Cascade Mechanism of Inflammaging-Driven Intervertebral Disc Degeneration: from Microenvironmental Evolution to Tissue Fibrosis and Frontier Intervention Strategies

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Abstract

As the core pathological basis of chronic low back and leg pain and spinal dysfunction, the etiology of intervertebral disc degeneration (IVDD) has long gone beyond simple mechanical wear, representing instead a gradual process in which mechanical imbalance and biological dysregulation are deeply coupled. The introduction of the concept of "inflammaging" provides a new dimension for elucidating its complex progression. Studies have shown that the pathological evolution of IVDD is not an accumulation of isolated events, but a multidimensional molecular cascade driven by inflammaging. Endogenous and exogenous stresses induce cells to enter a senescence program, triggering the persistent release of the senescence-associated secretory phenotype (SASP), which not only remodels the local immune microenvironment but also leads to the gradual loss of the native immune privilege of the intervertebral disc. Under the influence of chronic low-grade inflammation, cellular metabolic reprogramming becomes increasingly prominent: excessive lactate accumulation activates acid-sensing ion channels, forming a feed-forward loop of "microenvironmental acidification-inflammatory cascade-matrix degradation." As the lesion progresses, aberrant activation of the transforming growth factor-β signaling pathway further drives cellular phenotypic transition, causing the elastic matrix to transform into pathological fibrosis and ultimately leading to loss of function of the spinal motion segment. In view of these pathological processes, this article systematically reviews cutting-edge intervention strategies aimed at blocking this cascade, ranging from the use of senolytic drugs to selectively eliminate senescent cells and block the source of inflammation, to the use of functionalized carriers to targetedly inhibit the paracrine effects of SASP, and to the application of responsive hydrogels to remodel matrix homeostasis. In-depth elucidation of the molecular cascade mechanisms triggered by inflammaging, together with the use of biomaterials technologies to block pathological cycles, can provide important theoretical support for early intervention and tissue regenerative repair in IVDD.

Full Text

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【Abstract】 As the core pathological basis of chronic low back pain and spinal dysfunction, the cause of intervertebral disc degeneration (IVDD) has long gone beyond the scope of simple mechanical wear, but is a gradual process in which mechanical imbalance and biological disturbance are deeply coupled. The introduction of the concept of "inflammaging" provides a new dimension for elucidating its complex evolutionary patterns. Studies have shown that the pathological evolution of IVDD is not an accumulation of isolated events, but a multidimensional molecular cascade response driven by inflammaging. Internal and external stress induces cells to enter a senescent program and triggers the continuous release of the senescence-associated secretory phenotype (SASP), which not only reshapes the local immune microenvironment, but also leads to the gradual loss of the disc' s intrinsic immune privilege. Under the action of chronic low-grade inflammation, cellular metabolic reprogramming becomes increasingly prominent: excessive lactate accumulation activates acid-sensing ion channels, forming a positive-feedback loop of "microenvironmental acidification—inflammatory cascade—matrix degradation."As the lesion progresses, abnormal activation of transforming growth factor-β signaling pathways further promotes phenotypic transition of cells, causing the elastic matrix to transform toward pathological fibrosis, ultimately leading to loss of function of the spinal motion segment. In view of the above pathological processes, this article systematically reviews frontier intervention strategies to block this cascade reaction, including targeted elimination of senescent cells with senolytic agents to block the inflammatory source; targeted inhibition of SASP paracrine effects with functionalized carriers; and reshaping matrix homeostasis with responsive hydrogels. It also analyzes in depth the molecular cascade mechanisms triggered by inflammaging and the use of synergistic biomaterial technologies to block the pathological cycle, which can provide important theoretical support for early intervention and tissue regenerative repair of IVDD.

【Keywords】 intervertebral disc degeneration; inflammaging; cellular senescence; acid-sensing ion channels; TGF-β signaling pathway; pathological fibrosis; functionalized biomaterials

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【Abstract】 As the core pathological basis of chronic low back pain and spinal dysfunction, the cause of intervertebral disc degeneration (IVDD) has long gone beyond the category of simple mechanical wear, but is a gradual process of deep coupling

