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Integration of Innovative Materials and Biotechnology in Joint Repair and Regeneration

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Abstract

Musculoskeletal disorders, particularly osteoarthritis (OA), rheumatoid arthritis (RA), and post-traumatic osteoarthritis, are on the rise due to aging populations and increasing rates of obesity. The advent of regenerative medicine, particularly stem cell therapies, bioscaffolds, and growth factor delivery systems, has provided a new therapeutic direction for the treatment of musculoskeletal disorders by activating the body's self-repair mechanisms to restore joint structure and function. However, optimizing the integration, durability, and functional recovery of regenerated tissues remains a major challenge. To further address the potential of stem cell therapy, biomaterials, 3D bioprinting, and gene interventions in repairing and regenerating damaged joint tissues, this paper further traces the research advances of biomaterials, stem cell technologies, and gene therapies through in-depth analyses of relevant domestic and international studies and literatures, comprehensively evaluating their efficacy, safety, and potential clinical applications in joint repair and regeneration. At the same time, the paper focuses on the multidisciplinary integration of innovative materials and biotechnologies and the creative expansion from laboratory research to clinical applications. The role of nanotechnology, gene editing in orthopedics, and advances in 3D bioprinting in tissue engineering are also examined in some detail.It was found that mesenchymal stem cells (MSCs) show great potential for cartilage regeneration and inflammation reduction, and preliminary clinical trials have shown improvements in joint function and pain. Biomaterial-based strategies, such as collagen scaffolds combined with hydroxyapatite, have shown better results in repairing cartilage defects in animal models, which provides a low-cost, simple and environmentally friendly approach. In addition, nanotechnology and smart biomaterials are being explored for their potential for drug delivery and tissue repair, with nanocarriers protecting growth factors from degradation and enhancing targeted delivery. The convergence of innovative materials and technologies is bringing new therapeutic horizons to joint repair and regeneration. Multidisciplinary collaboration and the integration of innovative materials are opening up unprecedented therapeutic perspectives for joint repair and regeneration, and cross-disciplinary integration of materials science, regenerative medicine, and immunology is driving further development of precision medicine and personalized therapies. The integration of these technologies not only demonstrates great potential in the field of joint regeneration, but also provides new ideas for solving other complex biomedical problems. As these technologies continue to advance, the future of joint regenerative therapy is promising and will bring more benefits to patients with bone and joint diseases worldwide.

Keywords: fusion innovative materials, bone & joint, biotechnology, joint repair, joint regeneration, regenerative medicine, stem cell therapy, Mesenchymal Stem Cells (MSCs), biomaterials, 3D bioprinting, gene therapy, gene editing, nanotechnology, smart biomaterials, osteoarthritis, rheumatoid arthritis

1. Introduction

Joint diseases, particularly osteoarthritis (OA), rheumatoid arthritis (RA), and post-traumatic joint degeneration, are the leading cause of chronic pain, dysfunction, and reduced quality of life worldwide. Osteoarthritis affects more than 240 million people globally, and its prevalence continues to rise with the aging of the population and the increase in obesity, and is characterized by degeneration of articular cartilage, changes in the substructure of the bone, synovial inflammation and loss of joint function[1]. Although most current treatments focus on

symptomatic relief, most are ineffective in reversing structural damage to the joints. Medications (such as NSAIDs and glucocorticoids) provide only temporary pain relief and do not stop the progression of the disease. Joint replacement surgery, while providing significant pain relief and improved function, carries the same risks as any major surgical procedure, including infections, blood clots, nerve damage, and anesthesia complications, and artificial joints usually have a lifespan of 15 to 35 years, after which time replacement may be necessary. Replacement may be required after that time[2,3]. This problem is particularly acute for younger and more active patients, who may need to undergo surgery again before the life of the prosthesis. Hip or knee replacements, in particular , can improve the patient's function but usually do not fully restore the range of motion or natural feel of the original joint, and the patient may feel stiffness or limited movement in the joint after surgery. Therefore, the development of treatments that can repair joint structures and restore function has become an urgent clinical need. Osteoarthritis (OA) is the most common joint disease and one of the leading causes of disability, and studies have shown that the global increase in disability adjusted life years (DALYS) due to OA from 1990 to 2019 is mainly driven by population growth and aging, with the top three leading causes of the highest number of DALYs causes are: knee OA, females, and middle socioeconomic development index (SDI) quintiles[4].

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily involves the small joints, with a global prevalence of approximately 0.2%-1%[5]. Its onset is associated with genetics (e.g., HLA-DRB1), smoking, and female hormones, with higher prevalence in North America, Europe, and parts of the Middle East. Global gout incidence, prevalence and disability-adjusted life-years DALYS are on the rise. The incidence of patients of both male and female genders increased by 21.42% and 21.06%, the prevalence by 16.87% and 18.75%, and the DALYS by 21.49% and 20.66%, respectively, which was particularly significant in regions with westernized diets[6]. The main risk factors include a high purine diet, obesity and genetics. In addition, inflammatory diseases such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), although the prevalence was low, patients with PsA had significantly higher mortality rates for cardiovascular disease (RR=1.21), respiratory disease (RR=3.37), and infection-related disease (RR=2.43), and in the case of AS, the risk of death from all causes (RR=1.64), especially the risk of cardiovascular event mortality risk were higher than in the general population, and both men and women with AS had higher mortality rates[7]. Globally, the prevalence of joint diseases is increasing due to aging and obesity, with higher diagnosis rates in developed countries and significant underdiagnosis in developing countries, which may be due to inadequate resources. Joint diseases not only threaten the health of individuals , but also place a heavy burden on the healthcare system of the society , and there is an urgent need to strengthen the diagnosis and prevention strategies. In the field of regenerative medicine, stem cell therapies, especially mesenchymal stem cell (MSCs) therapies, have demonstrated their potential in cartilage regeneration and inflammation relief[8,9]. Stem cells can differentiate into connective tissues such as cartilage, and preliminary clinical trials have also shown their effectiveness in improving joint function and reducing pain. However, the effectiveness of stem cell therapy is affected by a variety of factors, such as the source of stem cells, the method of administration, and individual differences in patients, and the stability and standardization of the therapy still faces major challenges. In addition, gene therapy, as a means to promote tissue repair, has the potential to promote regeneration by delivering specific genes to activate the repair mechanism in the body, but its gene delivery efficiency, targeting and safety to avoid immune response still need to be further improved. In biomaterials and tissue engineering, innovative materials such as hydrogels and 3D printed scaffolds have been applied to articular cartilage repair[10]. These materials are able to mimic the structure and function of natural cartilage, provide support for cells and promote tissue regeneration. However, how to ensure the effective integration of these materials with natural tissues and how to subject them to long-term mechanical loading of the joints remains a challenge in the application of current technologies. Platelet-rich plasma (PRP) and exosome therapies have shown efficacy to a certain extent by utilizing their abundance of growth factors and bioactive molecules, which are able to promote repair and reduce inflammation, but standardization of their efficacy, reproducibility, and long-term effects still need to be validated by further studies[11,12]. In terms of innovative material technologies, smart biomaterials and 3D bioprinting offer new possibilities for personalized joint repair. Smart materials are capable of precisely releasing drugs or growth factors in response to environmental changes, such as temperature, pH, or mechanical forces, providing a high degree of therapeutic flexibility, while 3D printing technologies are capable of creating customized cartilage scaffolds based on patient-specific anatomical features, providing personalized repair solutions. However, these technologies also face some challenges, especially in ensuring long-term biocompatibility, stability of mechanical properties, and integration with natural tissues. Nanotechnology has also demonstrated potential for precision drug delivery and tissue repair, but its potential toxicity and biocompatibility issues still need to be explored in depth. In recent years, with the rapid development of innovative materials and biotechnology, breakthroughs have also been made in the field of gene editing. In the study of cartilage regeneration targets, Hye Jin Kim et al.[13,14] constructed cartilage-like organs using CRISPR-

