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REVIEW

Mechanisms and Factors Influencing Resorption of Herniated Part of Lumbar Disc Herniation: Comprehensive Review

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Abstract: This review systematically examines the mechanisms underlying the spontaneous resorption of lumbar disc herniation (LDH), focusing on vascularization, autophagy, apoptosis, macrophage activity, and the therapeutic potential of traditional Chinese medicine (TCM). We emphasize that resorption is influenced by factors such as herniation type, disease duration, and imaging biomarkers (eg, the bull's-eye sign). Additionally, this review summarizes recent progress in the study of resorption mechanisms following lumbar disc herniation, providing a reference for future clinical research.

Methods: Literature was systematically searched in PubMed, Web of Science, and CNKI (2000-2024) using keywords: 'lumbar disc herniation,' 'resorption,' 'autophagy,' 'TCM.' Inclusion criteria: (1) human/animal studies; (2) MRI-confirmed LDH; (3) English/Chinese full texts. Exclusion criteria: case reports (n<10).

Keywords: lumbar disc herniation, spontaneous resorption, autophagy, apoptosis, macrophage polarization, traditional Chinese medicine

Introduction

Low Back Pain refers to pain, stiffness, or discomfort occurring in the lumbar region, which is the area between the lower edge of the ribs and the gluteal fold, and may be accompanied by radiating symptoms in the lower extremities.[1] Lumbar disc herniation (LDH) is a prevalent cause of low back and leg pain, often leading to radiculopathy.[2] It is a degenerative disease of the lumbar spine, characterized by the protrusion of the intervertebral disc into the spinal canal. While the treatment of LDH typically involves conservative methods such as medication, physical therapy, and in some cases, surgery, recent research has focused on non-surgical treatments and the phenomenon of spontaneous resorption of the herniated disc material.[3]

Guinto et al[4] first reported spontaneous disc resorption in 1984, a phenomenon later explored as a potential alternative to surgical intervention. This process not only alleviates symptoms but also suggests new treatment strategies, underscoring the importance of understanding its mechanisms. Among the various conservative treatments, Traditional Chinese Medicine (TCM) has gained attention for its minimal side effects and ability to promote resorption through different biological pathways.[5] This review aims to provide a comprehensive understanding of the mechanisms behind spontaneous resorption and to explore the therapeutic potential of TCM in treating LDH.

Types of Disc Herniation Prone to Resorption

When the fibrous ring of the intervertebral disc ruptures and the nucleus pulposus penetrates the posterior longitudinal ligament, directly invading the spinal canal, this condition is referred to as a ruptured type of lumbar disc herniation.[6] A disc herniation exceeding 50% of the spinal canal diameter is defined as a giant lumbar disc herniation (Figure 1). [7] Recent studies

