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Intervertebral Disc Degeneration: Review Article

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ABSTRACT

Intervertebral disc degeneration is one of the serious problems in vertebral system damage. Symptoms that late detected and similar with other vertebral diseases make this process such a "silent disease". There are several theories regarding the risk factors and mechanisms of intervertebral disc degeneration, ranging from exogenous or endogenous factors related to the structure of the disc, the annulus fibrosus and nucleus pulposus. Some examples of mechanisms that are often discussed are apoptosis, autophagy, pro-inflammatory cytokine storm and increased matrix catabolism. This pathological process will accelerate the disc cell senescence due to reduced proliferation, compromised self-repair, increased inflammatory response, and enhanced catabolic metabolism. This review article aims to discuss the mechanism of intervertebral disc degeneration from various possible causative factors and possible therapies that can be used in accordance with the cell degeneration mechanism.

Keywords: Intervertebral disc (IVD), interverbtral disc degeneration (IDD), annulus fibrosus (AF), nucleus pulposus (NP).

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INTRODUCTION

The Intervertebral disc degeneration (IDD) is the one of chronic conditions that caused by several factors and mechanisms which had represent an important cause of morbidity and mortality.[1,2] The causes of intervertebral disc degeneration (IDD) are complex, but several studies have shown a role for cell apoptosis, autophagy, pro-inflammatory cytokine storm and increased matrix catabolism in IVD. Besides that, some human clinical trial and animal model studies have documented that cell death, particularly apoptosis and autophagy, significantly contributed to IDD and that this condition could be invoked by stressor and nutrient. In IDD, cellular senescence accumulates and is associated with reduced proliferation, compromised self-repair, increased inflammatory response, and enhanced catabolic metabolism. Nevertheless, the mechanism of IDD is still not well established.[3,4,5] According to meta analysis research in 2018[6] regarding the incidence and epidemioloy of IDD, the researchers found that 266 million individuals (3.63%) worldwide are diagnosed with lumbar disc degeneration yearly; the highest estimated incidence was in Europe (5.7%; 5668 per 100 000) and the lowest estimated incidence was in Africa (2.4%).

Therapy for IDD has been developed due to the limited ability to regenerate disc tissue. Apart from conservative treatment therapy with medication and physiotherapy, surgical interventions such as removing damaged discs are also often considered to minimize biomechanical complications that could occur. Nowadays, further studies focus on the use of stem cells and gene therapy to minimize damage and complications, especially in the field of biomechanics.[7,8,9]

The purpose of this review article is to determine the anatomical structure, physiology, molecular processes of IDD, and the effectiveness of existing therapies and new therapies of degenerating the intervertebral disc and minimizing biomechanical complications.

ANATOMY AND EMBRIOLOGY OF INTERVERTEBRAL DISC

Anatomy of Intervertrebral Disc

Intervertebral discs serve a number of vital functions in the realms of structural support and locomotion which is composed of several structures with their respective functions.[10] It is one of part of the spine, that allows the spine to be both a supportive, yet flexible structure. In carrying out its function, the spine is roughly composed of vertebrae, IVD, and ligaments.[10,11] In addition to its flexibility effect, it also acts as a "shock absorbent" by distributing the load throughout the spine evenly, thereby reducing the risk of fractures and degenerative changes in the disc; this is also called the protective function of the disc.[10]

An IVD consists basically of an annulus fibrosus (AF) and nucleus pulposus (NP).[11] However, as a functional unit, recent literature states that the intervertebral disc

consists of 3 parts, namely the AF, NP, and end plate cartilage that binds the disc to adjacent vertebrae (cranially and caudally).[12,13] Annulus fibrosus is a external fibrous ring that can be subdivided into an outer and an inner zone, which show different histological structures. The outer zone is composed of concentric lamellae of tight, collagenous fibers, whereas the inner zone is made of fibrous-cartilaginous tissue.[11] Located eccentrically at the transition between the middle and posterior IVD, NP contains a large number of glycosaminoglycans and a low fiber content, resulting in a sufficiently large capacity to hold water. Nucleus pulposus is composed of water, type II collagen, chondrocyte-like cells, and proteoglycans. This unique composite allows the NP to be elastic, flexible under stress forces and to absorb compression. Therefore, in order to keep NP from breaking, the AF encircled NP as a "cage", providing a gelatinous form.[10,11,12]

