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The application prospect of metal/metal oxide nanoparticles in the treatment of intervertebral disc degeneration

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With advancements in molecular biology and tissue engineering, significant progress has been made in the treatment of intervertebral disc degeneration (IVDD). In recent years, biomaterials have broadened therapeutic options for IVDD, particularly through the incorporation of metals, which impart antioxidant, anti-inflammatory, and cellular repair properties. The combination of metal ions, nanomaterials, and bioactive molecules further enhances the capacity of these materials to scavenge free radicals, regulate cell activity, and improve the microenvironment, thereby increasing their therapeutic efficacy and providing new opportunities for IVDD treatment. This review aims to provide a comprehensive analysis of the roles of metal-based and metal oxide nanoparticles in the treatment of IVDD, while addressing current challenges and future prospects related to their therapeutic applications.

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1. Introduction

Low back pain (LBP) is a widespread global public health concern, with its economic burden increasing significantly due to an aging population. Epidemiological studies indicate that over 80% of adults will experience LBP at some point in their lives.[1] Approximately 10% of these cases progress to chronic disability,[2] making LBP one of the leading causes of

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disability and imposing a substantial burden on public health and quality of life. The etiology of LBP is multifactorial, encompassing genetic predisposition, lifestyle factors such as occupational exposure, physical inactivity, alcohol consumption, and smoking, as well as aging.[3] Although the etiology of LBP is multifaceted, intervertebral disc (IVD) degeneration (IVDD) is its most common cause, characterized by distinct morphological changes resulting from aging or mechanical stress.[4,5] The IVD consists of three main components: The central nucleus pulposus, the surrounding annulus fibrosus (AF), and the cartilaginous endplates (CEP), which separate the disc from the vertebrae. Each region contains specific cell types, including nucleus pulposus, AF, and chondrocytes. Growing evidence indicates that three types of structural changes or cell injuries in the IVD contribute to the development of IVDD.[6] IVDD involves nucleus pulposus dehydration,[7] ECM degradation,[8] AF damage,[9] inflammation,[10] oxidative stress,[11] and cell senescence,[12] disrupting biomechanics and causing chronic pain. Current therapies are palliative, lacking regenerative efficacy and risking adjacent degeneration. Metal-based nanoparticles (NPs) offer targeted anti-inflammatory and regenerative potential for IVDD treatment.

In recent years, incorporating various metal ions into biomaterials to achieve specific biological functions has emerged as a promising strategy for enhancing the repair of disc degeneration. In the orthopedic field, metal ions contribute in two primary ways. First, they actively participate in the repair processes of bone[13] and cartilage[14] by promoting cell proliferation, differentiation, and extracellular matrix synthesis. Second, they regulate the synthesis and structural properties of biomaterials,[15–17] enhancing their biological functions and improving repair efficacy, thereby improving therapeutic outcomes. Nonetheless, the mechanisms through which metals influence material synthesis and function in IVDD repair remain poorly understood and lack systematic investigation.

This review aims to summarize the therapeutic mechanisms and functions of metal-based nanomaterials in the treatment of IVD injuries over the past three years, emphasize their advancements in the field of IVDD, and explore the potential challenges and future directions associated with the metallic intervention in spinal regenerative medicine (Scheme 1).

2. Multiple roles of metals in IVDD

2.1. Targeted drugs carrier and hydrogen generator

Magnesium and aluminum. Magnesium (Mg) is an essential component of biomedical materials supporting tissue regeneration, targeted drug delivery, antimicrobial activity, and neural repair,[18–21] Mg improves hydrogel mechanics and injectability while promoting glycosaminoglycan (GAG) secretion and cell proliferation, thereby contributing to IVD regeneration[22] (Fig. 1a–c). Mg plays a role in a mild-alkalization strategy that regulates aging pathways through sustained Mg^{2+} release, inhibition of Ca^{2+} influx, promotion of senescent cell proliferation, and improvement of the microenvironment favorable for disc repair[23] (Fig. 1d–h). By controlling its degradation to produce hydrogen (H_2), Mg effectively eliminates reactive oxygen species (ROS), inhibits apoptosis and extracellular matrix degradation, modulates the microenvironment, and supports the repair of IVDD[24] (Fig. 1i and j). Moreover, Mg^{2+} promotes cell proliferation and exerts anti-inflammatory effects through coordination with histidine-functionalized hyaluronic acid. This interaction helps maintain nucleus pulposus cell activity, enhances the microenvironment of IVDD, and supports tissue regeneration[25] (Fig. 1k and l).

Aluminum (Al) in biomaterials enhances mechanical properties, modulates the microenvironment, promotes cellular compatibility, and functions as an antimicrobial agent.[26–28] In a previous study, Al is also a key component of MgAl-LDH NPs,

