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Application trends and strategies of hydrogel delivery systems in intervertebral disc degeneration: A bibliometric review

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ABSTRACT

Hydrogels are widely used to explore emerging minimally invasive strategies for intervertebral disc degeneration (IVDD) due to their suitability as drug and cell delivery vehicles. There has been no review of the latest research trends and strategies of hydrogel delivery systems in IVDD for the last decade. In this study, we identify the application trends and strategies in this field through bibliometric analysis, including aspects such as publication years, countries and institutions, authors and publications, and co-occurrence of keywords. The results reveal that the literature in this field has been receiving increasing attention with a trend of growth annually. Subsequently, the hotspots of hydrogels in this field were described and discussed in detail, and we proposed the "four core factors", hydrogels, cells, cell stimulators, and microenvironmental regulation, required for a multifunctional hydrogel for IVDD. Finally, we discuss the popular and emerging mechanistic strategies of hydrogel therapy for IVDD in terms of five aspects: fundamental pathologic changes in IVDD, counteracting cellular senescence, counteracting cell death, improving organelle function, and replenishing exogenous cells. This study provides a reference and a new perspective for future research in this urgently needed field.

1. Introduction

Research indicates that approximately 700 million people worldwide, spanning various age groups and socioeconomic backgrounds, suffer from the torment of lower back pain (LBP) [1–3]. Intervertebral disc degeneration (IVDD) is one of the most common causes of LBP, and a significant burden on families and societies [4–6]. Unfortunately, for IVDD, the most prevalent degenerative spine disease, the current medical interventions are limited and may lead to significant challenges for patients, such as gastrointestinal drug reactions, reduced spinal mobility, and postoperative recurrence [7–9]. Due to the structural characteristics of IVD, the nucleus pulposus (NP) is almost inaccessible to the outside world and has no blood vessels, it is difficult to form or maintain an effective drug concentration locally through systemic administration. Therefore, local injection of IVD may be a more direct and effective treatment. However, there may be some risks, such as aggravating the injury to the anulus fibrosus (AF), leakage of drugs or mesenchymal stem cells (MSCs) occurs, ectopic ossification, and others. This not only limits the curative effect of drugs but also limits the clinical application of this treatment method.

Encouragingly, the cross-disciplinary field of medical-chemical engineering has experienced rapid and dynamic advancements, particularly in the realm of hydrogel materials [10–13]. With a high water content resembling that of NP tissue and a 3D network structure akin to that of the natural extracellular matrix (ECM), hydrogels can support cellular behaviors such as migration, adhesion, proliferation, and differentiation. The highly tunable mechanical properties of these materials make them suitable for the unique pressure environment of IVDs, with the potential to partially restore disc height [14,15]. Hydrogel delivery systems implanted into degenerated IVDs have shown effectiveness in prolonging drug release and action time, thereby enhancing therapeutic outcomes. These distinctive properties position hydrogel

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materials as among the most suitable tissue engineering materials for IVDD repair. Currently, injectable hydrogels are being investigated as a minimally invasive means to delay or even reverse IVDD [16–19].

Currently, some researchers have summarized the application of hydrogels in the field of IVDD [20–22]. However, these summaries often focus on specific types of hydrogels, such as decellularized matrix (dECM) hydrogels [23,24], silk hydrogels [25], electrospun nanofibrous hydrogels [26], and self-assembling peptide (SAP) hydrogels [27]. However, there is no review evaluating the overall research trends of various hydrogel delivery systems for the treatment of IVDD. Bibliometric analysis is an essential tool for quantifying the number of articles in a scientific field, and it has become a popular tool for statistically analyzing relevant features, offering a comprehensive overview of the literature. This enables researchers to more easily identify the developmental processes, current status, and future trends in related areas [28–31].

Therefore, this study employed bibliometric tools to conduct a detailed and comprehensive analysis of the research trends related to hydrogels in the field of IVDD. Subsequently, by integrating the bibliometric results with the trending mechanism directions, we provided a detailed description and discussion of the research hotspots in this field. Furthermore, we put forward the "four core factors" that should be possessed by multifunctional hydrogels for repairing IVDs. Finally, we summarize the current popular and emerging mechanisms of hydrogel therapy for IVDD, which provides a reference and a new perspective for future research in this crucial field.

2. Bibliometric analysis

2.1. Data sources and methods

In this study, bibliometric methods were utilized to elucidate the research trends, hotspots, and strategies in the field of hydrogel delivery systems for intervertebral disc degeneration. Web of Science (WoS) is the most appropriate influential, extensive, and trustworthy database for literature retrieval and analysis. On July 10, 2023, the WoS Core Collection database was used to identify documents on hydrogels and intervertebral discs. To ensure the breadth of the search scope, the search terms were constantly filtered. Finally, the following keywords were established: TOPIC = ((Intervertebral Disk Degeneration*) OR (intervertebral disk*) OR (intervertebral disc*) OR (disc herniation*) OR (disk herniation*) OR (disc disease*) OR (disk disease*)) AND TOPIC = (hydrogel OR hydrogels) AND Language = English AND Document type= (Article OR Review) AND Time span = 1985 to 2023. The data were exported and analyzed by removing duplicate entries using VOSviewer software 1.6.16 (Van Eck and Waltman, Leiden University, Leiden, The Netherlands) for network visualization. In addition, the documents were analyzed by the Bibliometrix package (http://www.bibliometrix.org/), which is an R-Tool for science mapping. This study is primarily descriptive without statistical analysis, the number and ratio (%) of each metric represent the distribution and changing patterns, respectively, in various years, nations, institutions, journals, and authors.

2.2. Annual publication

In total, 687 publications were retrieved, including 590 articles, 71 review articles, 25 meeting abstracts, and other types of papers. As document types such as meeting abstracts, book chapters, and other publications do not share the same citation rates, only document types that included original articles and reviews (657 publications) are included in the following analysis. First, we analyzed the growth of the obtained publications according to the publication year. As shown in Fig. 1A, the number of published articles increased in 2014 (reaching 45), and the second research peak occurred in 2021, with 68 articles. We found that the number of citations increased annually, indicating increasing interest in the biomedical community for the use of hydrogels in IVDD.

2.3. Most productive countries and institutions

More than 50 countries and regions worldwide are actively researching the application of hydrogels in the field of IVDD. The top 15 countries or regions with the most publications are shown in Fig. 1B. Researchers from the USA contributed the largest number of publications and had the highest H-index (202 articles, 45) in this field. China (167 articles, 32) and Switzerland (61 articles, 27) ranked second and third, respectively. A high H-index value indicates a high number of both publications and total citations of the same entity. Regarding the average citation ranking, Portugal ranked first (56 citations per record). To evaluate the most influential countries in the field more accurately, it is rational to consider as many key indicators (H-index, total citations, average citations) as possible. In this sense, China and the USA have made considerable contributions to the application of hydrogels in IVDD in terms of quality and quantity.

Among the most productive institutions, 833 institutions around the world are involved in the field of the application of hydrogels to IVDs. As shown in Fig. 1C, the top 15 research institutions in this field are from Europe, Asia, and America. Among them, the Ao Foundation and the University of Pennsylvania are in first and second place in terms of the number of papers published in this field, with 35 and 27 papers published, respectively. Additionally, the H-indexes of these two institutions are also far ahead of those of other institutions, reaching 22. Notably, although Drexel University ranks 14th in the number of published articles, its papers have been cited 56 times, ranking second, indicating that its papers have a high academic influence in the field.

Fig. 1D shows the geographic distribution of the number of authors affiliated with the country of publication. The USA has the darkest blue color. The USA and China are two core research powers for the application of hydrogels in IVDD. Fig. 1E shows the number of joint papers published by the top countries in the field of the application of hydrogels in IVDD. The USA seems to be the central country for any published document because there are so many scientific links between the USA and other countries. The USA and China are very cooperative in terms of scientific production, followed by Germany and Italy.

2.4. Most productive authors and sources

From 2001 to 2023, a total of 2609 researchers published their research findings in the field of hydrogel therapy for IVDD. This indicates that, within our analyzed dataset, each publication has an average of 5.00 authors and 6.39 co-authors. Fig. 2A displays the publications of the most relevant authors over the past decade (2012–2022). During this period, Zhang Y published 19 articles in the field of hydrogel therapy for IVDD, making him the author with the longest span of contributions, while Li Z had the highest annual total citation count in the field. Since 2020, several authors have published three or more highly cited papers. It is evident from the results that an increasing number of Chinese scholars are making significant contributions to this field. In addition, in the process of literature analysis, experts in the field of spine or biomaterials, such as Rui L. Reis [32], Abhay Pandit [33], Hans-Joachim Wilke [34], etc., have made great contributions to the field of hydrogel treatment of IVDD, although they are not presented in the data.

The most relevant journal sources in this field are illustrated in Fig. 2B. The journal "Acta Biomaterialia" stands out as the top critical journal, publishing approximately 39 articles from 2001 to 2023. The journal "Biomaterials" is the second with 31 published papers. The number of publications in other journals is less than 30. The top three journals are significant for researchers in the field of hydrogel therapy for IVDD and are the preferred choices for submissions. Additionally, through co-citation network analysis, the minimum citation threshold

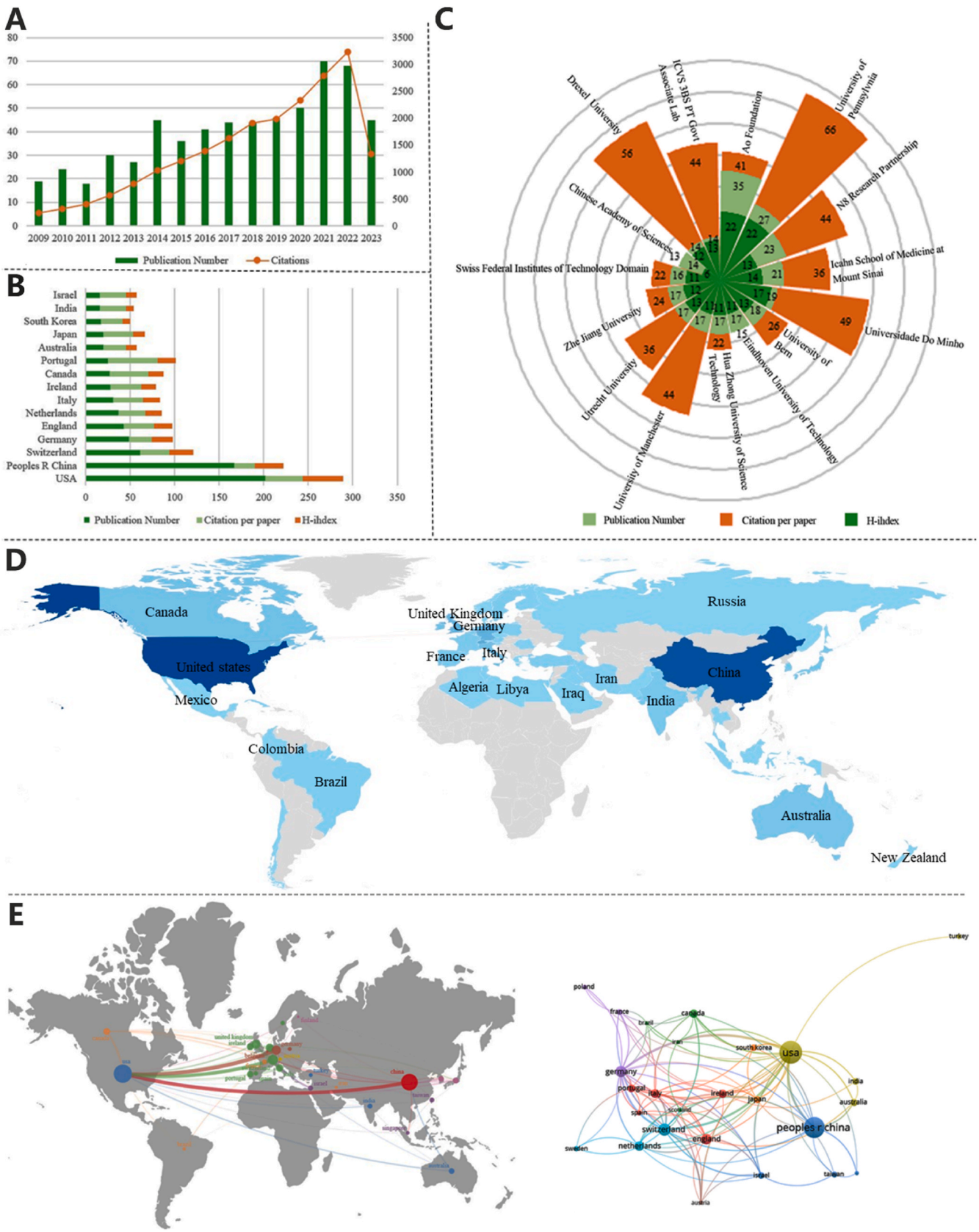

Fig. 1. **A**) The annual publication and citation growth of literature on the application of hydrogels in IVDD. The most contributing **B**) countries/regions and **C**) institutions to the application of hydrogels in IVDD. **D**) The geographic distribution of the number of authors affiliated with the country of publication (the shade of blue in the figure is proportional to the number of authors affiliated with each country). **E**) Geographic map and co-occurrence analysis of the number of joint papers published by the top countries (the size of the circle represents the number of articles published by the country, and the larger the circle is, the greater the country's contribution to co-authorship. The thicker the lines between the two countries are, the closer the cooperation between the two countries is).