Embryology of Intervertebral Disc

The vertebrae that develop from the embryonic structure are called the notochord, more precisely the sclerotome that develops axially around the notochord. Embryonic structure plays an important role, because the notochord will develop into the neural tube, a precursor to the vertebral nervous system, including the spinal cord and brain. The process in which the notochord would transform into an IVD will occur around the 5th week of embryonic development, where the perinotochordal basement membrane will develop into condensed cells (later developed into vertebral bodies) and loose cells (later developed into AF) through the action of several regulatory genes such as *Hox* and *Pax*. AF is a ring-shaped, or annular, condensation around the notochord between the cartilage-like tissue of the primordial vertebral bodies. NP is made up of most of the condensed notochordal tissue, which is located within the annulus fibrosus.[10,12,14]

AF consists of 2 collagen layers, the outside is composed of type 1 collagen, while the inside is composed of type 2 collagen. Type 1 collagen is composed of fibroblastic lamellae. The fibers, being arranged clockwise and counterclockwise in a helical circle, and connected by a spinal rim that would connect two adjacent vertebrae attribute to its strong property. The special configuration of these fibers is well suited to withstand the central and eccentric loads that transmitted from the NP which functions as a cushion for the spine.[10,14] Interspersed among AF, there are components of the extracellular matrix (ECM) including proteoglycans (PG), glycoproteins, and elastic fibers, in addition to the connective tissue cells that protect the AF.[15,16]

The IVD are mostly avascular, only the outer portion of the annulus is vascularized. Meanwhile, the NP and inner AF are supplied by the blood vessels near the bone-disc junction of the vertebral body. Glucose, oxygen, and other nutrients reach the avascular area by diffusion. The nerve fibers following the blood supply are detected in the peripheral vascular meniscus and there are mechanoreceptors in the menisci that can convert primarily mechanical stimulation into unique electrical nerve impulses.[10,11]

Structure of Nucleus Pulposus and Annulus Fibrosus

Cellularly, the NP consists of collagen type 2 with proteoglycan growth in ratio of 1:20. The ratio in aggrecan proportions is greater because of the function of the group as an air absorber. Aggrecan is a proteoglycan, and like all proteoglycans, it has a protein core with covalently attached sulfate glycosaminoglycan (GAG) with a high anion concentration, so the aggregate form is an aggregate proteoglycan.[17,18] Each proteoglycan aggregate is composed of a central HA filament and is maintained by protein links with molecules attached non-covalently at one end of the nucleus. The domains of the aggrecan core protein are G1, G2 and G3, globular regions; IGD, interglobular domain; KS, keratan sulfate-rich domain; CS1 and CS2, chondroitin sulfate-rich domains.[18] The presence of GAG components and other molecules causes the aggrecan size to become larger. Aggrecan is hydrophilic, where it would create an osmotic gradient that helps absorb water or retain air in the IVD so that it acts like a sponge and cushion in IVD. [17,18]

GAG chain easily sulfated and becomes hydrated to expand the distance between molecules, therefore, aggrecan would swell in an aqueous environment. The presence of type 2 collagen aids in removing a NP when aggrecan is stretched. When there is compression, a disturbance in balance causes the fluid to be displaced by compression, leading to closer relocation and a reduction in size. When compression is lost, it would swell back to its original shape. The higher in the number of waves and sulfated particles in the NP, the stronger the function of the IVD in suppressing compression.[18] In contrast to NP, the AF is more collagen-rich, of which 65% are collagen type 1 and 25% are aggrecan. This arrangement makes the annulus stronger and serves to protect the NP.[18,19]

The difference in the composition between NP and AF in general is the collagen tip and the amount of aggregate, the detail is described as in Table 1.