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of mechanical imbalance and biological disorder. The introduction of the concept of "inflammaging" provides a new dimension for elucidating its complex evolutionary law. Studies have shown that the pathological evolution of IVDD is not a stacking of isolated events, but a multi-dimensional molecular cascade response driven by inflammaging. Internal and external stress triggers the continuous release of the senescence-associated secretory phenotype (SASP) by inducing cells to enter the aging process, which not only reshapes the local immune microenvironment, but also leads to the gradual loss of the original immune privilege of the intervertebral disc. Under the action of chronic low-grade inflammation, cell metabolic reprogramming is becoming more and more significant: excessive lactic acid accumulation forms a feed-forward cycle of "microenvironment acidification-inflammation cascade-matrix degradation" by activating acid-sensitive ion channels. With the progression of the disease, the abnormal activation of the transforming growth factor-β signaling pathway further promotes the phenotypic transformation of cells, resulting in the transformation of the elastic matrix to pathological fibrosis, which eventually leads to the loss of spinal motor unit function. In view of the above pathological processes, this paper systematically reviews the cutting-edge intervention strategies to block the cascade reaction, including the use of senolytic drugs to target the removal of senescent cells to block the source of inflammation, the targeting of the inhibition of SASP paracrine effects with the help of functional carriers, and the reshaping of matrix homeostasis with the help of responsive hydrogels. In-depth analysis of the molecular cascade mechanism triggered by inflammaging and synergistic biomaterial technology to block the pathological circulation can provide important theoretical support for early intervention and tissue regeneration and repair of IVDD.

【Key words】 Intervertebral disc degeneration; Inflammaging; Cellular senescence; Acid-sensing ion channels; TGF-β signaling pathway; Pathological fibrosis; Functionalized biomaterials

Intervertebral disc degeneration (IVDD) is the common pathological basis of degenerative spinal diseases[^1-2], and is also the core inducement leading to chronic low back and leg pain and functional impairment worldwide[^3-4]. Epidemiological data show that 80% of individuals suffer from lumbodorsal symptoms in their lifetime[^4], and the resulting increase in medical expenditure and loss of labor force have imposed a heavy economic burden on global public health systems[^3]. Although conservative treatment and surgical decompression are widely used clinically, the former is difficult to reverse pathological outcomes[^5-6], while the latter carries an inherent risk of inducing accelerated degeneration of adjacent segments due to changes in biomechanical distribution[^7-8]. This dilemma has prompted researchers to re-examine the pathogenesis of IVDD.

Modern views hold that IVDD is a progressive process in which mechanical injury and biological disorder are deeply coupled[^9-10]. Changes in microstructure will deteriorate the microscopic mechanical environment[^10], inducing cellular dysfunction and matrix metabolic imbalance through mechanical-signal transduction[^11-12]; the concept of "inflammaging" provides a new perspective for this. Inflammaging is a chronic, systemic, sterile low-grade inflammatory state that appears with increasing age[^13-14]. Its core feature is the accumulation of pro-inflammatory factors and remodeling of the immune microenvironment driven by the senescence-associated secretory phenotype (SASP)[^14-15], which breaks intervertebral disc tissue homeostasis[^16-17]. Senolysis targeting the clearance of senescent cells has shown therapeutic potential in a variety of age-related diseases[^18]. This review aims to explore the cascade effects of chronic inflammation, cellular phenotypic transformation, tissue fibrosis, and matrix imbalance in the evolution of IVDD, so as to provide theoretical support for early precision intervention.

1 Inflammaging-induced evolution of the intervertebral disc microenvironment: cellular senescence-driven and immune response activation

In the specific physiological microenvironment of the intervertebral disc, nucleus pulposus (NP) and annulus fibrosus cells, driven by endogenous and exogenous stresses[^19-20], are prone to a tendency toward persistent cell-cycle arrest[^21-22], namely entering the stage of cellular senescence. Although these senescent cells lose proliferative potential, they still maintain vigorous metabolic activity and exhibit marked SASP. Through the release of pro-inflammatory factors, matrix-degrading enzymes, and chemokines, senescent cells locally construct a harmful microenvironment with catabolic dominance[^22], and drive phenotypic transformation of neighboring healthy cells through paracrine effects, promoting a trend of pathological signal amplification within the tissue[^23-24].

During this process, senescent NP cells, by upregulating the expression of matrix metalloproteinases and inflammatory factors, transmit stress signals at the cellular level into a degradation phenotype at the tissue level[^25]. Among them, N-acetylglucosamine-glucosamine-chondroitin sulfate serves as a key mediator[^26], triggering premature cellular senescence and disrupting redox homeostasis, systematically accelerating the apoptosis of functional cells and degradation of the extracellular matrix (ECM)[^27]. As the integrity of the fibrous ring structure is compromised and NP shifts or protrudes under mechanical imbalance[^28], the original immune privilege barrier is lost[^29], inducing infiltration of peripheral mononuclear cells into the tissue. Infiltrating cells trigger nuclear factor-κB (NF-κB)-mediated inflammatory cascade reactions through damage-associated molecular patterns[^29-30], and drive macrophage polarization toward the M1 phenotype[^31], ultimately inducing abnormal growth of nociceptive nerves into the deep layers of the tissue through the release of nerve growth factor[^32], forming the basis of discogenic pain hypersensitivity.