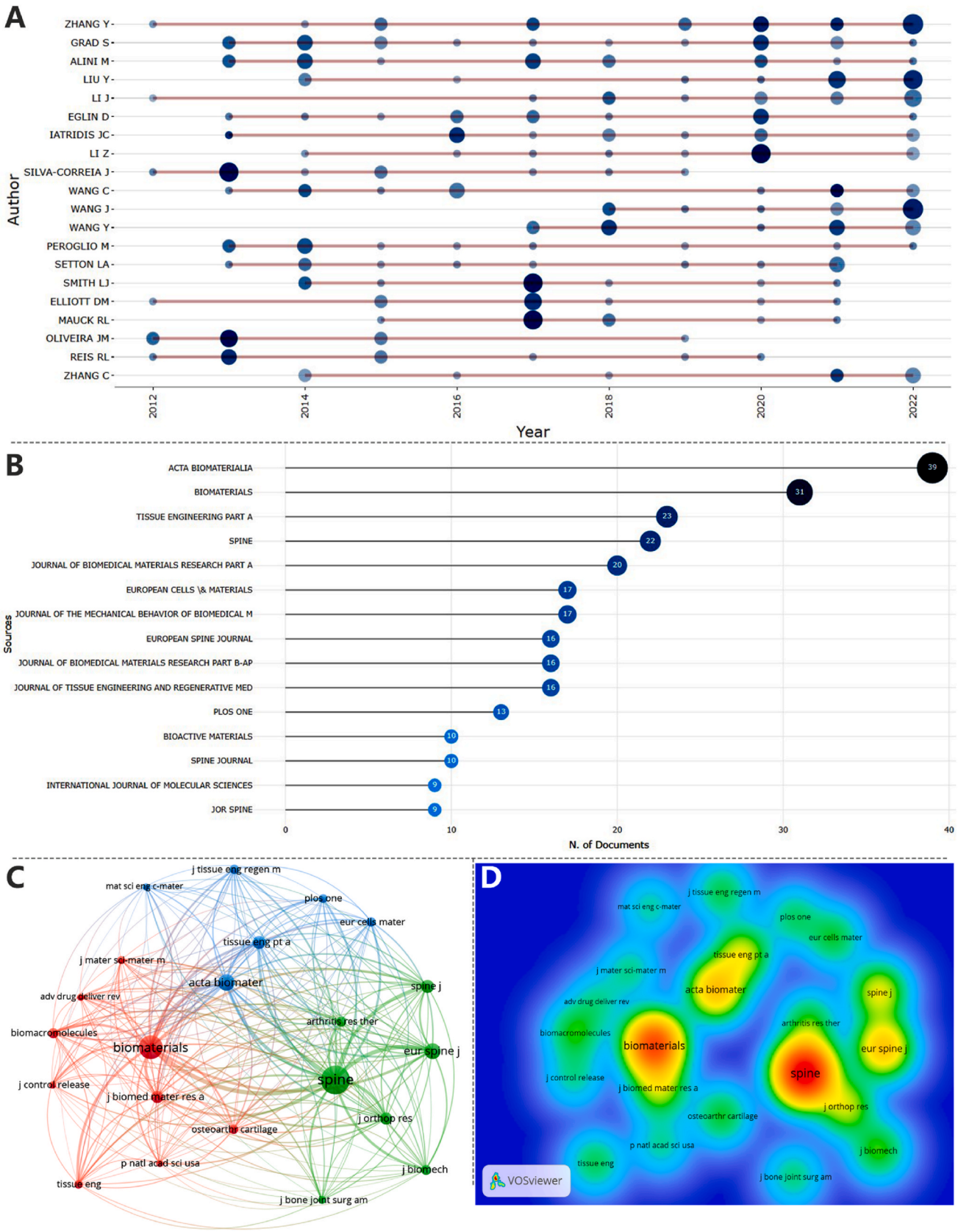

Fig. 2. **A**) The publications of the most relevant authors over the past decade (2012–2022) in the field of hydrogel therapy for IVDD. **B**) The most relevant journal sources. **C**) Co-citation network analysis and **D**) co-citation rate heatmap of the sources.

for sources is set to 250 times. Among 3820 sources, only 22 journals met this threshold (Fig. 2C). "Spine" leads with the highest total link strength (TLS) of 112923 (Citations = 3849), followed by "Biomaterials" (TLS = 95995, citations = 2693) and "Acta Biomaterialia" (TLS = 53264, citations = 1276). The strongest link (16368 times) occurs between "Spine" and "Biomaterials". This analysis identified three source clusters. Cluster 1 (green) includes 7 closely related journals, with "Spine" at its core. Cluster 2 (red) consists of 9 sources, with "Biomaterials" at its core. Cluster 3 (blue) includes 6 sources, with "Acta Biomaterialia" at its core. The co-citation rate heatmap for each source is shown in Fig. 2D, with "Spine" also displaying the highest activity. Fig. S1 displays the number of sources that occurred from 2001 to 2023, and reveals the optimal dynamic sources in the field of hydrogel therapy for IVDD. Over time, the annual publication rate of top journals gradually declined after an initial increase. Furthermore, the growth rate of the journal "Acta Biomaterialia," which experienced the fastest growth, slowed down after 2017.

2.5. Analysis of keywords

Keyword analysis is one of the most crucial indicators in bibliometrics. Three-field plots were created to provide a general understanding of the keywords in articles related to the application of hydrogels in IVDD (Fig. 3A). The figure illustrates the relationships between the top authors, keywords, and journals. The results revealed that authors such as Grad S, Liu Y, Zhang Y, Wang Y, Iatridis JC, Sliva CJ, Alini M, Li J, Li Z, and Wang J utilized almost all the top keywords in their publications. "Disc", "nucleus pulposus", "hydrogel", "tissue engineering", "intervertebral disc degeneration", "annulus fibrosus", "injectable hydrogel", and "biomaterial" were among the top-ranked and most frequently used keywords. The keywords "mesenchymal stem cells", "tissue", and "degeneration" are the most popular in journal articles.

Word clouds visually represent keyword metadata, enabling quick identification of the most important words in the research area. "Keyword-plus" extracted based on the reference titles of the articles, allows for a deeper exploration of the content of the papers. Fig. 3B displays keywords with occurrences ranging from 179 to 19, where the font size indicates their importance. The results showed that "degeneration," "intervertebral disc," "mesenchymal stem cells", and "*in vitro*" were the top-ranked terms and were considered the optimal keywords in our research area. Author keywords describe a set of words from the authors' perspective, as shown in Fig. S2, with occurrences ranging from 161 to 8. "Intervertebral disc", "hydrogel", "nucleus pulposus", and "tissue engineering" were among the top-ranked terms.

Further co-occurrence network analysis of keywords revealed that among 2715 keywords, 100 met the threshold (occurring more than or equal to 12 times). The keyword "intervertebral disc" (occurrences = 259, TLS = 1571) had the highest frequency, followed by "nucleus pulposus" (occurrences = 198, TLS = 1255) and "degeneration" (occurrences = 183, TLS = 1152) (Fig. 3C). These 100 keywords were concentrated in four clusters: IVDD model construction and treatment (red cluster), hydrogel material composition and properties (green cluster), IVD-related cells and cellular constituents (yellow cluster), and molecular and cellular biotherapy (blue cluster). IVD cell bioactivity can be modulated by adjusting the hydrogel material composition and hydrogel properties, assigning functions such as molecular or cellular therapies to the hydrogel, and constructing an animal IVDD model to validate its therapeutic effects. To further determine the evolution of the research themes over time, the evolution of the most frequent keywords was assessed using VOSviewer (Fig. S3). Purple and blue indicate that the keywords appeared early, while green and yellow indicate that the keywords appeared late. The results show that the evolution of keywords in this field has gradually shifted from an early stage focusing on "IVD tissues and their cells" to a new research trend of "biomaterials and their properties". Therefore, innovative research on hydrogel materials may receive wider attention in the future.

The yearly trends in the number of popular keywords in the field of hydrogel therapy for IVDD for the period from 2001 to 2023 were further visualized (Fig. 3D). Combining Figure S3 and Fig. 3D, we can observe the full picture of popular keywords over time. Among them, the keyword "intervertebral disc" has grown rapidly since 2005 and peaked in 2019. The keywords "hydrogel," "nucleus pulposus," "tissue engineering," and "intervertebral disc degeneration" have grown steadily. In particular, "intervertebral disc degeneration" is the fastest-growing term and will far outpace the other keywords in 2023. The number of most commonly used keywords is increasing every year, and research on these topics is expanding. Due to the dramatic increase in the frequency of use of these popular keywords over the past decade, a large number of studies on these topics are expected to emerge in the field of hydrogel therapy for IVDD research.

3. Hydrogel research hotspots in the field of IVDD

3.1. Microenvironment-responsive hydrogel

Numerous adverse factors in the microenvironment of IVDD, including osmotic pressure alteration, impaired glucose metabolism, decreased pH, hypoxia, and cellular pyroptosis, significantly affect the proliferation and differentiation of both endogenous and exogenous cells [35]. The results of the bibliometric analysis showed that "acid" and "inflammation" were considered popular keywords in the field of hydrogel therapy for IVDD. In the review process, microenvironment-responsive hydrogels, such as "acid-responsive," "reactive oxygen species (ROS)-responsive," and "enzyme-responsive" hydrogels, have received increasing attention and application.

3.1.1. Application of acid-responsive hydrogels in IVDD treatment

Because the diffusibility of metabolites and nutrients is reduced in degenerative IVDs, lactic acid, the main metabolite of anaerobic glycolysis gradually accumulates in local NP tissue, and its concentration reaches 8–10 times that of surrounding plasma [36]. Lactic acid accumulation recruits inflammatory cells, impairs resident cell mitochondrial function, and promotes intracellular ROS production, which leads to the downregulation of matrix synthesis and aggravates NP cell (NPC) apoptosis, to the detriment of tissue regeneration [37–39]. Lactate oxidase (LOX) can catalyze the oxidation of lactate to generate pyruvate and H_2O_2 [40]. However, the hypoxic conditions within NP tissues reduce the catalytic efficiency of LOX, and H_2O_2-induced oxidative stress further exacerbates IVDD. Interestingly, we found that a manganese dioxide (MnO_2)-based nanoplatform that catalyzes the H^+/H_2O_2 reaction to generate O_2 and Mn^{2+}, has catalase-like activity [41]. This can both increase the oxygen content in a local area to promote LOX oxidation catalysis and consume the H_2O_2 generated from lactate degradation. There are studies on combining LOX with MnO_2 to develop a composite nanoenzyme and loading it on hydrogel microspheres to obtain hydrogel microspheres with a lactic acid response (Fig. 4A) [42,43]. These enzyme-functionalized hydrogel microspheres can help nanoenzymes maintain stability for a long period and exhibit a delayed release curve. When injected into degenerated IVDs, they can significantly reduce lactic acid accumulation, inhibit lactic acid-mediated inflammation and ROS, activate TGFβ2 overlapping transcript 1 to promote autophagy and cell activity in NPCs, and upregulate the expression of ECM, which can significantly retard the deterioration of IVDD [42,43]. In addition, LOX-MnO_2 composite nanozymes also facilitated the loading of exogenous MSCs and prolonged the survival time of exogenous MSCs inside the IVD, thus realizing the endo-exocytotic cell-linkage IVDD repair strategy. Overactivation of acid-sensitive ion channel-3 (ASIC-3) in an acidic microenvironment induces the expression of proinflammatory factors in the NP tissue. Covalent coupling of the active peptide APETx2 to GelMA microspheres can endow NPCs with acid responsiveness, specifically

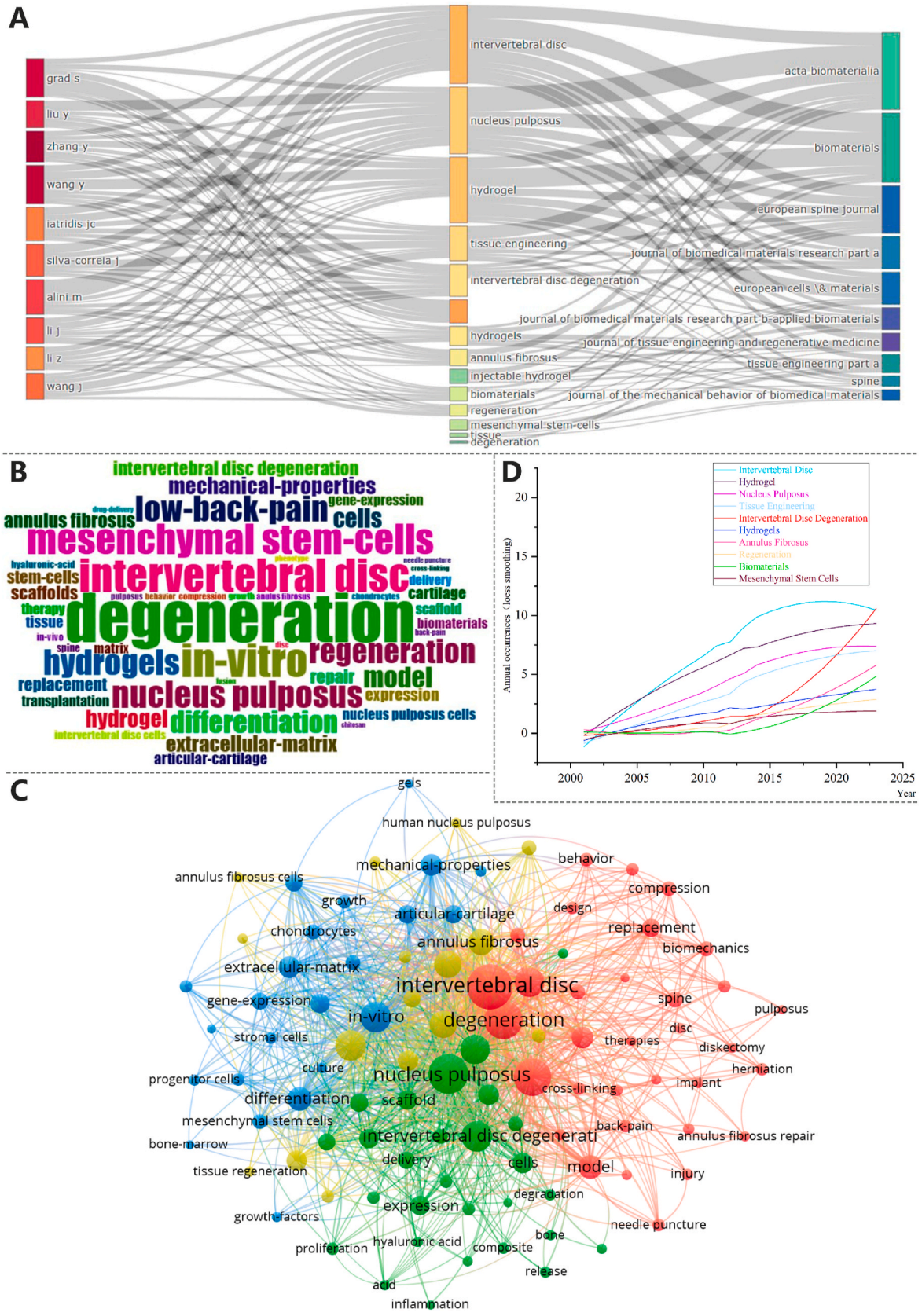

Fig. 3. Keyword analysis. **A**) Three-field plots for the relationships among top authors (the left field), top keywords (the middle field), and top journals (the right field). **B**) Word cloud of top keywords plus (font-size: word occurrences). **C**) Network visualization map showing cluster analysis of keywords. The larger the circle is, the more frequently words are used. The curves between the nodes represent the co-occurrence of the two keywords. **D**) Annual occurrences of the top keywords from 2001 to 2023.

