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REVIEW

Nanotechnology-Enhanced Pharmacotherapy for Intervertebral Disc Degeneration Treatment

Shaoyan Shi, Xuehai Ou, Chao Liu, Rui Li, Qianjin Zheng, Leiming Hu

Department of Hand Surgery, Honghui Hospital, Xi'an Jiaotong University, Xi'an Honghui Hospital North District, Xi'an, Shaanxi, 710000, People's Republic of China

Correspondence: Leiming Hu, Department of Hand Surgery, Honghui Hospital, Xi'an Jiaotong University, Xi'an Honghui Hospital North District, Xi'an, Shaanxi, 710000, People's Republic of China, Email huleiming0506@163.com

Abstract: Intervertebral disc degeneration (IDD) is a primary contributor to chronic back pain and disability globally, with current therapeutic approaches often proving inadequate due to the complex nature of its pathophysiology. This review assesses the potential of nanoparticle-driven pharmacotherapies to address the intricate challenges presented by IDD. We initially analyze the primary mechanisms driving IDD, with particular emphasis on mitochondrial dysfunction, oxidative stress, and the inflammatory microenvironment, all of which play pivotal roles in disc degeneration. Then, we evaluate the application of metal-phenolic and catalytic nanodots in targeting mitochondrial defects and alleviating oxidative stress within the degenerative disc environment. Additionally, multifunctional and stimuli-responsive nanoparticles are explored for their capacity to provide precise targeting and controlled therapeutic release, offering improved localization and sustained delivery. Finally, we outline future research directions and identify emerging trends in nanoparticle-based therapies, highlighting their potential to significantly advance IDD treatment by overcoming the limitations of conventional therapeutic modalities and enabling more effective, targeted management strategies.

Keywords: nanotechnology, drug delivery, intervertebral disc degeneration, regeneration, therapy

Introduction

Intervertebral disc degeneration (IDD) is a major contributor to chronic back pain, which is a leading cause of disability worldwide. IDD is characterized by the gradual deterioration of the intervertebral disc's structure, resulting in compromised mechanical integrity and function.[1–3] The etiology of IDD is complex and multifactorial, involving genetic, biochemical, and mechanical factors. These factors drive degenerative processes that include the breakdown of the extracellular matrix, heightened oxidative stress, and persistent inflammation.[4,5] This leads to the loss of disc height, reduced flexibility, and the onset of pain and functional impairment.

Conventional therapeutic approaches for IDD, such as pharmacological treatments, physical therapy, and surgical interventions, primarily focus on symptomatic relief but fail to address the underlying causes of degeneration.[2,6,7] Pharmacological treatments, including anti-inflammatory drugs, are limited to managing symptoms like pain and inflammation without halting disease progression. Surgical procedures such as discectomy and spinal fusion provide temporary relief but often result in further degeneration or complications. Thus, there is a critical need for more advanced therapies that can target the molecular and cellular mechanisms underlying IDD.

Nanotechnology has emerged as a promising avenue in the search for effective treatments for IDD.[8] Nanoparticles, with their small size and high surface area-to-volume ratio, offer distinct advantages for targeted drug delivery. Their nanoscale dimensions enable them to be directed precisely to the site of degeneration, concentrating therapeutic agents where they are needed most.[9,10] This targeted approach enhances drug efficacy while minimizing the systemic side effects often associated with traditional therapies, such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids.

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Nanoparticles can also be engineered to respond to the specific pathological conditions present in the degenerated disc environment, such as altered pH levels, oxidative stress, or increased enzymatic activity.[11,12] By designing nanoparticles that are responsive to these local stimuli, we can achieve controlled release of therapeutic agents directly at the site of degeneration.[9] This strategy allows for the sustained and localized delivery of drugs, providing a more effective treatment for the progression of IDD.

A particularly promising area of research is the use of nanoparticles to target mitochondrial dysfunction, which plays a crucial role in the pathogenesis of IDD.[13] Mitochondria are essential for energy production and cell survival, but in degenerated discs, mitochondrial dysfunction leads to increased ROS production and impaired cellular metabolism.[14,15] Nanoparticles such as metal-phenolic nanoparticles and catalytic nanodots have demonstrated the ability to selectively target mitochondria, delivering therapeutic agents that restore mitochondrial function, reduce oxidative damage, and improve cell survival.[16] By addressing mitochondrial dysfunction, these nanoparticles provide a novel therapeutic strategy for mitigating disc degeneration.

Multifunctional nanoparticles offer even greater potential by combining multiple therapeutic modalities into a single platform.[17] These systems can deliver a combination of anti-inflammatory agents, antioxidants, and growth factors to simultaneously address the degenerative and regenerative aspects of IDD.[12,18] Stimuli-responsive nanoparticles further enhance this precision by releasing therapeutic agents in response to specific changes in the disc environment, ensuring that treatment is delivered in a timely and targeted manner.[12,19]

In this review, we explore the role of nanoparticles in modulating the cellular and molecular pathways involved in IDD. We evaluate various nanoparticle systems, including metal-phenolic nanoparticles and catalytic nanodots, and their ability to deliver therapeutic agents effectively. Special emphasis is placed on how these systems target mitochondrial dysfunction, reduce oxidative stress, and modulate the inflammatory microenvironment within degenerated discs. We also examine the potential of these nanoparticles to promote tissue regeneration by supporting cell survival and extracellular matrix production.

The Underlying Mechanism of IDD

Mitochondrial Dysfunction and Its Impact on IDD

Mitochondrial dysfunction is critical in the pathogenesis of IDD, influencing numerous cellular processes crucial for disc health. This dysfunction primarily results in excessive production of reactive oxygen species (ROS), leading to oxidative stress, mitochondrial DNA damage, and disrupted cellular bioenergetics.[20] These conditions activate apoptotic pathways, especially in nucleus pulposus cells (NPCs), causing cell death and extracellular matrix degradation.[21] Furthermore, the interaction between mitochondrial dysfunction and endoplasmic reticulum (ER) stress aggravates cellular damage. Impaired mitophagy, the process of removing damaged mitochondria, results in their accumulation, heightening cellular stress responses.[22,23]

Key signaling pathways such as NF-κB pathway, activated by mitochondrial ROS, and the NLRP3 inflammasome, which contributes to inflammation and pyroptosis in NP cells.[23,24] Recent therapeutic strategies focus on targeting mitochondrial dysfunction to slow IDD progression. Mitochondria-targeted antioxidants like MitoQ reduce oxidative stress and restore redox balance.[21] Enhancing mitophagy with agents such as Urolithin A and promoting mitochondrial homeostasis with SIRT3 activators have shown promise in protecting cells from mitochondrial-induced damage.[25] Additionally, small molecule inhibitors that regulate mitochondrial dynamics, such as those targeting Drp1-mediated fission, and therapies that boost protective gene expression, including SIRT1 and PINK1, are under investigation.[26]

Moreover, oxidative stress plays a central role in the development of IDD by disrupting the balance between reactive oxygen species (ROS) production and the antioxidant defense system. In healthy intervertebral discs, ROS levels are tightly regulated by antioxidants. However, in IDD, factors such as aging, mechanical stress, and inflammation lead to an overproduction of ROS. Excessive ROS can cause cellular damage, including lipid peroxidation, protein oxidation, and DNA damage, leading to apoptosis or dysfunction of nucleus pulposus (NP) and annulus fibrosus (AF) cells, which are critical for maintaining disc structure and function. This damage compromises the extracellular matrix (ECM) by

degrading collagen and proteoglycans, which are essential for disc hydration and structural integrity.[27] As a result, the intervertebral disc becomes weakened, leading to the loss of disc height, reduced mobility, and pain.[28,29]

