

Potential of Cytokines in the Management of Intervertebral Disc Degeneration

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Abstract. The illness known as intervertebral disc degeneration (IDD) is characterized by discomfort in the intervertebral discs. The IDD is made up of the annulus fibrosus (AF) and nucleus pulposus (NP), which function as a joint and cushion for the spine. IDD can develop with ageing, which can cause the NP to herniate and cause pain. IDD patients experience detrimental effects on their quality of life and mental health in addition to their physical health. It also poses a critical economic burden on society as a whole. Imaging techniques used for the diagnosis are disc herniation, X-ray plain film, CT, and MRI are discussed as imaging modalities, with MRI being particularly useful for diagnosing disc herniation. Treatment approaches range from conservative methods to surgical intervention, related to the type of IDD. Nonsteroidal anti-inflammatory medications, rest, traction therapy, and physical therapy are examples of non-surgical therapies. Options for surgery include conventional open surgery, microsurgical lumbar discectomy, minimally invasive IVD removal surgery, and artificial IVD replacement surgery. Many studies are focused on the role of cytokines to explain the cause of IDD. And these cytokines can be classified as cell cycle inhibitor, proinflammatory factor and growth factor. The article highlights cell cycle inhibitors (p16INK4a and p53), proinflammatory factors (IL-1 β and TNF- α), and growth factor (TGF- β) involvement in IDD. However, currently, there are no cytokine-based treatments available for IDD in clinical practice. Future research could focus on developing new treatment or prevention targets for IL-1 β or TNF- α .

Keywords: Intervertebral disc; intervertebral disc degeneration; cytokines

1. Introduction

The intervertebral disc (IVD) is a round soft tissue between the vertebral bodies. It is a cushion to the spine, and act like a joint to allow the spine to move slightly. The IVD contains two different structures: the nucleus pulposus (NP) in the center and annulus fibrosus (AF) surround the NP. Each two parts takes half the diameter of the IVD. NP contains more water and is softer than AF. The plane that connected to the upper and lower vertebral is called endplate, which supply necessary nutrition to the IVD.

As people aging, a senescence of IVD is called intervertebral disc degeneration (IDD), and NP is prone to herniation and cause pain. There are still lots of people who has IDD without pain(asymptomatic), falling between 37% at age 20 and 96% at age 80 [1]. For those who are symptomatic, they have a doubled chance to have IDD [2]. Unlike a radiating pain caused by physical compression in cervical disc herniation, the etiologic analysis result of low back pain with lumbar disc herniation is not only physical compression, but moreover an inflammation around the disc. As the nutrition to IVD is delivered the endplate, the IVD itself doesn't have blood vessels and is immune-free. So, an initial inflammation can start a vicious circle of IDD, which seriously affects the physical condition and mental health of patients, resulting in poor quality of life. IDD places a significant financial strain on the healthcare system. The exact mechanism of IDD is still unknown. With the rapid development of molecular biology and its related disciplines and the thorough investigation of cytokines, increasing focus has been placed on their function in IDD.

This article focuses on the current management of IDD and cytokines that contribute to the progression and are potential treatment through accelerating NP cell senescence or inducing an inflammation [3].



2. Symptoms of IDD

The cervical disc herniation often occurs in the vertebra with large range of motion like C5~6 and C4~5. The majority of lumbar disc herniation is on L4~5 and L5~S1. The thoracic intervertebral disc herniation is not as common as the first two mentioned above, thus would not be included in the subsequent discussion [4].

Table 1. Symptoms of different compressed nerve root [5]