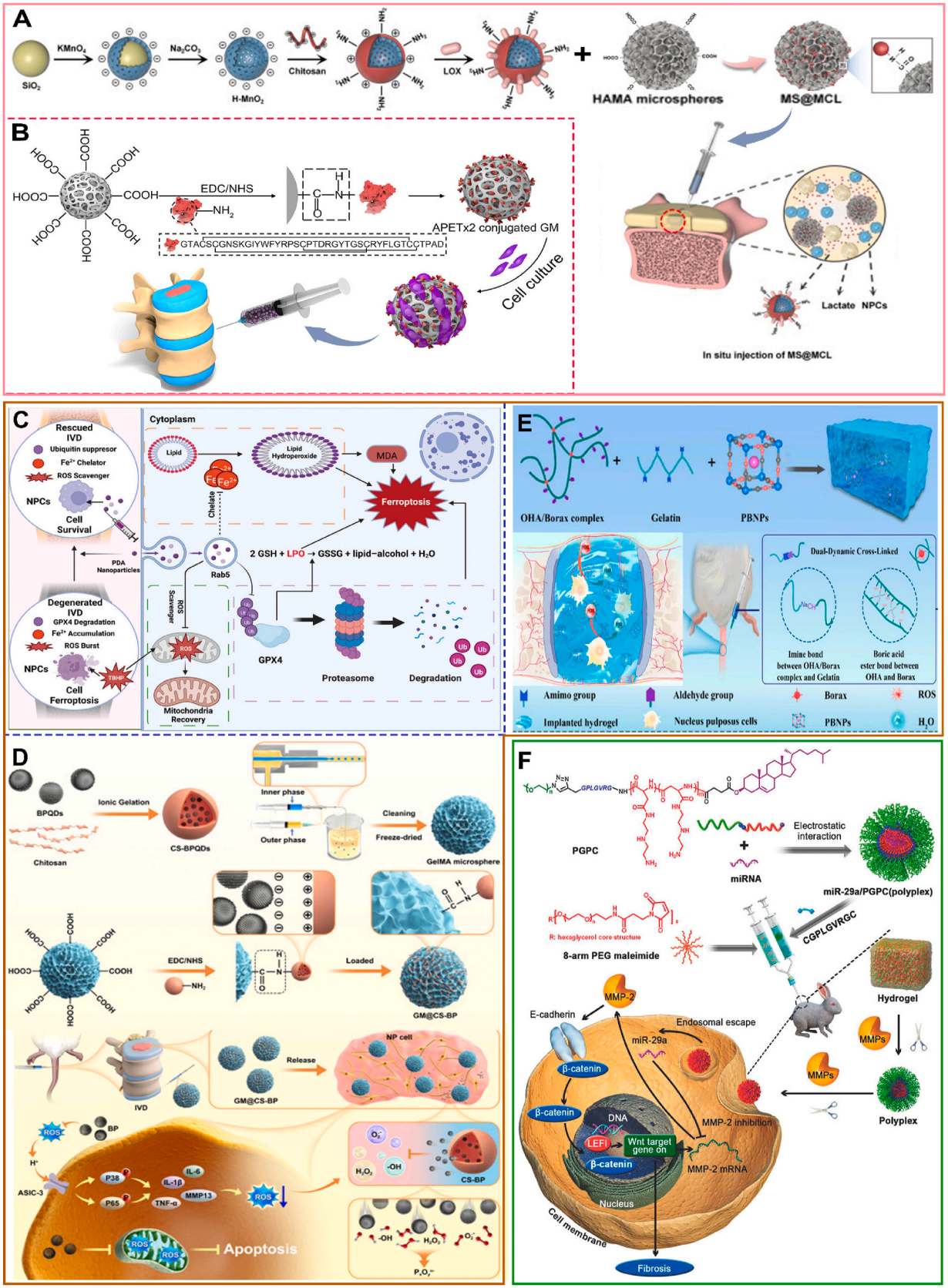

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Fig. 4. Several environmentally responsive hydrogel microspheres. **A**) HAMA hydrogel microspheres loaded with LOX-MnO_2 composite nanoenzymes with acid responsiveness and lactate scavenging ability. Reproduced with permission from Ref. [43]. Copyright 2023 Wiley. **B**) GelMA microspheres covalently coupled with the active peptide APETx2 specifically modulate ASIC-3 and reduce the toxic effects of the acidic environment on NPCs while delivering NPCs to compensate for the depletion of endogenous cells in the IVD. Reproduced with permission from Ref. [44]. Copyright 2021 American Chemical Society. **C**) ROS-responsive PDA-NPs repair IVDD by scavenging local ROS in degenerating IVDs and inhibiting ferroptosis in nucleus pulposus cells. Reproduced with permission from Ref. [45]. Copyright 2023 WILEY. **D**) GM@CS-BPQD composite microspheres scavenge reactive oxygen species and inhibit ASIC-3, improving the local pH and ROS microenvironment of IVDs. Reproduced with permission from Ref. [48]. Copyright 2021 Elsevier. **E**) A responsive hydrogel controlled-release PBNPs, which can eliminate ROS, improve the biological activity of NPCs, and delay the process of IVDD. Reproduced with permission from Ref. [52]. Copyright 2022 The Author(s). **F**) A hydrogel delivery platform with dual MMP enzyme responsiveness and controlled release of miR-29a regulates the balance between ECM degradation and synthesis. Reproduced with permission from Ref. [18]. Copyright 2018 WILEY.

downregulating the expression of ASIC-3 in NPCs, and inhibiting the activation of the NF-κB and p38 MAPK pathways. It further reduced the secretion of inflammatory cytokines such as IL-1β, IL-6, and TNF, leading to the downregulation of matrix metalloproteinase (MMP) expression, reducing the toxic effects of acidic environments on NPCs, and improving the anabolism of the ECM (Fig. 4B) [44]. Compared with the direct mixing of nanoenzymes in hydrogels, the loading method of hydrogel microspheres has the advantages of uniform and controllable size and high drug encapsulation efficiency. However, there are several limitations in the above studies: Direct injection of microspheres into the IVD increases the risk of drug burst release. Then, the degradation rate of the microspheres may be too fast, which may shorten the time of drug release. Additionally, there is a risk of drug leakage from the puncture hole, while reducing drug utilization Therefore, this study proposes that combining acid-responsive nanoenzyme hydrogel microspheres with an injectable hydrogel system can effectively overcome these limitations.

Moreover, the acidic environment can also be used as an "ON/OFF" switch for drug release. Acid-responsive hydrogels based on acid-sensitive functional bonds such as borate ester bonds, acyl hydrazone bonds, and imine bonds, which are locally degraded by H^+ in IVD, not only regulate the low-pH pathological environment but also effectively control and maintain the release of therapeutic small molecules, such as siRNAs, for more than 28 d [12]. Thereby, acid-responsive drug-controlled release hydrogels are also a worthwhile research direction for further investigations in the field of IVDD therapeutics.

3.1.2. *ROS-responsive hydrogels in IVDD treatment*

Oxidative stress is an important component of the adverse microenvironment of IVDD, and the imbalance between the production and removal of ROS, including superoxide anion (O_2^-), hydroxyl radical (OH^-), and H_2O_2, is the main cause of oxidative stress-induced injury. In degenerated IVDs, impaired cellular mitochondrial respiratory chain transmission leads to a metabolic imbalance in the massive production of ROS resulting in the accumulation of succinate and enhanced lipid peroxidation in tissues, which downregulates proteoglycan synthesis and triggers the degradation of the ECM. Moreover, ROS act as second messengers synergistically with Ca^{2+} enriched in mitochondria to stimulate the opening of the mitochondrial permeability transition pore, releasing numerous apoptotic factors to induce apoptosis. Meanwhile, the activation of inflammatory signaling pathways such as the NF-κB and MAPK pathways triggers the secretion of a large number of inflammatory factors, thus inducing an inflammatory cascade response and various secondary diseases. Oxidative stress induced by H_2O_2, IL-1β, LPS, or TBHP is also the most widely used research method to simulate the IVDD microenvironment *in vitro*.

Multifunctional nanoparticles with ROS scavenging ability and the ability to modulate NPC mitochondrial bioactivity have been shown to have a positive therapeutic effect. Polydopamine nanoparticles (PDA-NPs) are highly effective ROS scavengers capable of scavenging ROS products, regulating mitochondrial homeostatic imbalance, and inhibiting NPC ferroptosis (Fig. 4C) [45]. Black phosphorus (BP), especially BP quantum dots (BPQDs) with larger surface areas, which can scavenge excess ROS from intervertebral discs more efficiently, is another type of nanoparticles with equally efficient ROS scavenging ability [46,47]. Loading BPQDs onto GelMA@chitosan hydrogel microspheres through chemical grafting and electrostatic attraction extends the controlled release time of BPQDs and improves the oxygen metabolism microenvironment in IVDs. Moreover, the GM@CS-BPQD composite microspheres effectively modulated ASIC-3 expression, alleviated acidosis in NP cells, inhibited the MAPK and NF-κB signaling pathways, blocked inflammatory cascade responses, decreased MMP expression and reshaped the ECM (Fig. 4D) [48]. Prussian blue nanoparticles (PBNPs) are an approved antidote for cesium and thallium toxicity and have been broadly used in biomedical applications due to their good biocompatibility, photothermal properties, and antioxidant capacity [49,50]. PBNPs demonstrate remarkable enzyme-like activities, including peroxidase (POD), catalase (CAT), and superoxide dismutase (SOD), which enable them to efficiently scavenge ROS [51]. However, the absence of a suitable sustained-release vehicle leads to the need for repeated punctures to maintain local drug concentrations and the risk of leakage of hydrogel microspheres outside the IVD.

It has been investigated that loading PBNPs into a double power-bonded crosslinked hydrogel of oxidized hyaluronic acid, borax, and gelatin (PBNPs@OBG hydrogel) reduces ROS release from NPCs, improves mitochondrial membrane potential, and reverses the ECM anabolic imbalance in an acid-responsive manner. The PBNPs@OBG hydrogel sustained the release of PBNPs at the site of degenerated IVDs for 21 days and significantly delayed the height loss and deterioration of IVD after 8 weeks of treatment. (Fig. 4E) [52]. Moreover, the addition of MnO_2 mentioned above can also give the hydrogel the ability to scavenge ROS [43,53]. Hence, we are confident that utilizing hydrogels as drug delivery platforms for ROS-responsive nanodrugs or gel microspheres is a promising therapeutic strategy.

In addition to ROS-responsive nanomedicines, hydrogels with their ROS-responsive components can also be used as a "smart" means of controlled drug release. A multifunctional hydrogel is formed by self-crosslinking dopamine-functionalized gelatin and borax-coupled aldehyde-modified chondroitin sulfate via dynamic Schiff base bonds and borate bonds [19]. Dopamine enhances the adhesion of hydrogels to extracellular vesicles (EVs) through the formation of hydrogen bonds between catechol groups and EVs. The borate bonds and catechol groups in the hydrogel are ROS-sensitive and are easily degraded by oxidation. Therefore, the hydrogel scavenges extracellular ROS while intelligently controlling the release of functionalized EVs [54–56]. In addition, the ROS-responsive microspheres loaded with MR409, an antioxidant, were prepared using the ROS-responsive block polymer methoxy poly (ethylene glycol)-b-poly(propylene sulfide) (mPEG20-b-PPS30) [57]. A thermosensitive triblock poly(lactic-co-glycolic acid)-b-poly(ethylene glycol)-b-poly(lactic-co-glycolic acid) copolymer (PLGA-PEG- PLGA) hydrogel was used to deliver ROS-responsive microspheres to the IVD. This composite system has dual ROS scavenging capabilities for both hydrogel and drug. Therefore, the developed ROS-responsive hydrogel can eradicate the local accumulation of ROS in degenerated IVDs while intelligently controlling the release of loaded drugs. This provides a promising direction for local IVDD treatment.

3.1.3. *Enzyme-responsive hydrogels in IVDD treatment*

In the pathological IVDD microenvironment, the overexpression of MMP is the chief cause of ECM catabolic/anabolic imbalance. Therefore, some studies have designed enzyme-responsive hydrogel systems for

high MMP concentrations, among which collagen-based hydrogels are the most common. For instance, a mouse tail collagen hydrogel was used to encapsulate the pH-responsive H_2S donor JK1. The local MMPs in degenerated IVDs degrade collagen hydrogels, JK1 is released, and then H_2S is generated in response to pH, thus playing a therapeutic role [58]. MicroRNAs (miRNAs) regulate gene expression by directing target mRNAs and can significantly influence various pathological processes that modulate the development of IVDD [59,60]. The clinical translation of miRNA therapeutics is limited by the absence of a safe, convenient, effective, and stable delivery system. However, Ge et al. developed a two-stage MMP-responsive hydrogel that was able to sustain miR-29a locally in the IVD for more than 30 days [18]. miR-29a was efficiently encapsulated by an MMP-responsive cationic block copolymer and subsequently further encapsulated into an MMP-responsive hydrogel. The hydrogel was skillfully formed by cross-linking an MMP-cleavable peptide (CGPLGVRGC) with an eight-arm maleimide-terminated star PEG. This dual enzyme response efficiently depletes MMPs in the microenvironment, while consistently and responsively delivering miR-29a to NPCs, effectively slowing or reversing chronic IVDD (Fig. 4F). Thereby, enzyme-responsive hydrogels effectively regulate ECM metabolic homeostasis and enable controlled drug release for the treatment of IVDD.

In summary, the various unfavorable microenvironmental factors of IVDD are inextricably and intrinsically linked. Improvement of one unfavorable factor can be accompanied by positive therapeutic effects on other unfavorable factors. Follow-up studies should address the various microenvironmental factors of IVDD in an integrated manner, and the development of multiple environmentally-responsive hydrogel delivery systems is a promising avenue to achieve complementary benefits (e.g., environmental amelioration, controlled drug release, and cell mobilization).

3.2. Application of dECM hydrogels in IVDD treatment

NP-ECM is the main extracellular product of NPCs and is crucial for their survival. Therefore, the current hydrogel development strategy for IVDD treatment is mainly bionic ECM based on different materials. dECM is a 3D structure with a high water content that is effectively prepared using physical, chemical, and biological methods to remove cell components while retaining tissue components [61]. NP-dECM removes immunogenic cell substances while retaining natural NP tissue components such as collagen II and aggrecan. These components significantly impact cell growth, migration, proliferation, and differentiation. Furthermore, NP-dECM serves as an excellent carrier for local, sustained-release drugs. The hydrogel material based on NP-dECM can better adapt to the environment of the host IVD, which is crucial for regeneration and functional repair.