The chronic inflammatory cascade induced by inflammaging can negatively regulate the biosynthesis of core matrix components at the transcriptional level. In the degenerative environment, abnormally active NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways are regarded as major signaling pathways mediating ECM metabolic imbalance[^33–35]. Activation of these pathways is often accompanied by suppression of the expression of the cartilage lineage key transcription factor SRY-box transcription factor 9 (SOX9),

weaken the tissue' s repair potential at the source.

The biomechanical properties of the intervertebral disc are highly dependent on the content and structural integrity of the proteoglycan aggrecan[^36]. Aggrecan interacts with hyaluronic acid to form macromolecular aggregates, endowing the tissue with the ability to resist compressive loads. As the core regulator of type II collagen and aggrecan[^37], reduced SOX9 expression not only causes NP cells to gradually deviate from their physiological phenotype[^38–40], but also removes its inhibitory effects on chondrocyte hypertrophy and osteogenesis[^41]. This systematic suppression at the transcriptional level makes it difficult for the intervertebral disc to maintain structural homeostasis through endogenous synthesis while bearing catabolic pressure, thereby driving the evolution of pathological imbalance in the tissue toward systemic functional decline[^42–43].

2 Inflammatory senescence-mediated biochemical homeostasis remodeling: the pathogenic effects of lactic acid accumulation and acid-sensitive ion channels

Abnormal activation of the inflammatory microenvironment is often accompanied by marked metabolic reprogramming[^44]. The abnormal accumulation of intervertebral-disc metabolites is considered an important driver of the occurrence and development of IVDD[^45]. In the musculoskeletal system, aberrant lactylation is a key mechanism that mediates ECM homeostatic imbalance and decreased tissue repair capacity[^46], effectively linking cellular metabolic stress with pathological tissue remodeling.

As the largest avascular organ in the human body[^47], the NP tissue inside the intervertebral disc is, under physiological conditions, in a hypoxic and enclosed microenvironment. Because nutrient diffusion pathways are limited, anaerobic glycolysis becomes the main metabolic mode by which nucleus pulposus cells (NPCs) obtain ATP[^48]. However, during degeneration, this fragile metabolic balance is disrupted: limited material exchange leads to excessive accumulation of the metabolic product lactate in the central NP region[^44,49], where its concentration reaches a peak in degenerated NP regions[^49], thereby inducing a marked decrease in local pH[^50]. This imbalance of biochemical homeostasis not only marks insufficient nutrient supply, but also establishes a pathological feedback loop through lactic-acid-accumulation–induced acidosis. Studies have shown that high concentrations of lactic acid can directly inhibit ECM biosynthesis and induce NPC apoptosis[^51–52], accelerating structural collapse of the

intervertebral disc (IVD) at both biochemical and cellular levels.

As core receptors that sense the acidic microenvironment, acid-sensing ion channels (ASICs) are a class of proton-gated ion channels[^53] and belong to the degenerin/epithelial sodium channel family of exogenous sodium-ion channels[^54]. ASICs are widely expressed in the nervous system and in peripheral tissues such as the intervertebral disc[^53-54], and their activation is coordinately regulated by metabolic products such as acidosis, lactic acid, and arachidonic acid.

Studies have shown that upregulated ASIC expression is closely associated with the pathological progression of IVDD. As upstream regulatory factors, ASIC1 and ASIC3 directly drive premature senescence of nucleus pulposus mesenchymal stem cells by activating the p53–p21/p27 and p16–Rb1 axes[^55]. In addition, as important mediators of NP and endplate cells, activation of ASIC1a directly induces cellular apoptosis[^56]; at the level of tissue homeostasis, ASICs convert extracellular proton signals into transmembrane ion fluxes[^57-58], and the resulting intracellular calcium-signal dysregulation can further activate downstream MAPK and NF-κB pathways[^59-60], thereby establishing a vicious feed-forward cycle of "microenvironmental acidosis–inflammation–matrix degradation." In addition, ASIC-mediated extracellular lactic-acid effects also involve regulation of intracellular reactive oxygen species levels[^61], triggering activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and release of interleukin-1β (IL-1β), systematically aggravating the degenerative process of NP tissue. Beyond disrupting matrix homeostasis, the acidic microenvironment and the ASIC signal transduction it mediates are also core drivers of discogenic low back pain. As a nociceptive stimulus, the acidic microenvironment can directly activate damage receptors at peripheral nerve endings; in a chronic inflammatory environment, ASICs and inflammatory mediators mutually activate one another' s expression. While this interaction amplifies the local inflammatory cascade, it also constitutes the pathological basis for the induction and maintenance of chronic pain through sustained activation of damage receptors[^62].