Disc	Nerve root	Symptoms
C ₂₋₃	C ₃	Pain and numbness in the posterior part of the neck, particularly in the area around the mastoid process and auricle. No weakening of muscle strength or changes in reflexes.
C ₃₋₄	C ₄	Pain and numbness in the posterior part of the neck radiating along the levator scapulae, radiated to anterior chest. No weakening of muscle strength or changes in reflexes.
C ₄₋₅	C ₅	Radiating along one side of the neck and shoulder, feeling numb at the deltoid muscle, weakness and atrophy of the deltoid muscle, without any changes in reflexes.
C ₅₋₆	C ₆	Radiate pain along the upper arm and outer forearm towards the distal end to the thumb, index finger, and tip of the thumb. Numbness at the first dorsal interosseous muscle of the hand. Reduced biceps muscle strength and biceps reflex.
C ₆₋₇	C ₇	Radiate pain along the upper arm and dorsal center of the forearm towards the distal end to the middle finger, as well as to the index and ring fingers. Reduced strength and reflex of the triceps brachii muscle.
C _{7~T₁}	C ₈	Can cause weakened muscle strength in the flexor digitorum and hand interosseous muscles, as well as loss of sensation in the ring finger, little finger, and ulnar side of the palm, but without reflex changes.
L ₂₋₃	L ₂	Pain and numbness in the front and middle of the thighs. The strength of the iliopsoas muscle is weakened. Knee reflex weakened or disappeared.
L ₃₋₄	L ₃	Pain and numbness in the ankle of the femur. The strength of the quadriceps femoris muscle is weakened. Knee reflex weakened or disappeared.
L ₄₋₅	L ₄	Pain and numbness in the inner ankle. The strength of the tibialis anterior muscle is weakened. Knee reflex weakened or disappeared.
L _{5~S₁}	L ₅	Pain and numbness on the outer side of the calf and the back of the foot. The muscle strength of the extensor pollicis longus is weakened. Knee reflex weakened or disappeared.
Sacral	S ₁	Pain and numbness on the lateral side of the heel. The strength of the triceps calf muscle is weakened. Ankle reflex weakened or disappeared.

3. Pathology

3.1. Bulging

The fibrous ring is partially ruptured, but the surface is intact. At this time, the NP protrudes locally into the spinal canal due to pressure, but the surface is smooth. This type of conservative treatment can mostly alleviate or cure.

3.2. Protrusion

The fibrous ring is completely ruptured, the NP protrudes towards the spinal canal, but the posterior longitudinal ligament is still intact. This type often requires surgical treatment.

3.3. Extrusion

The NP penetrates the posterior longitudinal ligament, resembling cauliflower, but its root is still in the intervertebral space. Surgical treatment is required.

3.4. Sequestration

The free large NP tissue penetrates through the fibrous ring and posterior longitudinal ligament, completely protrudes into the spinal canal, and detaches from the original IVD. Surgical treatment is required.

3.5. Schmorl Nodules and Transosseous Protrusions

The former refers to the developmental or acquired fissures of the NP protruding into the trabecular bone of the vertebral body through both sides of cartilage plates; The latter is a protrusion of the NP along the vascular channel between the vertebral cartilage endplate and the vertebral body towards the anterior longitudinal ligament, forming a free bone block at the anterior edge of the vertebral body. These two types have no neurological symptoms in clinical practice and do not require surgical treatment [6].

4. Imaging

4.1. X-ray Plain Film

Usually used as a routine examination. Generally, spine anteroposterior and lateral radiographs are taken. If there is suspicion of spinal instability, flexion and extension dynamic radiographs and double oblique radiographs can be added. In patients with disc herniation, the appearance of plain films can be completely normal, but many patients may also have some positive findings. Scoliosis can be seen on the anterior view, while physiological lordosis can be reduced or disappeared and intervertebral space narrowing can be seen on the lateral view. On the plain film, degenerative symptoms such as fibrous ring calcification, bone hyperplasia, hypertrophy of articular processes, and sclerosis can also be seen.

4.2. CT

CT can better display the details of spinal bone structure. The CT manifestations of disc herniation include deformation and protrusion of the posterior edge of the intervertebral disc, compression and deformation of the dural sac, displacement of epidural fat, density shadows of soft tissue in the epidural space, and compression and displacement of nerve roots. CT can also observe the condition of intervertebral small joints and ligamentum flavum.

4.3. MRI

MRI can clearly display images of human anatomical structures, which is greatly helpful for the diagnosis of disc herniation. MRI can comprehensively observe the degeneration of various IVDs, as well as understand the degree and location of NP protrusion, and distinguish whether there are other space occupying lesions in the spinal canal. When reading the film, it is important to compare and observe the sagittal and cross-sectional images in order to accurately locate the image [4].

A Systematic Review and Meta-Analysis searched 280 independent studies with fourteen (5.0%) considered available to include in the analysis (over 3000 patients; 40% of them are asymptomatic; 61.4% are symptomatic). It demonstrates that for individuals under 50 years old, MRI evidence of IDD (disc bulge; degeneration; extrusion; protrusion; Modic I changes and spondylolysis) can explain the baseline back pain symptom to some extent [2].

