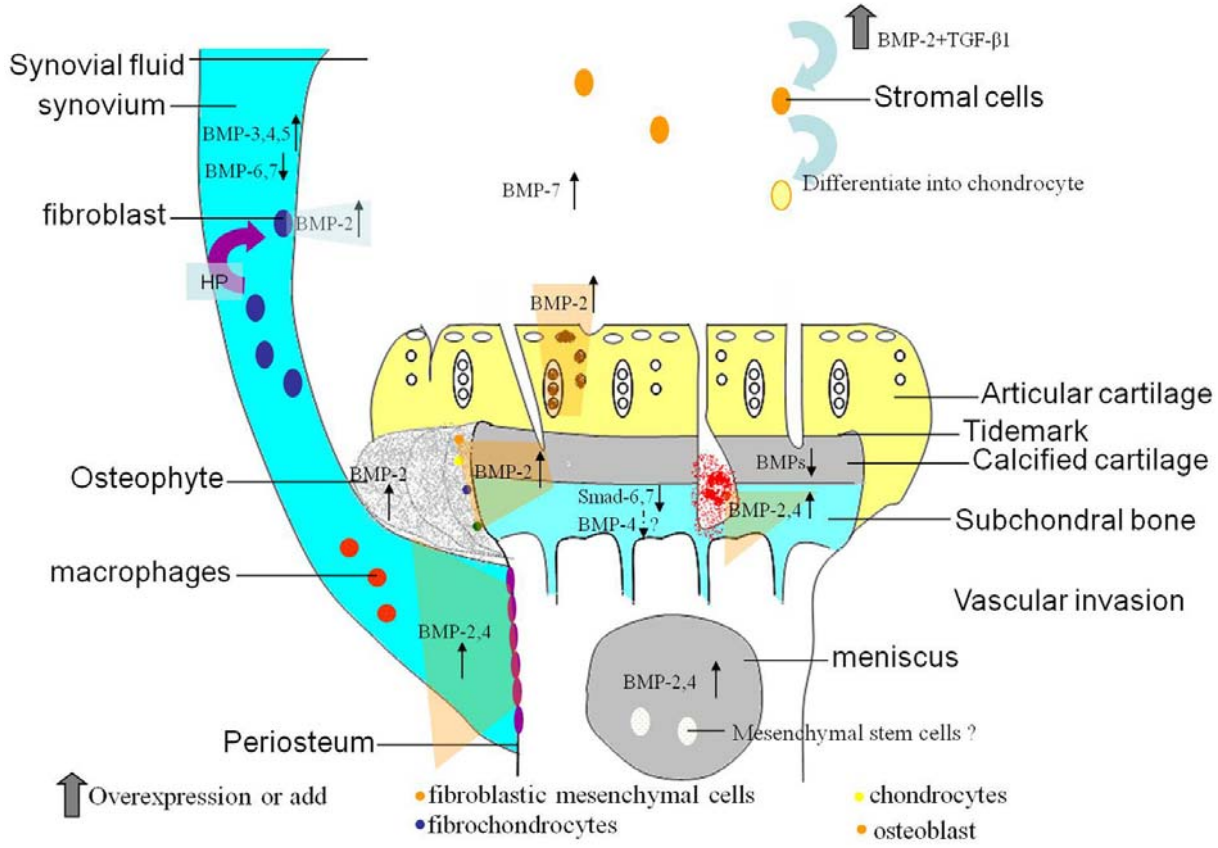

Figure 1. Molecular pathogenesis of OA. OA is characterized by progressive destruction of articular cartilage and subchondral bone accompanied by low-grade inflammation. Damaged chondrocytes secrete MMP1,3,8,9,13, ADAMTs, NO, PGs, Hh, etc, and the degradation products produce ColII, proteoglycans and fibronectin, which accelerate cartilage degeneration including chondrocyte apoptosis and ECM loss. Fibrocartilage would be formed as compensation by increased biglycan, decorin, perlecan, ColI, ColX expressed by fibrochondrocytes. Subchondral bone is characterized by fibrillation, sclerosis and osteophyte formation. Osteoclasts on the surface of destructed cartilage and subchondral bone express increasing cathepsin B,L,K, RANKL and decreasing OPG. The expressions of BMP-2,4 ,Wnt, PAR-2, Leptin are upregulated in the osteoblasts in the periosteum, and that of BMP-2, Wnt and Dkk-1 is also upregulated in the osteophyte. Upregulation of VEGF and downregulation of TIMPs and TGF-beta could be found in neovascularisation. The thickened synovium secretes several pro-inflammatory mediators such as MMPs, ADAMTs, IL-1,6,8,17,18, TNF-alpha, NO, PGE2, COX-2, LTB4, neuropeptides, adpokines etc by macrophages and fibroblasts. The anti-inflammatory mediators are downregulated such as IL-4,10,13,1Ra, TIMPs etc. Fibroblasts could transform into B cells by high level of CXCL-13 while into T cells by high level of IL-12. Macrophages could also transform into these immunocytes through V-CAM1 E-Seclectin by VEGF, bFGF, EGF etc.