DEGENERATION PROCESS OF INTERVERTEBRAL DISC

The risk for IDD is multifactorial, but several studies have shown a role for cell apoptosis, autophagy, pro-inflammatory cytokine storm and increased matrix catabolism. Among which, the most common cause are apoptosis and autophagy due to stress like un-physiologic loading (over loading, for example) and nutrition.[4,30] In IDD, cellular senescence accumulates and is associated with reduced proliferation, compromised self-repair, increased inflammatory response, and enhanced catabolic metabolism.[3,4,5] All of these factors cause degeneration resulted from cell death.

In this review, we must know what external factors can cause cell death. There are many factors, but in general they can be grouped into mechanical loading, biochemical stimuli, acute trauma force, and others. In mechanical loading, several examples are dynamic axial compression loading, static axial compression loading, hydrostatic compression and cyclic stretch. While in biochemical stimuli such as serum deprivation, hypoglicemia, high lipid peroxidation, and nicotine. In trauma, especially vertebral trauma can cause rapid or acute damage to the vertebral end plate.[30]

Inflamation

Vertebral trauma can cause damage to the cartilage end plate or the AF. This can lead to a natural compensatory mechanism in the form of angiogenesis and neurogenesis due to disruption of a cell or tissue, however, as IVD is avascular only the outer portion of the AF is vascularized from the branching of the pre-disc vessel while NP gets nutrients by diffusion if there is damage in IVD, it will easily degenerate the disc, especially in the avascular NP.[30,31] Trauma that occurs in IVD causes the activation of various pro-inflammatory cytokines, especially tumor necrosis factor-α (TNFα) and interleukin 1-β (IL-lβ), causing signs of inflammation and activation of the IVD catabolic pathway which results in the IVD degeneration process. TNFα and IL-lβ play an important role in the

degeneration of IVD. It was found that excessive TNF-α expression has anti-anabolic effects at the gene level and cause a catabolic shift. This effect inhibits the regeneration process of IVD after exposure to trauma which is exacerbated by the avascular condition of NP. In addition, TNF-α also stimulates genes for pain and accelerates the degradation process of aggrecan which disrupts the functional structures of AF and NP. Besides that, TNF-α exposure also stimulated mRNA production of IL-1β, and IL-6 supporting and strengthening its role as an initiator and regulator of multiple pro-inflammatory cytokines in intact IVDs.[30,32]

IL-1β has several effects on the IVD degeneration process, such as a greater ability to increase catabolic enzyme activity than TNFα. Furthermore, IL-1β and IL-6 could stimulate nerve promoting factors such as NGF (nerve growth factors) and BDNF (Brain Derived Neurotrophic Factor) which correlates with pain in disc degeneration.[32,33]

Nutrition

Nutrition plays an important role in IDD. In trauma, in which damage to the peripheral blood vessels around IVD or trauma that induces damage to the vertebrae resulting in clamping of the blood vessels, decreasing blood flow in IVD, thereby reducing nutrients supply. Blood vessels carry nutrients and oxygen necessary for the survival of normal tissues, especially in damaged tissues, vascular function as a nutrient supply is needed. If there is a lack of nutritional supply to damaged cells, the regeneration or recovery process of cells will be hampered which can interfere with cell metabolism and end in cell death. This further aggravates the aging process of the IVD and speeds up the degeneration of the IVD.[32] Furthermore, the survival of discus cells depends on several components such as mechanical signals (eg, deformation, stress, and fluid flow), electrical signals (eg, streaming potential), and biochemical signals (eg, osmotic pressure, glucose levels, pH, and growth factors) within the environment. When this balance is disturbed, there would be a decrease in nutrient supply, leading to failure in the tissue-level structure and its function and later, cell death.[32]