5. Treatment

5.1. Non-surgical Therapy

Non-operative treatment, also known as conservative treatment, is used to alleviate the symptoms of IDD and is first-line treatment for mild or moderate cases. Alternative treatments for IDD patients include rest in bed (gradually move down to the ground with a waist circumference), medication like NSAIDs, physical therapy like traction therapy, and complementary and alternative medicine, also known as Traditional Chinese medicine (TCM). Nonetheless, physicians and patients with IDD should aim for a complete plan that combines one or more conservative treatments to achieve more efficacy, fewer side effects, and reduced costs [7].

5.2. Surgery Treatment

Indications include symptom affecting quality of life, such as severe symptoms of lower back and leg pain, recurrent attacks or worsening after ineffective non-surgical treatment over six months; cauda equina syndrome in central type protrusion and sphincter dysfunction should be treated with emergency surgery; Individuals with obvious signs of neurological involvement.

There are traditional open surgery, microsurgical lumbar discectomy, minimally invasive IVD removal surgery and artificial IVD replacement surgery. Traditional open surgery includes total laminectomy, hemilaminectomy, and fenestration of the vertebral lamina. Microsurgical lumbar discectomy using a microscope to assist IVD removal. For minimally invasive IVD removal surgery, initially there were percutaneous NP resection and aspiration procedures. Later, percutaneous endoscopic lumbar discectomy (PELD) as well as microendoscopic discectomy (MED) were developed as a result of technological advancements. Nowadays, percutaneous spinal endoscopy technology, represented by PELD, has developed rapidly. Due to its advantages of minimal damage and fast recovery, its clinical application is increasingly widespread [8]. And there is still debate about indications of artificial IVD replacement surgery surgical, and caution should be exercised when choosing this surgery.

6. Cytokines in IDD

IDD is a result of the aging of IVD. At least three reasons are responsible for IDD: senescence of the NP cells, inflammation and change in extracellular matrix. They can either cause a weakness of the integral of the IVD and result in a herniation or directly induce a pain of the certain segments. Many cytokines are related to IDD, including cell cycle inhibitor(p50, p65, Notch), proinflammatory factor(IL-1, -2, -6, -9, -17, -18, -20, -21, -4, -10, -33, TNF- α , IFN- γ , PGE-2, MCP-1, -3, -4, ADAMT-4, -5, COX-2) and growth factor(TGF- β) [9-15]. As mentioned above, none of them (besides NSAIDs for COX-2) could be used as a clinical treatment to IDD.

6.1. Cell Cycle Inhibitor

The section headings are in boldface capital and lowercase letters. Second level headings are typed as part of the succeeding paragraph (like the subsection heading of this paragraph).

6.1.1. P16^{INK4a}

The P16^{INK4a} could block the cell cycle in the S1 phase, which induced cellular senescence. In the degenerated human disc, the expression of P16^{INK4a} is increased [13,16]. However, Novais's P16^{INK4a} knocked out mice doesn't have a significant decreased risk of IDD, but have a change of collagen composition [17]. This result suggested that P16^{INK4a} alone isn't enough to protect an individual from IDD, and the effect of P16^{INK4a} can be replaced by other mechanism.

6.1.2. P53

The P53 is a transcription factor with multiple biological function, mainly suppressing cell cycle by over hundred genes that it regulated. Its upregulation in NP cell accelerates the progression of IDD [15].

Studies have indicated that the degree and duration of stimulation affect how p53 reacts. The healing of cell damage and temporary growth arrest are brought on by mild and transitory stimulation. On the other hand, apoptosis and cell senescence can result from strong, prolonged stimulation. The majority of current research on p53 in IDD focuses on the dynamic alterations and function of p53 in severe stress and late degeneration. Nevertheless, the precise nature of the dynamic alterations and p53-related signaling pathway activation in early-stage IVD and sublethal stress remains unclear. In order to investigate targeted therapy approaches, future research should concentrate on the expression pattern of p53 in the early stages of IDD and its role in associated phenotypic alterations [10].