Several molecular mechanisms have been identified as key modulators of ROS in IDD, offering insights into potential therapeutic interventions.[30] One such mechanism is the activity of SIRT3, which has been shown to mitigate oxidative stress-induced senescence in nucleus pulposus cells (NPCs).[31] Additionally, the Keap1/Nrf2 axis plays a crucial role in bolstering antioxidant defenses, providing protection against ROS-induced damage.[31,32] Activation of this pathway helps counteract oxidative stress, thereby slowing the progression of disc degeneration. Antioxidant agents such as MitoQ and melatonin have been shown to effectively reduce ROS levels, while compounds like hesperidin and glycitin, which modulate specific cellular signaling pathways, have demonstrated efficacy in mitigating oxidative damage within the intervertebral disc.[21,33]

A particularly novel therapeutic target is the inhibition of ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation.[34] Since ferroptosis significantly contributes to ROS-induced cellular injury in IDD, targeting this pathway presents a promising strategy to preserve cell viability and maintain ECM integrity.[30,35] Taken together, ROS-induced oxidative stress is a fundamental mechanism underlying the molecular processes driving IDD. By influencing key signaling pathways and cellular processes, ROS accelerate disc degeneration. Therapeutic strategies aimed at reducing oxidative stress and enhancing cellular antioxidant capacity hold substantial promise for slowing IDD progression and preserving intervertebral disc health.

Inflammatory Microenvironment and IDD

The inflammatory microenvironment within the intervertebral disc (IVD) is a key factor in the progression of IDD. Elevated levels of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), activate signaling pathways that induce tissue degradation and cellular apoptosis.[35,36] Among these pathways, the NF-κB pathway is particularly prominent, upregulating matrix-degrading enzymes that contribute to the breakdown of the ECM, a critical event in disc degeneration[37] (Figure 1).

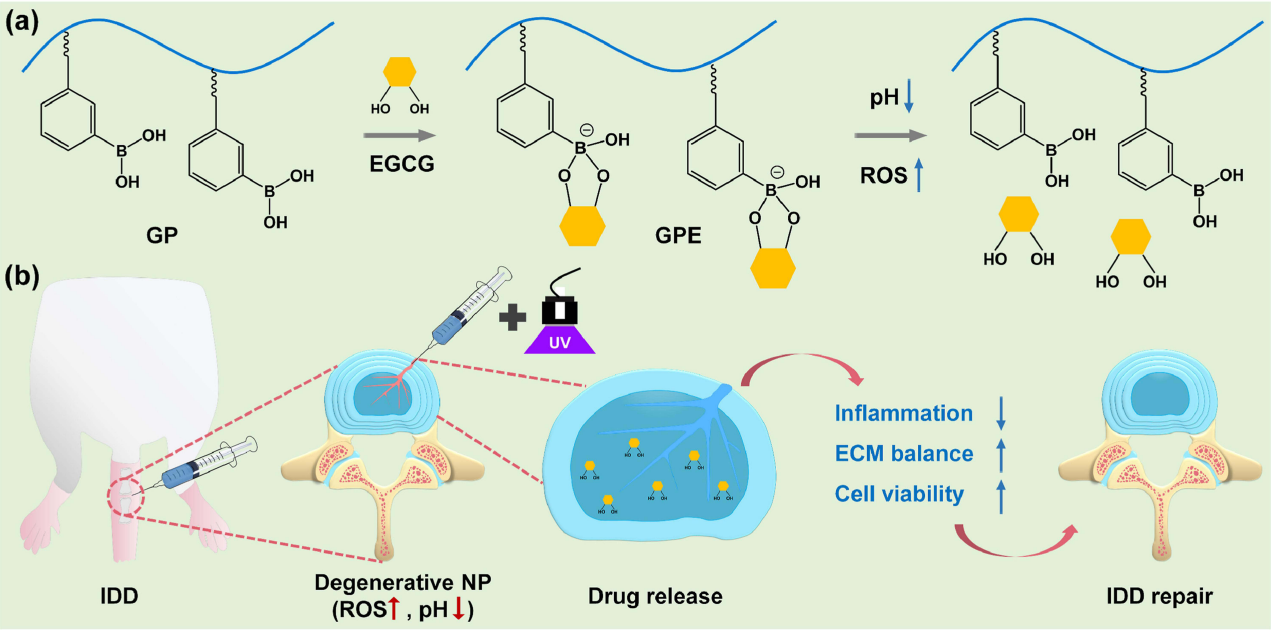

Figure 1 Illustrative representation of **(a)** the controlled release of epigallocatechin-3-gallate (EGCG) from gelatin methacryloyl (GP) hydrogel modified with phenylboronic acid, triggered by elevated reactive oxygen species (ROS) levels and acidic environments, and **(b)** the application of EGCG-loaded GP (GPE) hydrogel via in situ injection for the treatment of intervertebral disc degeneration (IDD) in a rat model. Reproduced with the permission from Liu L,Wang W, Huang L et al. Injectable pathological microenvironment-responsive anti-inflammatory hydrogels for ameliorating intervertebral disc degeneration, Biomaterials (306) (2024) 122,509. © 2023 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).[37]

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These pro-inflammatory cytokines not only drive catabolic processes but also inhibit anabolic pathways necessary for disc tissue repair and regeneration, thereby perpetuating the degenerative cycle.[38] A major consequence of inflammation is the elevated expression of matrix metalloproteinases (MMPs) and aggrecanases, enzymes responsible for degrading key structural components of the disc matrix, such as collagen and aggrecan. This degradation weakens the disc's biomechanical properties, accelerating its degeneration and further impairing its function.[38,39]

Additionally, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome plays a significant role in IDD pathogenesis. Activated by mitochondrial dysfunction and oxidative stress, the NLRP3 inflammasome promotes pyroptosis, an inflammatory form of programmed cell death in NPCs. This process exacerbates local inflammation, contributing to a vicious cycle of disc degeneration.[38,39] The involvement of the NLRP3 inflammasome underscores the complex interaction between oxidative stress, mitochondrial dysfunction, and inflammation in the advancement of IDD.

Targeting these inflammatory mechanisms presents promising therapeutic opportunities for mitigating IDD progression.[40] Several pharmacological agents have been investigated for their anti-inflammatory potential. For example, digoxin has been shown to inhibit NF-κB activation, reducing the production of matrix-degrading enzymes and slowing ECM degradation. Similarly, maltol has demonstrated efficacy in inhibiting the NLRP3 inflammasome, thus reducing inflammation and preventing pyroptosis within the IVD.[41] These compounds offer potential for modulating the inflammatory microenvironment and mitigating disc degeneration.

Nanoparticles for Targeting Cellular Dysfunction

Role of Mitochondrial Dysfunction in IDD and Targeting Strategies Using Nanoparticles

Mitochondrial dysfunction is a central factor in the pathogenesis of IDD, significantly contributing to the degradation of the ECM and the loss of NPCs. Mitochondria are critical regulators of cellular energy production and redox balance.[42] In the context of IDD, mitochondrial dysfunction disrupts cellular homeostasis by increasing the production of ROS, impairing ATP synthesis, and initiating cell death pathways such as apoptosis and necroptosis.[43] This mitochondrial impairment creates a toxic environment within the disc, characterized by oxidative stress and inflammation, which accelerates disc degeneration.[44] Given the crucial role of mitochondrial dysfunction in IDD, nanoparticle-based strategies have emerged as promising therapeutic interventions to protect and restore mitochondrial function.