However, the promotion of dECM-based hydrogels in the field of IVDD therapy depends on the following aspects: (1) Material source. The special location of IVDs, the high cost of obtaining them, and the low yield limit the possibility of obtaining NP-dECM from the patients themselves or from other volunteers. Therefore, animal-derived xenogeneic IVDs are currently the main acquisition route for NP-dECM [23,62]. However, different walking styles in different species lead to significantly different IVD stress distributions in humans versus other animals, which in turn leads to significantly different ratios of the composition of the components of the NP tissue [63]. Depletion of the composition of the ECM is inevitable due to the decellularization process. Therefore, it is crucial to consider factors such as the ease of material acquisition, high yield, and species source when developing dECM-based hydrogels for production. (2) Decellularization method. Although there are many kinds of decellularization methods, such as physical methods and chemical methods, we found that NP-dECM is often obtained by combining many kinds of decellularization methods, because it can effectively reduce damage to the ECM via a single method [23,24]. However, there is no unified preparation method at present. The development and formulation of an efficient and unified acellular standard is an important research direction for promoting the preparation of NP-dECM products. (3) Gel properties. NP-dECM hydrogels have a low elastic modulus and poor stability, so it is difficult to adapt to the local stress environment of IVDD [64]. Therefore, cross-linking agents (such as genipin [65]) or other components (such as hyaluronic acid [66] and collagen [67]) are often required to adjust the mechanical properties of hydrogels. However, the cross-linking agents used in different studies often have concentration-dependent toxic effects, which may have adverse effects on cell adhesion, proliferation, and differentiation. So, developing an ideal non-toxic crosslinking agent with highly adjustable mechanical properties is urgently needed for NP-dECM hydrogels. (4) Bioactive factors. During the preparation process, a large number of bioactive factors in NP-ECM are inactivated or eliminated by physical or chemical factors, and the activities of these factors play an important role in regulating the biological process of NPCs. Whether an NP-dECM hydrogel system can help maintain NP-related gene expression is still controversial [65,68]. Thus, researchers often supplement NP-dECM hydrogels with one or several bioactive factors to enhance their therapeutic effect.

Although NP-dECM, as a basic component of hydrogels, has great natural advantages in the treatment of IVDD, this study revealed that the latest research no longer only used this substrate but also combined it with other natural or synthetic materials as a loading and delivery platform for bioactive factors, drugs or cells. Therefore, this study suggests that the following research can prepare bionic ECM hydrogel based on the core components of NP-dECM, loaded with “seed” cells and supplemented biological factors to develop multifunctional composites closer to the original NP tissue.

3.3. Application of SAP hydrogels in IVDD treatment

In the process of bibliometric analysis, we found that a kind of SAP-based hydrogel (SAPH) has attracted increasing interest from scholars in the IVDD field in the past ten years. SAPH is usually defined as a physical peptide hydrogel formed by spontaneous assembly through intramolecular and intermolecular noncovalent interactions, including hydrogen bonding, π-π stacking interactions, van der Waals forces, electrostatic interactions, halogen bonds, and hydrophobic interactions [10,69–71]. Under specific conditions and careful design, SAPs can be assembled into nanofibers with different structures, including α-helix, β-spiral, β-turn, β-sheet, and micelle, and then crosslinked into hydrogels similar to ECM networks. SAPs have been widely developed and applied in nerve repair [72], wound repair [73], angiogenesis [74], and bone tissue engineering [10]. SAPH has the basic properties of traditional hydrogels, such as high water content, biocompatibility, biological function, environmental responsiveness, biodegradability, and injectability. It can also self-assemble into supramolecular hydrogel structures in response to changes in ionic strength, pH, enzyme activation, peptide concentration, illumination, and temperature without additional cytotoxic crosslinking agents [69,75–78]. Meanwhile, the configuration of the peptide sequence depends on the nature of the R group between two adjacent amino acids. The self-assembly of the peptide and its interaction with the surrounding environment can be adjusted by editing the amino acid sequence, which makes SAPH more adjustable and adaptive [79]. There are many reviews about SAPH in the field of biomedical materials for reference. This study only summarizes and analyzes the existing research on SAPH in the field of IVDD treatment.

In the process of bibliometric analysis, 25 directly related studies were retrieved (Table S1) [75,80–103]. Among them, the China scholar Ruan Dike has made the most contributions, with 7 works [82,84–86,89,90,97]. Among these studies, the most commonly used SAPs are RADA16-I (RADARADARADARADA) [75,80–82,84–86,89,90,95,97,98], F8(FEFKFEFK) [88,91,93,96], and KLD-12 (KLDLKLDLKLDL) [83,99,102,103]. In the initial research stage, based on SAPH’s characteristics of easy self-assembly into gels, shear thinning, and bionic ECM

network scaffold structures, the researchers verified its biocompatibility, cell delivery ability, and potential for use as an injectable NP tissue filler. Then, to improve the cell compatibility, cell adhesion, and bionic mechanical properties of SAPH, the preparation process of SAPH, such as the SAP concentration, pH, and vortex time, was adjusted [88,94,96]. Moreover, by adding NP-ECM components (such as chondroitin sulfate), hybrid SAPH can be more suitable for IVDD repair [87,94]. Graphene oxide (GO) has high water dispersibility, good biocompatibility, and the ability to promote cell adhesion. GO tablets contain a large number of hydrophilic groups such as carboxyl groups, hydroxyl groups, and oxygen groups, on their edges or basal surfaces, which significantly increases their hydrophilicity [104]. Because of their excellent characteristics, GO tablets are often used as a delivery platform for nanotherapeutic drugs, which can carry insoluble small molecule drugs, antibodies, DNA, proteins, and genes [105]. Therefore, Ligorio et al. added GO tablets to F8 hydrogels to adjust the mechanical properties of SAPH to make it more similar to NP tissue. Moreover, SAPH also improved the cell adhesion of SAPH and the cell viability and metabolic activity of NPCs [91]. GO tablets can also be used as drug delivery carriers to chelate TGF-β3 through strong binding interactions, thus achieving the sustained release of TGF-β3 from SAPH [93].

Interestingly, SAP, as an amino acid sequence, is well suited for the delivery of biologically active small molecule peptide drugs. Typically, bis-glycine (GG) is used as a linker to anchor bioactive peptides to the C-terminus of the SAP sequence. For example, P1R16, a new PTH-related supramolecular peptide recently developed by our group, is designed to anchor PTHrP-1 to the C-terminus of RADA16 by solid-phase conjugation and then coassemble with RADA16 to form a P1R16/RADA16 hydrogel, which achieves localized anchoring of PTHrP-1 to SAPH, thereby facilitating localized repair of bone defects [106]. BMP-7 not only stimulates the secretion of glycosaminoglycans and collagen II from NPCs *in vitro* but also plays a very important role in repairing degenerated IVDs *in vivo* [107–109]. The BMP-7 short peptide SNV (SNVILKKYRN), KPS (KPSSAPTQLN), and KAI (KAISVLYFDDS) were able to exhibit the major functions of BMP-7 [110]. Therefore, Ruan and Wang's groups anchored the BMP-7 short peptide to the C-terminus of RADA16-I to obtain a class of BMP-7-functionalized SAPs, which were then mixed with RADA16-I to form SAPHs [82,84–86,89,90,97]. Compared with SNV- and KAI-functionalized SAPHs, KPS-functionalized SAPHs have the best biological activity and ability to promote ECM expression in human degenerated NPCs, making them an ideal candidate scaffold for NP tissue repair [84]. The link protein is a glycoprotein that stabilizes the proteoglycan-hyaluronan and maintains IVD structural stability. Link N (DHLSDNYTLDHDRAIH) is the biologically active motif of the N-terminal fragment of the link protein [111,112]. Previous studies have shown that Link N promotes the accumulation of proteoglycans and collagen II in NPCs and chondrocytes [113,114]. Compared to RADA16-I hydrogels, LN-NS hydrogels functionalized with Link N significantly promoted the adhesion of rabbit NPCs and facilitated the migration of NPCs into the hydrogel, resulting in more significant ECM biosynthesis and deposition of encapsulated NPCs [80,81]. In addition, a novel functionalized peptide, RSA1, developed by coupling the acid-sensitive ion channel inhibitor Sa12b (EDVDHVFLRF) to the C-terminus of RADA16-I, significantly enhanced the ability of human NPMSCs to resist acidic environments. It can be demonstrated that, based on the SAP, it is possible to develop a unique and useful SAPH by the "head" editor according to the unique location and microenvironment of the IVD and the direction in which researchers are interested.

The present study revealed that the injectability and excellent shear-thinning properties of SAPHs make them suitable candidates and cell delivery platforms for minimally invasive therapy for IVDD [77]. However, although there have been countless explorations on the application of SAPH in biomedical materials, exploration in the field of IVDD is still relatively limited. This may be because researchers need not only an in-depth understanding of SAPs but also enough research experience in IVDD to combine the two. Moreover, the development of functional SAPs requires considerable screening and optimization, a long research and development time, and a high economic cost. Despite this, we still maintain a positive attitude toward SAPH as a candidate material for minimally invasive treatment of IVDD with promising research prospects.

3.4. Application of MSC/EV-hydrogels in IVDD treatment

Bibliometric analysis of this study revealed that "Mesenchymal stem cells" is one of the most popular keywords in the field of hydrogel therapy for IVDD (Fig. 3), which aroused our great interest. MSCs have excellent immunomodulatory and anti-inflammatory properties and can release bioactive molecules to regulate the microenvironment and promote tissue repair and regeneration. Due to their multidirectional differentiation potential and abundant sources, MSCs have become an ideal choice for the regeneration and repair of NPCs in degenerative IVDs. With its bionic ECM network structure and cell affinity, hydrogels provide a delivery platform and living environment for MSC implantation. MSCs encapsulated in hydrogels can improve the proliferation and functional activity of endogenous cells through paracrine, EV, or Exo crosstalk [67,115,116]. Using hydrogels to deliver MSCs can effectively overcome unnecessary cell migration or leakage, preventing ectopic ossification-induced bone hyperplasia [115,116]. More than 80 studies related to MSC-hydrogel therapy for IVDD have been reported in the last five years.

3.4.1. Application of MSC-hydrogels in IVDD treatment

Protecting the survival rate of transplanted MSC is an important prerequisite for MSC to supplement cell shortage. Studies have shown that loading kartogenin in hydrogels can protect ADSCs from ROS microenvironment toxicity through the Nrf2/TXNIP/NLRP3 axis increase ADSC viability, and stimulate ADSC differentiation toward an NP-like phenotype [117,118]. Salvianolic acid B can effectively reduce BMSC apoptosis in hydrogels by activating the JAK2-STAT3 pathway [119]. Thus, one of the important strategies for improving the survival rate of MSCs in hydrogels is the addition of bioactive components. Although some studies have achieved positive therapeutic effects by directly delivering NPCs to IVDs through hydrogel materials, the limitations of the NPC source and low yield limit its clinical popularization [120]. Therefore, promoting the differentiation of MSCs into an NP-like phenotype is the real purpose of cell therapy.

After summarizing the literature, we found that the following strategies can be adopted to develop hydrogel materials with the ability to induce MSC differentiation. Strategy 1: NP-dECM hydrogel. The structural environment in which cells reside plays a significant role in cell proliferation and differentiation. Hydrogels prepared by crosslinking with the natural biological crosslinker genipin and NP-dECM exhibit an elastic modulus similar to that of human NP tissue and demonstrate good biocompatibility [115,121,122]. When ADSCs were cocultured with this hydrogel, the expression of aggrecan, collagen II, and SOX9 increased significantly, and NP-specific marker genes such as Krt19 and Pax1 were highly expressed, which indicated that ADSCs differentiated into NP-like cells [122]. Strategy 2: Add inducible biochemical factors. At present, many studies have established that many inducible biochemical factors, including BMP-3, BMP-7, TGF-β 1, TGF-β 3, GDF-5, and GDF-6, can induce MSCs to differentiate into NP-like cells [98,123–126]. Therefore, encapsulating these biochemical factors and MSCs in hydrogels can continuously induce exogenous MSCs to differentiate into NPCs, thus controlling the probability of incorrect differentiation of MSCs and effectively replenishing the cell reserve of degenerated IVDs [98,123–126]. Strategy 3: mechanical signal-directed regulation. As IVDD continues to deteriorate, the mechanical microenvironment within the IVD changes, leading to an erroneous cell fate. Therefore, mechanically customized hydrogel microspheres with controllable elastic moduli and ligand densities have been prepared. Triggering

corresponding mechanical biological signals can support the NP-like differentiation of IVD progenitor cells/stem cells by transporting Yes-associated protein (YAP) without the addition of inducible biochemical factors [127]. Strategy 4 is preinduction treatment. Studies have shown that hypoxic (5 % O_2) preconditioning can significantly promote the expression of NPC markers HIF-1α, Pax-1, and Fox-F1 of MSCs in hydrogel, and promote the accumulation of NP-ECM components, without the need to supplement induced growth factors [128,129]. Some studies have mechanically stimulated MSCs within the hydrogel in a 3D system via a pressure cycling device (Fig. S4A), and MSCs showed differentiation toward NPC-like cell subtypes (Fig. S4B). The induced cell-hydrogel system injected directly into an animal model of IVDD showed more NP cells and NP-ECM deposition, and improved cell viability in a weight-bearing IVD environment (Fig. S4C) [130]. Therefore, directly inducing MSCs into NP-like cells before combining them with hydrogels may be a more efficient strategy for cell supplementation therapy. For severe IVDD patients, the use of an MSC-hydrogel system is a meaningful therapeutic approach for restoring endogenous cell depletion.

3.4.2. Application of EV-hydrogels in IVDD treatment

EVs are a class of nano-to micrometer-sized vesicle-like structures that originate from the cytokinesis of living cells and contain a variety of bioactive molecules. Their unique bilayer phospholipid shell enables them to home and seamlessly fuse with distant cell membranes, fulfilling their role as intercellular messengers to coordinate and regulate tissue regeneration and repair [131–133]. As intercellular messengers, EVs can establish crosstalk between transplanted cells and endogenous NPCs [134]. Especially, compared with MSCs, MSC-EVs have several advantages, such as abundant natural resources, lifelessness, no need for excessive external conditions, few safety problems, low toxicity, fewer immunogenicity problems, and engineering modifications [11].