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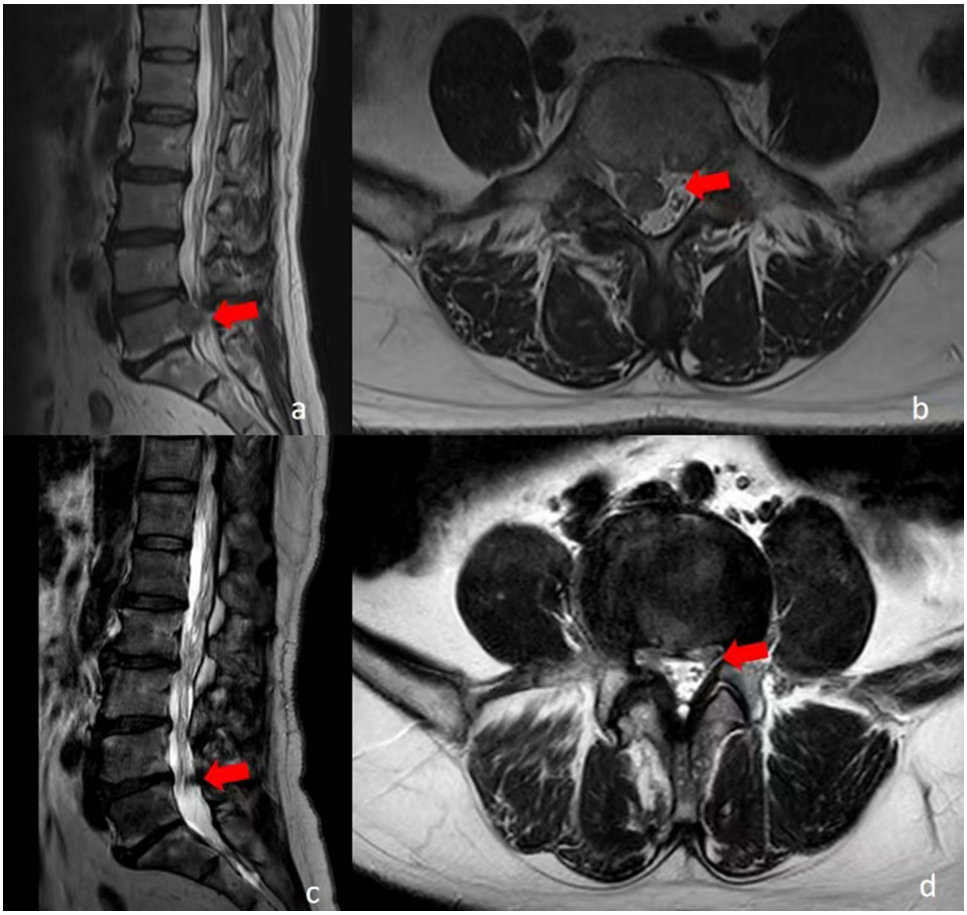

Figure 1 (**a**) is the first lumbar MRI in the sagittal view, and (**b**) is the first lumbar MRI in the coronal view, revealing a large ruptured lumbar disc herniation in the patient. After a period of conservative treatment, (**c** and **d**) show the last lumbar MRI in the sagittal and coronal views, respectively, with evidence of absorption phenomenon. The area marked by the red arrow is the protrusion and absorption of the lumbar disc tissue.

have shown that patients with giant ruptured lumbar disc herniation are more likely to experience resorption of the herniated material and achieve satisfactory outcomes through conservative treatment.[8] This is likely because, compared to other types of herniation, the giant ruptured herniation, due to its ruptured nature and direct contact with surrounding tissues, is more likely to trigger immune responses and inflammatory pathways, promoting the resorption of the protruding material.[9]

In MRI images, the characteristics of giant ruptured lumbar disc herniation include a large amount of nucleus pulposus material entering the spinal canal through the ruptured fibrous ring, manifesting as significant disc protrusion.[10] The rupture of the fibrous ring leads to a clearly discontinuous contour, and the protruding part may completely penetrate the fibrous ring, resulting in a complete rupture.[11] The dural sac and adjacent nerve roots may be significantly compressed, with MRI revealing changes in the shape of the dural sac, compression, and displacement or morphological changes of the nerve roots.[12] Additionally, the giant herniation may cause a more pronounced inflammatory response in the surrounding soft tissues.[13] In T2-weighted images, the signal of the protruding nucleus pulposus material is lower than that of the cerebrospinal fluid and fat in the corresponding segment,[14] clearly displaying the condition of the extradural fat, nerve roots, and spinal cord being compressed, manifesting as displacement or disappearance of the extradural fat, compression of the nerve roots towards the dorsal side, and deformation of the dural sac.[15]

Characteristics of Resorption

The Patient's Course of Disease, Age, and Size of the Herniated Tissue

The resorption of lumbar disc herniation tissue is closely related to the patient's disease duration and age.[16] An analysis of the resorption phenomenon in 409 patients with giant ruptured lumbar disc herniation showed that a shorter disease