One of the key approaches involves the use of polygallic acid-manganese (PGA-Mn) nanoparticles conjugated with mitochondrial-targeting peptides.[13] These nanoparticles are designed to specifically localize within mitochondria and enhance the organelle's redox capacity. By neutralizing excess ROS, PGA-Mn nanoparticles protect mitochondria from oxidative damage, thereby preserving NPC viability and maintaining the structural integrity of the intervertebral disc. The results have demonstrated that this targeted nanoparticle approach effectively maintains disc height and hydration, which are critical for disc functionality (Figure 2). In addition to mitigating mitochondrial damage, these nanoparticles help sustain the metabolic functions of NPCs, thereby reducing the catabolic processes associated with IDD.

Another innovative nanoparticle-based solution involves the use of manganese oxide (MnOx)-functionalized thermosensitive nanohydrogels.[45] These nanohydrogels have been developed as a platform for the transplantation of bone marrow-derived mesenchymal stem cells (BMSCs) into degenerative intervertebral discs. The nanohydrogel serves a dual purpose: it provides mechanical protection to the transplanted cells and creates a microenvironment that reduces oxidative stress by lowering ROS levels. This is particularly important in the context of IDD, where the high ROS environment not only damages resident disc cells but also reduces the viability of transplanted stem cells. The MnOx nanohydrogel shields the BMSCs from oxidative damage, enhancing their survival and integration into the damaged disc tissue. Furthermore, by reducing oxidative stress, this platform helps to restore cellular homeostasis and promote tissue regeneration within the disc, positioning it as a highly promising approach for IDD therapy.

These nanoparticle-based strategies target the underlying causes of mitochondrial dysfunction in IDD by addressing both the excessive production of ROS and the resulting oxidative damage. Mitochondria-targeted nanoparticles, such as PGA-Mn and MnOx nanohydrogels, offer a multi-faceted approach to mitigating oxidative stress while supporting

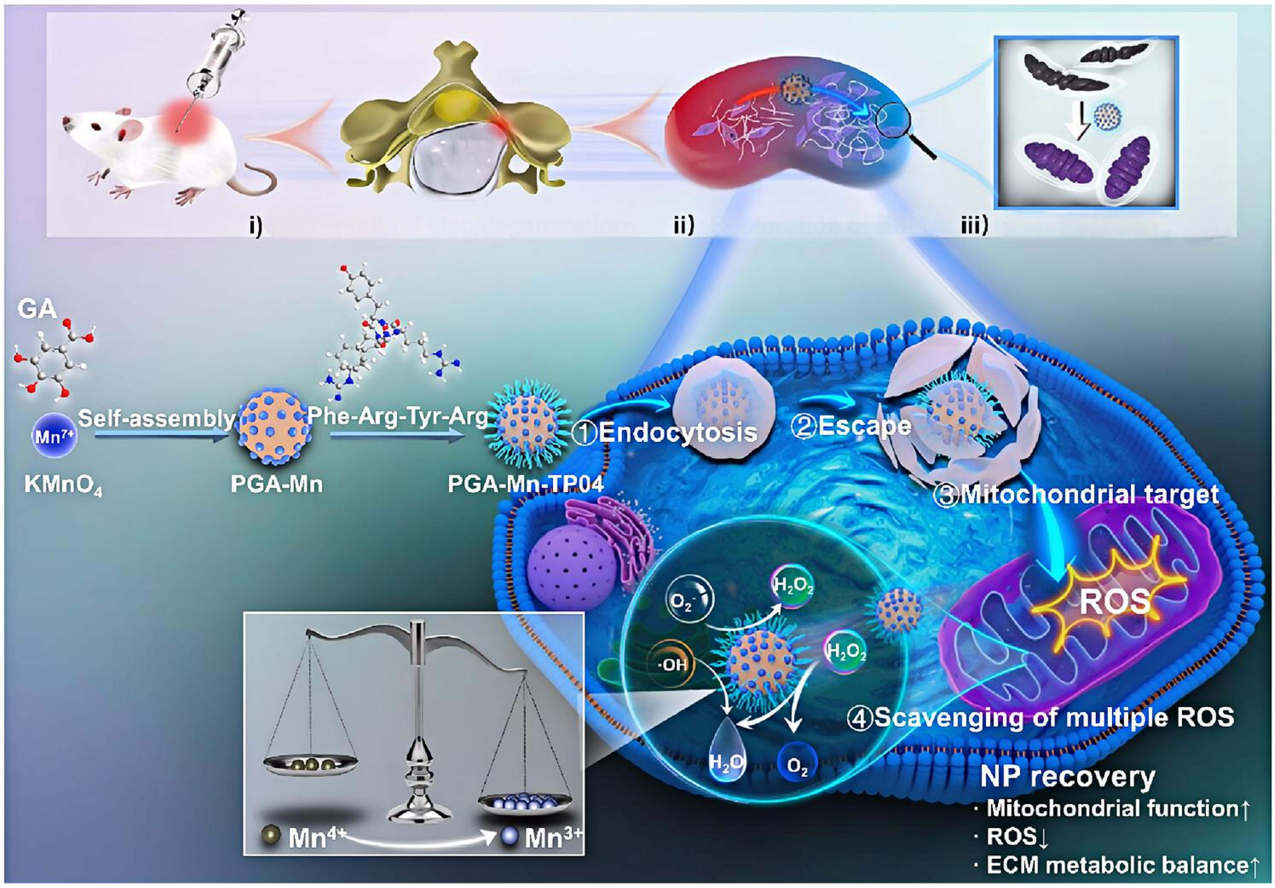

Figure 2 Schematic illustration of the underlying mechanism by which nanoparticles act inside NPCs. **i)** Intervertebral disc regeneration, **ii)** Restoration of extracellular matrix, **iii)** Mitochondria fusion. ↑, Increase; ↓, decrease. Reproduced with permission from Chen Q, Qian Q, Xu H et al. Mitochondrial-Targeted Metal-Phenolic Nanoparticles to Attenuate Intervertebral Disc Degeneration: Alleviating Oxidative Stress and Mitochondrial Dysfunction, ACS Nano. (18) (2024) 8885–8905. Copyright 2024, American Chemical Society.[13]

cellular repair mechanisms. The ability of these nanoparticles to precisely target the mitochondria within NPCs ensures that therapeutic effects are localized to the site of greatest damage, thus maximizing the efficiency of the treatment while minimizing potential side effects.

Metal-Phenolic Nanoparticles for Mitochondrial Targeting

Metal-phenolic nanoparticles have emerged as promising candidates for targeting mitochondrial dysfunction, particularly in the context of IDD.[13] Mitochondrial dysfunction plays a critical role in the progression of IDD, leading to increased oxidative stress and cellular damage within the disc tissue. Addressing this issue requires innovative therapeutic strategies that can specifically target and protect mitochondria, and metal-phenolic nanoparticles have shown significant potential in this regard.