OA cartilage, cellular localization of BMP-2 mRNA was limited in both upper and middle zone chondrocytes. In severely damaged OA cartilage, it extended to the deep zone chondrocytes(160). Phosphorylation of Smad-1, Smad-5, the downstream of BMP-2, were upregulated, meanwhile Smad-2 and -3 were degraded in a Smurf2-dependent manner in OA conditions(161,162). In a posttraumatic OA (PTA) model generated by a single high-energy impact load, proteoglycan loss was detected along with decreased BMP-2, indicating that BMP-2 may participate in PG synthesis(107). Furthermore, chondrocytes overexpressing BMP-2 showed increased aggrecan synthesis(163). On the other hand, genetic variation in BMP receptor signaling may be involved in human OA development(64, 164).

Asporin, an extracellular matrix protein up-regulated in disease states, binds to BMP-2 and negatively regulates its activity(165). The actin-binding protein calponin 3, which interacts with Smad-1 and -5, was reduced in OA cartilage. Since calponin 3 provides a negative regulatory mechanism for the BMP signaling pathway, its down-regulation could contribute to the increase of BMP-2 expression in OA joints(166). Noggin is one of the BMP binding proteins, and it acts as an antagonist. Noggin null mice exhibit defects in joint morphogenesis, indicating that the overexpression of BMPs plays a critical role in OA pathogenesis(167). Chordin is another antagonist of BMP. It was found not only in the superficial layers in normal cartilage, but also at a significantly higher level in the last two thirds of the OA

cartilage. However, the mRNA and protein levels of chordin were downregulated in OA(168).

It has been reported that Smad3 knockout (TGF-beta deficient) mice display OA phenotypes. The gene profiling and PCR examination showed that BMP signaling pathways involving Smad-1, Smad-5, BMP-2, and BMP-6, were more active in Smad3 knockout chondrocytes(169), suggesting a shift from TGF-beta toward BMP signaling. Thus, as an extracellular BMP inhibitor, noggin could abrogate its maturation (170). *In vitro* and *in vivo* OA models demonstrated that BMP-2 induced growth arrest and DNA damage, stimulated (GADD)45beta transcription factor depending on the suppression of COL2A1 by NF-kappaB, and upregulated matrix meatalloproteinase-13 (MMP-13) expression(171). Up-regulation of BMP-2 might be caused by pro-inflammatory cytokines IL-1beta and TNF-alpha (but not TGF-beta and IGF-1), which are known to be present in synovium and cartilage of patients with OA(172,173).

BMP-7 is considered an anabolic mediator. It may stimulate superficial zone protein, function as a key mediator of boundary lubrication of articular cartilage in joints, and it may also improve damaged intra-articular tissues by synthesizing and secreting chondrogenically differentiated infrapatellar fat pad (IFP) progenitor cells. These functions indicate that BMP-7 would potentially be a useful source for inducing superficial zone of articular cartilage(174). Furthermore, it generally had a more significant stimulatory effect in cultures of immature bovine cartilage explants than in cultures of mature explants(175).

Human meniscus cells, which came from meniscectomy of the knee joint in individuals with OA, also expressed BMP-2, and -4. These cells were stained with AS.02, which recognizes a protein on human fibroblasts that is highly homologous or identical to human Thy-1 antigen (CD90), which is one of the markers for mesenchymal stem cells (MSCs). These findings suggest a mesenchymal origin of human meniscus cells(176).

5.3.2. BMPs and subchondral bone

Interestingly, OA osteoblast mineralization in tibial plateaus was less than that of normal osteoblasts, even in the presence of BMP-2(177). The vascular invasion of bone marrow tissue into the subchondral plate was observed in articular cartilage in OA patients, who also expressed BMP-2 and -4 in reparative levels(178).