3 Inflammatory senescence-driven tissue morphological transition: fibrotic remodeling and functional decline mediated by transforming growth factor-β (TGF-β)

In the chronic sterile low-grade inflammatory environment constructed by inflammatory senescence[^63-65], multiple SASP components and pro-aging factors synergistically drive abnormal activation of fibrotic signaling. Among them, dysregulation of the TGF-β/Smad signaling pathway is regarded as the core mechanism inducing intervertebral-disc fibrosis.

As a key node regulating cell differentiation, apoptosis, and tissue fibrosis, the TGF-β/Smad signaling pathway plays a central role in maintaining intervertebral-disc homeostasis and coordinating environmental stress responses[^66]. As a multifunctional cytokine, TGF-β is indispensable for the

development and growth of the IVD[^67]: at physiological doses, it exerts endogenous tissue-protective effects by promoting matrix synthesis, inhibiting catabolism, and suppressing inflammatory responses. Studies have found that TGF-β and its receptors are widely distributed in NP and annulus fibrosus cells, but their expression levels diminish with age[^67-68]; this age-related decline in expression suggests attenuation of endogenous repair capacity. On this basis, appropriate upregulation of GATA-binding protein 4 (GATA4) and TGF-( )1 expression through bioengineering approaches has been shown to induce cartilage endplate stem cells to migrate into the NP and undergo directed transformation into NPCs, thereby inhibiting the progression of IVDD to a certain extent[^69].

Although TGF-β exhibits potential to promote repair[^70], recent studies suggest that pathological overactivation of TGF-β signaling is an important inducement driving the progression of IVDD[^67,71-72]. In the degenerative context, abnormal activation of TGF-β signaling mediates morphological remodeling of the IVD microenvironment[^71,73]. This abnormal activation is closely associated with endplate hypertrophy, intrachondral ossification, and accelerated vascularization[^73], and further worsens the biomechanical environment of the intervertebral disc by inducing narrowing of the IVD space. At the same time, this signaling pathway also participates in regulation of inflammatory responses during the fibrotic process[^71,74], jointly accelerating structural breakdown of the tissue. Overexpressed TGF-β binds to its receptors and activates downstream Smad signaling, thereby triggering transcription of pro-fibrotic genes[^75-76].

The most prominent pathological feature of fibrosis is manifested as an excessive tendency of ECM components.

reconstruction of properties[^72,^77-^78], with the core process being the phenotypic conversion of collagen types. During pathological fibrosis, highly hydrated and elastic type II collagen within the intervertebral disc is markedly lost and replaced by disordered, mechanically stiffer type I collagen. This evolution from a functional matrix toward a fibrotic matrix leads to the loss of the intervertebral disc' s ability to resist compressive loads[^79]. Because type I collagen cannot provide the necessary viscoelastic support, when the spinal segment bears physiological loads, the stress distribution changes from uniform conduction by the NP to local stress concentration, ultimately resulting in systemic decline of the functional spinal motion unit.

4 Frontier intervention strategies for IVDD driven by inflammaging: breaking pathological cascade reactions

Based on the core driving role of inflammaging in the progression of IVDD, emerging intervention strategies are no longer limited to traditional symptom relief, but are committed to blocking pathological cascade reactions. By targeted elimination of inflammatory sources, regulation of the pro-inflammatory microenvironment, and physical restoration of matrix homeostasis, it is expected

that substantive biological reconstruction of intervertebral disc tissue can be achieved.

4.1 Targeted clearance of senescent cells: using senolytics to block the inflammatory source

Targeting senescent cells and SASP, a key degenerative inducer, senescent-cell-clearing senolytic drugs have become an intervention direction with great potential[^24]. Their mechanisms of action mainly involve temporarily interfering with anti-apoptotic pathways specific to senescent cells, prompting these cells to initiate selective apoptotic programs, thereby fundamentally reducing the driving factors of tissue injury[^80]. Multiple preclinical studies have shown[^80–^83] that senolytics have clear efficacy in delaying the progression of age-related diseases in multiple organs, including musculoskeletal system-related lesions.