One notable example is the application of Prussian blue nanoparticles (PBNPs), which exhibit potent antioxidant enzyme activity.[46] PBNPs have been shown to alleviate intracellular oxidative stress by stabilizing superoxide dismutase 1 (SOD1), a key antioxidant enzyme that protects cells from oxidative damage. In the degenerative microenvironment of IDD, SOD1 is often degraded through the ubiquitination-proteasome pathway, leading to impaired antioxidant defense and further mitochondrial damage. PBNPs help counteract this process by preventing the degradation of SOD1, thereby improving mitochondrial structure and reducing ROS-induced degeneration in NPCs. By stabilizing mitochondrial function, PBNPs offer a novel therapeutic approach to mitigating oxidative stress and slowing the progression of disc degeneration.

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In addition to metal-phenolic nanoparticles, advances in drug delivery systems have further enhanced the therapeutic potential of nanoparticles in targeting mitochondrial dysfunction. Curcumin, a natural compound known for its antioxidant and anti-inflammatory properties, has shown limited bioavailability in its native form. However, when encapsulated in polylactic acid (PLA) nanoparticles, curcumin's bioavailability and therapeutic efficacy are significantly enhanced.[47] These PLA-curcumin nanoparticles not only improve the delivery of curcumin to target tissues but also amplify its anti-inflammatory effects, making it a promising candidate for the treatment of IDD. Moreover, these nanoparticles can be embedded in bioinks for three-dimensional (3D) printing, offering potential applications in tissue engineering and regenerative medicine. This approach allows for the creation of custom-designed scaffolds that can deliver therapeutic agents directly to degenerative disc tissues, promoting tissue repair and regeneration.

The ability of metal-phenolic nanoparticles to specifically target and protect mitochondria represents a major advancement in the treatment of degenerative diseases like IDD. These nanoparticles address the core issues of oxidative stress and mitochondrial dysfunction, which are key drivers of disc degeneration. By preventing mitochondrial damage and enhancing cellular antioxidant capacity, metal-phenolic nanoparticles offer a targeted, efficient approach to slowing or even reversing the progression of IDD.

Catalytic Nanodots-Driven Antioxidant Intervention

Catalytic nanodots are emerging as a potent therapeutic strategy for addressing oxidative stress in IDD, a condition characterized by the progressive breakdown of disc tissue due to various molecular and cellular dysfunctions.[48] ROS play a central role in exacerbating IDD by promoting damaging processes, which contribute to the degradation of ECM, inflammation, and loss of cellular viability. In this context, catalytic nanodots offer an innovative approach to mitigate oxidative stress and its detrimental effects, thus providing a promising avenue for IDD treatment.

One of the most promising developments in this area is the use of carbonized manganese-containing nanodots (MCDs), which have shown a strong ability to scavenge ROS.[48] By neutralizing ROS, these nanodots help protect NP cells from oxidative damage and suppress pyroptosis, a form of programmed cell death triggered by inflammation. Pyroptosis in NP cells accelerates disc degeneration by releasing pro-inflammatory cytokines that exacerbate local tissue damage and promote further ECM breakdown. MCDs have demonstrated efficacy in mitigating these harmful effects, thereby offering a protective mechanism that preserves cellular integrity and disc structure. Studies have confirmed that MCDs not only reduce ROS levels but also maintain mitochondrial function, which is crucial for sustaining cellular energy production and preventing apoptosis in NP cells.

In addition to MCDs, polydopamine nanoparticles (PDA NPs) represent another innovative solution for mitigating oxidative stress in IDD.[19] PDA NPs have shown significant promise in preventing ferroptosis, a form of cell death characterized by iron-dependent lipid peroxidation. Ferroptosis is particularly harmful to NP cells due to its ability to disrupt membrane integrity and lead to widespread cellular death. PDA NPs counteract ferroptosis by scavenging ROS, chelating free iron ions, and preventing the ubiquitination-mediated degradation of glutathione peroxidase 4 (GPX4), an enzyme critical for maintaining cellular redox balance. By protecting GPX4 from degradation, PDA NPs ensure that NP cells can maintain their antioxidant defenses, thus reducing the oxidative stress burden and preventing further cell death. This targeted approach to ferroptosis inhibition is highly effective in preserving NP cell viability and slowing the progression of IDD.

Another promising innovation in catalytic nanodots is the development of a dual-functional greigite nanozyme, which offers multifaceted protection against ROS-induced damage.[49] This nanozyme exhibits both superoxide dismutase (SOD) and catalase activities, mimicking the action of natural antioxidant enzymes to neutralize superoxide radicals and hydrogen peroxide, two major contributors to oxidative stress. Beyond its enzymatic activity, the greigite nanozyme also releases polysulfides, which further reduce ROS levels and restore mitochondrial function. By enhancing mitochondrial activity, the nanozyme helps alleviate cellular senescence state of irreversible cell cycle arrest often observed in aging and degenerative tissues, including the intervertebral disc. Cellular senescence contributes to the chronic inflammatory state within the disc, exacerbating tissue degradation and impeding repair mechanisms. By reducing ROS and reversing senescence in NP cells, the greigite nanozyme not only protects against oxidative stress but also promotes cellular rejuvenation, making it a highly promising therapeutic candidate for reversing the course of IDD (Figure 3).