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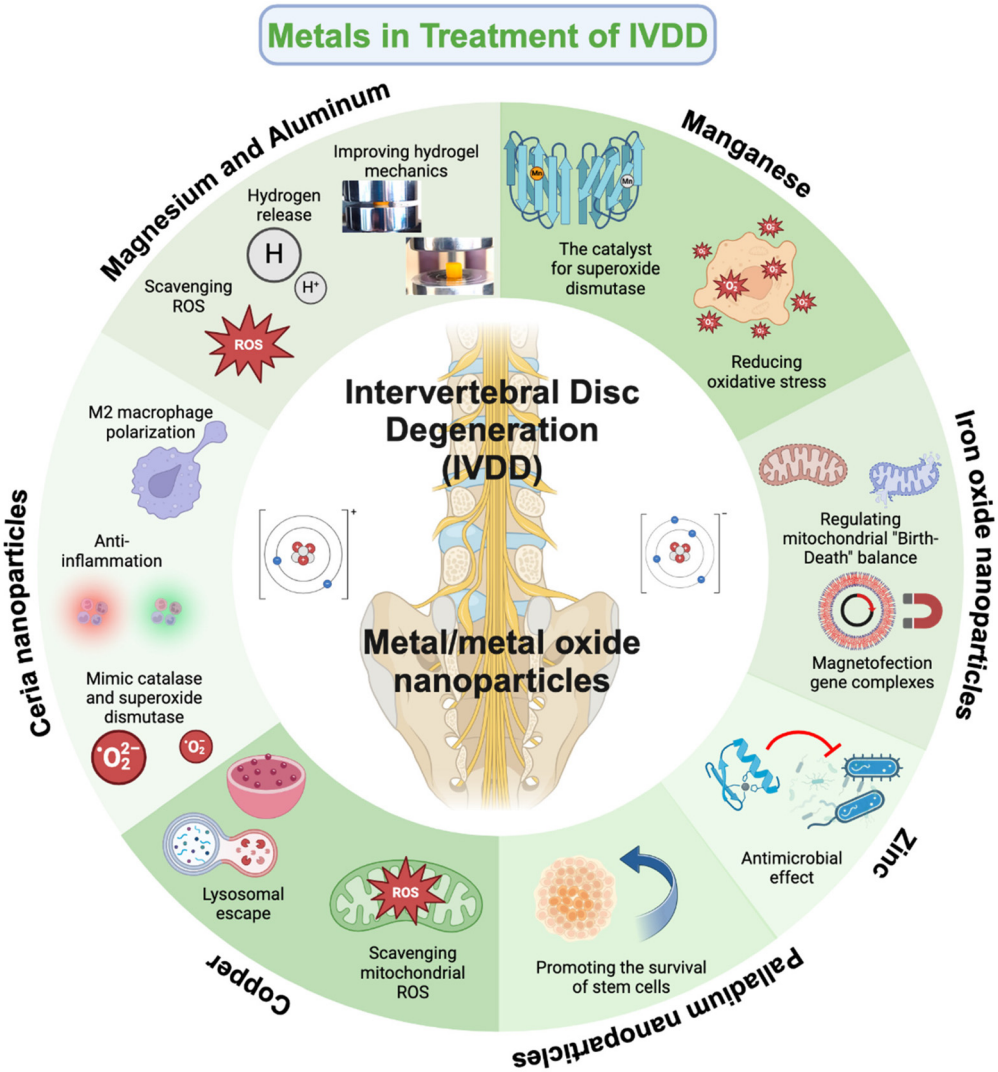

Scheme 1 Illustration of the involvement of various metal or metal oxide NPs in the treatment of IVDD (Created in BioRender. Zhang, L. (2025) https://BioRender.com/76ij58o).

contributing to the structure and functionality of the hydrogel system. It forms ionic interactions and hydrogen bonds, improving the mechanical properties and enabling the controlled release of the anti-inflammatory drug celecoxib, while maintaining biocompatibility and supporting the proliferation of nucleus pulposus cells in the IVD.[22]

2.2. Scavenging ROS and reducing inflammation in IVD cells

Ceria NPs. Ceria nanoparticles (CeO_2 NPs) enable efficient redox cycling between the Ce^{3+} and Ce^{4+} oxidation states, facilitated by oxygen vacancies in their crystal lattice. This cyclic redox process is crucial to the catalytic antioxidant function of CeO_2 NPs, aiding in the effective elimination of ROS. The activities of CeO_2 NPs, which mimic catalase (CAT) and superoxide dismutase (SOD), are central to their anti-inflammatory effects, highlighting their promising potential for applications in tissue repair and regeneration. In addition, CeO_2 NPs have been investigated as ROS scavengers in the treatment of Alzheimer's disease,[29] spinal cord injury,[30] atopic dermatitis,[31] and Parkinson's disease.[32] A study developed GelMA/HAMA composite hydrogels loaded with functionalized mesoporous silica NPs, CeO_2 NPs, and TGF-β3, demonstrating significant potential to regulate the annulus fibrosus (AF) defect microenvironment in IVDD. This regulation occurs through ROS scavenging (Fig. 2a–d), anti-inflammatory M2 macrophage polarization induction, and inhibition of inflammation[33] (Fig. 2e–g).

2.3. "Proton-sponge effect" of metallopolyphenol NPs

Copper. The metal nano-polyphenol particles exist widely in many plants in nature, and have antioxidant activity, antibacterial activity and pH response, exhibiting excellent biocompatibility.[34] Copper (Cu) serves as a catalytic oxidation center, while Epigallocatechin gallate (EGCG) possesses reducing properties, which interact and oxidatively polymerize into a