Direct injection of MSC-EVs can rapidly deliver them to their target sites of action. However, in a liquid environment *in vivo*, MSC-EVs are rapidly metabolized, making it difficult for them to maintain an effective concentration at the target site for long periods. The drug slow-release platform constructed by combining adipose-derived MSC-derived Exos (ADSC-Exos) and porcine NP-dECM hydrogels was able to maintain microenvironmental homeostasis in the early stage of IVD degeneration by cleverly combining the advantages of both [135]. In another study, MSC-Exos were delivered via hydrogels to alleviate oxidative stress-induced NPC senescence and improve NPC function, thereby alleviating the degenerative process in a puncture IVDD model [17]. However, Exos contains a variety of bioactive factors, and exploring the specific components of Exos that exert positive effects is a potential future research direction. Liao et al. reported that peroxiredoxin-2 (Prx2) in human MSC-EVs is a key component that inhibits the activation of inflammatory vesicles and attenuates NPC apoptosis [136]. MSC-EVs are also enriched with Vasorin, which promotes the viability of NPCs and maintains the metabolic homeostasis of the ECM via the Notch pathway [137]. Cells mediate the uptake of EVs via niche-dependent endocytosis. Conversely, NPCs are impaired in inflammatory environments and have a reduced ability to uptake EVs. The RGD peptide sequence, which consists of an arginine-glycine-aspartic acid tripeptide, specifically recognizes integrins on EV membranes, and RGD peptide-modified dECM hydrogels can enhance the anchoring ability to EVs, which significantly improves the residence time and bioavailability of EVs in IVD localization [138].

Due to the engineerable property of EVs, functional modification of them can improve the therapeutic effect of EVs. Cavin-2 binds to caveolin-1 and induces plasma membrane curvature, thus playing a key role in mediating EV uptake [139]. Therefore, the construction of Cavin-2-engineered EVs by gene editing technology can significantly improve the ability of EVs to be uptaken by damaged NPCs in sodium alginate hydrogels, thus enhancing the utilization of EVs and the therapeutic effect on IVDD [136]. Moreover, hypoxia pretreatment can enhance the expression of the endogenous antioxidant Glutaredoxin-3 (GLRX3) in MSC-EVs. Hydrogel delivery of hypoxia-pretreated MSC-EVs further enhanced the antioxidant capacity of NPC in degenerative IVDs [19]. In addition, MSC-EVs are rich in miR-3594–5p, which targets the homologous domain interacting protein kinase 2/p53 pathway, which can reduce the activity of β-galactosidase and alleviate cell cycle arrest, thus alleviating the aging of NPSCs [138]. Therefore, by precisely modifying Exos, we can not only improve the ability of Exos to treat IVDD but also better understand the underlying mechanism, thus providing a higher level of evidence for clinical application.

However, it must be emphasized that even though cell-free therapy based on MSC-EVs can play a therapeutic role similar to that of MSCs to a certain extent, it has lost the ability to compensate for the depletion of cells in degenerative IVDs. For patients with severe IVDD, it may be difficult for cell-free therapy based on EVs or other drugs to achieve the ideal therapeutic effect. Therefore, future research and clinical trials should design appropriate and targeted hydrogel implant materials for different degrees of IVDD.

According to the above bibliometric analysis and the summary of research status, we were the first to propose that multifunctional hydrogels for repairing IVDD should have the following “four core factors”: hydrogel delivery platforms, cells, cell stimulators, and microenvironment regulation. Factor 1: Hydrogel delivery platforms need to be biocompatible, injectable, biodegradable, compatible with the localized pressure environment of the IVD, and suitable for cellular delivery and controlled release of drugs. Factor 2: Cells. As mentioned earlier, severely degenerated IVDs suffer from cellular depletion. Therefore, hydrogels serve as an ideal cell delivery vehicle to replenish exogenous cells into degenerated IVDs, effectively overcoming this problem. Due to the source limitations of NPCs, MSCs from various sources with multidirectional differentiation potential are more commonly attempted to treat IVDD. Autologous ADSCs are ideal candidate cells due to their wide availability, ease of acquisition, expandability, inducible directional differentiation, and fewer allogeneic ethical issues. Therefore, inducing MSCs to stably differentiate towards NP-like cells is one of the key points. Factor 3: Cell stimulators. The presence of oxidative stress, low pH, and hypoxia in the localized adverse microenvironment of degenerating IVDs leads to endogenous cellular dysfunction and is not conducive to the survival and functionality of transplanted cells. Supplementing cell stimulators is an essential element in maintaining the stable survival, proliferation, and directed differentiation abilities of cells in hydrogels and IVDs. Factor 4: Microenvironment regulation. Various adverse microenvironmental factors in IVDD affect cell function, accelerate ECM degradation, and hinder IVDD repair. Therefore, on the one hand, the microenvironment can be utilized as a “switch” to regulate the degradation rate of hydrogels and the controlled release rate of cell stimulators. On the other hand, adjusting the microenvironment is of great significance to improve cell function, increase ECM accumulation, and promote IVDD repair. Overall, the four core factors are interconnected, mutually supportive, and mutually reinforcing, which align with the new hydrogel development strategy of the “four core factors” that will better achieve IVDD repair. The absence of any one of these factors will significantly diminish the efficacy of the hydrogel repair strategy.

4. Mechanistic strategy of hydrogel delivery systems for the treatment of IVDD

The pathomechanism of IVDD is the basis for the development of hydrogel delivery platforms. Based on bibliometric analysis and literature review, we found that hydrogel strategies can be developed in five directions.

4.1. Fundamentals of IVDD

Understanding the basic mechanism of IVDD to lay the foundation

for further diagnosis and treatment of IVDD. The IVD consists of three components: peripheral high-toughness AF tissue, internal high-water-content NP tissue, and upper and lower cartilage endplates (CEPs) [39]. The IVD has age-dependent degenerative properties, with degeneration occurring silently and continuously with age since the age of 30 years. Moreover, with the rapid development of the economy and technology, sedentary and prolonged head-down periods have become the norm for increasingly more workers. As a result, the age of onset of IVDD is gradually decreasing and the incidence rate is increasing [140]. The three components of the IVD exhibit different morphological and pathological changes. The degenerative changes in the IVD due to frequent compression-relaxation stress from accumulated trunk movements lead to gradual fissures in the AF, resulting in decreased toughness and significantly weakening the ability of the IVD to bear unexpected increases in load, thus sharply increasing the risk of AF rupture and disc herniation [39,141]. Because it is mostly isolated from the external environment, there are no blood vessels, nerves, or other components in the inner AF and NP tissues. Nutrients and oxygen are mainly diffused from the upper and lower CEP and outer AF. However, structural and functional disorders of the CEP caused by trauma, oxidative stress, and other adverse factors disrupt the energy supply of the NP tissue, leading to mitochondrial imbalance [142].Furthermore, due to contact with capillaries crawling from the AF fissure and degenerated CEP, NP tissue isolated from the outside for a long time gradually develops an immunoinflammatory response and oxidative stress stimulation [143]. Inflammatory mediators and ROS lead to pathological activities such as senescence, apoptosis, and pyroptosis of NPCs and NP progenitor cells (NPPCs) within NP tissue; gradual degradation of the ECM; accumulation of acidic metabolic byproducts; reduced water content; and a gradual decrease in the load-bearing capacity of the IVD [39,144,145]. Additionally, harmful components further stimulate nerve endings to enter the IVD, causing discogenic LBP (Fig. 5) [4,146]. Based on these factors, the degeneration of the three components of the IVD mutually reinforces each other, accelerating the degenerative process. Therefore, addressing the root cause is a fundamental and effective principle and approach for treating IVDD.

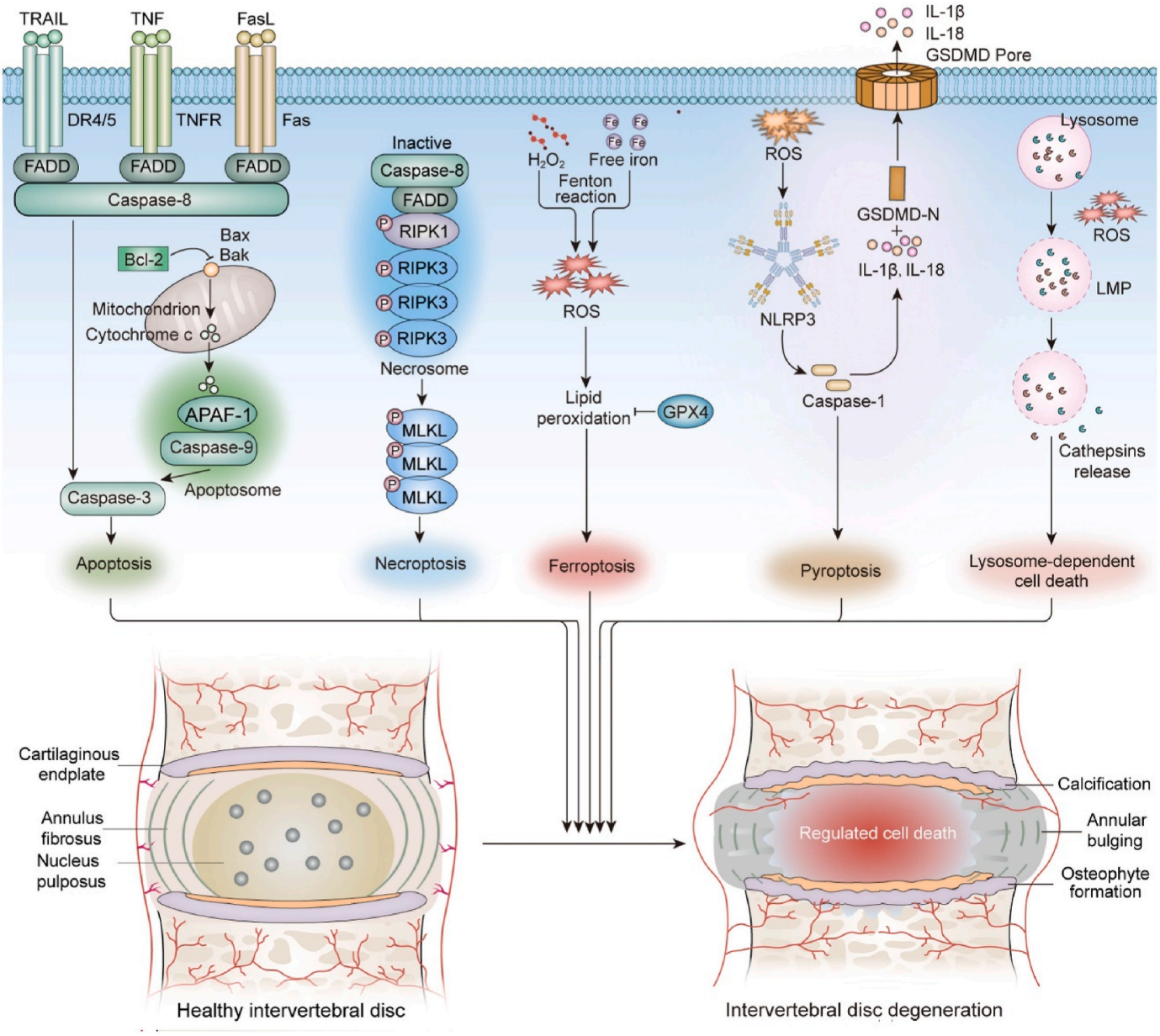

Fig. 5. The common forms and mechanisms of cell death in intervertebral disc degeneration. Reproduced with permission from Ref. [146]. Copyright 2022 Elsevier.

4.2. Regulating cellular senescence

Healthy and robust cells are the "combatants" that maintain normal function and self-repair in the IVD. However, an increasing number of studies indicate that one of the main pathological mechanisms of IVDD is the depletion and functional decline of endogenous cells [147–149]. Cellular senescence is a permanent state of cell cycle arrest and occurs in various diseases. As IVDD is an age-related degenerative disease, cellular senescence is a key feature of IVDD (Fig. 6A) [150]. Cellular senescence can be categorized into replicative senescence and stress-induced senescence [151]. Replicative senescent cells accumulate during physiological or accelerated aging processes, which are exacerbated by due to factors that either promote the accumulation of senescent cells or inhibit their degradation [152]. DNA damage, oxidative stress, and inflammation can induce stress-related cellular senescence, significantly increasing the burden of cellular senescence within tissues [153,154]. Furthermore, senescent cells induce an inflammatory microenvironment through the paracrine effects of the senescence-associated secretory phenotype (SASP), which damages surrounding healthy cells and impedes stem cell proliferation and regeneration. Moreover, the overexpression of MMPs associated with the SASP can induce autocrine ligand shedding, rendering senescent cells less susceptible to immune surveillance and clearance. These rapid accumulation, persistence, and amplification mechanisms lead to the accumulation of senescent cells in tissues, ultimately promoting the progression of IVDD [155–157].

A substantial amount of prior research has summarized the significant impact of cellular senescence on the progression of IVDD. Therefore, developing hydrogel materials that resist the senescence of NPCs is an important strategy for slowing the progression of IVDD. It was shown that delivery of bone marrow-MSC (BMSC)-derived exosomes (BMSC-Exos) via a self-healing hydrogel reduced the accumulation of senescent NPCs in degenerating IVDs, decreased the expression of senescence-associated proteins $p16^{INK4A}$ and $p21^{CIP1A}$, and reverse the excessive degradation of collagen II (Fig. 6B) [17]. Moreover, BMSC-EVs not only have therapeutic effects but can also be used as carriers for intracellular drug delivery. GLRX is an important component of the endogenous antioxidant system and can exert its cellular antioxidant stress effects by catalyzing protein deglutathionylation [158]. However, in senescent NPCs, the protein expression of GLRX3 is significantly downregulated, leading to a significant decrease in the capacity for endogenous antioxidant stress [19]. Therefore, EVs can be functionalized to overexpress GLRX3 as a carrier of bioactive factors. Delivery of GLRX3-functionalized EV through hydrogel can enhance the antioxidant defense and mitochondrial protection of aging NPCs in degenerative IVD, which significantly improves the course of IVDD (Fig. 6C) [19].

Studies have shown that oxidative stress, mechanical stress changes, inflammatory stress, genotoxic stress, and many other stress responses contribute to cellular senescence [159]. and numerous signaling factors/pathways are involved in regulating cell senescence [160]. However, the regulatory mechanisms by which most hydrogel materials alleviate NPC senescence are still unclear, posing a significant obstacle to the clinical translation of research outcomes. Therefore, using hydrogel materials to reverse NPC senescence trend and enhance the health and function of reserve cells is an important research direction for the endogenous repair of IVDD, and elucidating the specific regulatory mechanisms is an important step to promote the clinical translation of anti-aging hydrogel materials.

4.3. Reducing cell death

Although the accumulation of nonfunctional cells due to cellular senescence leads to cell cycle arrest in IVDs, the sharp decrease in cell numbers caused by cell death is the real cause of cell exhaustion in IVDs, and driving the progression of IVDD [146]. Various forms of cell death, including apoptosis, autophagic apoptosis, and necroptosis, participate in the pathological changes of IVDD (Figs. 5 and 7A) [146,161–163]. Our previous study has shown that modulating the PI3K/AKT signaling pathway to activate cellular autophagy, can significantly reduce oxidative stress-induced ROS overexpression and NPMSC apoptosis and improving the ECM synthesis/metabolism balance, thereby delaying the progression of IVDD [148,164]. Hence, the development of hydrogel materials resistant to cell death is an important approach for preserving and mobilizing reserve cells for IVD repair.