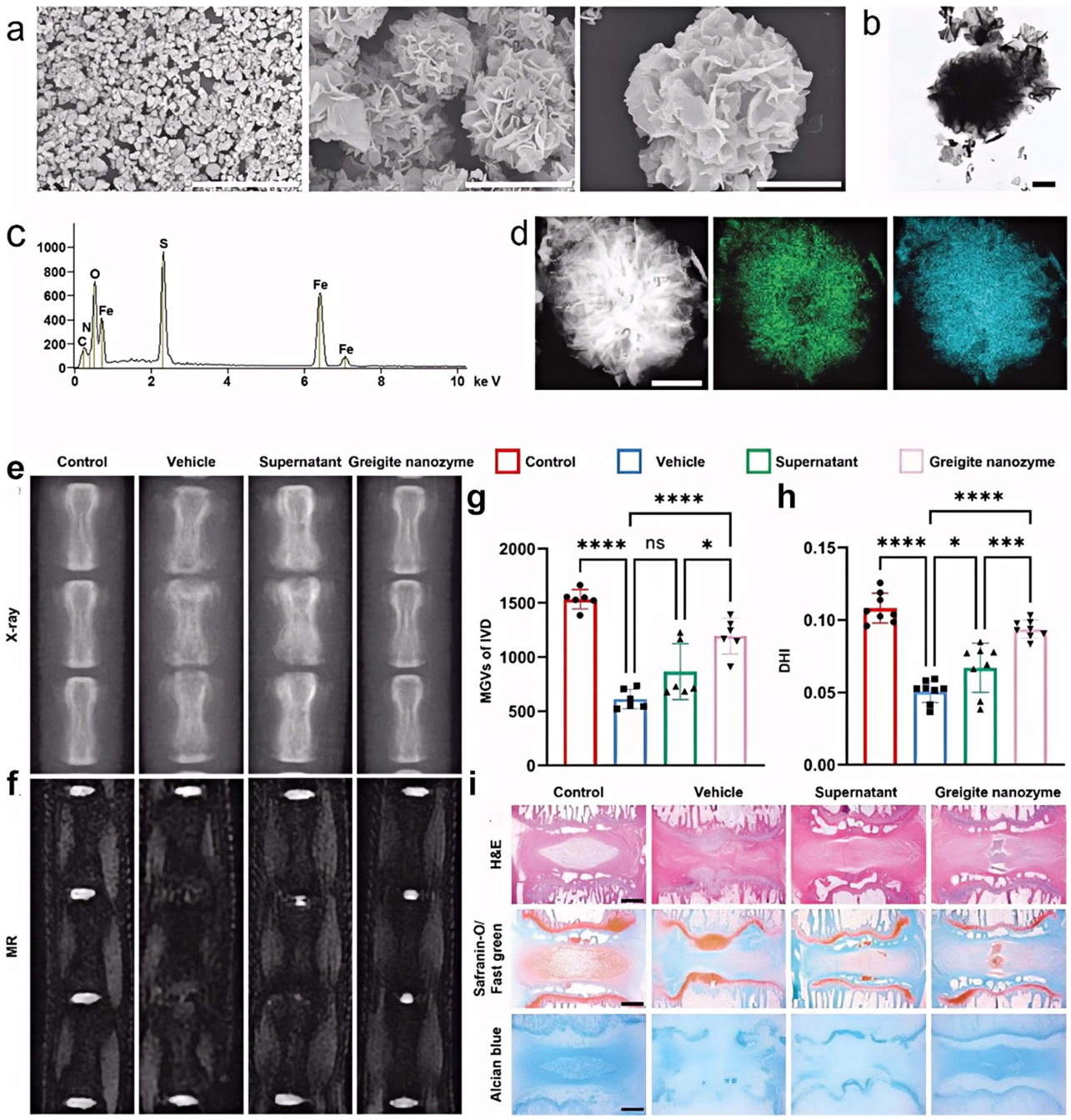

Figure 3 (**a**) SEM images revealed the formation of uniform greigite nanozymes with a flower-like microsphere structure (scale bars: 50 μm, 5 μm, 2 μm). (**b**) TEM images of the greigite nanozyme (scale bar: 1 μm). (**c**) EDS analysis confirmed the presence of sulfur (S) and iron (Fe) in the greigite nanozyme. (**d**) Elemental mapping displayed sulfur (green) and iron (blue) distribution within the greigite nanozyme. (**e**and **f**) X-ray and MRI scans of rat tails from the sham group, puncture group, puncture with greigite nanozyme supernatant (0.2 μg) injection group, and puncture with greigite nanozyme (0.2 μg) injection group. Samples were collected 4 weeks post-injection after the rats were sacrificed. (**g**) Mean gray value of the targeted intervertebral disc (IVD). (**h**) Caudal IVD hydration index in rats. (**i**) Hematoxylin/eosin, safranin-O/fast green, and alcian blue staining of the rat caudal IVD (scale bar: 1000 μm). Ns, no significance; *, $p < 0.5$; ***, $p < 0.001$, ****, $p < 0.0001$. Reproduced Shi Y, Li H, Chu D et al. Rescuing Nucleus Pulposus Cells From Senescence via Dual-Functional Greigite Nanozyme to Alleviate Intervertebral Disc Degeneration, Adv Sci (Weinh) (10) (2023) e2300988. © 2023 The Authors. Advanced Science published by Wiley-VCH GmbH. Creative Commons Attribution 4.0 International License.[49]

The ability of catalytic nanodots to specifically target ROS and modulate key cellular processes such as pyroptosis, ferroptosis, and senescence marks a significant advancement in the treatment of IDD. These nanodots offer a targeted approach that addresses the underlying causes of disc degeneration at the molecular level, rather than merely managing

symptoms. By focusing on the regulation of oxidative stress and restoring cellular homeostasis, catalytic nanodots have the potential to not only slow the progression of IDD but also promote the regeneration of damaged disc tissue.

Nanoparticle-Enabled Delivery Systems

Overview of Multi-Functional and Stimuli-Responsive Nanoparticle Delivery Systems

Multi-functional and stimuli-responsive nanoparticle delivery systems present advanced therapeutic strategies for IDD. Carbonized manganese-containing nanodots effectively scavenge ROS and suppress pyroptosis in NPCs, thus alleviating IDD.[50] Additionally, the local delivery of senolytic drugs using poly(lactic-co-glycolic acid) nanoparticles (PLGA-ABT) effectively eliminates senescent cells, reduces inflammation, and restores intervertebral disc structure.[51] These advanced nanoparticle delivery systems offer targeted and sustained drug release, maximizing therapeutic efficacy and minimizing adverse effects, thus representing a significant advancement in IDD treatment.

Nucleus Pulposus-Targeting Nanocarriers for Localized Therapy

Nucleus pulposus (NP)-targeting nanocarriers have emerged as a highly promising strategy for localized therapeutic interventions in IDD. These nanocarriers provide precise drug delivery to the NP, which is essential for preserving disc function and slowing the progression of degeneration. Among the approaches gaining attention is the use of microRNA (miRNA)-based therapeutics encapsulated in NP-targeting nanoparticles. For example, nanoparticles designed to deliver miR-22-3p inhibitors have shown success in alleviating IDD by modulating the JAK1/STAT3 signaling pathway and targeting SIRT1, a critical regulator of cellular senescence and inflammation.[52] This approach offers a targeted method for reducing disc degeneration while promoting NP cell survival and ECM maintenance.

Lipid nanocapsules (LNCs) loaded with miR-155 represent another innovative therapeutic strategy, especially for maintaining miRNA stability and ensuring a sustained release in vivo.[53] miRNAs are susceptible to degradation, which can limit their therapeutic efficacy. By encapsulating miR-155 in LNCs, researchers have found that it is possible to protect the miRNA from enzymatic degradation while maintaining its bioactivity for longer periods. This extended release offers a sustained therapeutic effect, allowing for more efficient targeting of molecular pathways involved in IDD progression.

The challenge of drug localization and controlling burst release has also driven the development of advanced injectable polymeric nanocarriers. These systems are based on a combination of cellulose acetate and polycaprolactone-polyethylene glycol (PCL-PEG), which provide a robust platform for delivering drugs with varying solubility profiles.[54] By efficiently maintaining drug localization within the NP cells, these nanocarriers prevent the premature release of the therapeutic agents, enhancing treatment efficacy while minimizing systemic exposure. This technology is particularly useful for ensuring that both high- and low-solubility drugs are effectively delivered to their target site within the degenerating disc.

Hydrogel-based nanocarriers have also gained attention for their ability to modulate the disc microenvironment and promote NP regeneration. One such approach involves engineered hydrogel microspheres encapsulating chitosan nanoparticles integrated with black phosphorus quantum dots (BPQDs).[55] These microspheres not only facilitate a balanced oxygen metabolism, crucial for preventing hypoxia and acidosis in the disc, but also reduce inflammatory cascades. The combination of chitosan nanoparticles and BPQDs fosters a regenerative microenvironment within the NP, promoting ECM synthesis and reducing oxidative stress-induced cellular damage (Figure 4).

A novel approach to IDD treatment involves ROS-responsive nanoparticles that simultaneously scavenge reactive oxygen species and enhance autophagy in NP cells. For instance, isoginkgetin-loaded ROS-responsive nanoparticles (IGK@SeNP) have been developed to mitigate ROS-mediated cellular damage in the NP.[56] By enhancing autophagy, these nanoparticles prevent ECM degradation and cell apoptosis, two key contributors to disc degeneration. Studies in IDD models have demonstrated significant therapeutic effects, positioning IGK@SeNP as a promising candidate for clinical translation.