5.3.3. BMPs and synovium

In the collagenase-induced OA model, BMP-2 and -4 are strongly expressed in deeper layers of the synovium, periosteum, and lining. Presence of BMP-2 and -4 in the lining is induced by synovial macrophages(179). On the other hand, overexpression of Smad-6 and -7, two BMP antagonists, caused a reduction in synovial thickening, indicating that BMPs are also involved in this process(180). Mechanical load would be one of the factors that stimulate BMPs. For example, exposure of synovial fibroblasts (SFs) of the rat temporomandibular joint (TMJ) to hydrostatic pressure (HP) causes significant up-regulation of BMP-2, which may influence pathological conditions, such as temporomandibular disorders(181). However, BMP-2 alone *in vitro* hardly induces chondrogenic differentiation of synovium-derived stromal cells; however, it can induce chondrogenesis and synthesis of cartilage-like matrix when combined with TGF-beta1(182).

The expression of BMP-4 and BMP-5 expression decreases in synovial tissue of OA patients, and their distribution varies within the lining and sublining of the layer(183). Levels of BMP-7 are found to increase in both plasma and synovial fluid of OA patients. Conclusively, there exists a positive correlation between BMP levels and OA: overexpression of BMP-7 in plasma and synovial fluid is associated with OA development(184).

5.3.4. BMPs and repair

Osteophyte formation is considered a repair process of bone. BMP-2 induced early osteophytes, which bulged from the growth plates on the femur and grew on top of the patella. Moreover, BMP-2 was strongly expressed in the late-stage osteophytes in STR/ort and collagenase-induced models(185). Other scientists found that BMP-2 mRNA was most prominently localized in fibroblastic mesenchymal cells, fibrochondrocytes, chondrocytes, and osteoblasts in newly formed osteophytes(160). This osteophyte formation could be completely blocked by Ad-Gremlin and significantly reduced by Smad-6 and -7(180). However, this osteophyte formation is different from those induced by TGF-beta and experimental OA(82).

BMP-2 has been proposed as a tool for cartilage repair and as a stimulant of chondrogenesis. In healthy cartilage, BMP-2 is hardly present, whereas it is highly expressed in cartilage of OA individuals. When BMP-2 was overexpressed in healthy murine knee joints, PG synthesis, aggrecan mRNA expression, collagen type II expression, and aggrecan degradation increased in patellar and tibial cartilage. BMP-2 boosts matrix turnover not only in intact but also in IL-damaged cartilage. Thus, BMP-2 contributes to the intrinsic repair capacity of damaged cartilage matrix(186). This may be related to increasing TIMP-1 production(187). Chondrocyte or stem cell transplantation with cells expressing BMP-2 may improve cartilage repair(188).

In vivo, skeletal muscle-derived stem cells (MDSCs) expressing sFlt-1(one of the VEGF antagonists) and BMP-4 demonstrated better repair without osteophyte formation, higher differentiation/proliferation, and lower levels of chondrocyte apoptosis in the OA model. *In vitro*, coculture of BMP-4-transduced MDSCs and OA chondrocytes produced the highest gene expression of type II collagen, and SOX9, as well as type X collagen, suggesting terminal differentiation of chondrocytes(189). In the OA rat model produced by excessive running or ACLT, periodical injections of BMP-7 could delay the cartilage degeneration (91,190). Furthermore, BMP-7 may be chondroprotective after traumatic injury in patients via an

increased survival of chondrocytes, which is evidenced by stimulating proteoglycan synthesis to participate in the repair process(191-193).

Others involved in potential prevention of OA include HrtA1 (high-temperature requirement protein A1), programmable cell of monocytic origin (PCMO), and Periodontal ligament-associated protein-1 (PLAP-1)/asporin. HrtA1 is a key regulator of physiological and pathological matrix mineralization *in vitro*, which is proposed to be related to TGF-beta/BMP signaling inhibition(194). PCMO is a new adult pluripotent cell derived from human peripheral blood monocytes. After 6 weeks of stimulation with BMP-2 and BMP-7, PCMO have the potential to differentiate into chondrocytes by producing collagen type II(195). PLAP-1/asporin is a member of the small leucine-rich repeat proteoglycan family, which has been proven to be a negative regulator of mineralization most understandably by regulating BMP-2 activity involved in ankylosis prevention(196).