4.3.1. Anti-apoptosis

Research has developed injectable glycerol cross-linked PVA gel with NP-matched viscoelasticity that can adapt to the mechanical environment of the IVD, maintain NPC synthesis metabolism markers, preserve cell proliferation and vitality, and reduce NPC apoptosis rates under pathological static and dynamic loading conditions [165]. However, the issue of cellular senescence and exhaustion within degenerated IVD cannot be solved solely by the hydrogel materials themselves. Loading effective ingredients that promote cell proliferation and inhibit cell apoptosis is the most commonly used strategy for developing anti-apoptotic hydrogels. H_2S is a gaseous signaling molecule that has been shown to protect cells from apoptosis by neutralizing toxic reactive species (such as oxygen radicals and peroxynitrite) and upregulating antioxidants (such as SOD, glutathione, and N-acetylcysteine) [166]. H_2S can prevent IL-1β-induced endoplasmic reticulum stress and mitochondrial damage in NPCs by activating the PI3K/Akt and ERK1/2 signaling pathways [167]. Due to the difficult loading properties of gaseous molecules, the acid-responsive donor JK1 can be encapsulated into a collagen hydrogel to achieve responsive release of H_2S in a degraded IVD [58,168].

However, compared to gaseous signaling molecules, intracellular regulatory proteins can more directly regulate cellular physiological processes. Platelet-rich plasma (PRP) can promote the migration and proliferation of various types of cells [169,170], due to its abundance of growth factors. A drug delivery system combining electrostatic spinning with hydrogels not only improved the sustained release of the active PRP component but also prevented leakage during transportation. This composite hydrogel significantly improved disc height and Pfirrmann grading in degenerating IVDs, with type II collagen levels approaching those of the normal IVD. (Fig. 8A) [171]. In addition, the above-mentioned MR409 is a synthetic growth hormone-releasing hormone analog that can downregulate ROS accumulation or block ROS signaling [57]. Delivery of MR409 by the dual controlled release method of hydrogel and microgel was able to downregulate intracellular ROS expression, thereby inhibiting secretory autophagy, reducing NPC apoptosis, and promoting ECM regeneration (Fig. 8B) [172]. However, further studies should enhance the mechanical properties of this hydrogel system and investigate whether the hydrogel degradation rate and drug release time can meet long-term requirements.

Furthermore, some small nucleic acid molecules can also serve as nanomedicines to regulate cellular biological processes. Research has shown that miR-155 is significantly downregulated in degenerated IVDs, while miR-5590–3p can directly target the 3′ UTR of FADD, caspase-3, and DDX5, directly inhibiting the expression of apoptosis-related genes and regulating mTOR phosphorylation, thereby affecting autophagy and cell apoptosis [174–176]. Using spherical nucleic acid embedded in DNA hydrogel to load miR-155 can prolong the release time in degraded IVD to some extent, and hinder the progress of IVDD by activating endogenous NPC autophagy and inhibiting apoptosis [177]. However, it must be noted that an appropriate hydrogel carrier is a prerequisite for the effective action of drugs. The degradation speed of DNA hydrogel used in this study is too fast, which cannot provide enough mechanical support and advantages for the sustained release of drugs. Multiple cross-linked hydrogels based on Zn^{2+}-oxidized alginic acid-gelatin (ZOGA) have been developed to adapt to the mechanical performance of the IVDs. The mechanical properties of the ZOGA were enhanced to 254.86 kPa. It not only exhibits strong antibacterial activity, biocompatibility, and biodegradability but can also form a

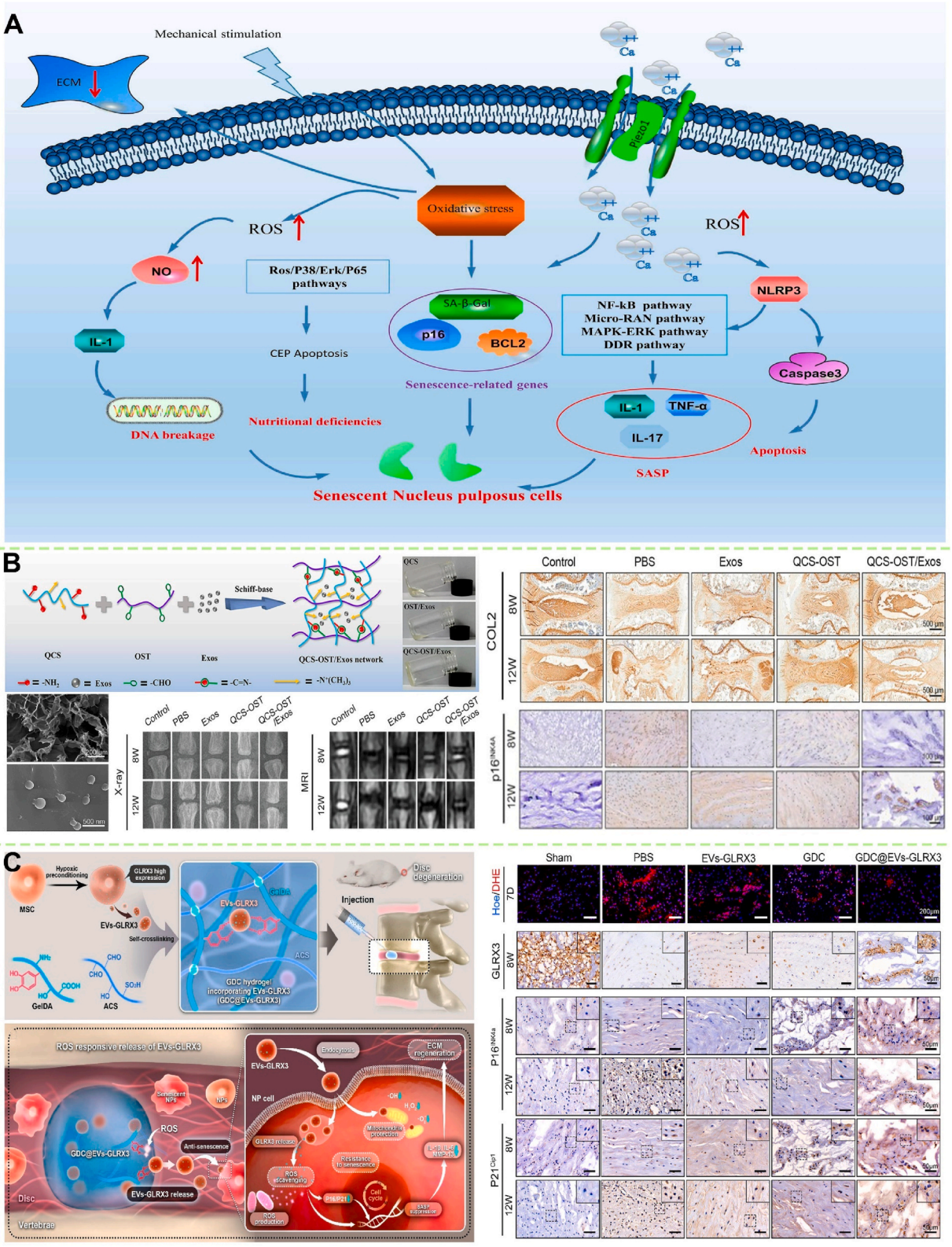

Fig. 6. Anti-senescence therapy for IVDD. **A)** Common pathogenic mechanisms of the senescence process in NPCs. Reproduced with permission from Ref. [150]. Copyright 2023 Elsevier. **B**) The quaternized chitosan/oxidized starch hydrogel-delivered BMSC-Exos reduced the expression of aging-related proteins (p16), reversed the metabolic imbalance of the ECM and delayed the process of IVD height loss and degeneration. Reproduced with permission from Ref. [17]. Copyright 2023 Elsevier. **C**) Hydrogels deliver GLRX3-functionalized EVs, which can enhance the antioxidant defense and mitochondrial protection functions of NPCs, reduce ROS expression, reduce the expression of aging-related genes, and significantly improve the process of IVDD. Reproduced with permission from Ref. [19]. Copyright 2023 American Chemical Society.

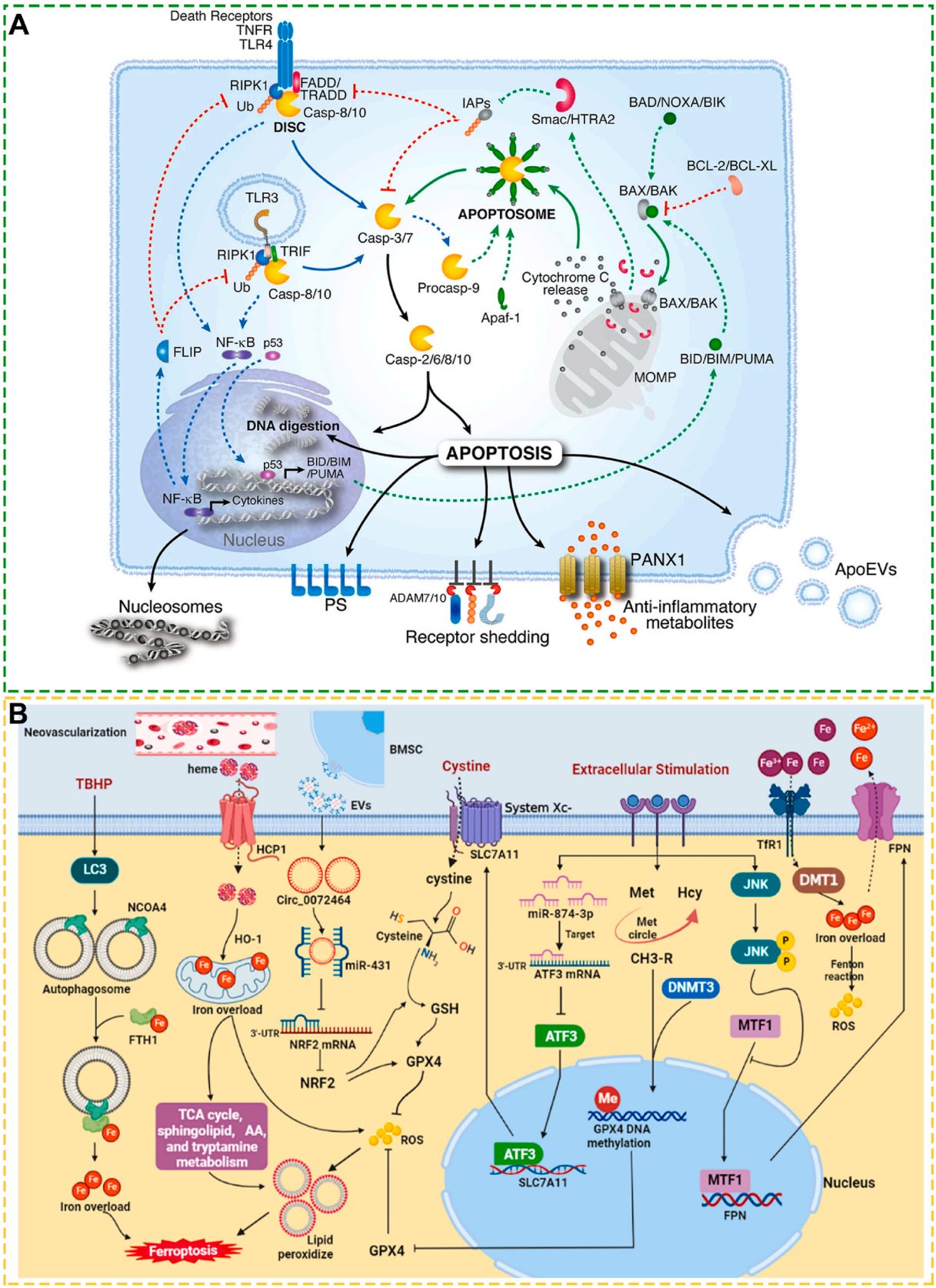

Fig. 7. **A**) Current modes of regulation associated with apoptosis. Reproduced with permission from Ref. [161]. Copyright 2021 the Author(s). **B**) Current modes of pyroptosis-related pathways. Reproduced with permission from Ref. [145]. Copyright 2023 MDPI.