Cas9 gene editing and stem cell-induced differentiation and screened α2 adrenergic receptor signaling as a therapeutic target for cartilage regeneration, a finding that provides a new therapeutic strategy for repairing cartilage damage. In terms of translational research on articular cartilage repair and regeneration, optimized human platelet-rich plasma (hPRP) combined with hyaluronic acid (HA) therapy was validated in in vitro and animal model tests, which showed that it promotes chondrocyte proliferation and attenuates inflammatory responses, and demonstrated in a clinical study that, after receiving continuous injections of hPRP/HA during a 6-month period, cartilage regeneration at the condylar process, synovial inflammation regeneration of cartilage at the condyle, reduction of synovial inflammation, decrease in disk displacement, pain relief, and an increase in maximal opening[15]. In the study of composite bone repair scaffold materials, Jia Rui et al.[16] showed that a high-performance bone repair composite scaffold composed of flat silk silkworm pupa cocoon (FSC) and polylactic acid (PLA). The structural design, mechanical properties and osteogenic mechanism of the scaffold were optimized. The FSC thermopressing parameters were established and the optimal conditions were determined by material mechanical testing .The FSC/PLA composite scaffold exhibited excellent biocompatibility, mechanical strength, and in vitro mineralization ability with suitable degradation rate. It promoted osteogenic differentiation and macrophage polarization toward an anti-inflammatory M2 phenotype, and in vivo experiments showed that the scaffold enhanced osteogenesis and reduced inflammatory responses, providing a new pathway for bone regeneration .The application of 3D bioprinting technology in bone and cartilage regenerative repair provides a new approach to solve the problems of traditional surgical methods by using biodegradable materials and cells to create bioactive and biocompatible bone and cartilage tissues. In addition, studies on the mechanism of activity and application of bone repair materials have shown the development of highly active and multifunctional bone tissue engineering scaffolding materials from autologous bone, allogeneic bone, and inert materials. Cristina López-Serrano et al.[17] developed PEGDA hydrogels with tunable mechanical properties and bioactivity by RGD and BMP-2 simulated peptide immobilization. The elasticity and viscoelasticity were fully characterized using compression testing, rheology and AFM micro indentation. After two weeks hMSC grown on such scaffolds expressed early osteogenic markers (Runx2), even in the absence of induced differentiation medium. Cells showed accelerated differentiation after one week using osteogenic medium. Rigid but stress-relaxing hydrogels resulted in overexpression of E11 osteoblast markers, suggesting that mechanical properties combined with functional modifications promote osteogenic differentiation. The research progress of innovative materials and biotechnology in joint repair and regeneration has provided a new theoretical foundation and clinical treatment strategy for the repair and regeneration of joint injuries, and these research results are not only of great scientific significance , but also offer a broad prospect for future clinical applications. By comprehensively analyzing the relevant research results at home and abroad, this paper will focus on the potential of stem cell technology, biomaterials, 3D bioprinting technology, and nanotechnology in joint repair, reveal their application value in regenerative medicine, and provide theoretical basis and practical guidance for the future development of joint regenerative therapy.

2. Pathologic Mechanisms of Arthropathy and Biological Barriers to Joint Repair

The main pathologic processes of osteoarthritis include degeneration of cartilage, stiffening of the joint capsule and ligaments, inflammation of the synovium, and changes in the sub-bone structures. Cartilage progressively thins, loses elasticity, and develops cracks, leading to decreased joint function. Synovial inflammation exacerbates cartilage destruction and promotes the synthesis of matrix-degrading enzymes (e.g., matrix metalloproteinases, MMPs)[18].In addition, the formation of subosseous sclerosis, bone cysts and bone spurs (osteophytes) further exacerbate pain and joint dyskinesia. At the cellular and molecular level, chondrocyte dysfunction is at the heart of osteoarthritis, with chondrocytes producing too many matrix-degrading enzymes during degenerative changes and failing to synthesize enough matrix components for repair. As shown in Fig. 1. inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), further exacerbate cartilage degradation by promoting matrix degradation and inhibiting cartilage synthesis. And oxidative stress plays an important role, reactive oxygen species (ROS) promote cartilage matrix degradation by increasing the activity of MMPs. In addition, biomechanical alterations of the joints play an important role in the development of joint injuries and degenerative diseases; imbalances in joint mechanics caused by injuries or degenerative changes exacerbate damage to articular cartilage and result in continuous tissue loss due to imbalances in the processes of cartilage matrix synthesis and degradation. In the weight-bearing regions of the joints, especially the knee and hip joints, overloading mechanical stresses can exacerbate degenerative changes and lead to limited joint function. Genetic and environmental factors, such as obesity and poor lifestyle, also play a key role in the development of joint damage and degenerative diseases. Obesity increases mechanical loading on joints, especially weight-bearing joints, which promotes cartilage wear and joint degeneration, and sedentary lifestyles or repetitive high-intensity activities increase the risk of joint damage and degenerative changes[19]. These mechanisms ultimately lead to cartilage degradation, inflammatory response, increased pain, and joint dysfunction, which will continue to deteriorate if not intervened.

On the other hand, the repair of joint trauma, especially cartilage injury, faces multifaceted challenges, mainly focusing on the lack of blood supply to cartilage, low regenerative capacity, damage to the cartilage-bone interface, and the complexity of cellular molecular mechanisms, which are intertwined with each other and severely limit the realization of effective repair. First, the lack of blood supply to cartilage is one of the most fundamental obstacles in the repair process. Cartilage, as an avascular tissue, is unable to deliver oxygen and nutrients through the bloodstream, which results in a low level of chondrocyte metabolism and a very slow repair process. This lack of blood supply means that cartilage is unable to repair itself after trauma, especially in degenerative joint diseases or traumatic injuries, where cartilage degradation is often not effectively curbed, leading to loss of joint function and persistent pain. Second, the low regenerative capacity of cartilage further exacerbates the difficulty of repair. Compared to other tissues, the cells of cartilage, chondrocytes, have an extremely limited ability to proliferate, so when cartilage is damaged, it cannot be repaired as quickly as other tissues. This limited regenerative capacity makes cartilage damage often impossible to heal on its own, especially in long-term degenerative diseases where cartilage degradation is usually unavoidable and causes great suffering to the patient. Currently, although some treatments such as microfracture and stem cell therapies are being explored, their results are still unsatisfactory and lack long-term efficacy. In addition, damage to the cartilage-bone interface is a challenge. The boundary layer between cartilage and bone is critical for the mechanical stability of the joint, and trauma-induced damage to the interface can disrupt the normal structural relationship between cartilage and underlying bone, thereby affecting the load-bearing capacity and function of the joint. Especially in the case of composite cartilage-bone injuries, repair is more difficult because not only cartilage but also bone must be repaired. Such complex trauma requires comprehensive consideration of cartilage-bone repair mechanisms, but current treatments often perform poorly in this regard. The complexity of the cellular molecular mechanisms involved in cartilage repair is also a major obstacle. Insufficient activation of molecular signaling pathways such as TGF-β, BMP, and Wnt after cartilage injury leads to abnormal cellular behavior and environmental responses during repair. Hypertrophy or apoptosis (cell death) of chondrocytes often makes repair difficult and is further exacerbated by destruction of the extracellular matrix. Dysregulation of these cellular and molecular mechanisms makes the process of cartilage repair extremely slow and erratic, and it is difficult for existing therapies to effectively modulate these mechanisms to promote cartilage regeneration. Although some potential therapeutic options exist, such as cell-based stem cell therapy, tissue engineering, and gene therapy, overcoming the lack of blood supply to cartilage, the low regenerative capacity, the damage at the cartilage-bone interface, and the complexity of cellular and molecular mechanisms remains a central problem in articular cartilage repair. Notably, it was shown that interleukin-1 β (IL-1β)-induced exosomes (C-Exos) from human umbilical cord mesenchymal stem cells (HucMSCs) remodeled the pro-inflammatory microenvironment of osteoarthritis (OA), enhanced its anti-inflammatory effects and promoted cartilage regeneration. miRNA profiling and pathway analyses confirmed the ability of C-Exos to improve chondrocyte function and chondrogenic matrix generation and promoted macrophage polarization. Encapsulation of C-Exos within hyaluronic acid hydrogel microspheres (HMs) enabled sustained release and significantly improved the inflammatory microenvironment and cartilage regeneration in a rat OA model[20].