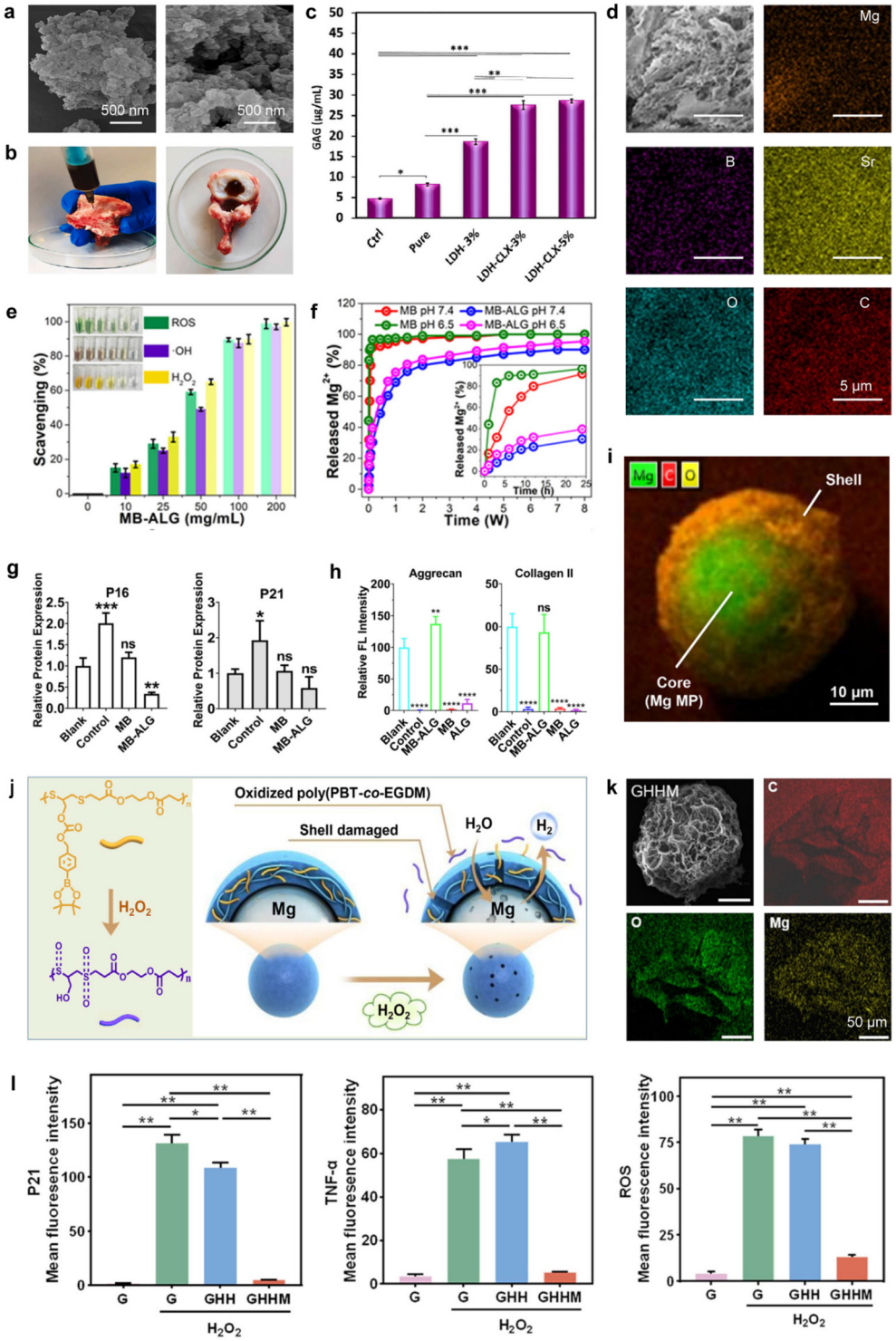

Fig. 1 (a) SEM images and particle size distribution of MgAl-LDH and LDH-CLX. (b) *Ex vivo* assessment of the injectability and cavity-filling capabilities of the composite hydrogel. (c) Total glycosaminoglycan (GAG) released by nucleus pulposus cells over 7 days (**$p < 0.01$; $n = 3$). The figures have been reproduced from ref. 22 with permission from Elsevier, copyright 2024. (d) Elemental mapping of MB–ALG hydrogels. (e) Scavenging activity of MB–ALG hydrogels against ROS, $^{\cdot}OH$, and H_2O_2 (mean ± SD, $n = 3$). The percentage of Mg^{2+} released from MB–ALG hydrogels and MB NPs over time under varying conditions. (f) Cumulative Mg^{2+} release percentage of MB–ALG hydrogel and MB NPs over time under different conditions. (g and h) Changes in the levels of P16, P21, Acan, and Col2. The figures have been reproduced from ref. 23 with permission from American Chemical Society, copyright 2024. (i and j) The fluorescence image of magnesium-containing microsphere (Mg@PLPE MS) labeled with Nile Red and the schematic illustration of the fabrication of ROS-responsive Mg@PLPE MS. The figures have been reproduced from ref. 24 with permission from Elsevier, copyright 2023. (k) SEM mapping of GHHM microspheres, scale bar = 50 μm. (l) Quantitative analysis of mean fluorescence intensity of P21 (left), TNF-α (middle), ROS (right). The figures have been reproduced from ref. 25 with permission from BioMed Central, copyright 2023.