Additionally, polyphenol nanosphere-encapsulated hydrogels have been explored for gene delivery systems targeting ECM regeneration. Specifically, antagomir-21, a small RNA inhibitor, is encapsulated within these hydrogels to inhibit

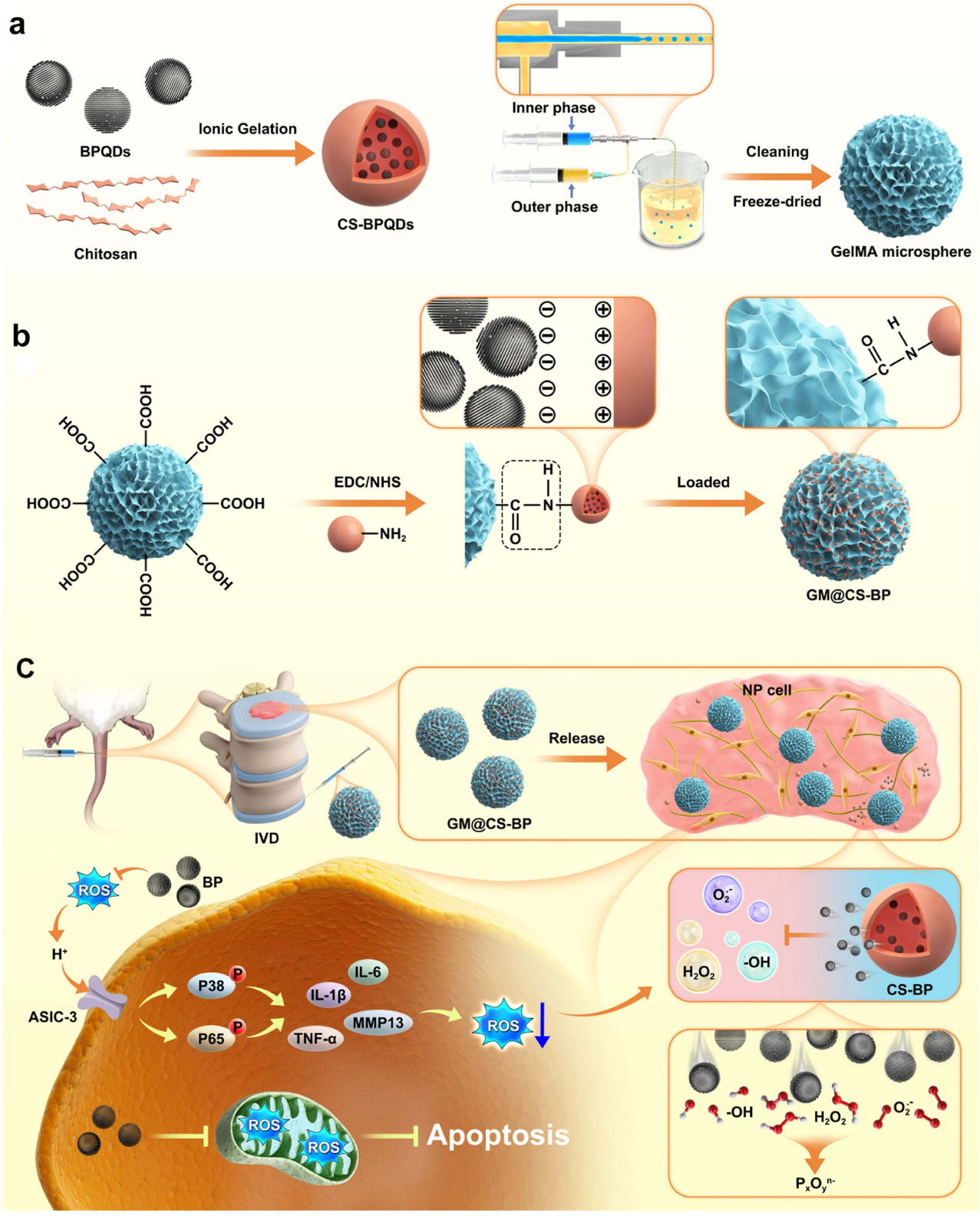

Figure 4 (**a**) Synthesis of BPQDs, CS nanoparticles, and GelMA microspheres. (**b**) Activation and grafting process for GelMA and CS-BP nanoparticles. (**c**) Targeted injection of oxygen metabolism-balanced engineered hydrogel microspheres into rat IVDs and exploration of the therapeutic mechanisms involved. Reproduced from Li Z, Cai F, Tang J et al. Oxygen metabolism-balanced engineered hydrogel microspheres promote the regeneration of the nucleus pulposus by inhibiting acid-sensitive complexes, Bioact Mater (24) (2023) 346–360. © 2022 The Authors. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).[55]

the MAPK/ERK signaling pathway, which is involved in inflammatory processes and ECM degradation.[57] The targeted delivery of antagomir-21 through these nanospheres not only reduces inflammation but also promotes the regeneration of NP tissue, highlighting their potential to reverse the degenerative changes associated with IDD.

Hydrogel-Based Nanoparticle Systems for Sustained Delivery

Hydrogel-based nanoparticle systems offer remarkable potential for sustained drug delivery in treating IDD, providing a promising avenue for addressing the complexity of this condition. One such system, hydrogen ion-capturing hydrogel microspheres (GMNP), composed of mineralized transforming growth factor-β (TGF-β) and catalase (CAT) nanoparticles, has shown the ability to neutralize the acidic microenvironment commonly associated with degenerated discs.[58] By releasing bioactive agents, GMNP suppresses the NLRP3 inflammasome cascade, a key player in inflammation, while simultaneously promoting extracellular matrix synthesis. This dual action not only mitigates inflammation but also supports tissue regeneration, making GMNP a valuable tool in IDD therapy.

In addition, a nucleobase-driven self-gelling hyaluronic acid hydrogel (HATMn) incorporating manganese dioxide nanoparticles has been developed to address oxidative stress within the degenerated disc.[59] Oxidative stress is a critical factor in the degeneration process, contributing to cellular dysfunction and disc degeneration. By effectively regulating oxidative stress and supporting cell viability, the HATMn hydrogel promotes NP regeneration, offering a targeted and efficient approach to restore disc health. This innovative hydrogel system demonstrates the therapeutic potential of combining hydrogel matrices with antioxidant nanoparticles in combating the degenerative effects of IDD.

Further advances in hydrogel-nanoparticle systems include the use of amphiphilic polycarbonate cationic nanoparticles (cNP) for targeted drug delivery. When combined with a decellularized annulus fibrosus matrix (DAF) hydrogel, cNPs deliver the TrkA-IN-1 antagonist, which significantly reduces inflammation and inhibits nerve growth within degenerative discs.[18] This approach addresses both the inflammatory response and the aberrant nerve growth associated with disc degeneration, presenting a comprehensive treatment strategy aimed at restoring disc function and alleviating pain.

Hydrogel systems have also demonstrated potential in the context of spinal tuberculosis (TB) and IDD. A 3D-printed scaffold loaded with gelatin hydrogel, platelet-rich plasma (PRP), and anti-inflammatory simvastatin offers prolonged drug release, coupled with significant regenerative effects.[60] The combination of these bioactive agents promotes healing while addressing both the infectious and degenerative aspects of spinal TB and IDD, further emphasizing the versatility of hydrogel-based systems in treating complex spinal conditions.