5.3.5. Others

Microarray expression profiling of osteoarthritic bone suggested altered bone remodeling and revealed many genes that are differentially expressed. Many of these genes are targets of either the WNT (wingless MMTV integration) signalling pathway (TWIST1, IBSP, S100A4, MMP25, RUNX2 and CD14) or the transforming growth factor (TGF)-beta/bone morphogenic protein (BMP) signalling pathway (ADAMTS4, ADM, MEPE, GADD45B, COL4A1 and FST). Other differentially expressed genes included WNT (WNT5B, NHERF1, CTNNB1 and PTEN) and TGF-beta/BMP (TGFB1, SMAD3, BMP5 and INHBA) signalling pathway component or modulating genes. In addition, a subset of genes was identified to be differentially expressed in OA between males and females such as GSN, PTK9, VCAM1, ITGB2, ANXA2, GRN, PDE4A and FOXP1, which were involved in osteoclast function(197).

At the present time, several therapies for OA have been used clinically and pre-clinically besides cytokines, such as BMPs. However, clinical efficacy is the gold criterion for evaluating the quality of therapy. Of course, the side effects, difficulties of execution, and level of grief for the patients are also taken into consideration. The effects of the treatment regarding pain relief and functional improvement are usually evaluated clinically for OA treatment.

6. THERAPIES

Current therapeutic strategies for OA include clinical and preclinical procedures.

6.1. Clinical therapy

A comparison of the clinical therapies available for OA patients is provided below and in Table 4.

6.1.1. Global treatments

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most popular therapy for OA, due to their effectiveness in relieving pain and improving function. These drugs significantly reduced PGE2 and downregulated COX-2 in the synovium and cartilage(198,199). However, NSAIDs are associated with significant adverse effects on the integrity of the gastrointestinal (GI) mucosa and on the cardiovascular system(200). The countermeasures for these side-effects include concomitant use of gastric-protective medicine such as misoprostol, a PGE1 analog(201), using an enteric coated formulation(200), improving health-related quality of life(202), or changing administration routine as mentioned in the section titled “External applied agent”. Nowadays, new lower-risk NSAIDs are available, but at a greater monetary value.

Non-opioid analgesics, such as acetaminophen, also known as paracetamol or Tylenol, is equally effective at achieving relief of mild to moderate joint pain as NSAIDs(203,204). However, NSAIDs appear to be more effective at relieving moderate to severe pain. A study including fifteen randomized controlled trials (RCTs) and 5986 participants demonstrated no significant difference between the safety of acetaminophen and NSAIDs(205), although previous meta-analysis indicated this compound was safer and should be the first line of treatment(206). Acetaminophen should be used cautiously in patients with liver defects and those who chronically abuse alcohol (207-209). Other drugs like tramadol could be used in patients in whom acetaminophen therapy has failed (210). When NSAIDS and non-opioid analgesics have no significant effect, opioid therapy (211) may be considered. However, tolerance, dependence, and other adverse effects may be not avoided while using this treatment.

Acupuncture & Traditional Chinese medicine may also be effective as treatment for OA. A systematic review of seven trials employing a total of 393 patients with knee OA revealed real acupuncture is more effective in pain relief than needles placed at non-acupuncture points on the body. However, real acupuncture has not conclusively shown better effects in functional improvement. Furthermore, the comparison of efficacy of acupuncture with other treatments need more evidence(212,213). Some Traditional Chinese medicines have been reported to be safe, tolerable, and effective for symptomatic improvement of pain and physical function, such as willow bark extract, ginger extract, boswellia-curcuma mixture, avocado-soybean unsaponifiables (americana Glycine max), boswellia serrata gum resine extract, cat’s claw extract, arnica tincture, comfrey extract, Tipi tea, stinging nettle leaf, the Chinese herbal mixture SKI306X, Duhuo Jisheng Wan (214,215), and a seaweed extract nutrient complex(216). Recently, it has been reported that human placenta extract (HPE) suppressed the histological changes in monoiodoacetate (MIA)-induced OA by inhibiting PG degradation and MMP-2 activity and that HPE may reduce deformity of knee joints (217). Other treatments such as exercise, Tai Chi, bracing and corrective footwear, pale vitamin E, behavioral interventions, spa, pulsed signal therapy, and hyperthermia have been shown to improve OA(4, 145, 218-224).