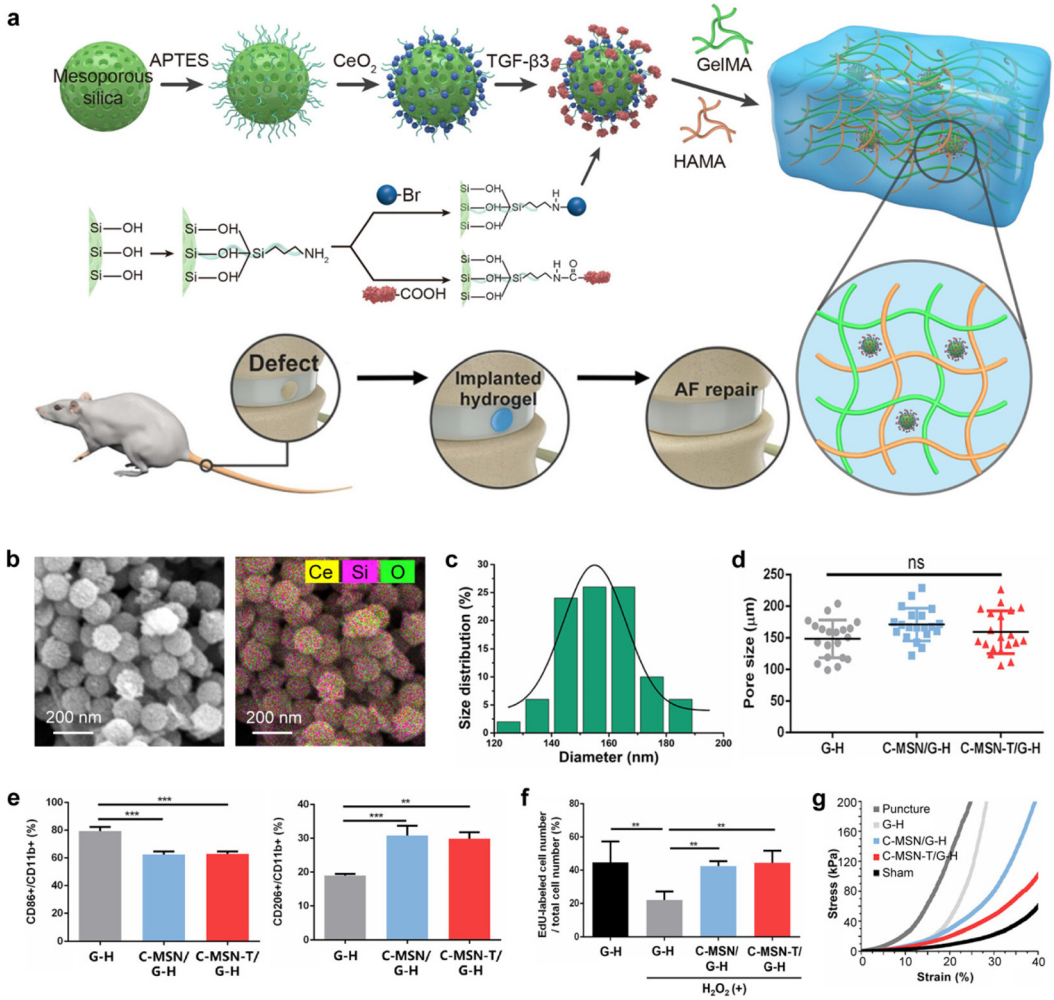

Fig. 2 (a) Schematic illustration of the composite hydrogels for AF repair. (b) Energy-dispersive X-ray spectroscopy (EDX) elemental mapping of silicium (purple). (c) Diameter distribution of MSN (n = 50). (d) Pore sizes of various hydrogels. (e) Antioxidant and anti-inflammatory properties of the composite hydrogels: quantitative analysis of cytometry results (n = 3). *p < 0.05, **p < 0.01, ***p < 0.001. (f) Cell status in oxidative damage microenvironment: quantitative analysis of the percentage of positive EdU-labeled cell (n = 5; blue, Hoechst staining; green, EdU staining). (g) Typical stress–strain curves of the IVD. The figures have been reproduced from ref. 33 with permission from American Chemical Society, copyright 2023.

quinone structure in an alkaline environment. The charged Cu-based polymer facilitates efficient intra-mitochondrial uptake and promotes lysosomal escape, overcoming the challenge of lysosomal phagocytosis and enhancing the intracellular delivery of functional NPs. A previous study[35] demonstrated that modifying PG@Cu with a mitochondrial targeting peptide significantly improved its mitochondrial specificity. This targeted approach effectively scavenged mitochondrial ROS, repaired oxidative stress-induced mitochondrial damage, and preserved the normal morphology of nucleus pulposus cells (Fig. 3a–d).

2.4. Modulating the behavior of bone marrow mesenchymal stem cells

Iron oxide NPs and ferrous NPs. Magnetic fields to guide iron-bound composites toward target seed cells have been commercialized under the term magnetic induction.[36–38] Iron (Fe) oxide NPs (IONPs) were synthesized by co-precipitating ferrous and ferric ions in an alkaline medium, resulting in magnetofection gene complexes that deliver therapeutic miRNAs for osteogenesis and angiogenesis. Subsequent results demonstrated that IONPs enhanced transfection efficiency by activating the p38 MAPK pathway[39] (Fig. 3e and f). In another study, Fe facilitated sustained H_2 production under the pathological microenvironment, neutralizing local acidity, alleviating oxidative stress, and regulating the mitochondrial "Birth–Death" balance, thereby promoting the repair of IVDD[40] (Fig. 3g and h). The greigite nanozyme (Fe_3S_4) emerges as a promising agent for attenuating disc degeneration by simultaneously scavenging ROS and releasing polysulfides, thereby mitigating oxidative stress and synergistically inhibiting ROS-induced senescence in nucleus pulposus cells[41] (Fig. 3i). GSH-CDs nanozyme containing $FeCl_3{\cdot}6H_2O$ mitigates ROS-induced mitochondrial damage