duration is more likely to be associated with resorption. Specifically, significant resorption (resorption rate ≥ 50%) occurred in 72 out of 269 patients (26.77%) within one year of disease onset, while it occurred in only 9 out of 140 patients (6.43%) with a disease duration of more than one year.[17] This indicates that patients with a shorter disease duration are more likely to experience resorption of the herniated disc material. Some studies have found that the herniated disc material in younger patients is more likely to undergo natural resorption, possibly because the disc tissue in younger patients has better metabolic activity and repair capacity. Kesikburun et al found that in a study of 40 patients receiving conservative treatment for LDH, patients with a mean age of 48.3 ± 10.1 years exhibited higher rates of complete resorption of their lumbar disc herniation tissue.[18] However, other studies suggest that age is not the primary factor affecting the resorption of herniated disc material, and other factors such as the type and size of the disc herniation and the inflammatory response of the disc may be more important.[19,20] Therefore, more research is needed to clarify the specific relationship between the resorption of herniated disc material and patient age. Additionally, when the degree of disc herniation exceeds 50% of the diameter of the spinal canal, the length of the herniated tissue extends more than 50% of the height of the adjacent vertebral bodies, or the area of the herniated tissue exceeds 50% of the area of the spinal canal, the probability of resorption significantly increases.[21] This indicates that the size of the herniated tissue is also related to the probability of resorption.[22]

Bull's-Eye Sign and Modic Changes

The neovascularization and granulation tissue formed around the protruding nucleus pulposus appear as a ring of high signal on T2-weighted MRI images, a phenomenon known as the "bull's-eye sign" (Figure 2). [23] A study by Dai et al[24] demonstrated that 42.53% of patients with the bull's-eye sign (37/87) exhibited significant resorption. This difference was statistically significant compared to patients without resorption ($P < 0.01$), indicating that the bull's-eye sign is an important factor in predicting the possibility of resorption. The presence of the bull's-eye sign may be a predictive indicator of resorption in patients with giant LDH. Even after clinical symptoms improve, patients with the bull's-eye sign are more likely to experience resorption of the herniated disc material.[25] Modic changes refer to signal changes in the vertebral marrow visible on magnetic resonance imaging (MRI), usually occurring in the vertebrae adjacent to the intervertebral disc.[26] The appearance of Modic changes suggests that the protruding disc tissue contains more fibrocartilage, making it difficult for new blood vessels to penetrate,[27] and that degenerated vertebral endplate cartilage may enter the spinal canal as part of the herniated material, making Modic changes unfavorable for the resorption of the protruding tissue.[28] The resorption of LDH tissue is evidently influenced by multiple factors, resulting from their synergistic interaction.

Mechanisms of Resorption

Although the precise mechanisms underlying disc resorption remain incompletely understood, current evidence suggests a multifactorial interplay involving neovascularization,[29,30] inflammatory responses,[31,32] MMP synthesis-degradation

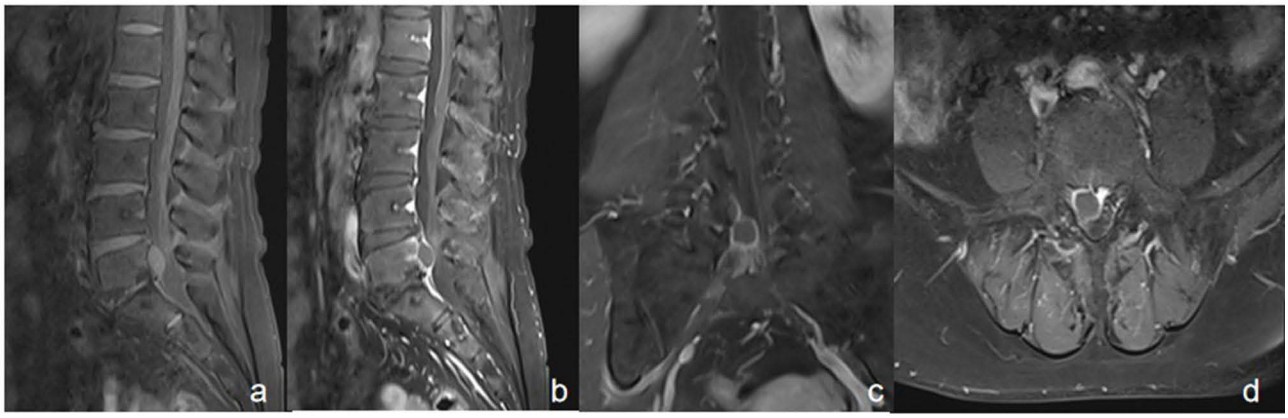

Figure 2 (**a**) is a sagittal fat-suppressed image, (**b**) is an enhanced MRI sagittal image, (**c**) is an enhanced MRI coronal image, and (**d**) is an enhanced MRI axial image. All show high signal of the protrusion, indicating a positive "bull's eye sign.".