One of the important components affected by the decrease in nutrient supply is proteoglycan, a significant matrix component that plays a crucial role in disc integrity and compressive supporting function. When the proteoglycan level decreases, the fixed charge density decreases in the disc, resulting in a loss of swelling pressure and loss of water content that ends with results in a smaller tissue pore size for transport of water, ions, nutrients and lactate, leading to lower values of solute diffusivity, hydraulic permeability, and electrical conductivity. The decrease in diffusion ability will further reduce the supply of nutrients in IVD, especially NP which gets nutrients from the diffusion process;[32,34] owing to the fact that NP is a source of stem cell / progenitor.[35,36]

However, due to its unsupportive structural arrangement such as low cell density, low cellular viability and activity, avascular, and nutrient insufficiency, its regeneration capacity is limited. Thus, in damaged and nutrition depleted IVD, NP regeneration is increasingly inhibited.[37]

In addition, AF is composed strongly of a layer of concentric rings arranged in continuous lamellar manner. This arrangement plays pivotal role in maintain NP when stretching or distention while holding the bed from torsion and bending. The minimal vascularization of the site makes AF prone to damage due to the limited healing process when exposed to trauma or herniation.[35,37]

Cell Senescence

Every cell would eventually degenerate; however, the process occurs within appropriate time and in accordance with the regeneration process of other cells. If aging occurs too quickly and is triggered by external stimuli, it could disrupt the balance of cell degeneration and regeneration processes, also known as cell senescence.[38] In general cell senescence is defined as irreversible cell cycle disruption due to the disturbances in telomeres and or due to external stimuli. These cells tend to cluster and fail to regenerate (mitogenic and replication failure), but still have the ability to pro-inflammatory cytokines, decreased protease matrix, growth factors and chemokines. Inflammatory phenotype of senescent cells associated with age-related disease is defined as senescence-associated secretory phenotype (SASP) via autocrine and paracrine modulation.[38,39] SASP is derived from golgi body vesicles, where it contains secreted cytokines and chemokines which can induce paracrine signaling of surrounding cells. There are many triggers of the aging process, especially from external stressors and oncogenic stimuli, which essentially inhibits cells from entering the mitogenic cycle and turning into oncogenic transformations.[39,40,41]

There are several biomarkers to detect senescence cells such as b-galactosidase (SA-b-Gal), p53 (tumor suppressor gene), cell-cycle kinase dependent (CDK) inhibitors (p16 and p21), cell cycle regulators (retinoblastoma protein, Rb), p38 and telomere length. However, SA-b-Ga is not specific because due to influence by lysosomes. These markers can appear in cell senescence depending on the molecular as well as the cause and type of cell.[38,42]

A vicious circle occurs in the cell senescence environment. This is due to the inability of senescence cells to regenerate plus the presence of SASP which can trigger senescent processes in neighboring cells. The process induce catabolism and pro-inflammation makes 'cell death' in IVD to be more progressive.[38,43]

Pro-inflammatory cytokines released by senescence cells such as TNF a, IL-1b, IL-17, IL-6, COX-2 and chemokines may promote senescence of neighboring disc cells and the infiltration of immune cells, thus worsening IVD degeneration.[38] Various causes of cell aging have been identified, including telomere shortening, DNA damage, oxidative stress, and activation of oncogenes pathway.[38,43]

The cell senescence mechanism is inability of cell to proliferate, inhibition SAb-gal activity and an increase on the expression of hallmark regulatory proteins such as SASP and p53/ p21 and p16/ RB tumors-suppressor networks that function to arrest proliferation and cause irreversibility of aging cells.[38,43,44,45] The trigger mechanisms are such follow.