6.1.2. Local treatments

Glucosamine and chondroitin naturally exist in the body to repair and maintain cartilage. These natural supplements have become popularized because of their safety and their effectiveness in relieving arthritis symptoms(225). Two RCTs, proceeded by a follow-up of 8 years, showed that treatment with glucosamine sulphate for 1 to 3 years may prevent total joint replacement for an average of 5 years after drug discontinuation(226). These compounds are absorbed through the gastrointestinal tract and are able to increase proteoglycan synthesis in articular cartilage(227,228). Animal experiments showed oral glucosamine sulfate not only attenuates the development of OA, but also reduces nociception and modulates chondrocyte metabolism. The mechanism would be related to mitogen-activated protein kinases (MAPKs), by inhibiting cell p38 and c-Jun N-terminal kinase (JNK) and increasing extracellular signal-regulated kinase 1/2 (ERK) expression(229). Chondroitin sulfate may reduce degradation of cartilage collagen and proteoglycans by partially inhibiting leukocyte elastase(230,231). However, recent meta-analysis found that chondroitin has minimal or insignificant benefits for OA symptomology(232). A meta-analysis of 15 RCTs of glucosamine and chondroitin compounds showed that all but one of these trials were classified as positive(219). Moreover the effects were greater for chondroitin than for glucosamine. Further studies are highly suggested to assess the relationship between time, dose, patient baseline characteristics, and structural efficacy; moreover, these studies may provide an accurate, disease-modifying characterization and a biological mechanism of these two compounds (233-235). It has been recently reported that undenatured type II collagen (UC-II) at a dose of 480 or 640 mg was more effective than glucosamine and chondroitin in arthritic horses and that it was tolerated well (236). However, it still needs clinical evidence. Other related compounds such as sodium hyaluronate and undenatured type II collagen have been reported to be efficacious in the treatment of knee OA(237,238). However, in a recent, multicentre, randomized, placebo-controlled, double-blind study of 337 patients followed for 1 year there was no clinical effect of intra-articular hyaluronan was shown(239).

Only 5% of OA patients need surgical treatment when conservative treatment displays no satisfactory effect. There are four categories of surgical procedures: osteotomy, arthroscopy, arthrodesis, and arthroplasty.

The purpose of the osteotomy is to transfer the load bearing from the pathologic to the normal compartments of the knee. Thirteen studies involving over 693 people indicated that valgus high tibial osteotomy is effective in improving knee function and relief of pain. However, it is uncertain which treatment, osteotomies or conservative treatment is more effective(240). Furthermore, a successful result of the osteotomy (about 60.3%) depends on proper patient selection, stage of osteoarthritis, and achievement and maintenance of adequate operative correction(241).

Arthroscopy is an alternative procedure to osteotomy(242). It is not only useful for the treatment of the same symptoms, but also for diagnosis of the disease. Although arthroscopic methods are widely used, they are not suitable for patients who have displayed OA symptoms for more than 2 years, or who display tibial osteophytes and joint space narrowing of less than 5mm (4 or more of these factors)(243). Arthroscopy is effective only temporarily in reducing the pain of mild to moderate hip OA(244).

Arthrodesis is an efficient procedure for OA of the hands, feet, ankles, and spine, but usually not for the hip and knees(245-248). In arthrodesis, multiple Kirschner wires, cannulated screwsiliac, and crest bone graft are frequently utilized to reduce nonunion rates(249).

Arthroplasty refers to the insertion of an artificial joint in order to restore the integrity and the function of the joint withered by OA. Joints commonly deteriorate after more than ten years, depending on the composition(250). The perioperative morbidity of unicompartmental knee arthroplasty would be less than total knee arthroplasty; furthermore, this arthroplasty has been reported to be used in very elderly patients (79-94 years) with tricompartment OA. Therefore, age is not a limiting factor for this surgical treatment(251)**.**

Use of local topical analgesics, such as capsaicin cream and NSAID gel (eltenac), function as either an adjunctive treatment or monotherapy for pain relief in OA patients(252, 253). These treatments have low incidence of local skin reactions, such as local burning sensations.

6.2. Preclinical therapy

Preclinical therapy is proven only effective in animals or cells, and marginally in clinical cases.