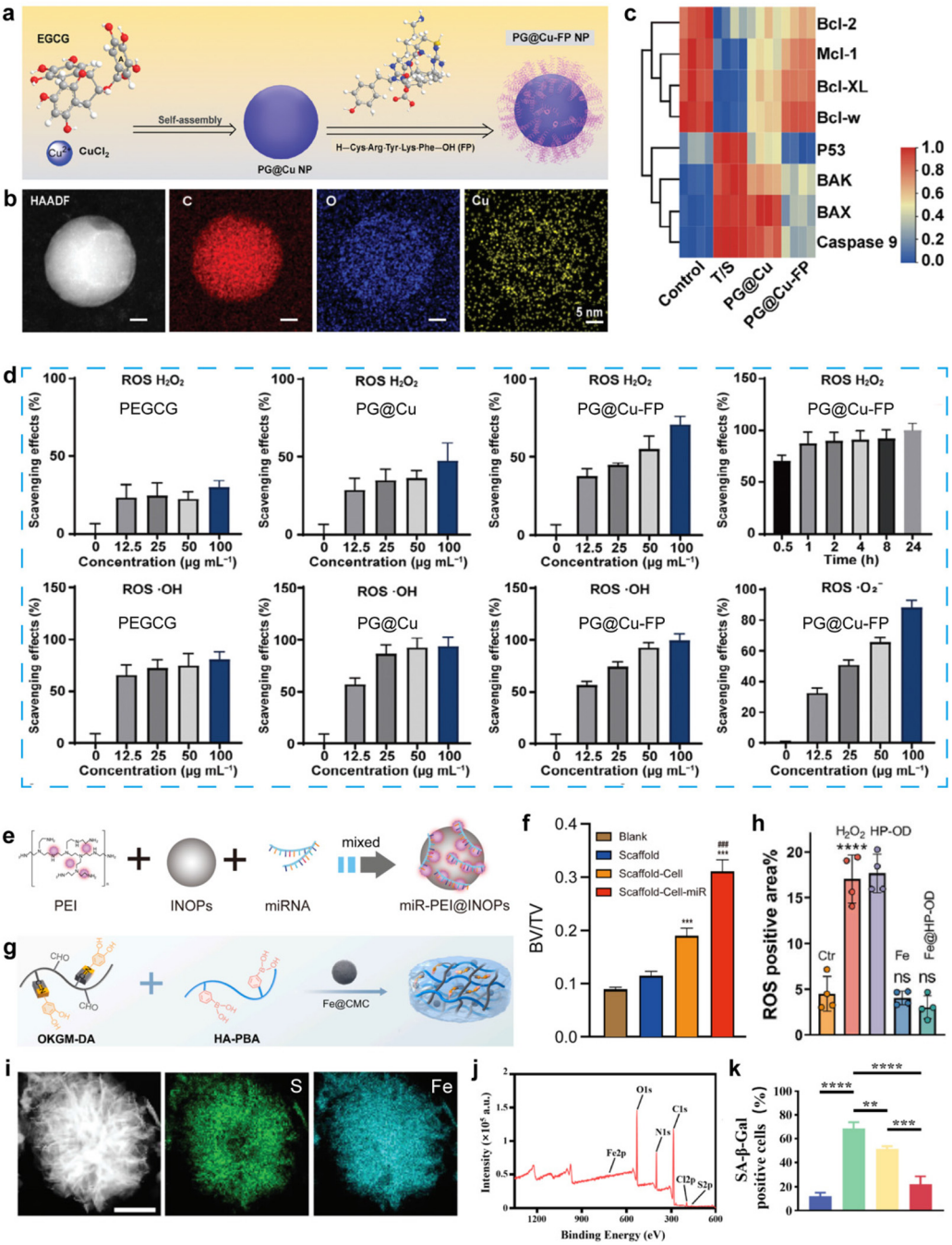

Fig. 3 (a) Schematic illustration of NPs catalyzed by Cu^{2+} and addition of peptides. (b) TEM (n = 3, scale bar: 25 nm) and elemental mapping microscopy. (c) Heat map of apoptosis-related genes. (d) The effect of multifunctional NPs in scavenging reactive oxygen species. The figures have been reproduced from ref. 35 with permission from Wiley, copyright 2024. (e) Schematic illustration of the synthesis process for magnetofection complexes (miR-PEI@IONPs) using polyethyleneimine (PEI)-coated IONPs for miRNA delivery. (f) Quantitative analysis of bone volume relative to total volume. The figures have been reproduced from ref. 39 with permission from BioMed Central, copyright 2023. (g) Schematic illustrating the fabrication and molecular mechanisms of the intelligent hydrogen nanogenerator (Fe@HP-OD). (h) Quantitative analysis of ROS across different groups. The figures have been reproduced from ref. 40 with permission from Elsevier, copyright 2023. (i) Element mappings of S (green) and Fe (blue) elements in greigite nanozyme. This figure has been reproduced from ref. 41 with permission from Wiley, copyright 2023. (j) XPS spectrum of GSH-CDs. (k) SA-β-gal analysis of the percentage of SA-β-Gal-positive cells in different groups. The figures have been reproduced from ref. 42 with permission from BioMed Central, copyright 2024.

