International Journal of Research in Orthopaedics
Singh A et al. Int J Res Orthop. 2022 Nov;8(6):765-774
http://www.ijoro.org

Review Article

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20222722

Osteoarthritis: insights into pathogenesis and futuristic treatment strategies

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Received: 30 August 2022
Revised: 28 September 2022
Accepted: 29 September 2022

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ABSTRACT

Osteoarthritis is the most common musculoskeletal condition world over that causes significant health, economic, and societal burdens. Till date, no therapeutic approaches have been able to stop or delay the progression of osteoarthritis satisfactorily. Structural and clinical features of the disease are characterized by a high inter-patient variability. This heterogeneity is believed to be a major factor associated with the complexity of osteoarthritis and the on-going difficulty to identify a single therapy for all sub-groups. The objective of this review is to highlight recent advances in the understanding of the pathophysiology of osteoarthritis and latest biological treatments available, their limitations and to bring to notice the latest state-of-the-art on-going research on novel therapies. For this study we searched different online databases such as PubMed and Cochrane Library from inception to January 2022. We identified eligible studies on the pathophysiologic findings, prevalence, or incidence of knee osteoarthritis, available treatments, and current research for future therapies. Besides the availability of vast literature on cartilage extracellular matrix and its changes in osteoarthritis, the complicated mechanism of the disease still has missing links in the chain. Presently, biological treatments such as platelet rich plasma, bone marrow mesenchymal stem cells and autologous fragmented adipose tissue containing structural vascular fraction are commonly used. In future, gene therapy could become a potential option for treating the disease. More extensive insights into the pathophysiology of osteoarthritis will be helpful in designing therapies that can curb structural progression and promote cartilage regeneration thus providing more potent relief from painful and disabling condition associated with osteoarthritis.

Keywords: Osteoarthritis, Pathophysiology, Platelet rich plasma, Mesenchymal stem cells, Gene therapy, Monoclonal antibodies

INTRODUCTION

Osteoarthritis (OA) is one of the most common enervating musculoskeletal conditions that affects the joints, mainly the chief weight bearing joints *viz.* the hip and the knee.[1] The prevalence of OA increased more than 113% between 1990 and 2019, making it the 6th leading cause of disability worldwide with the most cases appearing in China, India, and the United States. Figure 1 shows the percentage of population affected by OA in the five continents of the world.[2] There are over 654 million individuals world over aged 40 years and older with knee OA and there is a gradual increase in the global health burden of this disease.[3] There is a substantial variation in the incidence

and prevalence of the condition between different countries and a general increase in its incidence with age. It is estimated that knee OA incidence among older adults (60 years and older) is nearly 10% in men and 13% in women.[4] A significant increase in the prevalence of knee OA have been noticed over the last couple of decades and is continuously on the rise primarily due to life-style changes leading to obesity and other risk factors.[5] According to a study, approximately 85% of the burden of OA worldwide is associated with knee OA.[6] The same study also confirmed that between the year 2005 to 2015, there has been a substantial rise of 32.7% of occurrence of knee OA thereby making it one of the leading causes of global years lived with disability. OA causes the economic burden of nearly USD 89 billion of which major cost is with knee and hip joint replacements.[7]

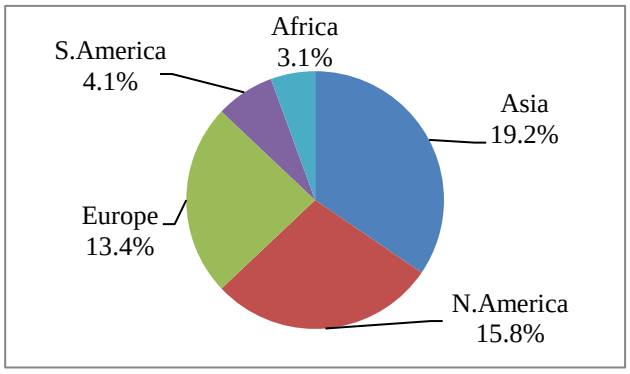

Figure 1: Global prevalence of osteoarthritis.