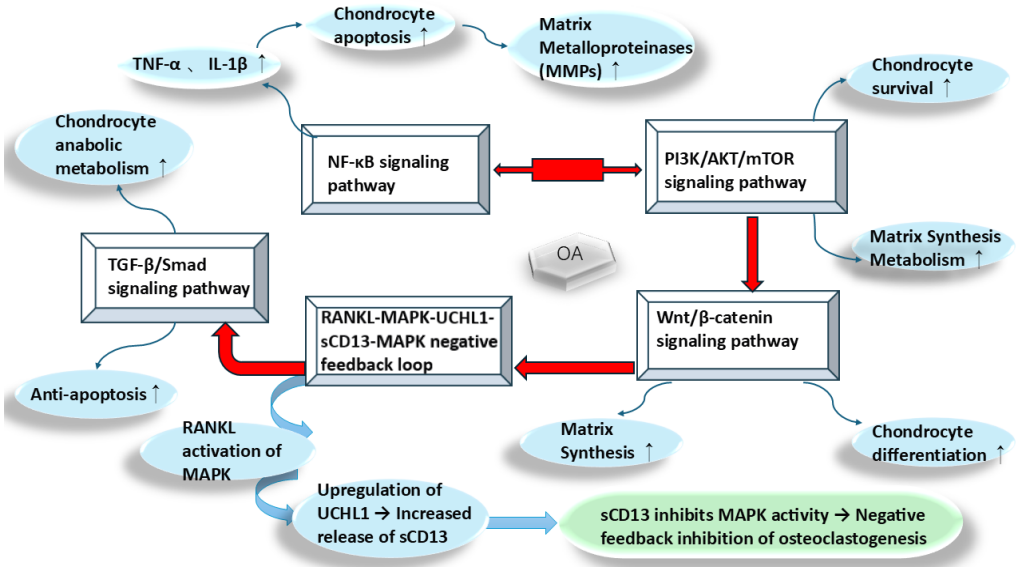

Figure 1. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), among others, further exacerbate cartilage degradation by promoting matrix degradation and inhibiting cartilage synthesis

In addition, features of the microenvironment of degenerative joint pathology that have a significant negative impact on the repair and recovery process of the joints include chronic inflammation, metabolic abnormalities, disruption of biological clock rhythms, cellular senescence, and activation of neural-osteocartilage coupling mechanisms, which together result in the degradation and damage of articular cartilage. In particular, chronic inflammation promotes the production of protein hydrolyzing enzymes, leading to degradation of the cartilage matrix, and also activates immune cells in the synovial membrane to secrete pro-inflammatory cytokines, creating an inflammatory cascade that sustains a chronic inflammatory environment. This inflammatory response further exacerbates the destruction of joint tissues and hinders the natural repair process of the joint. Second, studies have shown that intact (lateral tibial) cartilage is enriched with HomC or hypertrophic chondrocyte (HTC) types, whereas damaged (medial tibial) cartilage is enriched with prehypertrophic chondrocytes (preHTC), regulatory chondrocytes (RegC), and fibroblastic chondrocytes (FC)[21]. Metabolically, effector chondrocytes (ECs) primarily perform immune functions and elicit tissue inflammatory responses[22], the regulatory chondrocytes (RegCs), on the other hand, are active in a variety of signaling pathways, and the homeostatic chondrocytes (HomCs) are highly expressive of biological clock rhythm marker genes[23]. These imbalances in cellular metabolism may lead degenerative arthropathy into a vicious cycle. On the other hand, synovial fibroblasts develop degenerative changes earlier and to a greater extent than chondrocytes, a process that increases the transcription of senescence-associated secreted proteins (SASPs)and increases the expression and activity of matrix metalloproteinase MMP13, which ultimately leads to degenerative changes in synovial fibroblasts and degradation of the articular cartilage matrix. In addition, the activation of the nerve-bone coupling mechanism also plays an important role in the occurrence and development of bone degenerative diseases, and peripheral nerves can promote osteoarthritic degeneration by secreting a variety of neurotransmitters that act on a variety of osteoblasts or immune cells in the bone microenvironment. Together, these microenvironmental features not only lead to degradation and damage of articular cartilage,but also hinder the natural repair process of the joint. In recent years, the widespread application of functionalized innovative materials, such as biodegradable scaffolds, nanotechnology, and smart materials, has been able to regulate cellular behavior, improve cartilage regeneration, and facilitate tissue engineering at the molecular level, as well as to significantly improve the effectiveness of joint repair by modulating the local microenvironment and attenuating inflammatory responses. The application of these materials not only provides new solutions to overcome biological barriers in joint repair, but also provides more reliable support for long-term functional recovery and joint health.

3. Innovative Materials in Joint Repair

3.1 Biocompatible and Biodegradable Materials

Joint repair and replacement procedures are becoming more common as the population ages and the incidence of osteoarthritis increases. Biocompatibility is an essential requirement for any material used in joint repair procedures, ensuring that the material does not cause adverse reactions when in contact with living tissue. Biodegradable materials have the added advantage of being gradually absorbed by the body, thus avoiding the need for a second surgery to remove the implanted material. In recent years, bioceramics, such as bioactive glass, alumina, zirconia, calcium phosphate, and hydroxyapatite (HAp), have been widely used due to their excellent osteoconductivity and similarity to the inorganic composition of bone. These materials form an interfacial bond with human bone, stimulating bone composition and reducing the risk of implant failure. Biodegradable polymers and ceramics are already used in clinical settings, while magnesium-based biodegradable metals are a new class of materials still under development[24]. Changes in the surface structure of different materials can be observed in Fig. 2. A before and after treatment. After treatment, the surface of the material shows more pronounced structural features, such as changes in the distribution of particles or fibers. Such changes affect the physical, chemical or mechanical properties of the material, such as enhancing the strength of the material, improving its biocompatibility or adjusting its degradation rate. Degradation rate is another key factor to consider when designing scaffold materials. The degradation rate of the material should match the rate of new tissue formation and be gradually absorbed by the body over an appropriate period of time, while allowing the formation and maturation of new cartilage tissue to maintain joint stability and function. In terms of mechanical properties, the scaffold material should have stiffness and toughness similar to natural cartilage to withstand the stresses and impacts of daily activities. This is often achieved through material synthesis and processing techniques to ensure that the scaffold provides adequate support and stability in the joint. Despite the great potential of biodegradable scaffold materials for cartilage regeneration, a number of limitations remain, the balance between mechanical properties and degradation rate is a challenge as stiffness and toughness are often difficult to achieve simultaneously the modulation of cell growth and differentiation is also a key issue, the scaffold material needs to be able to promote the growth and differentiation of specific types of cells in order to form a functional cartilage

tissue. Fig. 2 B demonstrates significant differences in the surface structure of scanning electron microscopy (SEM) images of four different materials (AG, AG25SMu, AG50SMu, AG75SMu). Notably, Ajisaf et al.[25] prepared a novel gelatin-snail mucus hydrogel scaffold (AGSMu) for cartilage tissue repair using a freeze-drying method with an average pore size of 245 μm. FT-IR spectroscopy confirmed that snail mucus had been successfully introduced, which significantly enhanced the mechanical strength of the scaffolds by more than 80%, and that these scaffolds exhibited good biocompatibility and their controlled degradation behavior, which is expected to be an ideal matrix material for articular cartilage damage repair and regeneration.

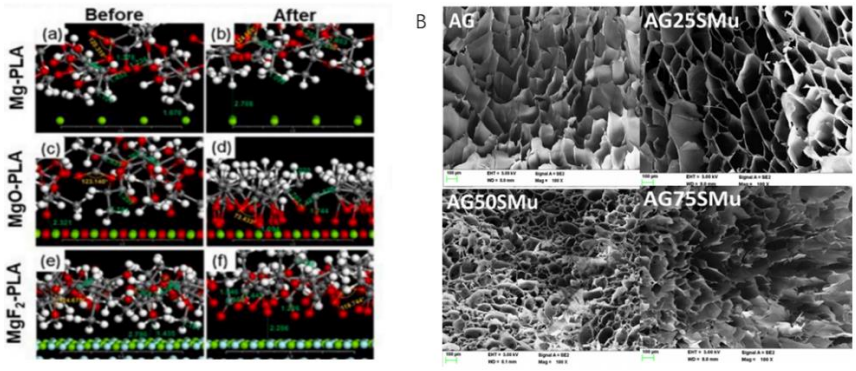

Figure 2. (A) The images of three different materials (Mg-PLA, MgO-PLA, MgF_2-PLA) before and after treatment are shown [24].(B) Comparison of scanning electron microscope (SEM) images of surface morphology of different materials [25]. Copyright 2024 KeAi, ACS APP LIED.