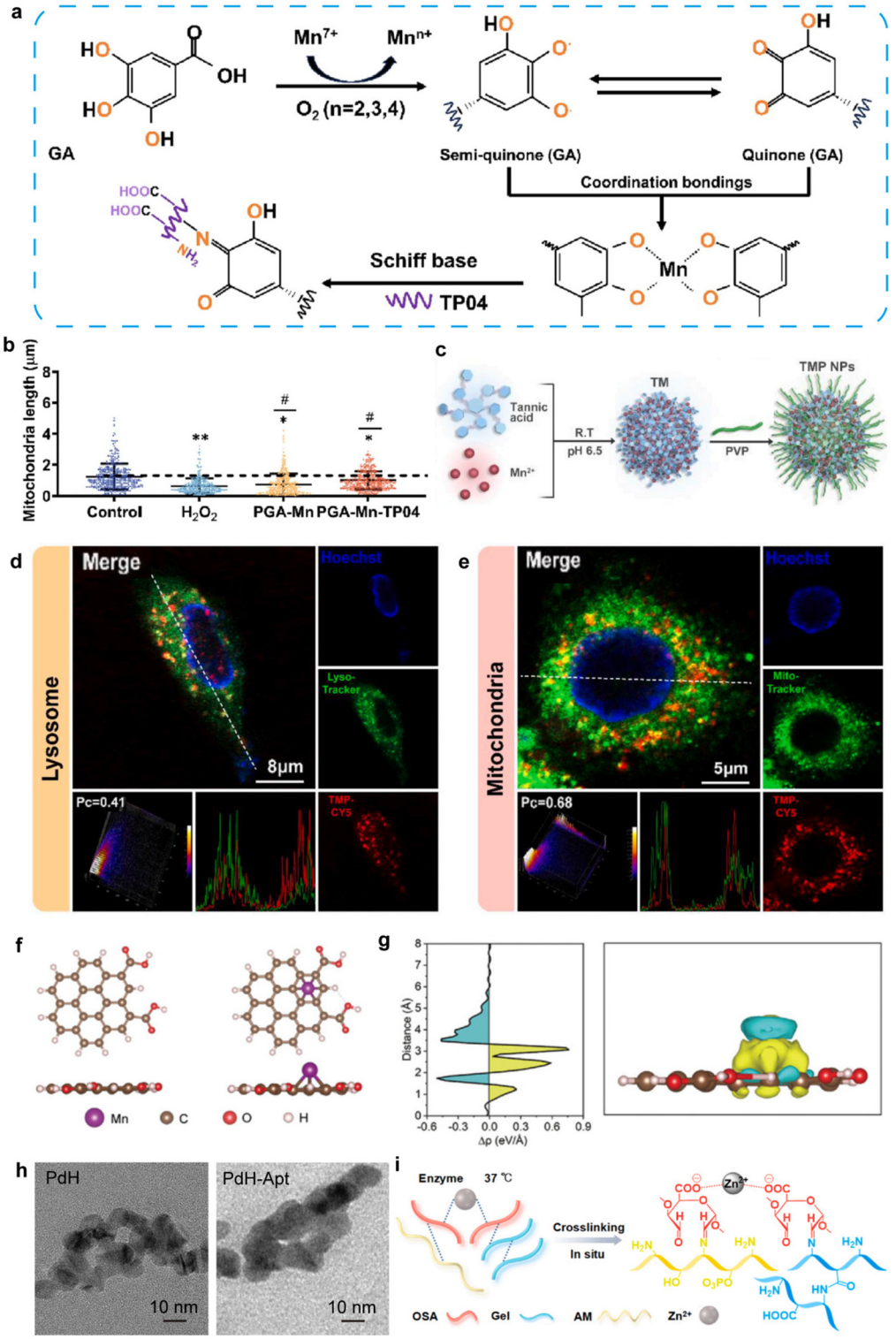

Fig. 4 (a) Schematic illustration of PGA-Mn-TP04. (b) Analysis of mitochondrial length. The figures have been reproduced from ref. 44 with permission from American Chemical Society, copyright 2024. (c) Schematic illustrating the synthesis of TMP. (d) Co-localization of the NPs (red) with lysosomes (green). (e) Confocal microscopy images of the co-localization of mitochondria (green) and NPs (red). Red: CY5-labeled TMP, green: lysosome or mitochondria, blue: nucleus. The figures have been reproduced from ref. 45 with permission from Elsevier, copyright 2024. (f) Atomic structures of CDs and MCDs. The purple, gray, red, and white balls denote the Mn, C, O, and H atoms, respectively. (g) Planar-averaged electron density difference and charge density difference plots for Mn interacting with monolayer CDs. The yellow and cyan colors indicate charge accumulation and depletion, respectively. The figures have been reproduced from ref. 46 with permission from Wiley, copyright 2024. (h) TEM images of fabricated PdH and PdH-Apt. This figure has been reproduced from ref. 50 with permission from Wiley, copyright 2024. (i) Preparation of ZOGA. This figure has been reproduced from ref. 52 with permission from Elsevier, copyright 2024.

and senescence in NP cells, thus attenuating IVDD progression[42] (Fig. 3j and k).

2.5. The catalyst for superoxide dismutase within mitochondria

Manganese. Manganese (Mn) is a vital trace element essential for human health, primarily acting as an activator for various enzymes.[43] Through coordination with tannic acid, Mn enhances its antioxidant activity, acts as a catalyst for superoxide dismutase (Mn-SOD), efficiently scavenges mitochondrial ROS, restores mitochondrial function, reduces oxidative stress, and supports IVD cell viability and tissue regeneration[44] (Fig. 4a and b). Moreover, Mn targets mitochondria *via* a metal–phenolic network (tannic acid-Mn–polyvinylpyrrolidone, TMP) to scavenge ROS, inhibit pyroptosis, and reduce extracellular matrix (ECM) degradation in IVDD[45] (Fig. 4c–e). Carbonized manganese nanodots (MCDs) function as ROS-scavenging nanozymes to inhibit pyroptosis in nucleus pulposus cells, offering an effective strategy for IVDD attenuation[46] (Fig. 4f and g).

2.6. The ability to overcome the hostile inflammatory environment during IVDD

Palladium NPs. Palladium (Pd) primarily serves as an anti-inflammatory and antioxidant in biomaterials research. It modulates the inflammatory microenvironment, reduces oxidative stress, enhances cell survival, and promotes tissue repair.[47–49] Furthermore, Pd supports the proliferation and differentiation of endogenous stem cells, improves the mechanical properties of biomaterials, and stimulates tissue regeneration. By modifying Pd hydride (PdH) nanostructures, Pd exerts significant anti-inflammatory and antioxidant effects, improving the inflammatory microenvironment in IVDD, promoting the survival of endogenous stem cells, and facilitating disc regeneration[50] (Fig. 4h).

2.7. Promoting crosslinking of the oxidized sodium alginate molecular chain

Zinc. Zinc (Zn), an essential trace element, exhibits potent antimicrobial properties and enhances the mechanical strength and biocompatibility of Zn-based biohydrogels.[51] A previous study[52] found that Zn could facilitate the crosslinking of oxidized sodium alginate (OSA) molecular chains, thereby improving the hydrogel's mechanical properties and promoting its affinity with nucleus pulposus tissues. Additionally, Zn provides stable antimicrobial effects within the Zn-containing platform, supporting the maintenance of extracellular matrix metabolic balance, thus aiding in the repair of IVDD (Fig. 4i).