Relevant research findings show that, in light of the specific pathological features of IVDD, senolytics can effectively clear senescent endplate chondrocytes within the marrow cavity beneath the endplate cartilage, while also suppressing the pro-inflammatory effects of SASP[^84–^86]. In experimental aging models, the value of this intervention is reflected not only in its ability to curb the processes of intervertebral disc height reduction and bone loss; more importantly, it can promote regeneration of microvessels in the marrow cavity. This provides critical nutritional support for the originally avascular intervertebral disc. Even if senolytics cannot directly reach the interior of the intervertebral disc, they can still improve angiogenesis in the endplate region and its coupling with bone formation, indirectly promoting the energy metabolism levels of NP and annulus fibrosus cells.

4.2 Regulating the immune microenvironment: SASP-targeted inhibition and local delivery based on functionalized carriers

In view of the low bioavailability of systemic anti-inflammatory drugs in the intervertebral disc and their significant systemic side effects, local drug delivery is regarded as a highly promising strategy for treating IVDD[^87]. In recent years, microspheres or nanoparticles have been used as functionalized carriers[^88–^92]. By means of microfabrication, specific pro-inflammatory factor inhibitors can be delivered directly into degenerated NP tissue, enabling sustained drug release and long-term maintenance of local immune homeostasis. For example, pH-responsive microspheres constructed from methacrylated hyaluronic acid[^93], or microspheres with immune-defense functions[^91], can release drugs in response to the biochemical features of the degenerative microenvironment, achieving controlled and sustained drug release and thereby maintaining local immune homeostasis over the long term. This precise intervention can not only effectively curb immune microenvironment remodeling driven by SASP, but also provide the necessary low-inflammatory, low-metabolic-stress environment for endogenous repair of the damaged matrix by reducing pro-inflammatory factor levels[^94], preventing degenerative cascade reactions in the intervertebral disc.

4.3 Reconstructing matrix homeostasis: physical support and biochemical repair mediated by responsive hydrogels

To address matrix mechanical instability caused by pathological fibrosis, functional materials developed through bioengineering technologies show dual repair potential. As a new type of scaffold[^95-^96], responsive hydrogels can not only compensate for tissue defects through their viscoelastic mechanical properties and simulate the biomechanical support of the NP[^97-^98], but also enable intelligent drug release according to changes in the microenvironment, such as decreased pH or increased enzyme concentration[^99].

Among various intervention approaches for intervertebral disc regeneration, functionalized hydrogels loaded with anti-inflammatory molecules, anti-fibrotic drugs, or growth factors exhibit therapeutic advantages distinct from other methods[^100-^101]. It should be emphasized that this strategy is not simply physical filling. Its core value lies in its ability to precisely intercept the cascade transmission of profibrotic signaling pathways such as TGF-β[^102], thereby suppressing the pathological transition of collagen phenotypes at the molecular level[^95], which can effectively delay the progression rate of matrix fibrosis.

The above synergistic model combining mechanical support with chemical microenvironment regulation logically realizes the reconstruction of intervertebral disc biochemical homeostasis from the bottom up. As an important bridge linking materials science and regenerative medicine, this type of composite intervention provides a feasible key technological route for functional restoration and tissue integration of spinal motion units by simulating the microenvironmental characteristics of the natural extracellular matrix.

5 Summary and outlook

Inflammaging plays a pivotal role in the pathological progression of IVDD. It is not only the starting point that induces chronic sterile low-grade inflammation, but also a deep-seated cause that drives changes in cell fate, metabolic reprogramming, and tissue fibrosis through SASP components. From immune microenvironment remodeling induced by cellular senescence, to activation of ASICs triggered by lactate accumulation, and then to the fibrotic outcome caused by pathological overactivation of the TGF-β pathway, this series of cascade mechanisms together depicts the trajectory by which the intervertebral disc shifts from physiological homeostasis to systemic functional decline.

In response to the above pathological cascade reactions, using senolytics to block the inflammatory source, functionalized carriers to precisely suppress SASP, and responsive hydrogels to reconstruct matrix homeostasis has established a core pathway for biological intervention in IVDD. However, clinical translation still faces multiple challenges: first, the precision of senolytic effects—namely, how to avoid potential off-target risks while clearing terminally senescent cells to rebuild nutritional supply; second, the dynamic regulatory performance of carrier design —how to ensure long-term maintenance of immune homeostasis in a complex mi-

croenvironment; and third, the need to focus on matching the biomechanics and biochemical signals of responsive hydrogels, aiming to rebuild physical support while strictly preventing the risk of pathological fibrosis mediated by TGF-β.

Looking to the future, in-depth elucidation of the molecular cascade mechanisms triggered by inflammatory aging, combined with cutting-edge biomaterials technologies to achieve physical–chemical dual blockade of pathological cycles, is expected to provide new entry points and theoretical bases for early precise intervention and tissue-regeneration research in IVDD.

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