6.2.1. Anticytokine/cytokine therapy

Anticytokine therapy targets the activity of catabolic cytokines, including proteinases, cytokine-induced signaling pathways, inflammatory factors (statin, recombinant IL-1Ra as anakinra), monoclonal anti-TNF antibody (adalimumab, infliximab), iNOS inhibitors SD-6010, MMP inhibitor PG-116800, cathepsin K inhibitor SB-553484(254-258), and chondrocyte apoptosis related to cytokines(259,260). Some growth factors, such as TGF-beta, BMP-7 and FGF-18, are perhaps effective in improving OA. Recently, an angiogenesis inhibitor thrombospondin-1 (TSP-1) has been reported to be intraarticular transferred and to inhibit OA development, probably by inducing TGF-beta production and by reducing microvessel density, macrophage infiltration, and IL-1 beta levels(261). Tanezumab, a humanized monoclonal antibody that inhibits nerve growth factor has been reported to reduce joint pain and improve function of patients with moderate-to-severe knee OA(262). However, these factors may be secreted from multiple cell types at different phases of OA, causing difficulties in their application.

Other anticytokines, such as the kinin B2 receptor antagonists, MEN16132, and icatibant are helpful for reducing pain, as evidenced in the monosodium iodoacetate-induced OA model(263). The highly selective A(3) adenosine receptor agonist CF101 was described as a cartilage protective agent by inducing apoptosis of

Table 3. Methods, application, limitation of OA animal models

Models	Methods	Application/ Advantages	Limitations
Factitious genetic modification	Knock-out/deficiency Cho/+(Coll11a1-/-), Dmm/+(Col2a1-/-), Cmd/+(aggrecan-deficient), alpha-1/beta-Integrin deficient, SLRP-deficient, Cre-Gdf5/Bmpr1a^{floxP} mice Knock-in/overexpression/transgenic mice Col2a1, Conditional MMP-13 transgenic, Bovine growth hormone(bGH) fusion , MT-DNIIR heterozygote (truncated TGF-beta-R2 overexpression), TNF-alpha transgenic mice	Molecular pathology	Questionable physiologic relevance, time-consuming, expensive, high requirement for researchers
Spontaneous disease model	rhesus macaques, Hartley albino guinea pigs, dogs STR/ORT, C57Bl/6, BALB/c mice	Epidemiology, pathogenesis, evolution, diagnosis, treatment, comparison, complication	Long time slow and mild changes relatively expensive individual differences
Pathogenic mimic model	Surgical procedure intra-articular injection	Short time, widely, successfully, stably used	External factor (trauma, inflammation)
a. Intra-articular surgery	patella dislocation, patellectomy, Hulth-Telhag model, ACLT, meniscectomy, tibial osteotomy, pelvic osteotomy, myomectomy, tendonotomy, groove	anti-inflammation cartilage protection	Ethical problem Surgical trauma and inflammation
b. Extra-articular surgery	Ovariectomy, myomectomy, tendonotomy	Imitate different etiological factor	Ethical problem exist Surgical trauma and inflammation
c. Immobilization	in forced fixed position(flexed, extending, intermediate posture)	elevate the motion of joint	fixture loosen
d. Overload	Compression, excessive exercise(treadmill running)	elevate the load of joint (overweight, obesity)	
e. Physical alteration	Freezing, surgical trauma induced by incision, shaving, abrasion, contusion	chondrocytes replication, matrix regeneration	
F. Chemical alteration	Intra-articular administration(papain, trypsin, hyaluronidase, collagenase) cytotoxic drugs(Thiotepa, nitrogen mustard, colchicines, osmic acid, iodoacetate) Indirect agents(vitamin A, Filipin)	Inflammatory for a very limited time	
G. Endocrine alteration	Intra-articular corticosteroid administration, a high fat diet, oral administration of quinolone analogues	endocrinic factor (obesity)	
H.Biochemical alteration	Croton oil, carrageenin, zymosan, dextran sulphate IL-1, TNF, substance P, TGF-beta2 Magnesium tetrasilicate, talcum powder		

inflammatory cells via deregulating the NF-kappaB signaling pathway(264). Calcitonin could promote matrix synthesis of chondocytes and inhibit cartilage degradation, which may involve in attenuation of MMP activity(265). Subcutaneous or intranasal administration of calcitonin has been shown to have effects on inhibition of bone resorption by binding to the calcitonin receptors on osteoclasts(266).

Since the equilibrium between OPG and RANKL plays a role in the pathology of OA, this system was expected as a new strategy for OA treatment(267).