OA is a whole joint disease characterized by the structural modifications of primary articular cartilage, the sub-chondral bone, Hoffa's fat pad, synovial ligaments, and muscles.[8] Studies have also established a link between OA and increased risk of developing cardiovascular disease and atherosclerosis.[9,10] There have been evidences to support that progression of lower limb OA is often associated with the development of symptoms of depression due to chronic pain which is the most severe consequence of OA limiting the physical activity.[11] Physical inactivity further contributes to greater knee pain and obesity. Figure 2 describes various risk factors of OA. Thus, in addition to being an economic burden, this disease has also become a social burden. OA is not yet curable, but management of risk and predisposing factors may slow down the disease progression. The management of the disease comprises multidisciplinary strategies with the objective to alleviate symptoms and enhance joint functions. The management of OA is broadly classified into pharmacological and non-pharmacological interventions. In the end stage disease, joint replacement surgery is the only option left to enhance the quality of life where symptomatic treatment does not yield satisfactory results considering it as a defeat of orthopaedics, medicine and science.[12]

The purpose of this review is to highlight the recent advances in the understanding of the pathophysiology of osteoarthritis and latest biological treatment methods available, their advantages and limitations and also future regeneration strategies. This review provides the available current information on on-going research on novel therapies in an effort to pass on better understanding of the progression of this multifactorial disease.

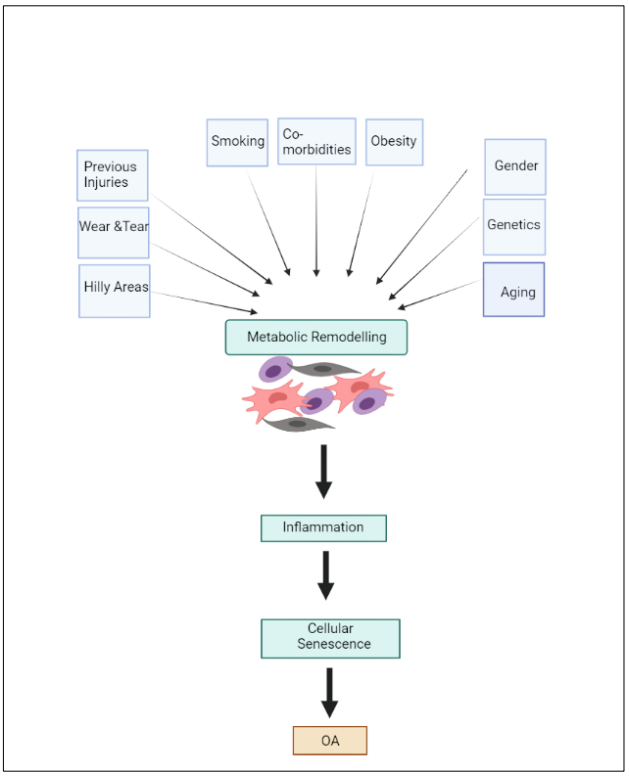

Figure 2: Various risk factors associated with osteoarthritis.

METHODS

For this study, the researchers searched the online databases PubMed, Cochrane Library, EMBASE and CrossRef from inception to January 2022 using MeSH terms "osteoarthritis", "pathogenesis", "treatment", "stem cell therapy", "gene therapy" using operators "OR" and "AND". References in languages other than English were excluded. We also identified the reference lists of relevant systematic reviews and included studies. We extracted the data related to prevalence, pathogenesis, and different treatment options.

PATHOGENESIS OF OA

OA is now recognized as a whole joint disease which is characterized by cartilage destruction, sub-chondral bone change, osteophyte formation and alterations of ligaments and meniscuses.[13] Extracellular matrix (ECM) is a complex molecular network that dynamically surrounds the cells. It is composed of different physical and biochemical components such as proteins, proteoglycans, glycoproteins, and polysaccharides which provide biochemical and biomechanical properties to the cells.[14,15]

The ECM composition and structural integrity is essential to the normal function of load-bearing tissues such as cartilage. Studies conducted in the recent years have indicated that ECM, directly or indirectly, regulates almost all cellular behaviours and is absolutely essential for key developmental processes.[16,17] Progression of OA is characterized by changes in ECM composition and structure (Figure 3). Healthy cartilage matrix is mainly composed of collagen type II that provides tensile strength for the tissue. Aggrecan, a negatively charged proteoglycan that is hydrophilic, provides compressive resistant and shock absorbing capability to cartilage under loading.[18] It has been shown that during OA, aggrecan content is decreased while collagen content is increased.[19] As a result, the change in ECM composition predisposes the tissue for mechanical fault resulting in significantly altered mechanical environments of the cells within the cartilage matrix. The reduced proteoglycan content decreases compressive modulus of cartilage and consequently making the tissues vulnerable to greater strains on exposure to mechanical stress. The rate of collagen synthesis increases in the early stages of OA and remains elevated. Also, the composition of collagen type II (healthy cartilage/matrix) has been found to change to type I (found in sub-chondral bone tissue).[20]