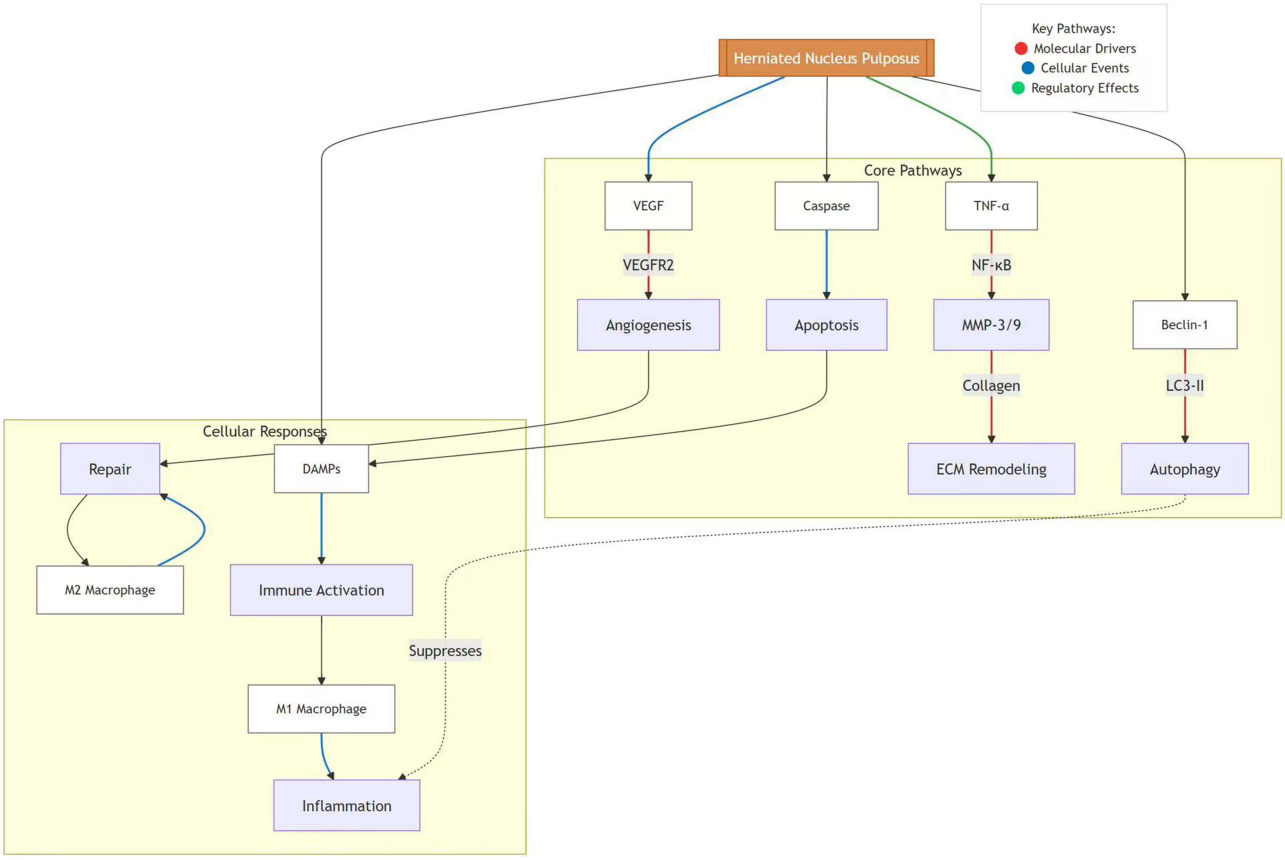

Figure 3 Simplified mechanisms of disc resorption. Molecular drivers (red line): VEGF-mediated angiogenesis and MMP-driven ECM remodeling. Cellular responses (blue line): Macrophage polarization and immune activation. Regulatory effects (green line): Autophagy suppresses inflammation while apoptosis releases DAMPs.

imbalance,[33,34] autoimmune activity,[35] and tissue dehydration.[36,37] These factors collectively promote the resorption of herniated disc tissue, leading to the dissolution and disappearance of the nucleus pulposus material. In addition to these mechanisms, recent studies have also highlighted the roles of apoptosis, autophagy, macrophage involvement, and nucleus pulposus rehydration in the resorption process of herniated discs (Figure 3).