6.2. Proinflammatory Factor

6.2.1. IL-1 β

Interleukin-1 β (IL-1 β) is the most studied among the 11 cytokines in IL-1 family. It can be find in degenerated or herniated IVD and epidural space [18]. Le Maitre and Hoyland found that IL-1, IL-1Ra, IL-1R, and caspase-1 are produced by IVD cells, and that with the exception of IL-1Ra, expression increased with progression of IDD [19]. IL-1 and IL-1Ra (the inhibitor of IL-1) restrict each other [20]. Later, they verified that people with IDD had a greater rise of IL-1 β than that of TNF- α . Kepler reported that the amount of chemokine ligand (CCL5) and IL-1 β were about triple in painful discs compared with normal discs, and the relation is corresponding to the grades of IDD [21]. Additionally, IL-1 β stimulates the synthesis of many inflammatory mediators, including MCP-3, MCP-4, and monocyte chemotactic protein (MCP)-1, which in turn promotes IDD [22].

IL-1 β also disrupting the extracellular matrix (ECM) of IVDs and promoting apoptosis of IVD cells. Proteoglycans, collagen, and water make up the majority of ECM. Normal disc ECM is rich of collagenII, but IL-1 β decreased the level of collagenII by NF- κ B pathway. IL-1 β can stimulate the synthesis of matrix metalloprotease (MMP)-1, MMP-2, MMP-3, MMP-4, MMP-13, and A disintegrin-like and metalloprotease with thrombospondin type-4 motif (ADAMTS-4) and ADAMTS-5, which are able to break the collagenII[20, 22].

IL-1 β promotes to cell senescence. Senescence associated β -galactosidase (SA- β -Gal) was employed as a dependable cell senescence detector. An in vitro study showed SA- β -Gal positive cells are upregulated when exposed to external IL-1 β . Wang found a upregulated in NOTCH pathway after IL-1 β treatment, and this phenomenon is depend on the function of NF- κ B and MAPK. p53 and p16 are also cell senescence markers, and IL-1 β can elevate the level of p53 and p16 [14].

Comprehending the signalling pathways associated with IL-1 β could potentially result in a novel class of targets that facilitate remission in individuals with IDD.

6.2.2. TNF- α

TNF- α is another proinflammatory factor that can induce IDD. TNF- α can upregulate the level of IL-1 β , as well as other proinflammatory factors include IL-6 and IL-8. TNF- α also disrupt the ECM and induce cell senescence. The ECM degradation effect of TNF- α is also related to the NF- κ B pathway, and its cell senescence effect is the result from the production of p53 and p16 [14]. Wang also proved the cell senescence induced by TNF- α is related with NF- κ B and MAPK [9].

Andrade examined the herniated disc tissue and found increased expression of TNF-R, the receptor of TNF- α , and showed a relation between TNF- α and pain evaluated by the visual analogue scale (VAS) [23].

An increasing amount of data indicates that TNF- α is a critical activator of IDD, which is linked to inflammatory responses, apoptosis, metabolic disorders, and other pathological processes in IVD.

TNF- α antibody is therefore a useful therapeutic target for mitigating IDD, particularly in terms of preventing the destruction of extracellular matrix and decreasing inflammatory reactions.

6.3. Growth factor (TGF- β)

TGF- β is protective within the process IDD. Proinflammatory cytokines mentioned above could accelerate the process of IDD. By contrast, TGF- β reverse these effect by suppressing those proinflammatory cytokines. Li made IDD modules in Beagle dogs, whose TNF- α were 4 times as the normal dog. Then the TNF- α is half reduced with a 24h TGF- β treatment, but still twice as the normal [24]. In addition, TGF- β may also participate in the process of IDD by impacting the equilibrium between extracellular matrix production and breakdown. Interestingly, the influence of TGF- β is a “U” curve, which means it is protective at low dose, and could has an adverse effect at higher dose [25].

Therefore, the molecular biological therapy strategy using TGF- β targeting abnormal expression has become a novel strategy for IDD treatment [26].

7. Conclusion

A full understanding of the role of various factors is helpful to grasp the pathological mechanism of the disease from the molecular level, and explore new ideas for clinical treatment of this kind of disease. Despite the fact that a great deal of research has been done at the genetic and molecular levels, it is still far from clear how many cytokines interact with each other, how to balance anabolism and degradation metabolism, and how to be regulated by intracellular signaling pathways. Only by understanding the mechanism of intervertebral disc degeneration from the root can scientific theoretical basis be put forward for its treatment. Currently, there is no available cytokine treatment for IDD in clinical practice. Among the cytokines that plays a role in IDD, IL- β and TNF- α are of the most importance. Future studies could investigate new treatment or prevention target to IL-1 β or TNF- α .

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