As a result, the decreased collagen type II content during OA sabotages the integrity of ECM networks formed by collagen and proteoglycan. Further, due to shortening of collagen fibril lengths, elastic modulus decreases as the extent of OA increases.[21] Due to these changes, osteoarthritic cartilaginous tissue shows reduced ability to store elastic energy and this in turn leads to fibrillation and fissure formation.

As OA progresses, multiple factors may be involved in ECM changes in the cartilage tissue. One of these factors is inflammation that affects the ECM qualitatively as well as quantitatively. Age related wear and tear and mechanical damage trigger series of inflammatory responses in the tissues housing in close proximity of the joint including articular cartilage, sub-chondral bone, synovial membrane and ligaments (Figure 4).[22] In addition, chondrocytes, the only cells residing in the cartilage, respond to such inflammatory conditions and participate in catabolic activities, thus leading to the degradation of cartilaginous ECM.[23] The elevated levels of nitric oxide (NO) are also reported to enhance the degenerative activities of matrix degrading proteins. NO upregulated by the transcriptional activity of NF-kB perpetuates the chronic inflammation that enhances matrix degradation and mediates apoptosis of chondrocytes by creating oxidative environments.[24] The use of NO inhibitor in canine model of OA, reduces degenerative changes in the cartilage possibly highlighting the critical role of NO in the progression of OA.[25]

Simultaneously with matrix degradation, the inflammation mediated down regulation of chondrogenic growth/transcription factors mediating chondrocyte ECM synthesis, such as transforming growth factor β, sex determining region Y-box9, connective tissue growth factor and insulin like growth factor are also found to suppress the anabolic activities of chondrocytes.[26] Thus, these results demonstrate the significant influence of inflammatory mediators in the progression of OA by altering homeostasis of cartilage ECM. As the disease progresses, the tissue gradually loses aggrecan content and collagen fibril stiffens.

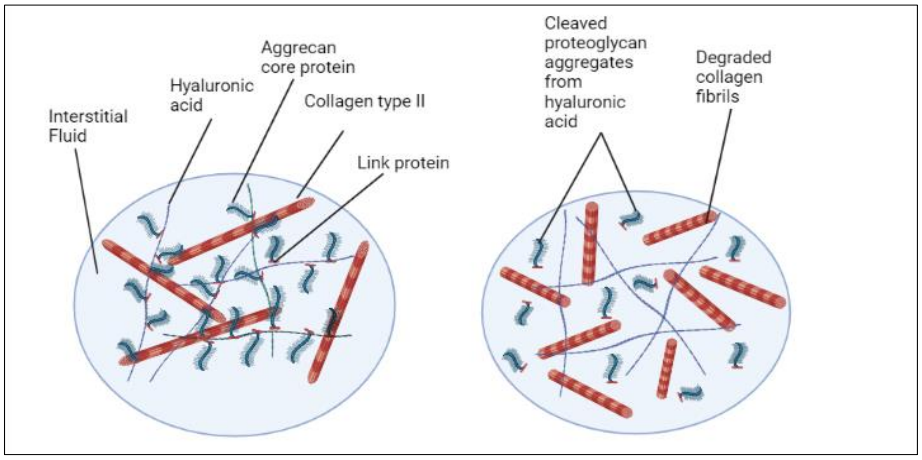

Figure 3: Cartilage extracellular matrix and its changes in osteoarthritis (a) healthy network of proteoglycan aggregates entangled with type II collagen fibres; and (b) cartilage matrix changes in osteoarthritis defined by degradation of proteoglycans and cleavage of type II collagen fibres.