3.2 3D Printing and Personalized Joint Prostheses

3D printing technology, a revolutionary manufacturing process, has shown great potential for application in the field of orthopedics and joint prosthetics due to its ability to accurately manufacture complex structural components. This technology makes it possible to customize personalized implants based on a patient's specific anatomical structure and defect characteristics, thus meeting the need for individualized treatment[26]. In bone and joint repair, 3D printing technology is used in two main ways: firstly, to create personalized biological models and surgical guides, and secondly, to directly print biocompatible implants. Combined with medical imaging technologies such as CT and MRI, 3D printing is able to accurately replicate the anatomical structure of injured tissues, which in turn creates metal implants that meet the specific needs of the patient. These personalized implants not only reduce excessive mechanical strength and avoid stress-shielding effects, but also improve biocompatibility and functionality, increase cell and nutrient permeability, and promote angiogenesis and bone growth[27，28]. The process of porous Ti-Ta coating on the surface of Ti6Al4V acetabular cups by laser directed energy deposition (DED) technique can effectively form porous Ti-Ta coating on the surface of Ti6Al4V acetabular cups, which can improve its stability and functionality in orthopaedic implants, (Fig. 3A,B) the effect of BMP-2 on the migration of cells at different voltages: comparison of microscope images In the presence of BMP-2, the cell migration and distribution were more obvious, especially at 250 μC and 500 μC voltage.

In addition, 3D printing technology has been used to fabricate biodegradable scaffolds with specific pore structures, which provides suitable conditions for cell implantation and opens up new research directions for bone tissue engineering. Studies have shown that 3D printed poly(lactic acid)/hydroxyapatite (PLA/HA) composite scaffolds are capable of forming bone-like apatite in in vitro degradation experiments, and antimicrobial experiments have shown that scaffolds containing 30% HA + 5% chitosan (CS) + PCL have good antibacterial effects, and both in vitro and in vivo experiments have demonstrated the excellent bioactivity and ability to promote tissue regeneration of such scaffolds[29]. This composite scaffold has appropriate compressive strength and good osteogenic properties, providing a low-cost, stable, simple, and rapid method for achieving personalized printed bone repair scaffolds. Despite the many advantages of 3D printing technology in orthopedic applications, there are still some challenges. For example, the use of modeling software, operating methods of printing equipment, high demand for metallic implant materials, and the lack of relevant laws and regulations limit its further application. Conventional prostheses often lead to problems such as stress masking, wear and loosening due to mismatch with the patient's anatomy . To address these issues, researchers have adopted a variety of strategies.Ankush Pratap Singh et al.[30] The use of patient CT scan data to create a solid model of the femur and personalize it can be effective in reducing the rate of stress masking. (a), (b), and (c) in Fig. 3 C show the stress distribution in the proximal-lateral femoral region with different implants. The color changes from blue (low stress) to red (high

stress). (d) shows the side, posterior, and anterior views of the femoral implant, with the proximal-lateral femoral region (burgundy color) specifically labeled. As can be seen from the graphs, the Type 2 metal implant produced the highest average Von Mises stress in the proximal-lateral femoral region. This individualized design not only improves the fit of the prosthesis to the patient's bone structure, but also helps to distribute the stress and reduce wear. The study showed that low-stiffness implantable polyether ether ketone (PEEK) hips fabricated by fused deposition modeling showed more natural stress distribution, reduced stress shielding (up to 95%) and slowed the rate of bone loss (up to 72%) compared to Ti6Al4V implants. The stiffnesses of the titanium and PEEK implants were 2.76 kN/mm and 0.276 kN/mm, respectively.The simulation results showed that the PEEK implant is generally a safer joint for daily activities; however, it is prone to failure during high-intensity activities due to the presence of large stress peaks in specific areas. Overall, the use of PEEK materials can effectively reduce the degree of stress shielding and help mitigate the bone loss problem[31]. By optimizing the design using a sacral tray, the peak strain on the sacral pedicle screws could be reduced by 18.6%, while the maximum strain of the prosthesis increased by 60.7%. The addition of the lumbosacral pedicle strip system further reduced the maximum strains on the sacral pedicle screws and the entire prosthesis by 30.2% and 19.4%, respectively[32]. Second, advances in materials science have opened up new possibilities for surface modification of prostheses. Surface microtexture modifications, such as micro-pit designs, can store wear debris and provide secondary lubrication, thereby increasing the wear resistance of the material[33]. In addition, the application of wear-resistant coatings such as Titanium Nitride (TiN), Titanium Niobium Nitride (TiNbN), Zirconium Oxide (OxZr), and Zirconium Dioxide Nitride (ZrN), while coatings under investigation are Diamond-Like Carbon (DLC), Silicon Nitride (SiN), Chromium Nitride (CrN), and Tantalum-Based coatings, significantly improves the wear-resistant properties of the prosthesis[34]. Notably, hydroxyapatite (HAP) nanocoatings applied to titanium alloys (e.g., Ti6Al4V) have been widely used as artificial bone implant materials in recent years due to their osseointegration properties, bioactivity, and good biocompatibility. However, problems such as the brittle nature of HAP, its low mechanical strength, and its poor adhesion to the metal substrate limit its service life and overall bioactivity[35]. On the other hand, antibiotic-coated collagen-hydroxyapatite scaffolds adjusted antibiotic release kinetics utilizing an iterative approach of freeze-drying and chemical cross-linking, resulting in a hierarchical dual-release system capable of clearing infection and promoting fracture healing[36]. Implantation of strontium-enhanced amorphous calcium phosphate (Sr-ACP) particles into collagen/collagen-magnesium-hydroxyapatite (col/col-Mg-Hap) osteochondral scaffolds improves subchondral bone repair[37]. Fig. 3. D demonstrates that the effects of ACP and Sr-ACP on new bone formation and tissue mineralization can be assessed by tissue sections under different processing conditions. The application of computer technology, image processing, and artificial intelligence techniques has made it possible to observe the characterization of the process, form, and extent of wear. The combined and comparative analysis of these techniques provides additional solutions for prosthetic wear behavior.

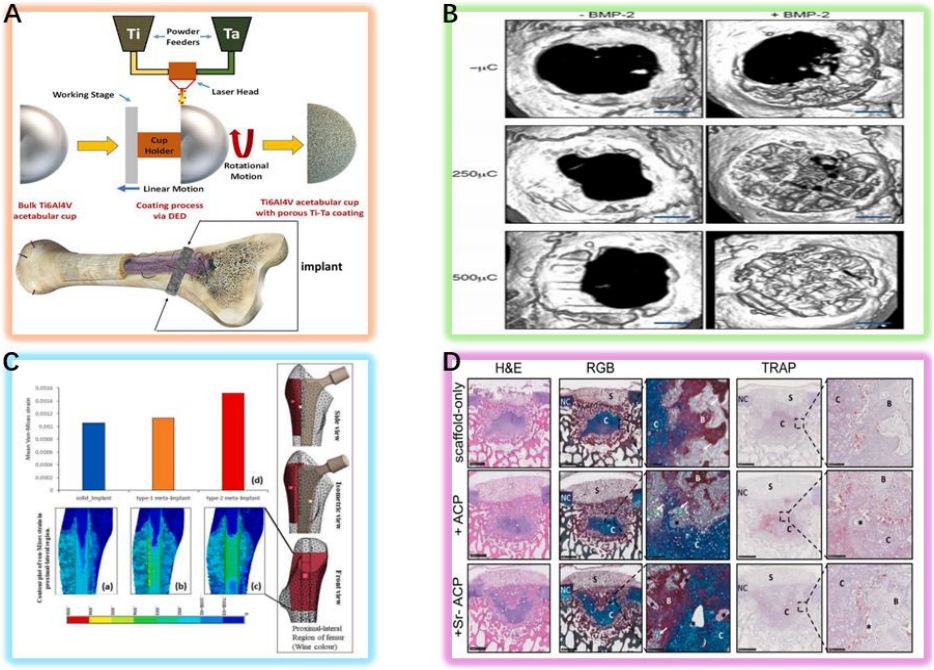

Figure 3. (A) Application of laser directed energy deposition technique to Ti6Al4V acetabular cups [27]. (B) Synergistic effects of voltage and BMP-2 on cell migration: microscopic image analysis [28]. (C) Stress