6.2.2. Gene therapy

OA has a surprising degree of heritability and multiple interacting loci; thereby, much progress has been made to genetically modify synovium, cartilaginous matrix(268,269). However, the successful modification of relevant gene mutations that are associated with OA seems impossible to accomplish in the near future. Nonetheless, gene therapy is believed to be a powerful tool in gene modification techniques.

6.2.3. Tissue/Cell transplantation

In 1994, Brittberg *et al.* introduced autologous chondrocyte implantation. However, due to articular cartilage defects exhibited in OA patients, usage of this technique poses some difficulty. Recently, several researchers are attempting to treat OA by tissue-engineering methods, which are based on stem cells and scaffolds, but not on chondrocytes (270). Ideally, the most effective approach is to combine these methods to promote cartilage regeneration and inhibit destruction(271).

7. SUMMARY AND FUTURE DIRECTIONS

Although several genes have been found to be associated with OA, genetic epidemiology demonstrates that these genes rarely undergo mutation, are limited to the human species and demographic location of these species, and do not have a sufficiently high frequency to confer significant population risks of primary OA(272). Moreover, molecular studies of larger cohorts may be required to yield more conclusive results concerning the genetic factors of OA and to exclude false positives. Table 2 lists several target genes recommended for further validation and study in animal models.

No consensus currently exists regarding which animal model is most relevant to the study of OA. Each model offers advantages and disadvantages (Table 3). Genetically modified mice are the best tools for mechanistic studies aimed at understanding the functional role of specific molecules in OA pathology; still some reservations remain concerning the mouse model, particularly their physiological relevance to the human disease, and their use as drug-screening tools. Furthermore, mouse models are also time-consuming and expensive, and they require cooperation between researchers in different fields. Spontaneous OA models are less affected by external factors such as these, so the consequences resulting from manipulation could be eliminated. These models are beneficial in studying the primary onset of OA, biochemical changes of articular cartilage, prevention and treatment, and the causation in several physiopathological

Table 4. Comparison of clinical therapies for OA patients

Agent	Administration route	Effects	Adverse effects
NSAIDS	oral	Moderate to severe pain relief	Gastrointestinal toxicity Cardiovascular risks Hepatic & renal toxicity
Nonopioid analgesics	oral	Mild to moderate pain relief	Gastrointestinal reaction drowsiness
Opioid analgesics	oral	Moderate to severe pain relief	Tolerance Dependence Respiratory depression constipation
Acupuncture	puncture	Pain relief	Relatively safe
TCM	oral	Pain relief, physical function improvement	Relatively safe
Glucosamine Chondroitin	Injection	Symptoms relief	Potential effect on OA progression
Osteotomy Arthroscopy Arthrodesis Arthroplasty	Surgical methods	Pain relief Function improvement	Invasion Motion limitation
Topical analgesics	External applied	Local pain relief	Local skin reaction

changes. However, similar to the factitious models, they are time-consuming, and more individual differences exist in the progression of the disease (as in humans). Surgically induced models develop rapid and reproducible damage. They are especially useful for studying anti-inflammation and cartilage protection. However, these models are not suitable for observation of biochemical and metabolic changes associated with the progression of OA because surgical trauma and inflammation may have an affect. Intra-articular administration of agents may generate models in little time, and can mimic the final step of cartilage injury. Thus, these models are valuable for investigating cartilage pathology and the therapeutic effect of drugs. Despite this, agent-dose should be monitored in the joints of different OA models. Clearly, the biochemical and structural models of OA are complementary. In practice, they are usually combined. The utilization of several species increases the number of models available. However, the discrepancies in the animal size, lifespan, disease progression, and response to treatment should be taken into consideration.

So far, the mechanisms of OA development seem clear both at the gross anatomical and the molecular levels. However, the global effects, such as the connection between individual molecules, have been modestly revealed. Even single cytokine families, such as the BMPs, play different roles in different phases of OA. These varying effects present more difficulties when studying signaling crosstalk. It is of great necessity to discover the precise actions and interactions of these cytokines in further studies. Interestingly, studies have suggested that rheumatoid arthritis and OA share some common characteristics (264).