The first stressor is oxidative stress. NP cells are a source of reactive oxygen species (ROS) that are elevated in IDD. ROS that most often causes damage is H_2O_2 which would induce several pathways such as inhibit the proliferation of NP cells, increase the number of SA b-Gal positive disc cells, and activate the senescent signal pathways to induce the cycle arrest of NP cells at the G0 / G1 phase.[38,46]

Secondly, pro-inflammatory cytokines such as TNF-a, IL-1a, IL-1b, IL-6, IL-17, and various chemokines could promote ECM catabolism and disc inflammation, leading to disc component damage. The cytokine that specifically plays a role in this process is TNF-a, which increased the number of SA-b-Gal positive cells and induced the ECM metabolism shift from anabolism to catabolism.[31,47] The third and fourth, about decrease in nutrition that has been discussed above and mechanical trauma.

All of the risk factors discussed above could induce a initial trigger for cell senescence by telomere shortening due to incomplete replication of the end of DNA. This shortening of the telomere will trigger the DNA damage response (DDR). Apart from shortening of telomere, oxidative stress and inactivation of DNA repair genes, including Brca1, Xrcc4 and DNA ligase IV can also induce DDR. In the end, activated DDR would stimulate the p53-p21-Rb and p16-Rb signaling pathway.[38] As discussed previously, when there is stress or trauma to the vertebrae nutrition transport to IVD is impaired. Thereby, when this condition is accompanied by exposure to oxidative stress and an increase in pro-inflammatory cytokines, the stress-induced premature senescence (SIPS) would be accelerated.[42,45]

Due to telomere shortening and DDR activation, the molecular process of cell aging can be divided into 2 lines, namely cell cycle arrest and induction of phenotype senescent cells to surrounding cells. In the DDR pathway. the process is related to m-ToR, whereas in telomere shortening it is related to Caveoline-1 which synergized with p53 and p16 in accelerating the aging of disc cells. The p38-MAPK pathway is active due to various stimuli such as nutritional deficiency, trauma and due to pro-inflammatory cytokines which will trigger overactivation of the p53-p21-Rb and p16-Rb pathways. Over-activation of the p53-p21-Rb and p16-Rb pathways triggers the WNT-b-catenin pathway and therefore induce disc cell senescence (a positive feedback), which together with m-ToR triggers accelerated cell aging.[31,42,46]

TREATMENT

There are many types of treatment that have been developed in accordance with the pathophysiology of IDD, some of which are growth factor (GF) therapy to stimulate angiogenesis, TGF-βl to suppresses inflammation, and exosomes as potential alternatives to stem cells.[16,47,48] This therapy goes hand in hand. Time will increase with the rapid development of theoretical findings about the pathogenesis of IDD. In accordance with the anatomy of IVD, especially avascular NP, angiogenesis triggers are needed, especially in cases of IDD. Some GH has been shown to increase angiogenesis, but what will be discussed in this review are platelet-derived growth factor (PDGF), Growth and Differentiation Factor-5(GDF-5), and Transforming Growth Factor Beta-1 (TGF-β1).[16]

PDGF belongs to the category of anti-catabolic mitogens, which acts to slow down cell damage and cell turnover. The PDGF family consists of four homodimeric proteins (PDGF-AA, -BB, -CC, and -DD) and one heterodimeric protein (PDGF-AB), a major growth factor on platelet-rich plasma. PDGF acts as an anti-catabolic and anabolic trigger. PDGF's properties to induce angiogenesis are exerted via modulation the expression of vascular endothelial growth factor (VEGF) and its ability to act as a chemoattractant, thus increasing anabolic processes in IVD and prevents catabolism. Thus, PDGF could reduce the number of AF cells apoptosis induced by serum depletion and inhibit IVD cell apoptosis.[16,49,50]

GDF-5 belongs to the bone morphogenetic proteins (BMP) family which is also known as cartilage-derived morphogenetic protein-1 (CDMP-1) and BMP-14. GDF-5 plays important role not only in the musculoskeletal system, but also in Parkinson's disease and myocardial infarction.[51,52] In a study conducted by Bucher et al[53] in which GDF-5 was transfected with mesenchymal stem cells (MSCs) with electroporation, MSC expresses GDF-5 efficiently for up to 21 days and there was an upregulation of chondrogenesis markers, namely GDF-5 aggrecan and SOX9. In other study by Wei et al[54], it was found that GDF-5 increased disc height and the number of AF cells, and in another study on the effect of adenovirus GDF-5 (Ad-GDF-5) in increasing ECM metabolism in human NP cells by Luo XW, Liu K, Chen Z, et al[52]., it is known that ad-GDF-5 can be increased synthesis of proteoglycan, and up-regulation of the expression of collagen II and the aggrecan genes. Therefore, the role of GDF-5 is related to improve the synthesis of proteoglycan, collagen II, and aggrecan as well as increase cell numbers and improve the structure of IVD.