Another mechanism that could possibly change the mechanical microenvironment is the accumulation of advanced glycation end products (AGEs) which can cross link to the collagen network and increase the stiffness of human adult articular cartilage.[27] This leads to the formation of fibrocartilagenous tissues that exhibit more bond-like properties replacing the completely degenerated cartilage in addition to osteophyte formation at the periphery of the articular surface.[28] In addition to affecting the mechanical environments of the chondrocytes, the

changes in matrix composition during OA also alter the interactions of matrix proteins with the cells. Matrilin-3 (MATN3) is a matrix protein which is highly upregulated during OA.[29] Although the protein is a part of healthy cartilage matrix, the soluble form of MATN3 is upregulated and released to synovial fluid in OA.[30] The studies have revealed that this MATN3 can change the behaviour of chondrocytes, demonstrating the direct involvement of ECM in the progression of OA by interacting with the cells as well as indirectly by changing the mechanical environment of the cells.

Changes in the composition of the ECM also affects chondrogenic differentiation of mesenchymal stem cells (MSCs). Several studies have demonstrated that changes in the mechanical properties of the cartilage during OA may favour the differentiation of MSCs towards non-chondrocytic lineages further intensifying the degeneration of cartilage.[31,32] Altered environments in ECM composition and mechanical properties during progression of OA significantly limit the chondrogenesis of MScs inhibiting the regeneration process of cartilage damage.

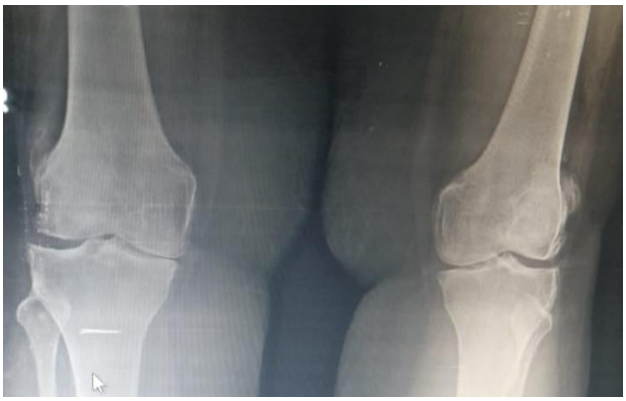

Figure 4: Radiograph of osteoarthric knees.

BIOLOGICAL TREATMENT OPTIONS

Most of the OA management guidelines designed by professional organizations suggest that patients with OA should be offered a core set of non- pharmacological interventions including education, weight loss for those who are obese, and strengthening, cardiovascular and mind-body exercises such as Yoga and Tai Chi.[33] Structured exercise interventions that typically focus on strengthening the lower extremity muscles offer improvements in pain and functional status. In addition, a combination of diet and exercise can result in substantial weight loss, pain relief, improvement in functional status, and reduction in inflammatory markers. While, lateral wedge shoe inserts have not yielded positive outcomes, a recent trial of individualized external orthotic, which is attached below the sole, has been reported to improve pain and functional status than a control orthotic.[34] However, more trials are needed to prove the efficacy of this tool.

Modern medicine is still looking to find an answer to stop the progression of OA in early stages to avoid surgery altogether. So far there is no non-surgical treatment that can control the progression of the disease. Therefore, a lot of focus in research has been put into discovering a better understanding of its pathogenesis, genetics, and biomarkers. These new findings have provided clinicians with new biological treatments of OA that have the potential to slow down the advancement and reverse the course of the disease. Although these therapeutic options are in clinical practice, a rising number of replacement surgeries performed still demand the development of new therapies or optimization of already existing options.

Platelet rich plasma

Platelet rich plasma (PRP) is obtained by high-speed spinning of patient's blood to separate RBCs from plasma. PRP affects synovial cells, endothelial cells, cells of innate immunity, and components of metabolism in cartilage. Platelet activation results in the release of over 800 proteins and the molecules contained in their cytoplasmic granules whose function is related to vasoconstriction, inflammation, immune reaction, angiogenesis, and tissue regeneration. The beneficial effect of PRP is mediated by kemokines, cytokines, growth factors, adhesive proteins, proteases and other small molecules such as, ADP, serotonin, calcium, histamine and epinephrine. PRP is safe with no reported infections, adverse clinical features or serious complications. However, due to repeated intra-articular PRP injections, some adverse events have been reported. These may include moderate pain, swelling and effusion for a couple of days.[35] Although numerous studies confirm the impact of PRP on pain reduction in knee OA in short and medium term at 6-12 months, different methods of product preparation and application make it difficult to obtain conclusions regarding clinical results from such therapy.[36,37] There is a need to standardize product characterization and dosage, proper timing, treatment repetition period, location and application technique. New trends are emerging more frequently, which is best portrayed by the application of PRP intra-osseously into the sub-chondral bone, one of the key pathophysiological components of OA pathogenesis, which was not addressed in previous development of non-surgical treatment options. A recent systematic review indicated the great potential of this approach and a recent observational study demonstrated better outcomes at 6 and 12 months when PRP is applied both intra-osseously and intra-articularly compared to intra-articular application only.[38,39]