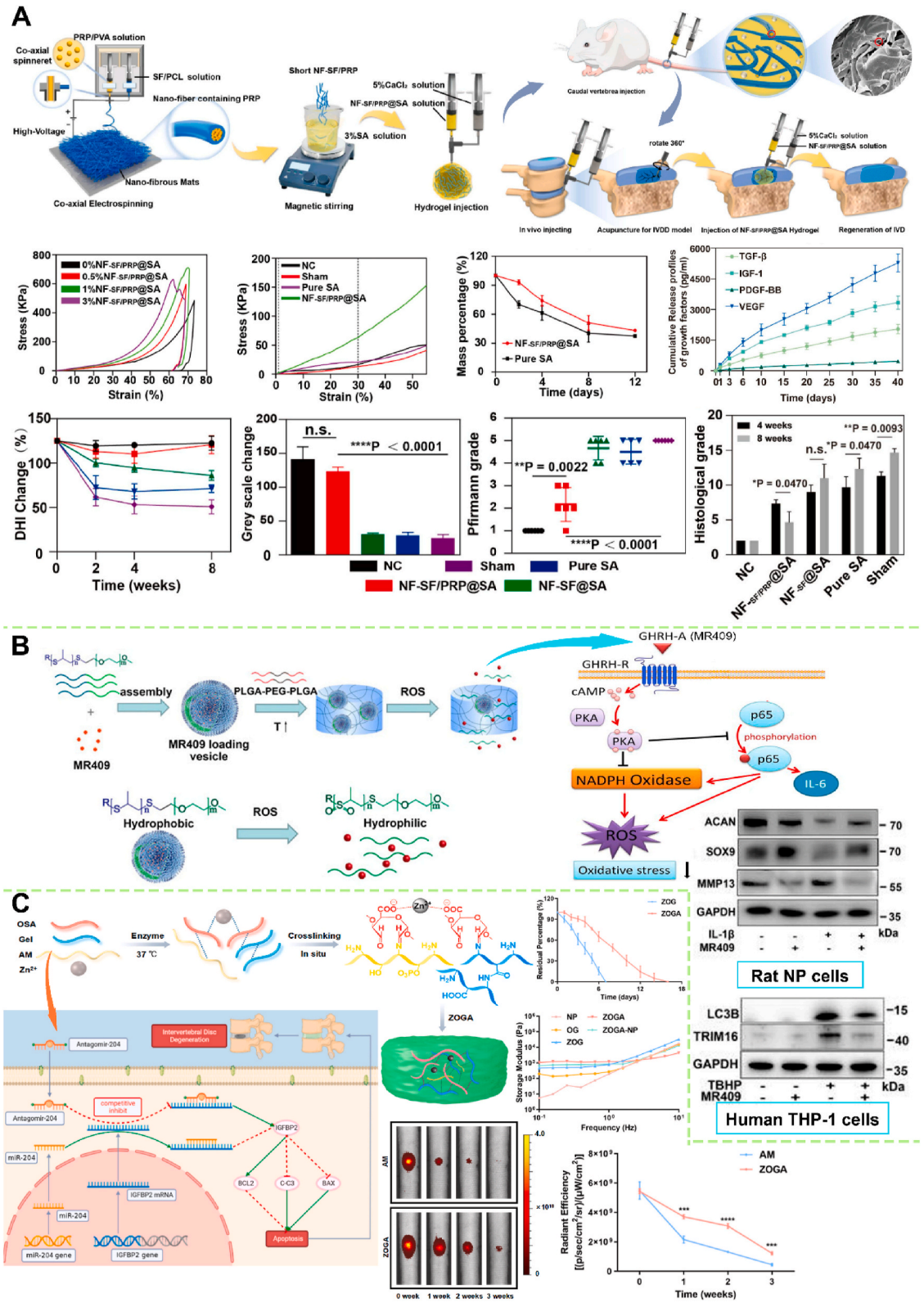

Fig. 8. Anti-apoptosis treatment of intervertebral disc degeneration. **A**) PRP was encapsulated in core-shell nanofibers and then uniformly dispersed in alginate gel to construct a dual-controlled drug release system. Reproduced with permission from Ref. [171]. Copyright 2022 Elsevier. **B**) Hydrogel-loaded microspheres released MR409 in response to localized ROS, and MR409 inhibited secretory autophagy to downregulate intracellular ROS expression, attenuate NPC apoptosis, and ameliorate inflammation-induced metabolic imbalance in the extracellular matrix. Reproduced with permission from Refs. [57,172]. Copyright 2018 American Heart Association, and 2024 Ivyspring International Publisher. **C**) The enhanced mechanical properties, biodegradability, and drug release capabilities of the ZOGA hydrogel make it suitable for the treatment of IVDD. The delivered antagomir-204–3p (AM) reduces NPC apoptosis by competitively inhibiting the IGFBP2 gene. Reproduced with permission from Ref. [173]. Copyright 2023 Elsevier.

high-strength hydrogel network by cross-linking with collagen components in NP tissue. This makes it more suitable for local IVDs [173]. Using this hydrogel to load miR-204–3p inhibitor antagomir-204–3p can delay the release rate of the latter, because it forms a dynamic Schiff base bond with oxidized alginic acid, one of the hydrogel components. The released antagomir-204–3p inhibited miR-204–3p overexpression-induced NPC apoptosis by competitively binding to the downstream target gene IGFBP2 (Fig. 8C) [173].

In conclusion, the controlled release system of anti-apoptosis drugs based on hydrogel can effectively resist the depletion of endogenous cells in degenerated IVDs and mobilize the vitality of endogenous reserve cells. This provides a highly promising and selective therapeutic approach for the prevention and treatment of IVDD.

4.3.2. Anti-pyroptosis

Pyroptosis is another form of programmed cell death triggered by various inflammasomes and mediated by the gasdermin protein family. This leads to cell rupture and the release of cell contents, activating a more severe inflammatory response and further worsening the cell survival environment (Fig. 7B) [145,161]. In particular, IL-1β and nucleotide-binding domain-like receptor protein 3 (NLRP3), key molecules involved in pyroptosis, play crucial roles in the pathogenesis of IVDD [178,179]. By inhibiting the NF-κB signaling axis or activating the SIRT1 signaling axis, the expression and activity of the inflammasomes NLRP1 and NLRP3 can be suppressed, reducing the inflammatory response of NPCs and promoting autophagy, thus inhibiting the pyroptosis of NPCs.

BMP-7 can regulate the inflammatory response in diabetic rats, inhibit the activation of NLRP1 inflammasomes, and reduce NPC cell pyroptosis, thus improving IVDD in diabetic rats. As mentioned previously, SAPH functionalized with KPS, a peptide sequence with BMP-7 bioactivity, promotes the proliferation of NPMSCs and inhibits lipopolysaccharide (LPS)-induced pyroptosis in NPMSCs [97,180]. However, the protective effect of RADKPS on NPMSCs was significantly weakened after inhibiting the ERK1/2 and RhoA signaling pathways. Further elucidation of the regulatory mechanisms involved will contribute to the clinical translation of RADKPS. Additionally, studies have shown that miR-410 in MSC-Exos can directly bind to the mRNA of the inflammasome NLRP3, reducing its expression to inhibit LPS-induced NPC pyroptosis [181]. BMSC-EVs can deliver Prx2 to NPCs to attenuate TNF-induced pyroptosis [136]. Umbilical cord MSC (UCMSC)-derived Exos can reduce the abundance of m6A methylation in degenerated NPCs by delivering miR-26a-5p, which targets METTL14 mRNA, to decrease the expression levels of METTL14 and its downstream target NLRP3, thereby inhibiting NPC pyroptosis [182]. These studies demonstrated that stem cell-derived EVs are rich in regulatory small nucleic acid molecules or active factors. Sustained delivery of them to degenerating IVD using hydrogels may delay or even improve IVDD by modulating NPC pyroptosis [135].

Interestingly, in the process of bibliometric analysis, we have found that an increasing number of scholars have focused on the significant potential of traditional Chinese medicine therapy for IVDD in recent years. For instance, active pharmaceutical ingredients such as maltol and paeoniflorin, traditional Chinese medicine compound formulas such as Duhuo Jisheng Decoction and Qiangjin Zhuang Qufeng mixture have been found to improve IVDD by regulating cell pyroptosis mediated by inflammasomes [183–186]. However, there is currently no herb-hydrogel treatment system available to combat pyroptosis. Many herbs contain flavonoids, triterpenoids, anthraquinones, and other compounds that have antioxidative, anti-inflammatory, antimicrobial, cell proliferation-promoting, anti-pyroptotic, anti-senescence, and anti-apoptotic effects [149,185–187]. Therefore, developing an herb-hydrogel system may be a promising frontier research direction for local IVDD treatment.

4.3.3. Anti-ferroptosis

Ferroptosis, a new special form of regulated cell death, has been proposed by researchers in recent years. Its characteristics include iron-dependent lipid peroxidation of cell membranes, unstable iron deposition, excessive generation of ROS, mitochondrial contraction, and increased mitochondrial membrane density [188]. With the continuous advancement of bioinformatics technology, scholars have identified the overexpression of ferroptosis-related genes in degenerative IVDs or degenerative NPCs [189,190]. The regulatory role of ferroptosis in the process of IVDD has also been summarize (Fig. 9A) [191]. Studies have found that by regulating multiple signaling pathways such as the HMOX1/GPX4 [192], NRF-2 [193], NF-κB [194], Circ-STC2/-miR-486–3p/TFR2 [195], and USP11/SIRT3 pathways [196], oxidative stress-induced ROS overexpression and iron overload can be reversed, and the lipid peroxidation could be inhibited, which led to the improvement of the NPC active function. NRF-2 is the main regulatory factor of antioxidants and cellular protection pathways, regulating intracellular iron metabolism. GPX4 is a downstream target of NRF-2 that maintains the cellular redox balance and is considered a major component of antioxidant defense. It can convert active phospholipid hydroperoxides (PLOOH) to inactive phosphatidylcholine (PLOH), thereby blocking the free radical chain reaction responsible for lipid peroxidation. By binding with glutathione, GPX4 can convert harmful membrane lipid hydroperoxides into nontoxic lipids. GPX4 can also prevent ferroptosis by neutralizing active Fe^{2+}, converting H_2O_2 to H_2O, and through various other methods [191,197–200]. In summary, the main strategy to combat NPC ferroptosis is to activate the NRF-2/GPX4 regulatory pathway to enhance cell antioxidant capacity. The development of anti-ferroptosis biomaterials is an emerging and promising research strategy.

The PDA-NPs mentioned above could alleviate iron overload by chelating Fe^{2+} and regulating the expression of iron storage proteins, inhibiting GPX4 ubiquitination and converting and scavenging phospholipid hydroperoxides, thus inhibiting ferroptosis in NPCs. Weekly local injection of PDA-NPs in a rat IVDD model retarded the IVDD process to some extent [45]. However, due to the lack of a transport medium, PDA-NPs cannot exert sustained effects locally in the IVD, suffer from a range of side effects associated with repeated puncture administration, and have limitations such as cumbersome administration and increased therapeutic pain. Unfortunately, no anti-ferroptosis hydrogels for the treatment of IVDD have been developed yet. Fortunately, research on anti-ferroptosis hydrogels has been conducted in areas such as skin ulcers, diabetic wounds, radiation-induced oral mucositis [202], diabetic wounds [203,204], radiation-induced oral mucositis [205], and spinal cord injuries [206], achieving satisfactory therapeutic effects. These studies provide technical and feasibility support for its application in IVDD treatment, offering new strategies for IVDD treatment.

4.3.4. Anti-PANoptosis

As discussed earlier, the same injury can often participate in different cell death pathways, and these pathways have intersections of signaling regulation [207]. Therefore, there may be interactions between various forms of death. In 2019, Professor Kanneganti summarized the discovery of a new form of death in infectious diseases, PANoptosis. It is characterized by the simultaneous occurrence of apoptotic, pyroptotic, and necroptotic cell death, which cannot be explained by individual forms of death [208]. PANoptosis is regulated by cell death signaling complexes, which are assembled by integrating components from other programmed cell death pathways. Z-DNA binding protein 1 (ZBP1) and transforming growth factor β-activated kinase 1 (TAK1, also known as MAP3K7) were initially identified as key regulatory factors of PANoptosis. ZBP1 is considered the main switch of PANoptosis, where activated ZBP1 interacts with serine/threonine protein kinase 3 (RIPK3) and recruits caspase-8 to form the ZBP1-RIPK3-CASP8 cell death signaling complex, which is involved in RIPK3-mediated necroptosis,

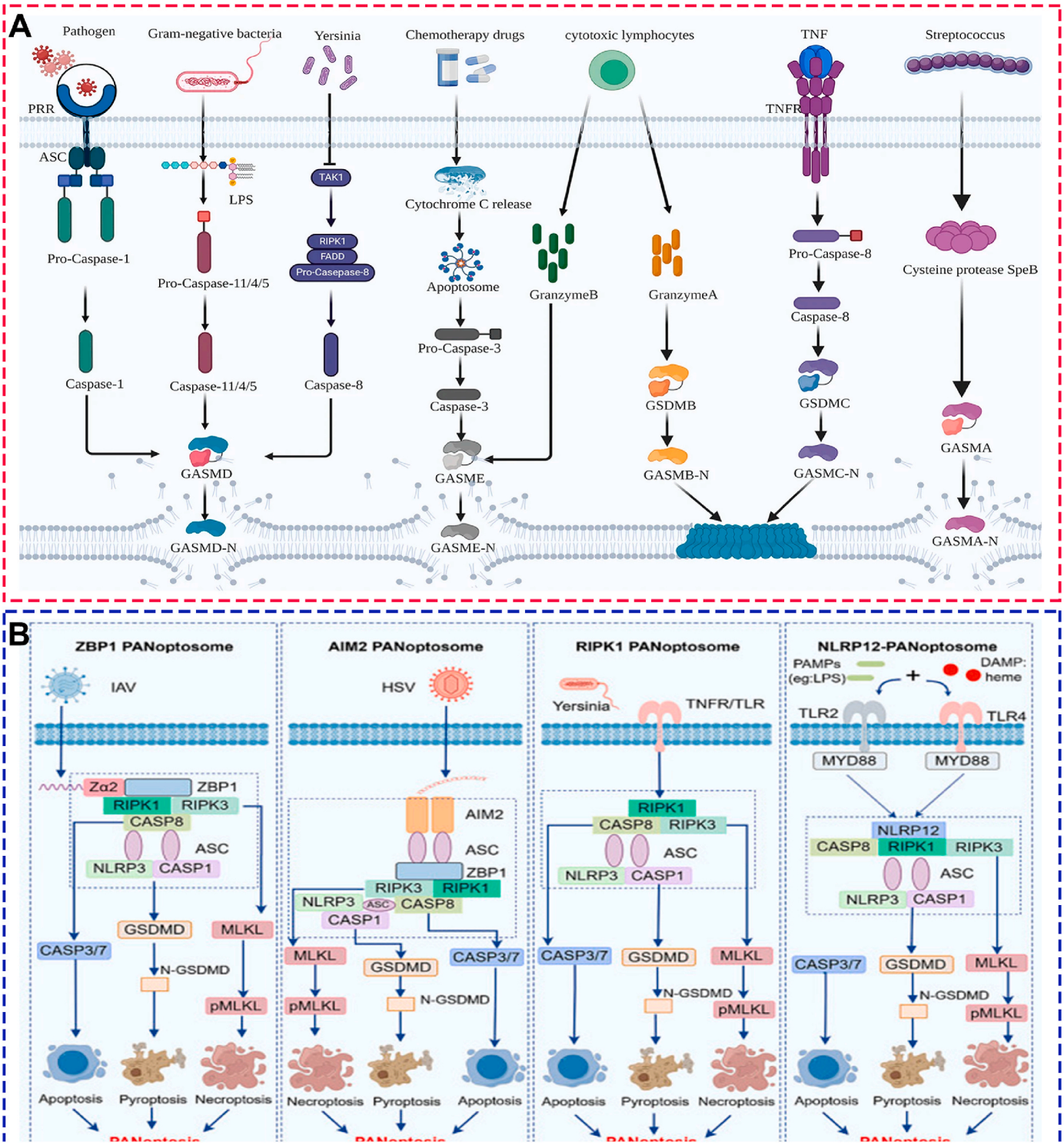

Fig. 9. A) Potential ferroptosis-related pathways in NPCs. Reproduced with permission from Ref. [191]. Copyright 2021 the Author(s). **B**) The potential PANoptosis-related pathways. Reproduced with permission from Ref. [201]. Copyright 2023 Elsevier.