TGF-β1 not only functions as a growth factor, it also functions as an anti-inflammatory in IDD. TGF-β1 is a polypeptide that acts in several cells, and functions in the process of cell proliferation, growth, and differentiation. One of the most effective roles of TGF-β is to regulate β1,3-glucuronosyl transferase-1 expression and chondroitin sulfate synthesis in NP cells through mitogen-activated protein kinase (MAPK) signaling, transcription factors such as AP1 and Sp1, and positive TonEBP52 affect the cell function of the disk to be stronger.[16,55,56]

Apart from being a growth and differentiation factor, TGF-β1 is also a strong immune suppressor. In the study of Yang Ha et al.,[47] it was concluded that TGF-β1 inhibits Iκ-B phosphorylation and NF-κB activation. NF-κB is a core protein factor found in several tissue cells which has activity as a transcription regulation and plays a role in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacteria or viruses. In anti-inflammatory role, NF-κB plays a key role in regulating the immune response to infection while IκB is a gene that inhibits NF-κB activity. so that when phosphorylation of Iκ-B is inhibited, there will be an increase in the activation of NF-κB which functions as an important factor in the cell defense mechanism.[46,57,58]

In IDD, mainly due to IVD cell senescence, there is a decrease in the number of viable and functional cells. One of the therapies considered to treat cell senescence is stem cell-based therapies which aim to increase the number of viable cells. With the increase in viable cells, it is hoped that there will be an increase in the production of an appropriate and functional NP-like matrix to enhance the regeneration process in IVD. One type of stem cell is an exosome produced by mesenchymal stem cells (MSCs) which have a differentiation ability similar to NP cells.[48] According to Yuan et al.[59] the extracellular matrix derived from NP cells also has the ability to induce differentiation of mesenchymal stem cells.

Exosomes are one of 3 types of extracellular vehicles (EVs) that is formed after the fusion of multivesicular bodies (MVBs) with the plasma membrane. Based on the differences in characteristics, there are 3 types of EVs, namely exosomes (diameter <150 nm), microvesicles and apoptotic bodies (both> 100 nm). Exosomes themselves have a complex composition, consisting of proteins, nucleic acids, lipids and other metabolites. Due to their small size (<150 nm diameter), exosomes are best visualized with an electron microscope.[60,61,62] The function of exosomes was originally only as cellular waste to maintain homeostasis. However, recent research showed that exosomes are important vesicles in communication between cells for cellular modulation or mediation. The role of exosomes in IVD regeneration was demonstrated by the study of Lu K et al.[48] which showed that some NP cell exosomes could promote bone marrow mesenchymal stem cells (BM-MSC) to differentiate into cells similar to NP cells. In addition, due to its role as a modulation of the

communication system, exosomes increase cell recruitment from the surrounding environment to replenish the role of functional cells damaged by IDD.[48,63,64]

PREVENTION

There are several preventive measures to prevent and slow down IVD damage, one of the factors that affect the inhibition of IVD cell degeneration is a healthy lifestyle such as maintaining BMI and regular exercise. For example, research by Schumann et al.[65] on the relationship between lifestyle-related factors (smoking, body mass index [BMI], and sports activities) and lumbar disc disease (lumbar disc herniation and lumbar disc narrowing) on the basis of data of the EPILIFT Study in people aged 25-70 years, which shows that the higher a person's BMI, the easier degeneration of the intervertebral discs will occur. This is related to biomechanical and atherosclerotic processes, because the higher the body weight, the faster the disc mechanical damage. Being overweight also increases cholesterol and blood fat levels which can stimulate atherosclerosis in the IVD vascular so that the regeneration process of the disc can be hampered due to vascular insufficiency.[65,66]