However, lack of consistent measurements of the treatment outcomes that would enable more precise cross-referencing of study results is the greatest limitation of these studies.[40] The application of PRP products combined with other procedures like stem cell or hyaluronic acid application remains an interesting area of research. Further studies are needed to focus on possible therapeutic potential of PRP products in OA.

Bone marrow mesenchymal stem cells (BM-MSCs)

Mesenchymal stem cells (MSCs) are specialized precursor cells found in various tissues that retain the ability of self-renewal and can differentiate into different tissue specific adult cells. MSCs can replace aged and damaged cells, and thereby potentially maintain the function of the tissue or organ in the adult.[41] As chondrocytes are the only cells present in the articular cartilage, the potential of the MSCs to differentiate into adult cells makes them a potential therapeutic method for OA treatment. So far, this effect has been observed only in in vitro, however, their alternative effect observed in injured tissue is to secrete immune-modulatory and trophic signalling molecules that prevent an over-aggressive immune response and promote local regeneration by secretion of anti-apopotic, anti-scarry, angiogenic and mitotic signalling molecules. In addition, these are also known to inhibit bacterial growth by secreting LL-37.[42,43] Due to their paracrine signalling and lack of evidence for in vivo differentiation of MSCs into chondrocytes, a new term "medicinal signalling cells" was coined for these cells indicating a new understanding of MSC function in the treatment of OA.[44,45] With the onset of OA, MSCs start accumulating in joints and adjacent bone marrow lesions. Thus, suggesting that they may play a natural role in response to joint pathology or injury but the mechanism by which stem cell therapy may be effective in OA still remains ambiguous.[46]

The bone marrow is the first investigated and excellent source of stem cells (BM-MSCs).[47] Autologous BM-MSCs are safe at all tested doses, clinical trials of BM-MSCs have reported efficacy at higher doses ranging from 25×10^6 cells and 40×10^6 cells.[48,49] BM-MSCs treatment in patients with OA results in overall improvement in pain and symptoms and reduces synovial inflammation. But, still there is ambiguity in literature related to cartilage-regenerative ability of BM-MSCs.[50] There are also some therapeutic possibilities combining MSCs with biodegradable materials that seem promising but need to be further investigated.[51] However, there are some studies showing that intra-articular use of MSCs for the repair of cartilage is questionable, due to insignificant pain relief and functional improvement in patients with knee OA.[52]

Intra-articular application of autologous micro-fragmented adipose tissue (AMFAT) with stromal vascular fraction (SVF)

A group of researchers conducted four clinical studies over last few years, investigating use of AMFAT in treatment of knee OA.[53] In one of the trial, a standard lipo-aspiration technique was performed, and harvested fat was introduced into Lipogems® ortho kit (Lipogems International SpA, Milan, Italy) for the process of micro-fragmentation. The final product of microfragmented adipose tissue was applied intra-articularly into patients' affected knee joints. Pain estimated measured by VAS at 3, 6 and 12 months), decreased significantly, both for resting and movement estimates. Additionally, cartilage GAG content, measured by dGEMRIC index, significantly improved in 52.9% of measurements and deteriorated in only 11.2% of measurements, which would be a normal disease course for late-stage OA.