The Role of Apoptosis

Apoptosis, also known as programmed cell death, is a process that induces cells to die in a regulated manner through the control of genes and their products.[38] The main mechanisms of apoptosis include the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway.[39] The intrinsic pathway involves the loss of mitochondrial membrane potential and the release of cytochrome c, which triggers the activation of caspases, ultimately leading to cell death.[40] The extrinsic pathway, on the other hand, is initiated by the activation of death receptors, such as Fas and TNF receptors, promoting the activation of caspases and apoptosis.[41] Apoptosis not only affects the survival of cells themselves but also indirectly influences tissue resorption by promoting the degradation of the extracellular matrix (ECM).[42] During apoptosis, specific caspases are activated, which can directly or indirectly break down components of the ECM, such as collagen and elastin.[43] This degradation disrupts the physical structure of the tissue, providing a pathway for resorption.[44] Apoptotic cells release signals and cellular contents that attract and activate surrounding immune cells, such as macrophages and neutrophils.[45] These cells release inflammatory factors (such as IL-1β, TNF-α) and enzymes (such as MMPs) that further promote the degradation of the ECM. At this point, the inflammatory factors not only recruit immune cells but also activate tissue cells such as fibroblasts, prompting them to secrete more MMPs, accelerating the breakdown of the ECM.[46]

Apoptotic cells can interact with surrounding cells through the release of apoptotic inducers, such as Fas ligand, which can bind to Fas receptors on neighboring cells, promoting their apoptosis and leading to the reduction or disappearance of nucleus pulposus cells within the herniated disc tissue.[47] This intercellular signaling can amplify the apoptotic response, accelerating tissue remodeling and resorption.[48] Apoptotic cells can also influence the behavior of surrounding cells through the release of signaling molecules, activating autophagy mechanisms in adjacent cells in some cases.[49] Autophagy, as an intracellular degradation pathway, helps cells remove damaged organelles and proteins, playing a crucial role in maintaining cellular homeostasis and tissue resorption.

The Role of Autophagy

Autophagy in the human body can be classified into macroautophagy, chaperone-mediated autophagy, and microautophagy,[50] with macroautophagy being the main type involved in resorption. The primary purpose of autophagy is to reabsorb and recycle cellular organelles and intracellular substances, and its molecular mechanisms are gradually being elucidated.[51] Currently, about 35 autophagy-related genes (ATG) and signaling pathways such as PI3KC3, Beclin-1, and JNK/p38 have been identified.[52,53] With the deepening of autophagy research, some researchers believe that autophagy plays a significant role in the resorption of nucleus pulposus after disc herniation.[54] Autophagy is highly inducible, and studies have shown that when cells are stimulated by adverse factors, mitochondria can automatically release apoptotic factors to induce cell death, while cells can initiate autophagy to clear damaged mitochondria, thereby avoiding apoptosis and necrosis.[45] Other studies have shown that autophagy regulates cellular metabolism by recycling and reusing intracellular molecules such as fatty acids and amino acids,[55] ensuring the survival of disc cells under low-nutrient conditions, and playing a protective role for the intervertebral disc. The phagocytic action of nucleus pulposus cells and macrophages together protects the undegenerated cells in the disc, promoting the self-regulation and repair of the disc.[56] Recent work by Márcia et al[57] *and* Wang et al[58] *demonstrated that ATG5 knockdown exacerbates apoptosis via autophagy inhibition, highlighting autophagy's protective role. Therefore, the specific* mechanisms of autophagy still need to be clarified, and further research is required to accurately control the occurrence of autophagy.[59]