Distribution in Femoral Implants, Effect of Different Types of Implants on Von Mises Stresses [30]. (D) Optimization of tissue engineering scaffolds, promotion of new bone formation and mineralization by ACP and Sr-ACP [37]. Copyright 2021,2023, 2024 ELSEVIER

3.3 Ceramics and Composites

In the application of joint prostheses, ceramic materials are favored for their high hardness, high wear resistance and good biocompatibility. However, the high brittleness of ceramic materials, which is prone to rupture upon impact, limits their application in joint prostheses. In order to optimize the application of ceramic materials in joint prostheses, Shao-Meng Wen et al.[38] improved the impact toughness of ceramic-polymer composites through a bionic structuring strategy coupled with a graded structure and a twisted thin-wood laminated (Bouligand) structure, and prepared bio-based ceramic-polymer composites with gradual fabrication gradient Bouligand structure by in-situ impregnation method on the resulting products, and showed that the introduction of the gradient structure improves both the peak damage load and the total energy absorption capacity of the composites. Bioceramics have good chemical resistance, bioactivity and anticorrosion protection properties. Surface-modified bioceramics for metal implants can improve their biomedical properties and corrosion resistance. Surface modification techniques, such as chemical vapor deposition (CVD), physical vapor deposition (PVD), sol-gel, and electrochemical deposition, can be used to improve the mechanical properties of metal implants, corrosion resistance, antimicrobial resistance and biocompatibility[39]. These treatments not only reduce the generation of wear particles, but also reduce the risk of osteolysis and prosthesis loosening due to wear particles. It is worth noting that the UV curing-assisted droplet writing (DIW) technique allows for the preparation of dense, crack-free and high-performance zirconia-based composites with ordered layers of alumina flakes, and the development of new composites, zirconia-toughened alumina-tempered composite ceramics (ZTAs), offers new possibilities for improving the strength and toughness of ceramic materials[40]. This composite material outperforms conventional alumina ceramics in a number of ways and is seen as a potential replacement for alumina ceramics in the future.

3.4 Surface Coating and Functionalized Materials

The optimization of antimicrobial, anti-wear and bioactive coating technologies in the research and application of surface coatings and functionalized materials is essential to prolong the service life of prostheses and improve their biological function. Antimicrobial coating technologies are key to preventing prosthetic infections. Prosthetic infections can be prevented either by precise release of antimicrobial agents or by using contact killing strategies, or by creating antimicrobial surfaces on implants and devices. These antimicrobial coatings can employ embedded antimicrobial nanoparticles, functionalized polymers, and inorganic-organic hybrid materials . For example, sea urchin-like microporous organic polymer composites (Ag2O@UMOPs) modified by silver dioxide showed excellent bacterial inhibition against Escherichia coli and Staphylococcus aureus[41]. The boron grafted urethane composite coating (BWOB) consisting of three morphologies of Bi2WO6 nanoparticles in the form of nanosheets, flowers, and microspheres and boron grafted urethane (ITB) has excellent bacteriostatic and anti-silicone algal adhesion properties, reaching 95.43% and 98.38% against Escherichia coli and Gluconococcus aureus, respectively, and 98.62% against Acropora pinnatifida[42]. Furthermore, in a study by Kavian Cooke et al.[43] a hard Ni coating containing nanoscale Al2O3 and TiO2 particles was embedded into the surface of a Ti-6Al-4V alloy by a surface modification technique using an electric arc during inert tungsten gas welding. Microstructural analysis revealed the presence of a hard martensitic structure driven by surface critical chemical modifications and the presence of nickel at a depth of about 2 mm, leading to grain size reduction and strengthening. The hardness of the treated layer increased by more than 180% and the wear resistance improved by 100%. The effect of strontium-containing montmorillonite (Sr-MMT) coating on magnesium-calcium alloys was found to have optimal corrosion resistance for bone repair. Both in vitro studies and in vivo experiments showed that the Sr-MMT coating has good biocompatibility and promotes osteoblast proliferation and differentiation as well as adherence to the wall, and this coating technique provides a new strategy for degradable Mg alloys that combine good corrosion resistance and biocompatibility[44]. Bioactive coating technology is also important for improving the biocompatibility of prostheses and promoting tissue integration. Yihang Gao et al.[45] showed that genetically engineered proteins, such as Mfp-AFP, which combines mussel adhesion proteins and antifreeze proteins, exhibit good biocompatibility and have the potential to be used in anti-icing coatings and biomedical materials. Fig. 4 well demonstrates that the properties of materials can be significantly optimized in the field of surface coatings and functionalized materials by accurately controlling the material's composition, structure and preparation process. , the properties of materials can be significantly optimized. These techniques not only improve the mechanical properties and stability of the materials, but also enhance their potential for biomedical applications.

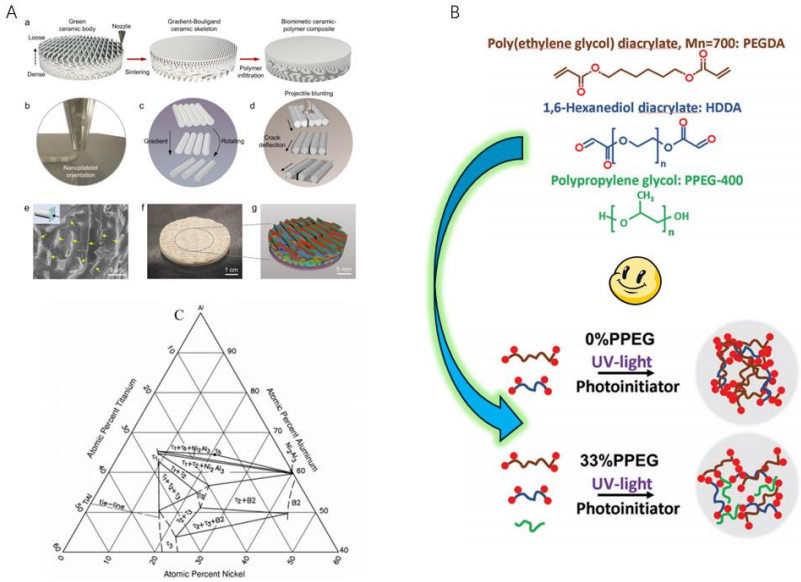

Figure 4. (A) Preparation process and structural characterization of biomimetic ceramic-polymer composites. a Shows the steps from loose green ceramic bodies through nozzle molding, sintering to form a gradient-Bouligand ceramic skeleton, and finally polymer infiltration to form biomimetic ceramic-polymer composites. b Shows the nanosheet orientation, which affects the final properties of the material. c Shows the process of rotational and gradient changes to control the structure of the material. d Illustrates the process of particle grooming, including crack deflection, which helps to improve the mechanical strength of the material. e Provides an electron microscope image of the nanosheet orientation, which shows the microstructure of the material. f Demonstrates the macroscopic appearance of the final product. g Provides a detailed view of the internal structure of the material, showing the alignment and size of the nanosheet[38]. (B) Schematic representation of polymer network formation by monomer polymerization during ultraviolet (UV) light curing at different monomer contents [40]. (C) Phase diagram analysis of the Ni-Al-Ti ternary alloy system, describing the phase compositions of the nickel (Ni), aluminum (Al), and titanium (Ti) ternary alloy system at different compositional ratios [43]. Copyright 2023, 2024 Wiley; 2022 Springer Nature.