In this review, we use the gold criterion to elevate therapeutic effect. However, the clinical trials in meta-analysis usually only measured the symptoms, which might omit the effect of therapies on the pathological progression of OA. Furthermore, larger cohorts of patients for longer time periods are needed to verify the usefulness of these therapies. In the future, preclinical therapies call for more validation and application. For example, replacing OA tissues with ideal scaffolds, introducing proper stem/progenitor cells, creating a suitable microenvironment for their function, and rehabilitating the function of the regenerated tissues, is recommended for future exploration. Moreover, it takes a long lead-time for the development of OA, therefore, the structural failure might begin several years before symptoms appearance. So preventive treatments could be used in adult populations (273).

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Abbreviations: OA: osteoarthritis, ECM: extracellular matrix, Col2a1: collagen type II, alpha 1, HIF-

2alpha:hypoxia-inducible factor-2alpha, SNP: single nucleotide polymorphism, COL11A1: collagen type XI, alpha 1, SLRP: small-leucine-rich-proteoglycan, Agc1: aggrecan 1, TGF-beta: transforming growth factor beta, COMP: cartilage olgomeric matrix protein, MATN3: matrilin 3, FRZB: frizzled-related protein, CILP: cartilage intermediate-layer protein, VDR: vitamin D receptor, KL: koltho, ESR1: oestrogen receptor alpha, BMP: bone morphogenetic protein, OPG: osteoprotegerin, IL-1: interleukin 1, IL1R1: interleukin 1 receptor 1, PGE2: prostaglandin E2, COX2: cyclooxygenase 2,: TXNDC3: Thioredoxin domain containing 3, RHOB: Ras homolog gene family, member B, BLP2: BBP-like protein 2, CIAS1: cold auto-inflammatory syndrome 1, CD36: cluster of Differentiation 36, NCOR2: nuclear receptor co-repressor, DIO2: type II iodothyronine deildinase, TNA: tetranectin, MT-1-MMP: membrane type 1 matrix metalloproteinase, BGN: biglycan, FM: fibromodulin, Gdf5: growth differentiation factor 5, Hh: hedgehog, SmoM2: SMO homolog protein, TNF: tumor necrosis factor, Ca: calcium, P: phosphorus, Mg: magnesium, S: sulfur, K: potassium, GAG: glycosaminoglycan, ACLT: anterior cruciate ligament transaction, OSM: oncostatin M, MSCs: mesenchymal stem cells, MMPs: matrix metalloproteinases, TIMP: tissue Inhibitor of metalloproteinase, NO: nitric oxide, TRAP: Tartrate-resistant acid phosphatase, nfat2: nuclear factor of activated T cells 2, Oscar: osteoclast-associated receptor, ALP: alkaline phosphatase, IGF-1: insulin-like growth factor 1, EP: E prostanoid, PI3K/Akt: phosphatidylinositol 3-kinase, CTGF: connective tissue growth factor, FGFs: fibroblast growth factors, VEGF: vascular endothelial growth factor, RANKL: receptor activator of NF-kappaB ligand, TRAF3: TNF receptor-associated factor 3, OCPs: osteoclast precursors, SA-β-gal: senescence associated beta-gal, p53: tumor protein 53, p21: cyclin-dependent kinase inhibitor 1, p16: cyclin-dependent kinase inhibitor 2A, SOD2: superoxide dismutase 2, ROS: reactive oxygen species, ULK1: Unc-51-like kinase 1, LC3: light chain 3, Smad: proteins that modulate the activity of transforming growth factor beta ligands, Smurf-2: E3 ubiquitin-protein ligase, PTA: posttraumatic osteoarthritis, PG: proteoglycans, GADD45beta: growth arrest DNA damage 45 beta, WNT: wingless MMTV integration, IFP: infrapatellar fat pad, CD90: human Thy-1 antigen, SFs: synovial fibroblasts, TMJ: temporomandibular joint, HP: hydrostatic pressure, MDSCs: muscle-derived stem cells, sFlt-1: one of the VEGF antagonists, HrtA1: high-temperature requirement protein A1, PAR-2: proteinase-activated receptor, PCMO: programmable cell of monocytic origin, PLAP-1: periodontal ligament-associated protein-1, NSAIDs: Non-steroidal anti-inflammatory drugs, GI: gastrointestinal, RCTs: randomized controlled trials, HPE: human placenta extract, MIA: monoiodoacetate, MAPKs: mitogen-activated protein kinases, ERK: extracellular signal-regulated kinase, UC-II: undenatured type II collagen, TSP-1: thrombospondin-1

Key Words: Osteoarthritis, Gene, Animal model, Mechanisms, Therapies, Articular cartilage, Subchondral bone, Synovium, BMPs, Review

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