The Role of Macrophages

Macrophages play a central role in immune-mediated resorption of herniated discs.[60] The primary mechanism for macrophages to be recruited to the LDH region is through chemokines, such as monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), MIP-1α, TSLP, etc.[61] These factors are secreted by damaged disc cells or existing immune cells, forming a gradient that attracts macrophages to the damaged area. Macrophages recognize these chemokines through specific receptors on their surface, such as CCR2 (the receptor for MCP-1), guiding them to migrate to the inflammatory region.[62] Studies have shown that macrophages in the LDH region produce pro-inflammatory and anti-inflammatory factors. Pro-inflammatory factors promote inflammation and tissue degradation, while anti-inflammatory factors help limit inflammation damage and promote tissue repair.[63] Therefore, macrophages can be divided into two phenotypes based on their function: M1 (pro-inflammatory) and M2 (anti-inflammatory or reparative).[64] M1 macrophages participate in tissue degradation by producing pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and enzymes (MMPs),[65] while M2 macrophages promote tissue repair and resorption by secreting growth factors and anti-inflammatory cytokines (such as IL-10).[66] Based on these mechanisms, some scholars have proposed a pro-inflammatory treatment approach, which involves avoiding the use of non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, utilizing the natural healing process of inflammation rather than suppressing it, which is beneficial for the occurrence of resorption and effective for patients with acute LDH.[67]

Beyond their direct role in inflammation, macrophages promote disc tissue degradation via activation of matrix metalloproteinases (MMPs), including MMP-3 and MMP-9.[68] MMPs are a family of structurally similar zinc-dependent endopeptidases that are important degrading enzymes of the extracellular matrix.[69] Studies have shown that after macrophages are recruited to the LDH region, they are activated by recognizing and responding to signals released by damaged disc tissue.[70] These macrophages release a series of inflammatory factors, which, after binding to receptors on the surface of target cells (such as chondrocytes and other immune cells), activate a series of signal transduction pathways, including nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathways.[71] The

activation of these pathways leads to the activation of transcription factors, which enter the nucleus and promote the expression of MMPs genes.[72] With the increase in MMPs gene expression, MMPs (especially MMP-3, MMP-9, and MMP-13) are transcribed and translated into proteins, which are then secreted from the cells. These enzymes specifically break down components of the disc's matrix, such as collagen and proteoglycans.[73] The activity of MMPs is also regulated by tissue inhibitors of metalloproteinases (TIMPs), which are natural inhibitors of MMPs, maintaining a balance between tissue degradation and reconstruction.[74] Some studies suggest that during the resorption process of LDH, macrophages and other cell types regulate the expression of TIMPs, thereby modulating the activity of MMPs and affecting their degrading function.[75]

Macrophages also play a key role in angiogenesis. Ultrastructural analysis of disc specimens removed during surgery by Kobayashi et al[76] revealed the presence of many macrophages around newly formed blood vessels. Studies have shown that vascular endothelial growth factor (VEGF) secreted by macrophages binds to specific receptors (such as VEGFR-1 and VEGFR-2) on the surface of endothelial cells (ECs), activating signal transduction pathways and promoting the proliferation of endothelial cells.[77] VEGF stimulates endothelial cells to migrate to the area of new blood vessel formation.[78] The VEGF gradient serves as a directional signal, guiding endothelial cells to migrate to areas with higher VEGF concentrations.[79] As endothelial cells proliferate, migrate, and organize, VEGF also promotes the branching and maturation of new blood vessels,[80] including the recruitment of surrounding smooth muscle cells and pericytes, which surround the endothelial cells, stabilizing and maturing the new blood vessels.[81] Newly formed blood vessels provide necessary nutrients and oxygen to the resorption and repair areas, while also helping to remove waste and inflammatory products.[82]

