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REVIEW

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Immunological Considerations and Biological Consequences of Intradiscal Needle Procedures: Implications for Chemo-Nucleolysis and Oxygen–Ozone Therapy

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ABSTRACT

Intervertebral disc (IVD) procedures, including chemo-nucleolysis and oxygen–ozone therapy (OOT), are increasingly used as minimally invasive approaches for disc herniation and radiculopathy. Although generally considered safe, these interventions may induce biological and immunological consequences that remain insufficiently characterized. This editorial discusses the immunobiology of the nucleus pulposus (NP) and the potential effects of annular disruption caused by intradiscal needle procedures. Under physiological conditions, the NP behaves as a relatively immune-privileged tissue because of its avascular structure, extracellular matrix composition, and local immunomodulatory mechanisms. Mechanical disruption of the annulus fibrosus may expose NP-derived antigens and damage-associated molecular patterns (DAMPs) to immune surveillance, activating inflammatory pathways involving Toll-like receptors, NF-κB signalling, inflammasomes, cytokine release, oxidative stress, and extracellular matrix degradation. Although chemo-nucleolysis and OOT may reduce intradiscal pressure and alleviate symptoms, current evidence does not demonstrate restoration of annular integrity or complete recovery of disc immune privilege. A deeper understanding of IVD immunobiology may improve patient selection, procedural safety and long-term therapeutic strategies in minimally invasive spine care.

Keywords: intervertebral disc, oxygen–ozone therapy, chemo-nucleolysis, immune privilege, disc degeneration.

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BACKGROUND

In this Editorial, we aim to highlight the biological and immunological implications of invasive procedures involving the intervertebral disc (IVD), particularly intradiscal interventions performed to relieve pain and disability associated with disc herniation and radiculopathy, with a specific focus on IVD immunology.

Ozone-mediated chemo-nucleolysis and direct intradiscal oxygen–ozone therapy (OOT) for disc herniation have generally been described as minimally invasive procedures associated with relatively low complication rates according to the available literature (1-4). Nevertheless, although most published clinical series report favourable safety profiles, serious adverse events have occasionally been documented, including paradoxical gas embolism, vertebrobasilar stroke, infectious complications and neurological injury associated with inadvertent gas migration into the spinal canal or circulation, particularly in predisposed individuals (5, 6). Additional complications described in isolated reports include paraesthesia, hypoesthesia, transient headache and vitreoretinal haemorrhage following high-volume ozone administration (1-8). Spondylodiscitis and local inflammatory reactions have also been reported (2, 4). However, the overall incidence of severe complications remains difficult to quantify because current evidence is based largely on retrospective studies, case reports and relatively small clinical series.

During the past two decades, increasing attention has been directed toward the immunobiology of the intervertebral disc and the interaction between disc tissue and the peripheral nervous system. The nucleus pulposus (NP) is widely considered a relatively immune-privileged tissue because of its avascularity, its specialized extracellular matrix and the presence of local immunomodulatory mechanisms capable of limiting immune surveillance and inflammatory cell infiltration. Nevertheless, the exact mechanisms regulating NP immune privilege and their alteration during degeneration, trauma, or aging remain incompletely understood.

Similarly, the nerve root and its dural sleeve represent highly specialized structures in which even limited mechanical injury may disrupt local anatomical barriers and trigger neuroinflammatory responses. Consequently, any invasive procedure involving puncture of the annulus fibrosus or neural foramen, including intradiscal infiltration procedures, may induce a degree of biomechanical and immunological perturbation independent of the injected compound itself. ❑

CONTENT

Under physiological conditions, the immune privilege of the NP is maintained by several anatomical and molecular mechanisms, including the annulus fibrosus, cartilaginous endplates and the absence of direct vascularization, all of which restrict immune cell trafficking and antigen exposure. In addition, NP cells express immunomodulatory molecules such as Fas ligand (FasL), capable of inducing apoptosis in activated T lymphocytes and contributing to local immune tolerance (9). Through these mechanisms, NP antigens normally remain sequestered from systemic immune recognition.

However, mechanical disruption of the disc, whether caused by spontaneous herniation or iatrogenic needle puncture, may compromise these barriers and expose NP-derived antigens to the immune system. Experimental evidence suggests that this process can trigger the release of damage-associated molecular patterns (DAMPs), including HMGB1, extracellular ATP, S100 proteins and matrix degradation fragments, which activate Toll-like receptors (TLR2/TLR4), RAGE signalling and inflammasome pathways (10). Subsequent NF-κB activation promotes the release of inflammatory mediators such as IL-1β, TNF-α, IL-6, nitric oxide, prostaglandins and reactive oxygen species, thereby contributing to matrix degradation through metalloproteinases and ADAMTS-mediated catabolism of collagen II and aggrecan (10, 11).