In another trial conducted by the same set of researchers describing cell types contributing to the effect of treatment.[54] A stromal vascular fraction from lipoaspirate (SVF-LA) and stromal vascular fraction from microfragmented lipoaspirate (SVF-MLA) samples were characterized and the CD45- fraction identified several population phenotypes such as endothelial progenitor cells (EPC), endothelial mature cells, transitional pericytes, pericytes, and supra adventitial-adipose stromal cells (SA-ASC). The immune-phenotyping profile of SVF-MLA was predominant by reduction of leukocytes and SA-ASC, and an increase in EPC, indicating their unavoidable involvement in the observed effect of the SVF- mediated cartilage treatment. Together these studies suggest that the application of AMFAT with SVF in patients with knee OA increases GAG levels in hyaline cartilage, consequently reducing pain and improving movement abilities. The procedure is safe for patients, minimally invasive, quick, one-step and economic, posing lesser complications and great compliance.[55-59]

Till date there are no comparative trials between the outcomes of BM-MSC and AMFAT directly, but a comparative literature review indicates that both provide an excellent safety profile and favourable patient outcomes on the basis of perceived pain, joint function and OA progression.[60] There is a need for more structured experimental trials regarding the application of MSCs and standardization of applicable doses.

Extracellular vesicles (exosomes)

Exosomes are surrounded by a phospholipid bilayer that contain different cell specific receptors and integrins which are vital for cell-to-cell communication.[61] Being the main component of MSC secretome, extracellular vesicles after entering the cells regulate gene transcription and the function of recipient cells.[62,63] A recent pre-clinical study that used MSC exosomes for cartilage repair, reported that exosome treated animals show increased cellular proliferation, augmented matrix deposition, and better histologic scores.[64] Some researchers argue that in comparison with MSC treatment, exosome-based therapy is more sustainable, reproducible, and safe, primarily because of reduced toxicity and immunogenicity.[65,66] Limited studies have been reported on exosomes from the synovial fluid and chondrocytes thus, calling for more research to understand their role in OA.

FUTURISTIC APPROACHES FOR OA MANAGEMENT

As stated earlier, OA is a multifactorial disease with complex pathology and multiple underlying pathophysiological mechanisms triggering cartilage

destruction and inflammation in the joints ultimately causing pain, stiffness, swelling, restricted motion and loss of function. Apart from surgery, no ideal non-surgical treatment has come up for OA till date. OA is a disease in which same set of treatments do not work for all the patients. Putting the patients in specific sub-groups on the basis of their clinical, biochemical, radiographic and molecular characteristics could, in future, prove to be the right course of action for providing more specific treatment options targeting specific mechanisms in OA pathogenesis.

Phenotyping OA patients

Dividing OA patients into sub-groups or phenotypes for understanding individual patient needs. The researchers of a study propose chronic pain, inflammatory, metabolic syndrome, bone and cartilage mechanism, mechanical overload, and minimal joint disease phenotypes.[68] For the patients who do not fit into any of these sub-groups due to overlapping of characteristics, a seventh phenotype named "complex knee OA phenotype" was observed. The OA phenotype research is in infancy, further research could provide the patients and the clinicians a tool to give a prognosis, facilitate the decision on a conservative or surgical treatment, and eventually lead to designing treatment protocols and development of drugs for treating OA.[69]

Bone morphogenetic protein (BMP-7)

The intra-articular injection of BMP-7 inhibited the advancement of OA in a rabbit ACL transaction model of knee OA.[70,71] BMP-7 is a member of transforming growth factor β (TGF-β) super-family possessing anabolic and chondroprotective effects in vitro, providing a base for its therapeutic effect in human OA.[72]

Furthermore, a phase I double-blind randomized, multicentre, placebo-controlled, single dose escalation trial demonstrated its safety with no dose-limiting toxicity.[73] The outcomes of further phases are expected to determine the efficacy of BMP-7 on OA treatment.

Sprifermin

With the recent discovery of fibroblast growth factor 18 (FGF 18), it has induced a novel treatment options for stimulating chondrocyte proliferation, inducing type II collagen expression and matrix production.[74] The intra-articular application of sprifermin demonstrated a beneficial effect on cartilage, increasing the cartilage thickness and reducing cartilage loss in vitro, in vivo and several pre-clinical and clinical trials in humans. It has been found that FGF 18 suppressed the matrix metalloproteinase production.[75]

Since Sprifermin is currently non-approved drug under development, its application for OA should be considered with caution.