The Role of Nucleus Pulposus Rehydration

The nucleus pulposus of the intervertebral disc is composed of a large amount of water and proteoglycans, which help the disc withstand pressure and maintain elasticity.[83] With aging or due to injury, the nucleus pulposus may dehydrate, leading to disc degeneration. However, recent studies have shown that after degeneration or injury, the nucleus pulposus can partially recover its water content and function, a phenomenon known as nucleus pulposus rehydration.[84] Rehydration of the nucleus pulposus helps restore the normal biomechanical properties of the disc, including its height and elasticity.[85] Nucleus pulposus rehydration improves the internal nutrient supply of the disc, promoting the repair and regeneration of damaged cells. The increase in water content enhances the efficiency of nutrient and metabolic waste exchange, providing necessary growth factors and nutrients for disc cells, thereby promoting cell health and vitality, and indirectly affecting the resorption of the herniated disc region.[86] Additionally, improved hydration status helps stabilize the extracellular matrix, reduce the excessive release of inflammatory mediators, and decrease the accumulation of inflammatory cells, thereby alleviating the inflammatory response around the disc.[87] In summary, nucleus pulposus rehydration creates a favorable environment for the resorption of herniated disc material. Improved biomechanical properties and cellular metabolic conditions promote the repair and regeneration of disc cells, while reduced inflammation reduces the risk of further tissue damage, collectively promoting the natural resorption process of the herniated material.[83]

Imaging Biomarkers and Clinical Implications

Factors such as disease duration, herniation size, and the presence of imaging biomarkers like the "bull's-eye sign" on MRI significantly affect the likelihood of resorption. The bull's-eye sign, a ring of high signal intensity around the herniated nucleus pulposus, has been identified as a reliable predictor of successful resorption. Moreover, Modic changes in the vertebral endplate, visible on MRI, can inhibit resorption by preventing vascular infiltration and new tissue formation.

Traditional Chinese Medicine Treatment for LDH

There are many options for conservative treatment of LDH, including medication, physical therapy, epidural injections, and traditional Chinese medicine (TCM). Traditional TCM treatments, such as acupuncture, massage, and herbal medicine, are favored by patients due to their low cost, simplicity, and apparent effectiveness.[88] Research has confirmed the effectiveness of TCM in treating lumbar disc herniation and its ability to promote the absorption of herniated material.[25] Xiaosui Huahe Decoction is a traditional Chinese herbal formula used to treat lumbar disc herniation. The

combination of herbs in the formula can promote the absorption of herniated disc material, reduce its volume, and thereby relieve symptoms caused by the compression of nerve roots by the herniated material. The formula also has anti-inflammatory, dehumidifying, and blood-activating effects, which can alleviate swelling and inflammation around the nerve roots, reducing pain and other symptoms. The formula synergizes qi-tonifying herbs with blood-activating and stasis-eliminating agents to harmonize qi and blood, improve local blood circulation, and provide a favorable environment for the absorption of herniated disc material and the recovery of nerve roots.[23] *Xiaosui Huahe Decoction was shown to upregulate M2 macrophage markers (CD206+ cells increased by 40%, P<0.01) and suppress MMP-9 expression (↓62%, P=0.004) in a rat LDH model, as confirmed by immunohistochemistry and qPCR*.[22]

In summary, traditional Chinese medicine treatment for LDH is effective, providing intelligent solutions to the global challenge of lumbar disc herniation. As research into the mechanisms of TCM treatment for lumbar disc herniation deepens, it opens up new avenues for the treatment and prevention of lumbar disc herniation and the exploration of the therapeutic value of Chinese herbal medicine.

Conclusion

Macrophage polarization (M1/M2) and autophagy synergistically regulate ECM degradation and tissue remodeling, offering potential therapeutic targets.Integrating imaging biomarkers (eg, bull's-eye sign) with patient-specific factors (eg, disease duration) may enhance resorption prediction, guiding personalized non-surgical strategies. Growing clinical evidence supports the safety and efficacy of non-surgical approaches, including traditional Chinese medicine.[16] Of course, if symptoms worsen progressively during conservative treatment or cauda equina syndrome appears, surgical treatment should be performed promptly to avoid delaying the condition. Although a consensus has not yet been formed on the related mechanisms, factors such as vascularization, autoimmune responses, apoptosis, and autophagy have become common ground in most studies. In clinical practice, the possibility of resorption of the herniated disc can be preliminarily assessed based on the degree of herniation, duration of the disease, and imaging examinations, to timely select the most suitable treatment plan for the patient.

Consent for Publication

All authors agree to publish. All authors approved the final version.

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Disclosure

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