3. Conclusions and outlook

In recent years, biomaterials have garnered considerable attention in the treatment of IVDD, a prevalent age-related degenerative condition characterized by nucleus pulposus degeneration, annulus fibrosus rupture, and cartilage endplate calcification, resulting in severe LBP.[53] Given the complex structure of the IVD and its limited self-repair capacity, the application of biomaterials offers a promising therapeutic strategy. Previous research has shown that biodegradable hydrogels, nanomaterials, and composites can facilitate the growth and repair of IVD cells and enhance the disc microenvironment. For instance, hyaluronic acid,[54] gelatin,[55] and polymer-based hydrogels demonstrate excellent cellular compatibility, mechanical properties, and the ability to release growth factors, anti-inflammatory molecules, and other bioactive compounds, thereby supporting disc repair in preclinical studies. Moreover, integrating metal ions, nanozymes, and bioactive molecules has significantly enhanced these hydrogels' antioxidant, anti-inflammatory, and cellular activity regulation properties.

Life processes result from intricate interactions among bioactive substances engaged in chemical reactions, where metal ions play a pivotal role. These ions are omnipresent and are indispensable components of all life forms, contributing significantly to fundamental biological processes and maintaining human homeostasis.[56] As efficient catalysts, metal ions are central to metabolic reactions, driving essential biochemical pathways. Metal ions and their oxides find extensive application in tissue engineering and regenerative medicine due to their multifunctional properties, including antibacterial, antioxidant, and cell proliferation-promoting effects. They contribute to enhancing mechanical properties, regulating biological signaling pathways, facilitating tissue regeneration, and controlling drug release in biomaterials. Besides, numerous enzymes depend on metal ions to sustain their catalytic activity, highlighting their indispensable role in biological and therapeutic processes. Research has shown that over half of metabolic pathways rely on metal ions, underscoring their vital role in cellular function. For example, Mn^{2+} and Zn^{2+} are essential cofactors for various glycosylases located in the Golgi apparatus, and their balanced homeostasis is critical for the proper functioning and stress response of this organelle.[57,58] Given their significance in maintaining tissue homeostasis, exogenous metal ions have the potential to act as therapeutic agents, promoting tissue healing and regeneration. While the application of metal ions in bone tissue engineering has attracted growing interest, their potential in addressing IVDD remains largely underexplored, warranting further investigation into their therapeutic efficacy and mechanisms. Mechanistically, metal NPs exert therapeutic effects in IVDD by modulating multiple intracellular signaling pathways. For instance, manganese-based NPs attenuate oxidative stress-induced nucleus pulposus cell degeneration by scavenging ROS and inhibiting the activation of the ERK pathway, thereby suppressing downstream pro-inflammatory cytokines such as IL-17.[45] Iron oxide nanozymes have also been shown to interfere with the MAPK cascade, particularly by downregulating phosphorylated p38, thus reducing ECM degradation and apoptosis.[39] Additionally, certain metal ions (*e.g.*, Mg^{2+}) released from biodegradable nanocarriers can activate the

PI3K/Akt/mTOR signaling axis, promoting nucleus pulposus cell survival and autophagy while mitigating mitochondrial dysfunction.[23] These multifaceted regulatory effects highlight the potential of metal NPs to restore homeostasis in the degenerative disc microenvironment.

Biomaterials, especially those enhanced with metal ions, hold significant promise for advancing the treatment of IVDD. These materials, including biodegradable hydrogels, nanomaterials, and composites, have demonstrated considerable potential in fostering cell proliferation, improving mechanical properties, and modulating biological processes within the IVD microenvironment. By addressing the challenges of IVDD through such innovative strategies, the future of treatment approaches appears highly promising. Metal ions enhance the mechanical strength and biocompatibility of biomaterials, while simultaneously supporting tissue regeneration and enabling controlled drug release. With continued progress in tissue engineering and regenerative medicine, future research is expected to emphasize the creation of hybrid biomaterials that integrate the distinct advantages of metal ions with sophisticated drug delivery systems, potentially transforming therapeutic strategies for IVDD. These systems can potentially provide more effective solutions for overcoming the intricate challenges of IVDD by promoting tissue regeneration and preventing further degeneration. Furthermore, combining metal ion-based therapies with stem cell-based approaches offers significant promise for restoring IVD function and mitigating the chronic pain commonly associated with IVDD. Emerging hypotheses suggest that metal NPs may modulate redox signaling, inhibit ferroptosis, and reprogram nucleus pulposus cell fate. Future studies should explore their integration with gene editing or exosomal delivery systems to enable targeted, regen-