Additionally, the development of an enzymatically initiated keratin methacrylate (KeMA) hydrogel has shown promise for controlled exosome release in IDD therapy. Exosomes, which play a critical role in cell communication and tissue regeneration, are delivered more efficiently through this hydrogel system, leading to enhanced exosome kinetics, reduced inflammation, and improved extracellular matrix regeneration. The KeMA hydrogel's ability to regulate exosome release over time ensures sustained therapeutic effects, contributing to long-term disc repair.[61]

Lastly, an injectable microgel assembly (MA-TNS) with sequential release of bioactive factors, such as stromal cell-derived factor-1α (SDF-1α) and TGF-β1, has demonstrated remarkable potential for endogenous disc repair. This system promotes stem cell recruitment and differentiation, facilitating long-term NP reconstruction.[62] By orchestrating the timely release of these key factors, the MA-TNS hydrogel assembly fosters a regenerative microenvironment within the disc, enabling sustained tissue regeneration and disc restoration.

These innovative hydrogel-based nanoparticle systems exemplify the cutting-edge approaches being developed for the treatment of IDD. Their ability to provide sustained and controlled release of therapeutic agents, while simultaneously addressing the underlying mechanisms of degeneration, positions them as promising solutions for advancing the field of regenerative medicine for spinal disorders.

Modulation of Inflammation and Immune Responses

Use of Nanoparticles to Inhibit Inflammatory Cascades and Promote Disc Regeneration

Nanoparticle-based therapies have shown immense potential in mitigating inflammation and promoting disc regeneration in IDD. One promising strategy involves a smart microgel gene delivery system, which encapsulates functionalized nanoparticles loaded with siGrem1. This system effectively modulates the inflammatory response, scavenges ROS, and reduces apoptosis in NPCs.[17] By maintaining ECM homeostasis and curbing degenerative processes, this approach delays the progression of IDD and supports long-term disc health.

Another innovative development in the field is a pH-responsive delivery system using ammonia borane-loaded hollow polydopamine (AB@HPDA) nanoparticles. These nanoparticles are designed to release hydrogen in a controlled manner within the acidic microenvironment of degenerated IVDs. The release of hydrogen helps rebalance oxidative stress and inflammation, two key contributors to disc degeneration.[63] By preventing ECM degradation, this system not only protects the structural integrity of the disc but also creates a more favorable environment for tissue regeneration.

Immune modulation is another promising avenue for IDD therapy, as demonstrated by immune-defensive microspheres. These microspheres, which combine neutrophil membrane-coated polylactic-glycolic acid copolymer nanoparticles with TGF-β1, offer sustained anti-inflammatory effects while improving the biomechanical function of the nucleus pulposus.[64] The coating mimics the immune-evasive properties of neutrophils, allowing the nanoparticles to evade immune detection and prolong their therapeutic action. This sustained release of anti-inflammatory agents helps maintain a balanced microenvironment, contributing to disc repair and functional recovery.

Additionally, the use of enhanced cell-penetrating peptides (CPPs) complexed with microRNAs represents a novel approach for targeting inflammation and ECM degradation in NPCs. For example, the delivery of a miR-221 inhibitor and miR-149 mimic via CPPs has been shown to effectively reduce inflammatory cytokines and matrix-degrading enzymes.[65] By promoting matrix deposition and reducing inflammation, this strategy enhances the overall regenerative capacity of the disc, offering a targeted and efficient solution for IDD treatment.

Collectively, these nanoparticle-based strategies highlight the advantages of using targeted, sustained delivery systems for therapeutic agents in IDD therapy. By addressing the multifaceted nature of disc degeneration—through modulating inflammation, rebalancing oxidative stress, and preventing ECM degradation—these approaches significantly improve treatment outcomes while minimizing potential side effects. The precision and efficacy of these nanoparticle systems make them a promising avenue for future advancements in the treatment of IDD, offering hope for more effective and long-lasting solutions to this complex and debilitating condition.

Immune-Defensive Microspheres and Their Roles in IDD

Immune-defensive microspheres have emerged as a critical tool in addressing IDD by modulating the inflammatory microenvironment and promoting disc regeneration. One innovative approach involves the use of a nanocomposite hydrogel composed of epigallocatechin-3-gallate (EGCG)-coated hydroxyapatite nanorods and O-carboxymethyl chitosan cross-linked with aldehyde hyaluronic acid. This hydrogel system plays a dual role in enhancing ECM anabolism through MSC differentiation while reducing catabolism by inducing the polarization of M2 macrophages. By promoting tissue repair and reducing inflammation, this nanocomposite hydrogel presents a minimally invasive yet highly effective therapeutic strategy for managing IDD.[66] Its capacity to create a favorable microenvironment for MSCs underscores its potential in reversing disc degeneration and facilitating long-term disc regeneration (Figure 5).

Another innovative strategy centers on the use of an engineered bionic nanoparticle sponge, which encapsulates manganese dioxide (MnO_2) nanoparticles within a TrkA-overexpressed macrophage cell membrane, creating the MnO_2@TMNP system. This system offers a multi-pronged approach to managing IDD by binding inflammatory factors and nerve growth factors, effectively curbing inflammation-induced NPC apoptosis, matrix degradation, and nerve ingrowth.[28] The MnO_2 nanoparticles inside the macrophages are particularly effective at scavenging intracellular ROS, which are key drivers of oxidative stress and inflammation. Moreover, MnO_2@TMNP prevents the polarization of M1 macrophages, which are associated with pro-inflammatory responses, while promoting M2 macrophage polarization, thus