Figure 1 summarizes the principal immunological pathways potentially involved following annular disruption and NP exposure.

Despite these biological considerations, intradiscal procedures guided by fluoroscopy or CT remain widely used in selected patients because they may provide relatively rapid pain relief while avoiding more invasive surgery. Chemonucleolysis using agents such as chymopapain, collagenase, or oxygen–ozone mixtures aims to reduce disc volume and mechanical nerve root compression, while potentially modulating the

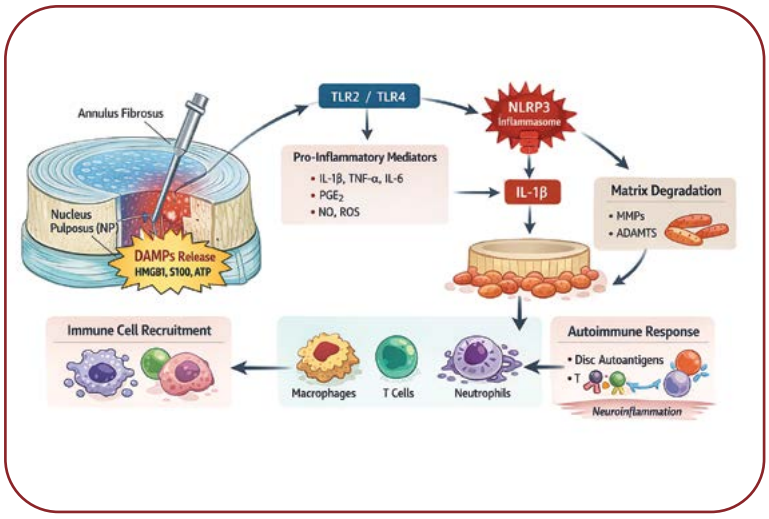

FIGURE 1. Schematic representation of the principal immune and inflammatory pathways activated following annular disruption and exposure of nucleus pulposus tissue. Needle puncture or disc herniation may expose NP-derived antigens and damage-associated molecular patterns (DAMPs) to immune surveillance, activating TLR/RAGE signalling, NF-κB pathways, inflammasome activation, cytokine release, oxidative stress and extracellular matrix degradation.

inflammatory microenvironment surrounding the affected nerve root.

When NP material escapes through a damaged annulus fibrosus, exposure of normally sequestered antigens may contribute to sterile inflammatory responses mediated by DAMP signalling and cytokine release (12). By reducing intradiscal pressure and partially decreasing the amount of herniated NP material, chemo-nucleolysis may indirectly reduce mechanical irritation, oedema and local inflammatory activation. In the case of OOT, some experimental and clinical observations using only paravertebral/intramuscular approaches have suggested possible anti-inflammatory and oxidative modulatory effects, including partial modulation of phospholipase activity and prostaglandin synthesis, although these mechanisms remain incompletely characterized and require further confirmation. ❑

COMMENTS

However, currently available evidence does not indicate that chemo-nucleolysis restores annular integrity or fully re-establishes the immune privilege of the disc. Consequently, although symptomatic improvement is frequently achieved, particularly in contained disc herniations, immune activation and degenerative processes may persist at a subclinical level in susceptible patients. Paravertebral-intramuscular approaches are better recommended

This limitation may have several potential clinical implications. Persistent structural disruption of the annulus fibrosus may allow continued exposure of NP antigens to immune surveillance, contributing to chronic low-grade inflammation and recurrence of symptoms. In parallel, inflammatory mediators such as IL-1β and TNF-α may sustain extracellular matrix degradation, progressive disc degeneration and biomechanical instability. Moreover, the persistence of annular defects may increase susceptibility to recurrent herniation under adverse biomechanical conditions.

The currently available evidence suggests that the biological response to annular puncture and intradiscal manipulation is likely multifactorial, involving mechanical, inflammatory, immunological and degenerative components. Nevertheless, many mechanistic aspects remain incompletely elucidated, and further translational and prospective clinical studies are necessary to clarify the long-term consequences of repeated or extensive intradiscal interventions.

CONCLUSIONS

For these reasons, although chemo-nucleolysis and OOT may provide clinically meaningful symptomatic relief in selected patients, these procedures should also be regarded as biological interventions involving a complex immune-regulated tissue environment and should be avoided. A more comprehensive understanding of IVD immunobiology may help optimize patient selection, procedural safety, and long-term therapeutic strategies in minimally invasive spine care. ❑

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