4. Biotechnology in Joint Repair and Regeneration

Biotechnology in joint repair and regeneration is an interdisciplinary research field that combines research advances in several disciplines, including biomaterials, cell biology, molecular biology, and regenerative medicine, to provide new directions and possibilities for the treatment of articular cartilage injuries. The development of smart biomaterials provides new strategies for the repair and regeneration of articular cartilage. These materials are capable of responding to exogenous or endogenous stimuli and modulating cell behavior by controlling the release of drugs or bioactive factors, thus providing an excellent microenvironment for tissue repair and regeneration. Xiaoqing Lu et al. [46]demonstrated that the smart drug release system is able to respond to exogenous or endogenous stimuli in a specific and predictable manner to promote chondrocyte proliferation and differentiation. Second, carbonic anhydrase IX siRNA (siCA9) modulates inflammatory microenvironmental regulation to promote the role of Kartogenin (KGN)-induced cartilage-directed differentiation of Mesenchymal Stem Cells (MSCs) A novel strategy for the role of carbonic anhydrase IX siRNA (siCA9) modulated inflammatory microenvironmental regulation to promote cartilage-directed differentiation of Mesenchymal Stem Cells (MSCs) was demonstrated to be effective in reducing synovial inflammation and OARSI scores by BMSCs in combination with AHK-CaP/siCA9 NPs in an OA mouse model, suggesting that it can effectively inhibit synovial inflammation and promote cartilage regeneration[47]. In a study of cartilage regeneration targets, Xiaocui Wei et al.[48] screened 2,040 FDA-approved drugs and found that α-adrenergic receptor antagonists, particularly phentolamine, stimulated cartilage formation and prevented cartilage hypertrophy. Phentolamine also prevented cartilage degeneration and promoted hyaline cartilage-like cartilage regeneration without causing fibrosis. Mechanistically, α2-AR signaling triggered the proliferative effects of chondrocyte hypertrophy through cGMP-dependent protein serine kinase (SLPI) production, and SLPI deficiency resisted cartilage degeneration and helped large cartilage defects heal. Of interest is that tissue-engineered cartilage offers a new therapeutic avenue for articular cartilage repair, and a large number of products are already being used in preclinical trials. Tissue-

engineered cartilage includes the organic integration of chondrocytes, signaling stimuli, and scaffolding materials, in vitro culturing to improve its overall biochemical and biomechanical capabilities, and the use of fixation techniques to enable it to better fill the defect. In terms of clinical applications, osteochondral grafting techniques and chondrocyte transplantation have been shown to be effective for specific types of cartilage defects. Autologous osteochondral grafting is indicated for smaller osteochondral defects, while allogeneic osteochondral grafting is indicated for larger defects. Autologous chondrocyte transplantation (ACI) and matrix-induced autologous chondrocyte transplantation (MACI) are indicated for cartilage defects that do not reach the subchondral bone at depth and are graded at grade 3 to 4[49]. In addition, MSCs play an important role in the field of regenerative medicine and are considered to be one of the most promising seed cells in achieving cartilage repair and regeneration.

4. The Role of Stem Cell Technology in Joint Repair

Stem cell technology has received much attention in recent years for its potential in the medical field. As the limitations of traditional treatments, such as surgery and medication, are becoming apparent, stem cells, as an innovative treatment that promotes tissue regeneration and repair, have emerged as a potential avenue for addressing bone and joint trauma. Stem cells are unique in their ability to self-renew and differentiate to repair and regenerate damaged joint tissues, especially important structures such as cartilage, bone, ligaments and tendons. Stem cells are capable of differentiating into many types of mature cells under appropriate conditions. Depending on their differentiation potential, stem cells are mainly divided into two categories: embryonic stem cells and adult stem cells. Embryonic stem cells are totipotent and capable of differentiating into almost all types of cells, but their clinical application is somewhat limited due to their origin and ethical issues. Adult stem cells, on the other hand, are derived from adult tissues, usually from bone marrow, adipose tissue, synovial fluid and other parts of the body, and have become the main type of stem cells used in joint repair due to the relative simplicity of obtaining materials and the elimination of ethical controversies. The key advantage of stem cell technology in joint repair is its strong regenerative ability, especially for cartilage repair. Articular cartilage is a tissue with low regenerative capacity, which is often difficult to be restored by traditional treatment methods. However, stem cells can promote cartilage regeneration by differentiating into chondrocytes (osteoblasts) and accelerate the repair of the surrounding tissues through the secretion of growth factors and cytokines. In addition, stem cells are able to regulate the immune response and reduce inflammation, further improving joint function. In the treatment of some degenerative joint diseases, such as osteoarthritis, umbilical cord mesenchymal stem cells (MSCs) have been used to treat osteoarthritis of the knee, and the WOMAC scores have shown significant improvements in pain and function[50]. In addition to cartilage repair, stem cells also show an important role in bone repair and ligament and tendon repair. In the treatment of bone defect or fracture,stem cells are able to differentiate into osteoblasts and promote the regeneration of bone tissues, especially in the treatment of diseases such as femoral head necrosis. Statistical analysis shows that the age of the patient is significantly correlated with the results of his/her active treatment, which suggests that autologous bone marrow cell implantation is an effective and safe method. The majority of patients (87.5%) reported complete relief of pain, while 10.42% showed significant improvement in symptoms[51]. For ligament and tendon injuries, stem cells are also able to promote the repair of these tissues and improve motor function by differentiating into the appropriate cell types, characteristics that make stem cell technology promising for application in joint trauma, degenerative diseases and the aging process .This minimally invasive treatment not only reduces the patient's postoperative recovery time, but may also be effective in delaying the loss of joint function and delaying or even avoiding joint replacement surgery. However, although stem cell therapy has shown promising results in clinical studies, it still faces some challenges. The process of stem cell extraction, processing and application has not yet been fully standardized, leading to variations in results in different studies and clinical applications. Secondly, the long-term effects of stem cell therapy are not yet clear, especially in terms of the durability of tissue repair, which still needs to be supported by more clinical data. In addition, safety issues that may be triggered by stem cells, such as tumor formation or immune rejection, remain a major concern for the medical community. In terms of avoiding immune rejection and achieving autologous cell repair, induced pluripotent stem cells (iPSCs) offer significant advantages in terms of their prospects for biomedical applications. iPSCs enable autologous-sourced cellular therapies by reprogramming a patient's own somatic cells into pluripotent stem cells. iPSCs are autologous by virtue of their autologous properties, which allow the cells, when implanted into a patient's body, to be recognized by the immune system as the “self”, thus effectively avoiding immune rejection[52]. In addition, in terms of quality control and standardization, iPSCs can be clonally expanded and differentiated under strictly controlled conditions, ensuring consistent and high quality cell products and reducing the risk of immune rejection due to cellular variation . Creating a library of iPSC lines covering a wide range of human leukocyte antigen (HLA) types can minimize the risk of immune rejection through HLA matching, making iPSCs safer and more effective for treatment . The safety and efficacy of iPSCs-derived

cell products are continuously being evaluated in preclinical studies and clinical trials covering the potential of using iPSCs to treat a wide range of diseases such as Parkinson's disease, diabetes, and retinal degeneration[53]. Studies have shown that electric field stimulation (ES) combined with neurotrophic factor (NF) significantly improves the efficiency of generating functional neurons from human iPSCs and increases inter-synaptic interconnections, advancing the understanding of neuronal development and providing new possibilities for modeling neurodegenerative diseases. Notably, gene editing, through CRISPR technology, can further improve the targeting and differentiation potential of stem cells, cross tumor microenvironmental barriers, overcome graft-versus-host-disease (GvHD) and lymphatic depletion, and optimize their effects in joint repair[54]. Meanwhile, by combining with other regenerative medicine techniques, such as platelet-rich plasma (PRP) or growth factor therapy, stem cell therapy is expected to achieve better efficacy in joint repair, promoting functional recovery and improved quality of life for patients.