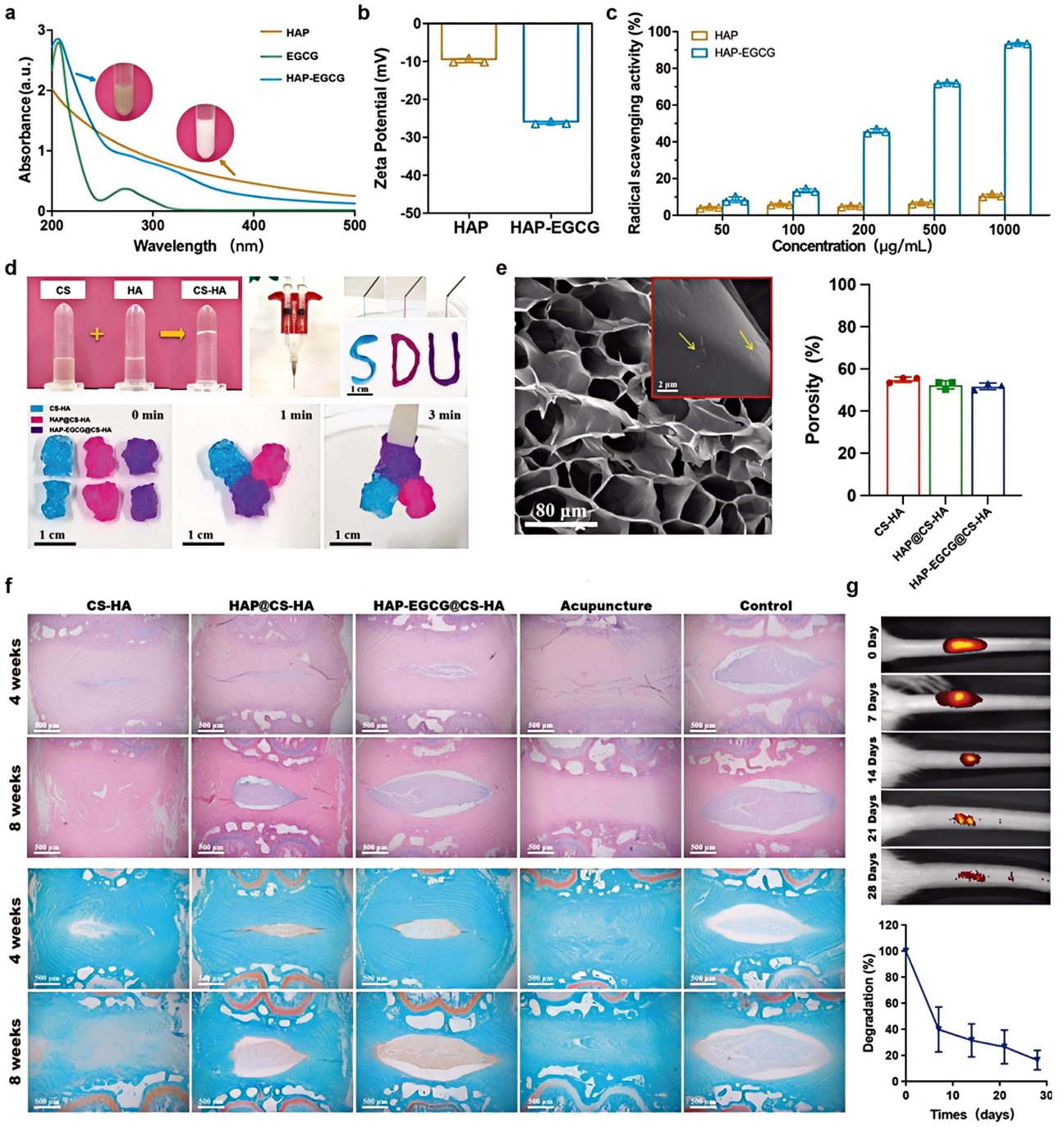

Figure 5 (**a**) UV–vis spectra of HAP nanorods, EGCG, and HAP-EGCG nanorods. (**b**) The zeta potential measurements of HAP nanorods and HAP-EGCG nanorods. (**c**) DPPH scavenging activity of HAP and HAP-EGCG across varying concentrations. (**d**) Photographs of the hydrogels formed by mixing CS and HA solutions, with blue representing CS-HA, red for HAP@CS-HA, and purple for HAP-EGCG@CS-HA. The process also illustrates injectability and self-healing. (**e**) SEM images of HAP-EGCG @CS-HA hydrogels (with arrows indicating HAP-EGCG nanorods) and the porosity percentage of the hydrogels. (**f**) HE and Safranin O staining of the IVD at 4 and 8 weeks post-injection. (**g**) In vivo degradation rate evaluation of the IVD delivery system using the HAP-EGCG@CS-HA hydrogel. Reproduced from Zhao DW, Cheng Q, Geng Het al, Decoding Macrophage Subtypes to Engineer Modulating Hydrogels for the Alleviation of Intervertebral Disk Degeneration, Adv Sci (Weinh) (11) (2024) e2304480. © *2023 The Authors. Advanced Science published by Wiley-VCH GmbH*. Creative Commons Attribution 4.0 International License.[66]

facilitating matrix regeneration and alleviating discogenic pain. This targeted intervention not only addresses the structural degradation of the disc but also mitigates pain by reducing nerve ingrowth, offering a comprehensive approach to IDD treatment.

Further expanding on the role of oxidative stress in disc degeneration, a polydopamine-based nanoplatform for spermidine delivery (SPD/PDA) has been designed to provide sustained regulation of oxidative stress within degenerated discs.[67] By enhancing the local bioavailability of spermidine, this system promotes the polarization of M2 macrophages, leading to a reduction in inflammation and facilitating disc regeneration. The sustained release of spermidine ensures long-term therapeutic effects, making SPD/PDA a promising candidate for the management of chronic degenerative changes in IDD. The ability of this system to modulate oxidative stress and inflammation simultaneously addresses two key contributors to the degenerative process, positioning it as an important tool in disc repair.

In addition to these approaches, polymeric nanoparticles have demonstrated the ability to deliver mRNA, enabling the expression of anti-inflammatory cytokines and growth factors specifically in human joint and intervertebral disc cells.[68] By excluding M1 macrophages, which drive inflammatory processes, this system promotes the production of anti-inflammatory mediators that contribute to disc repair. The targeted delivery of mRNA offers the advantage of localized therapy, reducing systemic side effects while providing the cells with the necessary signals for regeneration. This mRNA delivery strategy holds considerable promise for halting the inflammatory cascade and promoting disc regeneration in IDD patients.

A novel class of nanoparticles, functionalized trimetallic nitride endohedral metallofullerenes, also shows significant potential in IDD treatment. These nanoparticles possess potent radical scavenging properties, reducing ROS production and the expression of pro-inflammatory mediators in macrophages.[69] Their anti-inflammatory and analgesic effects make them a powerful tool for treating both the degenerative processes and the pain associated with IDD. The ability of these nanoparticles to target oxidative stress and inflammation concurrently opens up new therapeutic possibilities for addressing the multifaceted nature of disc degeneration.

Together, these immune-defensive microspheres and nanocarrier systems represent cutting-edge advancements in IDD therapy. By modulating the inflammatory microenvironment, scavenging oxidative stress, and promoting tissue regeneration, they significantly enhance therapeutic outcomes while minimizing adverse effects. Their targeted, sustained delivery of bioactive agents makes these nanotechnologies a cornerstone for future regenerative strategies in spinal health.

Conclusion

Our review systematically explores the growing potential of nanoparticle technologies in treating IDD. Nanoparticles offer distinct advantages over conventional therapies, particularly through their capacity for targeted, localized, and controlled drug delivery.[9,70–72] These properties are critical in addressing the complex pathophysiology of IDD, which involves chronic inflammation, oxidative stress, and degradation of the ECM. By enabling the precise administration of therapeutic agents directly to the degenerated disc, nanoparticles may mitigate or even reverse these pathological processes, thereby promoting tissue regeneration and improving clinical outcomes in IDD.[73]

However, despite promising preclinical results, the translation of nanoparticle-based approaches into clinical practice remains challenging. Future clinical research should focus on addressing challenges related to large-scale manufacturing consistency and long-term biocompatibility of nanotechnology-based treatments for IDD. First, research should aim to standardize the synthesis of nanomaterials to ensure batch-to-batch consistency, exploring advanced manufacturing techniques like microfluidic platforms to improve precision and scalability. Additionally, long-term in vivo studies are needed to assess the potential toxicity and immune responses of nanomaterials in spinal tissues, focusing on chronic inflammation, immune reactions, and bioaccumulation. Furthermore, the targeting delivery systems of nanomaterials should be optimized with strategies such as ligand targeting and peptide functionalization to enhance treatment specificity and minimize side effects.

Second, future research should address the mechanical integration of nanomaterials with intervertebral disc tissue to ensure that treatment materials restore disc function without compromising its biomechanical properties. Personalized treatment strategies should be prioritized, developing therapies to individual patients through genomic and proteomic analyses to improve efficacy. Finally, establishing clear regulatory frameworks and clinical trial standards for nanotechnology-based treatments is crucial for accelerating clinical translation. Through these research priorities, the challenges of nanotechnology-based therapies for IDD can be overcome, leading to safer and more effective treatments.

In conclusion, while significant progress has been made in applying nanoparticle technologies to IDD, their clinical implementation remains complex, requiring resolution of production, biocompatibility, and regulatory challenges. Cross-disciplinary collaboration will be crucial in overcoming these obstacles. Continued innovation in nanoparticle design and application holds substantial promise for more effective, targeted, and durable therapeutic outcomes.

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Disclosure

The author(s) report no conflicts of interest in this work.

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