Table 1 Some recently reported examples of metals for the treatment of IVDD

Metal	Material style	Characteristics	Application	Published year	Ref.
Mg	(1) An injectable, self-healable, and shear-thinning hybrid GEL-QCS-LAP hydrogel	(1) The localized celecoxib delivery system for nucleus pulpous repair	(1) IVD	(1) 2024	(1) 22
	(2) Magnesium boride–alginate (MB–ALG) hydrogels	(2) Ameliorating the local aging microenvironment and reinstating normal functionality in senescent cells	(2) IVD	(2) 2024	(2) 23
	(3) A ROS-responsive magnesium-containing microsphere (Mg@PLPE MS)	(3) Alleviating IVDD through controlled release of hydrogen gas	(3) IVD	(3) 2023	(3) 24
	(4) A keep-charging hydrogel microsphere	(4) An ideal platform for the nucleus pulposus cells to grow on	(4) IVD	(4) 2023	(4) 25
Ce	A composite hydrogel integrating ceria and TGF-β3	Eliminate ROS and induce anti-inflammatory M2 type macrophage polarization	AF	2023	33
Cu	A metal polyphenol particles (PG@Cu-FP)	PG@Cu-FP exhibits enhanced escape from lysosomal capture, enabling efficient targeting of mitochondria to scavenge excess reactive oxygen species	IVD	2023	35
Fe	(1) An electromagnetic field and iron oxide NPs	(1) Delivering miR-21 into bone marrow mesenchymal stem cells and HUVECs promoted osteogenesis and angiogenesis	(1) Various orthopaedic diseases	(1) 2023	(1) 39
	(2) An intelligent hydrogen nanogenerator (Fe@HP-OD)	(2) Releasing H_2 in response to the unique micro-environment in degenerated IVDs	(2) IVD	(2) 2024	(2) 40
	(3) A dual-functional greigite nanozyme	(3) Scavenging ROS	(3) IVD	(3) 2023	(3) 41
	(4) The glutathione doped carbon dots	(4) Scavenging ROS	(4) IVD	(4) 2024	(4) 42
Al	An injectable, self-healable, and shear-thinning hybrid GEL-QCS-LAP hydrogel	The localized celecoxib delivery system for nucleus pulpous repair	IVD	2024	22
Mn	(1) Polygallic acid-manganese NPs	(1) Scavenging mROS and restore the mitochondrial function after targeting the Mitochondria	(1) IVD	(1) 2024	(1) 44
	(2) A metalphenolic network release platform	(2) Released from the platform targeted mitochondria to efficiently scavenge ROS and reduce ECM degradation	(2) IVD	(2) 2024	(2) 45
	(3) Carbonized Mn containing nanodots	(3) ROS-scavenging and suppressing pyroptosis of NP cells to alleviate IVDD	(3) IVD	(3) 2024	(3) 46
Pd	A super paramagnetically-responsive cellular gel	PdH modification provided an anti-inflammatory microenvironment, optimizing the healing outcome of IVD	IVD	2023	50
Zn	A high-strength biohydrogel based on zinc-oxidized sodium alginate–gelatin (ZOG)	ZOG loaded with AM (ZOGA) exhibits hygroscopicity, antibacterial activity, biocompatibility, and biodegradability, forming a high-strength collagen network that improves the mechanical properties of the IVD	IVD	2023	52

Magnesium: Mg, cerium: Ce, copper: Cu, iron: Fe, aluminum: Al, manganese: Mg, palladium: Pd, zinc: Zn

erative disc therapy. Future research should focus on refining these strategies to optimize therapeutic outcomes. Despite notable advancements, further investigation is required to optimize the clinical application of these materials, particularly concerning their long-term efficacy, biodegradability, and *in vivo* safety. Incorporating metal ions into IVDD therapy presents promising opportunities for developing non-invasive, regenerative treatments, potentially revolutionizing the clinical management of this challenging condition. To comprehensively assess long-term biosafety, we recommend implementing chronic *in vivo* toxicity evaluations, employing advanced imaging techniques for nanoparticle tracking, and conducting systematic histological analyses over extended periods. For delivery system optimization, we propose the development of stimuli-responsive carriers and the incorporation of disc-targeting modifications (*e.g.*, peptide ligands). These proposed methodological advancements are designed to bridge existing translational gaps, improve clinical applicability, and systematically address current technical barriers in the field. Additionally, to facilitate clinical translation, future studies should optimize the metabolic clearance and biosafety of metal NPs. Engineering biodegradable, renally excretable platforms and conducting long-term *in vivo* safety evaluations will be critical to ensure the therapeutic feasibility in IVDD.

Although most current studies on metal-based NPs in IVDD are confined to *in vitro* or small animal models, emerging translational efforts indicate growing clinical interest. For instance, IONPs have shown promise in modulating inflammation and oxidative stress in disc cells, and several early-phase clinical trials have evaluated their safety in related musculoskeletal applications such as osteoarthritis.[59] Gold[60] NPs are also under investigation for their anti-inflammatory and antimicrobial properties, with ongoing translational studies aiming to develop injectable formulations for spinal disorders. While direct clinical trials for metal-based NPs specifically targeting IVDD remain scarce, these efforts highlight the therapeutic potential and future directions of nanomedicine in disc degeneration. Continued optimization of biocompatibility, targeting specificity, and delivery systems will be critical for successful clinical translation.

This review offers a detailed overview of research conducted in the past three years on using metal ions and their oxide NPs in IVDD treatment. It underscores the multifaceted roles of metal ions such as Mg, Ce, Cu, Fe, Al, Mn, Pd, and Zn in modulating the pathophysiology of IVDD (Table 1). These ions influence key cellular processes, including reducing oxidative stress, anti-inflammatory effects, extracellular matrix remodeling, and promoting cellular proliferation and differentiation. Importantly, this review critically evaluates the potential of these metal-based therapies to enhance tissue repair and regeneration in IVDD.

Author contributions

Long Zhang: writing – original draft, investigation, conceptualization, data curation, formal analysis, funding acquisition. Haijiang Ren and Fang Cai: formal analysis, investigation. Bin Ru, Nannan Zhang, Wenlong Liu, and Wenjun Cai: methodology, validation. Yun Xu: Resources. Xiang Wu: software. Shibo Wang: visualization. Han Zhang: writing – review & editing, project administration. Han Zhang, Shun Li, and Xiangdong Kong: writing – review & editing, supervision, project administration.

Data availability

Permission has been acquired for the use of all figures' copyright in this review.

This is a review paper. No primary research results, software or code have been included and no new data were generated or analysed as part of this review. This review cited some data from published papers, and matched data can be obtained from the matched published papers.

Conflicts of interest

There are no conflicts to declare.

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