5. Exploring the Application of Gene Therapy and Gene Editing Technology in Joint Repair and Regeneration

In the study of cartilage regeneration, gene editing of chondrocytes using CRISPR/Cas9 technology can effectively enhance their self-repairing ability, thus improving cartilage repair. Cartilage tissue usually has limited self-repairing ability, especially in joint injury or degenerative diseases (e.g., osteoarthritis), and the repairing ability of chondrocytes is even more insufficient.CRISPR/Cas9 technology can accurately modify key genes related to chondrogenesis and maintenance, such as Sox9, Aggrecan, and Col2A1. By editing these genes, the proliferation, differentiation and synthesis of chondrocytes can be enhanced, enabling them to better maintain the structure and function of cartilage. It was shown that activation of Sox9 and inhibition of RelA by applying CRISPR-dCas9 technology enhanced the chondrogenic induction potential of mesenchymal stem cells (MSCs) and reduced the inflammatory response. This modification improved cartilage integrity, reduced catabolic enzyme production, and suppressed immune cells, leading to a significant reduction in cartilage degradation and relief of OA pain[55]. In addition, CRISPR/Cas9 can be used to knock down some genes associated with cartilage degradation. Knockdown of the TGF-β-activated kinase 3-associated structural domain 1 kinase (TAK1) gene in chondrocytes to construct inflammation-resistant cartilage by CRISPR-Cas9 technology can improve their resistance to pro-inflammatory and catabolic NF-κB pathway signaling. TAK1 KO chondrocytes loaded with sodium hyaluronate hydrogel vesicles were able to produce abundant chondrocyte extracellular matrix proteins and better integrate into natural cartilage even under inflammatory conditions, and in vivo experiments showed that these engineered chondrocytes recruited fewer pro-inflammatory M1 macrophages due to reduced cytokine secretion[56]. In the application of gene therapy, the existing gene delivery technologies mainly include two types of viral vectors and non-viral vectors. Genetically engineered viral vectors and organic matrix non-viral nano-delivery systems address the limitations of traditional drug delivery systems such as toxicity and adverse reactions. Viral vectors, such as adenoviruses, lentiviruses, and adeno-associated viruses, are capable of efficiently introducing genes into cells, and have been approved for clinical applications in treatments for cancers, hematologic disorders, inherited metabolic disorders, and neurodegenerative disorders; however, the potential for immune response and gene integration issues have limited their widespread use. Non-viral vectors, such as liposomes, nanoparticles, and polymeric vectors, on the other hand, offer better biocompatibility and lower immune response, and ionized lipid nanoparticles (CrLNPs) can be finely tuned for efficient delivery of CRISPR / Cas9 ribonucleoprotein (RNP) in vitro and in vivo. These CrLNPs enable efficient gene editing of a wide range of cancer cell lines and tumor tissues, providing a low-risk alternative to viral delivery methods[57]. In addition, to address possible side effects and immune responses in gene therapy, Lorenzo D'Antiga et al.[58] evaluated gene therapy using an adeno-associated virus serotype 8 vector encoding the UGT1A1 gene, with two patients receiving a dose of 2 × 1012 vg/kg (number of copies of the vector genome per kilogram of body weight), and three receiving a dose of 5 × 1012 vg/kg. kg. No serious adverse events were reported, but elevated liver enzymes were observed in four patients and may be related to the immune response. Patients in the high-dose group had bilirubin levels below 300 μmol/L and did not require phototherapy, indicating that the therapy was effective. Gene therapy can effectively repair cartilage tissue damage and slow down the process of cartilage degradation through molecular-level interventions and has shown great potential for clinical application. With the continuous optimization of gene delivery technology and therapeutic methods, gene therapy is expected to become one of the main therapeutic tools in the field of joint repair.

6. The Role of Growth Factors and Biological Factors

In medical research, cell growth factors significantly regulate the biological behavior of chondrocytes, and these factors promote chondrocyte proliferation, differentiation, and repair through a complex signaling network, which is essential for maintaining the health and function of articular cartilage. Among them, members of the

transforming growth factor-β (TGF-β) family play key roles in chondrocyte proliferation, differentiation, and extracellular matrix synthesis.TGF-β1 is particularly capable of promoting chondrogenesis in MSCs and supporting chondrocyte function by regulating the expression of Sox9 and COL2, ACAN, TGFBR1A, and TGFBR2[59,60]. The TGF-β signaling pathway promotes osteogenic progenitor cell enrichment and differentiation in the early stage, and its signaling upregulation positively regulates Sox9 expression and affects the proliferation level of condylar chondrocytes. In the late stage, TGF-β negatively feedback regulates osteoblast differentiation and mineralization, and interacts with the Wnt/β-linker protein signaling pathway to inhibit osteoblast differentiation and induce chondrogenesis . Bone morphogenetic proteins (BMPs) activate the Smad signaling pathway by binding to cell surface receptors, thereby regulating the expression of target genes.BMPs promote the differentiation of mesenchymal stem cells (MSCs) to chondrocytes and induce the synthesis of cartilage matrix, such as type II collagen and proteoglycans. On the other hand, BMPs regulate chondrocyte proliferation and hypertrophy by inhibiting the FGF signaling pathway, thus playing an important role in endochondral osteogenesis[61]. Insulin-like growth factor (IGF) promotes chondrocyte mitosis and synthesis of cartilage matrix components through its receptor activation of the downstream PI3K-Akt and MAPK signaling pathways .IGF-1 synergistically interacts with BMPs to further enhance chondrocyte anabolism and differentiation[62]. FGF2 (basic fibroblast growth factor), a member of the fibroblast growth factor (FGF) family, is a mitogen of chondrocytes that promotes chondrocyte proliferation and directs their differentiation to mature chondrocytes.FGF supports chondrocyte proliferation and differentiation by activating its surface receptor, which promotes the expression of cell-cycle-related genes.The Wnt/β-catenin signaling pathway plays a key role in the osteogenic differentiation of MSCs and also affects chondrocyte function. The Wnt/β-catenin (Wnt/β-catenin) signaling pathway plays a key role in the osteogenic differentiation of MSCs and also affects chondrocyte function.Wnt signaling activates the expression of downstream genes, such as cyclin D1 and c-myc, which are involved in cell cycle regulation and cell proliferation, by stabilizing the β-catenin protein, facilitating its entry into the nucleus, and binding it to TCF/LEF transcription factors. proliferation. In addition, the Wnt/β-catenin pathway affects osteoblast differentiation and proliferation by regulating the expression of Runx2.These growth factors work together to promote the healthy development of cartilage tissue and repair after injury by precisely regulating the behavior of chondrocytes[63]. By modulating the levels of these growth factors or their signaling pathways, the proliferation, differentiation and repair of chondrocytes can be promoted, providing a potential therapeutic strategy for the treatment of cartilage injuries and joint diseases .

In the field of regenerative medicine, the design of growth factor delivery systems is critical for tissue repair and regeneration, and nanotechnology and microcarrier-based delivery systems play an important role in improving the stability, targeting, and therapeutic efficacy of growth factors. Nanocarriers such as liposomes and polymeric nanoparticles provide a protective environment in vivo, preventing growth factors from enzymatic degradation and reducing their inactivation in the hostile environment of the body, and can also control the rate of release of growth factors for sustained and stable therapeutic efficacy. Increased targeting is achieved by modification of the surface of the nanocarriers with specific ligands or antibodies that specifically recognize and bind to the receptors on the target cells, allowing for precise delivery of the growth factors to the site of the lesion[64]. This targeted delivery not only reduces non-targeted effects but also reduces systemic side effects and improves the therapeutic index of growth factors . In addition, the use of microcarriers has shown great potential in improving the therapeutic efficacy of growth factors. microcarriers can provide uniform and controlled release of growth factors, and microcarriers fabricated by microfluidic technology are capable of sequentially releasing growth factors to mimic the time-release profiles required during natural tissue repair. the use of bioscaffolds and engineered biomaterials, which mimic the extracellular matrix (ECM), can enhance the biological activity and differentiation potential of growth factors at the target site[65,66]. Nanotechnology- and microcarrier-based delivery systems have significantly improved the stability, targeting, and therapeutic efficacy of growth factors by protecting them from degradation, improving the precision of targeted delivery, and controlling release, which not only provide new strategies for the treatment of a wide range of diseases and injuries, but also point to the direction for future research as well.