Monoclonal antibodies

Monoclonal antibodies (mAb) have already been approved as novel therapeutic method used for approximately 30 targets and diseases such as autoimmune diseases, cancer, asthma, gout and hypercholesterolemia. When compared to small molecules, mAbs have target selectivity and less toxicity.[76] In knee OA, mAbs have shown promising results in mice models and in vitro studies. Tanezumab is mAb that blocks the nerve growth factor (NGF) from activating Tropomyocin-receptor-kinase (TrK) receptors on nociceptic neurons.[77] Hence Tanezumab is a potential therapeutic option for treating chronic pain and improving physical function in patients with symptomatic OA having moderate to severe symptoms of knee OA.[78] In addition, a recombinant, fully human, anti-nerve growth factor antibody Fazinumab also showed improvement in walking knee pain and WOMAC scores.[79] Human mAb ADAMTS-5 showed slowed cartilage degeneration and osteophyte growth but did not affect subchondral bone sclerosis in mice that underwent surgery.[80] Other therapeutic drugs of interest that could potentially halt the progression of OA include adalimumab, infliximab and etanercept that inhibit TNF-α and anakinra that inhibits IL-1 and IL-1Ra genetic therapy that is in a pre-clinical stage on animal model.[81] Anakinra demonstrated encouraging results in animals but not in human clinical trials. In contrast, TNF inhibitors may prove their potential in the treatment of an inflammatory phenotype OA in future. Having said, present available data suggest that mAbs may exhibit a favourable risk-benefit ratio considering future targeted therapeutic methods for OA. But, patient phenotyping is an essential approach for potential benefits of mAbs.

Gene therapy in OA

Gene therapy offers an ideal combination of locally administered therapeutics and long-term effects, and thus could be the future option for OA management. The use of helper-dependent adenovirus (HDAd) – mediated intra-articular gene therapy approach for long-term expression of interleukin-1 receptor antagonist (IL-1Ra) was investigated in small and large animal models.[82] Since IL-1 is an inflammatory mediator involved in numerous catabolic processes in OA pathophysiology, the continuous prevention of binding to its receptors could offer a sustained symptomatic and disease modifying treatment for OA. Authors reported non-significant improvement in cartilage status with respect to cartilage volume and bone surface covered by cartilage and prevention of osteophyte formation in mice treated with HDAd-IL-1Ra. Whereas, in a horse model, a reduction in symptoms, decreased level of synovitis and improved cartilage status were observed.

The modern gene editing methods such as clustered regularly inter-spaced short palindromic repeat (CRISPR), CRISPR-associated (Cas) endonuclease system, also served as a therapeutic potential for the disease. Targeted CRISPR-mediated ablation of NGF significantly

decreased the level of pain on one hand and induced progressive cartilage and osteophyte formation on the other. Additionally, NGF loss-of-function was associated with the upregulation of cartilage-degrading enzymes such as MMP-13 and ADAMTS-5, and aggrecan degradation products.[83] Whereas, the targeted ablation of MMP-13 and IL-1β both not only lead to reduced cartilage degradation, lessened synovial hyperplasia, and decrease in osteophyte development, but also to downregulation of catabolic enzymes involved in cartilage matrix deterioration. Multiple gene editing of NGF, MMP-13 and IL-1β resulted in alleviation of pain and decelerated OA progression. These results are indicative of potential of CRISPR/Cas 9 gene editing for OA treatment in the near future.

CONCLUSION

Complex pathogenesis and a large number of mechanisms leading to the same outcome, make OA an interesting disease for the investigators. Current biological treatment of knee OA, including PRP and MSCs offer significant results in terms of clinical outcome, seen as a reduction in knee pain, but also in the increase of GAG content in hyaline cartilage after intra-articular application of AMAF with SVF. Therapeutic options (Sprifermin, BMP-7, mAbs and gene therapy) offer promising solutions, but more clinical studies are needed to confirm the safety and efficacy of these methods. In conclusion, multidisciplinary studies are required for better understanding of the pathogenesis of this disease. Also, use of a wide range of biochemical markers to objectify the results of novel gene therapies using different OA phenotypes could improve our knowledge of OA pathophysiology and help in directing researchers towards more patient specific treatments for the disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Singh A, Rai V, Pandey S, Chavan M, Ketha D. Osteoarthritis: insights into pathogenesis and futuristic treatment strategies. Int J Res Orthop 2022;8:765-74.