CASP8-mediated apoptosis, and NLRP3 inflammasome-dependent pyroptosis. On the other hand, TAK1 is considered the main suppressor of PANoptosis, inhibiting RIPK1 phosphorylation and limiting the formation of the RIPK1-FADD-caspase-8 signaling complex, thus preventing the spontaneous activation of PANoptosis [208]. With further research, this complex composed of various pyroptotic, apoptotic, and necroptotic molecules has been named PANoptosome. The PANoptosome consists of three structural domains: the assembly domain, catalytic domain, and sensing domain [209,210]. In addition to the ZBP1- (or NLRP3-) PANoptosome and the RIPK1-PANoptosome, the AIM2-, NLRC4-, and Pyrin- (or NLRP12-) PANoptosomes have successively unveiled their "mysterious veils" (Fig. 9B) [201,209–211]. However, research on PANoptosis in musculoskeletal diseases is currently limited [212–215]. Studies have explored PANoptosis-related biomarkers in osteoarthritis through bioinformatics, identifying three genes (NFKBIA, RNF34, and SERINC3) [213]. Apelin-13 was also found to play a crucial role in the treatment of osteoporosis, fracture healing, osteoarthritis, and periprosthetic osteolysis by regulating multiple

programmed cell death pathways such as autophagy, apoptosis, inflammatory responses, and the NLRP13 inflammasome. Therefore, apelin-13 is considered a potential regulator that may exert bone-protective effects by modulating PANoptosis [214].

Similarly, the characteristic manifestations of PANoptosis such as apoptotic, pyroptotic, and necroptotic features coexist within degenerated IVDs, with PANoptosis-related factors such as IL-1β, caspase-1, caspase-3, caspase-8, and the NLRP3 inflammasome participating in various death pathways of IVD cells. Hence, it is cautiously speculated that PANoptosis may be involved in the process of IVDD. Unfortunately, there is currently no research exploring the potential relationship between PANoptosis and IVDD. Consequently, we believe that exploring the regulatory mechanism of PANoptosis in IVDD and developing anti-PANoptosis hydrogel materials may be able to counteract multiple cell death pathways more comprehensively within IVDD, thus exerting a more comprehensive and efficient therapeutic effect. This is a novel and unprecedented perspective with significant research prospects and value.

4.4. Correcting organelle damage

Based on the above summary and citation analysis, we found that the current therapeutic strategy using hydrogel materials to preserve reserve cells by resisting cell aging and death mainly achieves the goal of IVD repair in two directions. On the one hand, it is about protecting mitochondria. Mitochondria are the energy generation and supply centers of cells and the core parts of oxidative metabolism. Mitochondrial membrane homeostasis is crucial for cell survival. The mainstream research direction is to improve the self-repair ability of IVD cells by counteracting the imbalance in mitochondrial homeostasis induced by various adverse factors and enhancing mitochondrial antioxidant capacity, energy metabolism, and autophagy [216]. On the other hand, it is about combating excessive endoplasmic reticulum stress. The endoplasmic reticulum is the quality control organelle for protein homeostasis. The protein quality control system involves endoplasmic reticulum-related degradation, protein folding partners, and autophagy. When the accumulation of misfolded and unfolded proteins in the endoplasmic reticulum disrupts protein homeostasis, endoplasmic reticulum stress is activated [217]. There is an interaction between the endoplasmic reticulum stress response and redox signal transduction, where the excessive accumulation of ROS may disrupt the redox homeostasis of the endoplasmic reticulum, leading to the accumulation of dysfunctional proteins and excessive endoplasmic reticulum stress [218]. Weakening the phosphorylation of overactivated unfolded protein reaction (UPR)-related proteins, such as PERK, IRE1α and ATF6, and the protein expression of transcription factor 4 (ATF4) and X-box binding protein 1 (XBP1) activated by genes downstream of the UPR can improve the correct synthesis of proteins, lipids, polysaccharides and other cell components and cytokines in IVD cells, thus saving IVD cells [219]. There is significant crosstalk between mitochondrial dysfunction and endoplasmic reticulum stress, which can form positive and negative feedback loops through inflammatory factors, signaling pathways, Ca^{2+} transfer, ROS, or C/EBP homologous protein (CHOP) [142]. Therefore, rescuing the organelle function of endogenous cells will provide ideas and directions for the research and clinical translation of hydrogel materials for IVDD treatment.

4.5. Supplementing exogenous cells

According to the above findings, we can preserve endogenous cells to repair degenerated IVDs by inhibiting endogenous cellular senescence and death. However, the number of endogenous cells remaining within heavily degenerated IVDs is almost depleted to the point where it is insufficient to meet the repair needs of degenerated IVDs. Implanting exogenous MSCs into degenerated IVDs can effectively address the dilemma of insufficient endogenous cell numbers. This represents a significant breakthrough in IVDD treatment. As mentioned earlier, the MSC-hydrogel delivery system is one of the popular research directions in the field of IVDD. Fortunately, cell therapy has been thoroughly and high-quality research in the field of IVDD, and have been verified to have a positive therapeutic effect on IVDD [67,116,122,182]. The application of the MSC-hydrogel system in IVDD has been summarized in the previous section, and here we focus on the advantages and dilemmas faced by cellular therapies.

Through extensive research, the pathways by which stem cell therapy exerts a positive therapeutic effect can be summarized as follows: First, the multidirectional differentiation potential of MSCs allows them to differentiate into IVD cells, thus overcoming the depletion of endogenous cells. Second, supplemented MSCs can interact with endogenous IVD cells, reducing the pathological states of senescence, apoptosis, necroptosis, and ferroptosis. Third, MSCs can improve the metabolic balance of the local ECM in the IVD. Last, supplemented MSCs can, to a certain extent, regulate the adverse local microenvironment of IVDD through immune modulation.

However, stem cell therapy does not necessarily mean it is flawless. Although numerous studies have confirmed the potential of different types of stem cells for IVDD treatment, each type of stem cell has advantages and disadvantages. For example, BMSCs have been studied the most deeply, but the acquisition method is bone-invasive. ADSCs are abundant and have low immunogenicity, but their differentiation ability is relatively poor. UCMSCs have broad differentiation ability, no ethical barriers, low immunogenicity, and no tumorigenicity, but the possibility of autologous sources is minimal, with high preservation and amplification costs. NPPCs are best suited for the IVD microenvironment and are capable of stimulating proliferation and differentiation in situ, but the yield and survival rate of NPPCs in IVDD patients are low. iPSCs have strong multidirectional differentiation ability, self-renewal, and proliferation capabilities, but they also have safety concerns, especially in the presence of tumorigenicity [220]. Some early clinical trials have shown that local injection of stem cells in degenerated segments of IVDD patients can partially repair IVDD [221,222]. These promising treatment results from early studies have made significant contributions to the clinical promotion of stem cell therapy. Nevertheless, compared to stem cells from IVD sources, stem cells from other exogenous sources have a lower tolerance for the unfavorable microenvironment of IVDD, making it difficult to control the quantity and quality of direct differentiation into IVD cells. Different studies have used different MSCs, with varying treatment doses and no unified treatment standards. Additionally, current clinical research reports mainly focus on the direct injection of MSCs without cell delivery vehicles, which may lead to unnecessary cell migration or leakage, resulting in ineffective treatment and osteophyte formation [223].

According to our bibliometric analysis outcomes, MSCs are one of the hottest keywords in the field of hydrogel treatment for IVDD, with research intensity increasing annually (Fig. 3). Therefore, despite the limitations of stem cell therapy, researchers still maintain a positive attitude toward the use of stem cell therapy in IVDD treatment. This may be because hydrogels can to some extent compensate for the shortcomings of stem cell therapy. However, it is essential to emphasize that selecting the appropriate cell source, inducing cells through efficient directed differentiation, and relying on appropriate hydrogel vehicles are crucial to fully realizing the immense potential of cell therapy in IVDD treatment.

5. Conclusions and prospects

Over the past decade, hydrogel materials have gradually gained popularity among researchers in the field of orthopedics, especially in the field of IVDD. This study has summarized the trends in the investigation and application of hydrogel materials in the treatment of IVDD through bibliometric analysis, including annual publication growth, most contributing countries and institutions, most prolific authors and

publications, and keyword analysis. This is the first comprehensive bibliometric analysis of this research area, which provides scholars with an efficient and insightful overview of research trends in the field.

According to the co-occurrence of keywords and literature summaries, the corresponding research topics and hot spots in this field are determined. The microenvironment-responsive hydrogels, NP-dECM hydrogels, SAPH, and MSC/EV-hydrogels are hot topics in the field of IVDD treatment. Therefore, we discuss the current hot research status and limitations with examples and propose potential solutions. We found that not only can we improve the living environment of local cells by consuming harmful microenvironmental factors, but these microenvironments can also be used as a "switch" for drug release in hydrogels to regulate the time-space effect of drug release. Moreover, there are internal relationships among various adverse factors, and the comprehensive consideration of various adverse microenvironments can realize the complementary advantages of improving the living environment, time-space controlled drug release, cell mobilization and repair, and other functions. In addition, NP-dECM hydrogels have unique advantages in terms of composition, while their further popularization and mass production are constrained by limited material sources, high cost, difficult preparation, and insufficient mechanical properties. We believe that the development of biomimetic ECM hydrogels with proper mechanical properties based on the core components of NP-dECM combined with bioactive factors and cellular therapies, may be a more suitable alternative. Moreover, SAPH has gradually attracted the interest of researchers in the spine field in recent years, research on the use of SAPH for the treatment of IVDD is much more limited than that in other areas. We believe that highly editable functionalized SAPH is an ideal candidate scaffold for NP tissue repair and deserves more attention. Referring to the research progress on SAPH in other fields, understanding the unique pathological mechanism of IVDD and combining them is crucial for future breakthroughs in this field. Furthermore, benefiting from the multifunctional bioactivities of MSCs and MSC-EVs and the ideal cell/drug carrier ability of hydrogels, MSC/EV-hydrogel systems are the hottest research direction in this field. However, we suggested that it should be specifically designed according to the degree of degeneration of IVD. It is difficult to achieve satisfactory therapeutic effects with EV-hydrogels alone for severe IVDD with endogenous cell depletion without exogenous cell support. Based on the above discussions and thoughts, we have innovatively concluded that "hydrogel delivery platform, cells, cell stimulators, and microenvironmental regulation" are the "four core factors" that a multifunctional hydrogel for the repair of IVDD should possess. Based on the results of bibliometrics, we reviewed and summarized the mechanistic strategies of hydrogel delivery systems for the treatment of IVDD. Based on these mechanistic strategies, the development of hydrogel delivery systems with "four core factors" is an important direction for research and translation.

There are still some great challenges in facilitating the clinical translation of hydrogel therapies in the field of IVDD and these challenges are the most promising research directions for the future:

(1) The IVDD microenvironment is intricate. Current popular hydrogel research primarily focuses on overcoming oxidative stress, low pH, and ECM metabolic disorders. However, research on designing hydrogels to address hypertonicity, hypoxia, and pressure load within the microenvironment is relatively scarce. Therefore, a multifaceted approach to microenvironment modulation represents a critical direction for future hydrogel development. The average internal pressures of the IVD in supine, sitting, and standing positions are 0.22 MPa, 0.75 MPa, and 0.59 MPa respectively, with maximum pressure values of 0.41 MPa, 1.50 MPa, and 1.07 MPa [224]. While some studies initially consider matching the mechanical properties of hydrogels with NP tissue or IVD structure, the mechanical strength of most hydrogels falls short of meeting the conditions of the IVD. The main reason is that mechanical property evaluations of these hydrogels are predominantly conducted under unconstrained *in vitro* conditions, failing to replicate the *in vivo* IVD pressure environment. This discrepancy makes it difficult to confirm the hydrogel material's effective load-bearing and dissipation capabilities *in vivo*, posing a significant obstacle to clinical translation. Using finite element analysis, *ex vivo* IVD structures or *in vivo* modeling to examine the mechanical properties of hydrogels can provide more direct and effective evidence for hydrogel therapy in treating IVDD.

(2) The selection of animal models for IVDD is diverse. Various animals such as SD rats, New Zealand rabbits, goats, and macaques have been utilized in constructing IVDD models, and there are some differences in IVD structure between species [63,225]. Currently, most studies have used the IVDD modeling method of fine-needle puncture of the SD rat caudal, which deviates from the mechanism of physiological degeneration models. This raises doubts regarding whether hydrogel materials developed at present can yield equivalent therapeutic effects in the human body, thereby impeding their clinical translation. Utilizing stress-induced degeneration models with pressure applied at both ends may present a closer resemblance to physiological degeneration conditions [226]. Animal experiments are an indispensable step before clinical translation, and effectively simulating human IVDD conditions poses a major challenge in the development of hydrogels, warranting further exploration in future research endeavors.

(3) Controllable hydrogel degradation. Hydrogel degradation rates faster than the rate of tissue regeneration will make it difficult to meet the need for continuous mechanical support, and drug and cell delivery; degradation rates that are too slow will hinder the space and rate of tissue regeneration. Matching the controlled rate of hydrogel degradation with the rate of tissue regeneration remains a challenge for biomaterials in the field of tissue engineering.

(4) Although hydrogel materials for treating IVDD have been rapidly developed with increasingly enriched functionalities, current research mostly remains at the stage of preclinical experiments involving cells and small animals, with few hydrogels progressing to the clinical trial phase. Conducting large animal experiments to validate these hydrogel materials and advancing them to phases I, II, and III clinical trials are essential steps toward clinical translation. This should be a focal point for researchers and a future direction of work. Without achieving clinical translation, these studies will struggle to truly benefit IVDD patients.

In conclusion, the prevention and treatment of IVDD is an urgent field, which has a wide range of global beneficiaries. Facilitating the clinical translation of hydrogel materials will contribute to the minimally invasive treatment of patients with discogenic LBP and the structural repair of IVDs after foramenoscopic minimally invasive nucleus pulposus removal in patients with herniated discs. This study analyzed the research hotspots and application trends of hydrogel materials in treating IVDD utilizing bibliometric tools. We innovatively summarized the "four core factors" that multifunctional hydrogels should possess, offering a more comprehensive and effective approach to the treatment of patients with degenerative IVD diseases. Finally, we summarize the mechanism of hydrogel therapy for IVDD from five aspects: the fundamentals of IVDD, regulation of cellular senescence, reduction of cell death, correction of organelle damage, and introduced the concept of "PANoptosis" into the field of IVDD. These outcomes will provide novel design ideas for the future development of hydrogel materials for IVDD.

CRediT authorship contribution statement

Junwu Wang: Writing – original draft, Visualization, Project administration, Conceptualization. **Yu Zhang:** Writing – original draft, Visualization, Software, Methodology. **Yilong Huang:** Visualization, Software, Methodology, Investigation. **Zhuowen Hao:** Software, Data curation, Conceptualization. **Guang Shi:** Software, Data curation, Conceptualization. **Lanhong Guo:** Validation, Supervision, Methodology, Investigation. **Chunyu Chang:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Jingfeng Li:** Writing – review & editing, Validation, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mtbio.2024.101251.

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