7. Interdisciplinary Fusion - Combining Innovative Materials and Biotechnology

7.1 Nanotechnology Meets Smart Materials

In joint repair, nanomaterials show great potential due to their unique physical, chemical and biological properties. The large specific surface area and controllable structure of nanomaterials give them an advantage in improving the strength, toughness and biocompatibility of materials. Through nanotechnology, the surfaces of materials can be precisely modified to improve their biological response in vivo. For example, nanoparticles can improve therapeutic efficacy by modulating drug release while reducing drug toxicity. For the regeneration of articular

cartilage, nanomaterials can effectively mimic the microstructure of cartilage, promote cell growth and differentiation, and thus improve the efficiency of cartilage repair. nanocomposite microgel assemblies with microporous structure, injectability, tissue adhesion, and furoic acid contractile peptide (KGN) slow release. The cyclodextrin nanoparticle-bone marrow mesenchymal stem cell (BMSC)-loaded microgel system containing KGN was prepared by a droplet microfluidic device and ultraviolet cross-linking, and used for repair of cartilage defects in a rabbit knee injury model, and the experimental results showed that the newborn cartilage had typical synovial cartilage properties, which showed a good prospect for application in the field of cartilage regeneration[67]. Meanwhile, the role of smart materials in joint repair has been increasingly emphasized. Smart materials are a class of materials that can undergo self-regulation or self-repair in response to external stimuli (e.g., temperature, pH, magnetic field, etc.). In joint repair, scaffolds made with smart materials can adaptively adjust their properties according to changes in the tissue environment. In addition, smart materials can regulate the release of biological signals and promote cell proliferation, migration and differentiation, thus accelerating the regeneration of cartilage and bone tissue. Hydrogels synthesized from hyaluronic acid-polyacrylic acid (HA-pAA) combined with poly (lactic acid-poly(glycolic acid)) (PPM) microcapsules (PPMMs) containing glutathione (GSH) and iron oxide nanoparticles (IOs) with pore structures enable two-stage release of GSH, promote hydrogel self-repair and immobilize chondrocytes. Hydrogels containing chondrocytes can be delivered to the site of injury through the CD44 receptor on the hyaluronic acid polymer chain, which is guided using its internal magnetic field[68].

7.2 Cell-Material Synergies

In addition, cell-material synergy is one of the key factors in joint repair. Through well-designed cell carrier materials, a suitable microenvironment can be provided for stem cells to promote their adhesion, proliferation and differentiation, thus accelerating the process of tissue repair. The use of biodegradable scaffold materials can provide the necessary mechanical support for stem cells during the repair process, and with the advancement of the repair process, the scaffold materials are gradually degraded and eventually replaced by newly generated tissues. The surface properties of scaffold materials, such as pore structure and surface chemical functional groups, can regulate cell behavior. In a study by Leisha Cui et al.[69], an injectable degradable organic-inorganic hybrid hydrogel composed of polyhedral oligomeric silsesquioxanes (POSS) with a core of tricalcium phosphate and sugars was used as a cartilage scaffolding material, which was able to enhance the adherence of stem cells and resisted cyclic compression, and promoted their directed differentiation into chondrocytes which enhances cartilage repair. The interaction between stem cells and materials is not limited to physical contact, but also involves more complex biological reactions. In addition, scaffold materials can effectively transmit biological signals to promote the directed differentiation of stem cells into chondrocytes, thus achieving more efficient and precise joint repair. For example, SIM@CACM microgel scaffold can slowly release stabilized simvastatin (SIM) to recruit bone marrow mesenchymal stem cells (BMSC), and its hydrophilicity and high specific surface area are conducive to the rapid adherence, proliferation and infiltration of BMSC. Through the integration of nanotechnology, smart materials, 3D printing technology and cell-material synergy, the field of joint repair is moving towards a more personalized and precise treatment. The integration and innovation of these technologies not only bring new therapeutic hope for joint disease patients, but also provide more research directions and practical opportunities for related basic research and clinical applications.

Table 1. Evaluation of the effectiveness and safety of different techniques in cartilage restoration, conclusions.

Technology/material category	Evaluation of efficacy	Security Assessment
bio-materials	Promotes cartilage or bone tissue repair, is biocompatible and enhances healing speed. Studies have shown that biomaterials improve healing by approximately 30-50%.	Biocompatibility is good with no immune reaction or rejection in 99% of patients. Anaphylactic reactions may occur in rare cases (<1%).
Biotechnology, Biocompatible and Biodegradable Materials	Biotechnology improves the efficiency of cartilage repair and tissue regeneration by about 40-60%. Studies have shown that biodegradable materials	Certain biotechnologies, such as gene transduction, may trigger the risk of an immune response or foreign body reaction, and about 3%-5% of patients may experience adverse reactions.Due to the uncontrollable nature of the degradation process, incomplete degradation or

	increase the efficiency of repair by 35-55%.	adverse reactions may sometimes result (2%-3%). However, in most cases, degraded materials do not leave behind harmful substances.
Stem cell technology	Stem cells are able to increase the efficiency of cartilage regeneration and treat cartilage damage with a repair rate of 70-85%. For example, stem cells are 78% effective in treating knee osteoarthritis.	Long-term use of stem cell technology may result in an increased risk of tumorigenesis, with approximately 1-2% of patients potentially experiencing tumorigenesis or immune rejection.
Gene therapy and gene editing technology	Gene therapy can significantly improve joint repair, and studies have shown that gene editing for repairing cartilage damage has a 75-85% success rate.	As gene editing involves genome modification, there is a high risk (5%-10%) that unintended gene mutations may occur.
3D Printing and Personalized Joint Prosthesis Technology	Individualized prostheses are better adapted to the patient's joint, with a 25%-45% increase in the success rate of the repair and a reduction in postoperative complications.	3D printing technology and personalized prostheses are safer, but there is still a need to focus on the selection and quality of the printed material, and the prosthesis rejection rate is less than 1%.
Nanotechnology and Smart Materials	Nanotechnology enhances the bioactivity of materials and promotes cartilage repair. Studies have shown that nanomaterials can enhance repair by 25-50%.	Nanoparticles may accumulate in the body and cause immune responses or toxicity, safety data are still incomplete, and long-term effects are unknown.
Cell-material synergies	The synergistic effect of the cells and materials significantly improves the efficiency of cartilage regeneration, and the combined technique increases the efficacy by 40-70%.	The synergistic effect of the cells and materials significantly improves the efficiency of cartilage regeneration, and the combined technique increases the efficacy by 40-70%.

This paper provides an in-depth review of research advances in the field of joint repair and regeneration by integrating innovative materials and biotechnology, focusing on the integrated application of multidisciplinary technologies such as stem cell therapy, biomaterials, 3D bioprinting, and genetic interventions, as well as their clinical translational potential. The findings suggest that mesenchymal stem cells (MSCs) exhibit significant potential in cartilage regeneration and inflammation relief, and preliminary clinical trials have confirmed their effectiveness in improving joint function and reducing pain. Biomaterial-based repair strategies, such as collagen scaffolds incorporating hydroxyapatite, have shown promising results in animal models and offer a low-cost, environmentally friendly solution for joint repair. In addition, the development of 3D bioprinting technology has opened up new possibilities for personalized joint repair, enabling the fabrication of customized cartilage scaffolds based on the anatomical characteristics of patients, which further promotes the clinical application of tissue engineering. The application of nanotechnology and smart biomaterials has also provided new ideas for drug delivery and tissue repair, significantly improving therapeutic efficacy by protecting growth factors from degradation and enhancing targeted delivery. However, the field of joint repair and regeneration still faces many challenges. The effectiveness of stem cell therapy is affected by the source of stem cells, the mode of administration, and the individual differences of patients, and its stability and standardization need to be improved; gene therapy still needs to be further improved in terms of the efficiency of gene delivery, targeting, and the safety of immune response. The integration of materials, stability of mechanical properties and long-term compatibility with natural tissues in biomaterials and tissue engineering still need to be solved. In addition, the potential toxicity and biocompatibility issues of nanotechnology need to be studied in depth. By optimizing the source and application methods of stem cells and combining gene editing techniques to improve their targeting and differentiation potential, it is expected to further enhance the effectiveness of joint repair. Advances in single-cell technologies, such as single-cell sequencing and time-of-flight mass spectrometry flow cytometry, have enabled

detailed molecular characterization of human joint tissues, providing valuable insights into soft-tissue engineering strategies and therapeutic interventions for chronic arthritis, such as osteoarthritis and rheumatoid arthritis[70]. Meanwhile, the development of efficient drug delivery systems and tissue engineering scaffolds by utilizing the properties of nanotechnology and smart materials will provide stronger support for joint repair. In addition, the continuous advancement of 3D bioprinting technology will provide a broader application prospect for personalized joint repair. Interdisciplinary collaboration and innovation are the key to advancing the field of joint repair and regeneration. By integrating the research results from various disciplines, it is expected that more effective treatment options will be brought to patients with joint diseases, which will significantly improve their quality of life and reduce the burden of healthcare on the society.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

None declared.

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Ethical approval

Not required.

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