In addition, the study of Schumann et al.[65] also assessed body building and strength training in subjects with the 'FIT' screening tool, which results showed a decrease in the incidence of intervertebral disc degeneration in men undergoing high levels of cumulative body building and strength training. Sports that are considered effective for increasing intervertebral disc resistance are endurance sports such as water aerobics, yoga, pilates, stretching, and walking. This exercise must be done regularly, in order to increase muscle, joint, and bone strength and help maintain optimum nutrition for your disc.

CONCLUSION

This review article describes the role of IVD as an important component of the vertebral system, including the patophysiology of IDD and some therapy developed based on the pathophysiology that has been identified. IVD not only acts as a realm of structural support and locomotion, but also has the flexibility needed by the axial system such as vertebrae which is called "shock absorbing". Therefore, the IVD system has a "special" structure that synergizes with each other in maintaining its functions, namely AF, NP, and cartilage end plate. IDD is one of the causes of disruption of the "shock absorbing" system with a very wide range of risk factors, as described above, including differences in anatomical structure, trauma, lack of nutrition (decreased angiogenesis function), massive pro-inflammation, and cell senescence. The pathophysiology of each risk factor is uncertain but it's hoped that it can be used as a therapeutic innovation for IDD, not only as a curative therapy but also as a preventive therapy. Some therapies that are expected to successfully treat IDD are growth factor (GF) therapy to stimulate angiogenesis, TGF-βl to suppress inflammation, and exosomes as potential alternatives to stem cells whose mechanisms have also been described in this review.

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Table 1. The Difference structures and anatomy between annulus fibrosus (AF) and nucleus pulposus (NP)

Feature	AF	NP
Origination	Interzone cells[20]	Mesodermal somites[21]
Shape formation	Between the 8th and 10th week of gestation[20,21]	Tenth week of embryonic development[21]
Cell shape	Elongated, fifibroblast-like[16,21]	Rounded, chondrocyte-like[20-1]
Dominant collagen type	Type I collagen (80% by dry weight) and other collagen variants (types II, III, IV, VI and XVIII) (<1%)[16,23,24]	Collagen Type II (60%) and type I collagen (40%)[16,18,23,24]
Proteoglycan content	1–2% of dry weight; the major PG (aggrecan) and other smaller PGs (e.g., decorin, biglycan, fibromodulin and lubricin)[25]	High (~70%)[22], 60%[18]
ECM water content	Low[16,21]	High[21]
Phenotypic marker	C1QR; CA12; COL1A1; COL1A2; ESTs; FLJ20831; HPCAL1; LIMK2; PDLIM1[22]	HIF1/2α, GLUT1, KRT 18/19, CA-3/12, CD24, A2M[22]
Tissue function	- Transferring vertical compressive load into circumferential hoop stresses[25] - Shock absorption, stability, lubrication, nutrition and proprioception to the knee joint[25]	- Absorb the loads and equalize the compressive stress on the vertebral CEP[26]
Blood Supply	Peripheral 10–25% are vascular for LM and 10–30% for MM[18,27]	Avascular[18,28]
Innervation	Most abundant on the periphery and the anterior and posterior horns[22,29]	No innervation[18,28]

Notes : C1QR complement component C1q receptor, CA12 carbonic anhydrase XII, COL1A2 collagen, type I, alpha 2, FLJ20831 hypothetical protein FLJ20831, HPCAL1 hippocalcin-like 1, LIMK2 LIM domain kinase 2, LM lateral meniscus, GLUT1, glucose transporter 1, HIF1α hypoxia inducible factor 1 alpha, KRT18 keratin 18, MM medial meniscus, CEP cartilage end plate.

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