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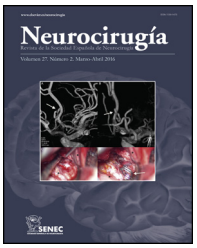

Review article

Biology and mechanobiology of the intervertebral disc☆

Emilio González Martínez[a], *José García-Cosamalón*[b,*], *Iván Cosamalón-Gan*[c], *Marta Esteban Blanco*[c], *Olivia García-Suarez*[c], *José A. Vega*[c]

[a] *Servicio de Neurocirugía, Complejo Asistencial Universitario de León, León, Spain*
[b] *Instituto de Biomedicina, Universidad de León, León, Spain*
[c] *Departamento de Morfología y Biología Celular, Facultad de Medicina, Universidad de Oviedo, Oviedo, Spain*

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ABSTRACT

The intervertebral disc (IVD) is noted for its low cell content, and being the largest avascular structure of human body. The low amount of cells in the disc have to adapt to an anaerobic metabolism with low oxygen pressure and acidic pH. Apart from surviving in an adverse microenvironment, they are exposed to a high level of mechanical stress. The biological adaptation of cells to acidosis and hyperosmolarity conditions are regulated by mechanoproteins, which are responsible for converting a mechanical signal into a cellular response, thus modifying its gene expression. Mechanobiology helps us to better understand the pathophysiology of IVD and its potential biological repair.

Biología y mecanobiología del disco intervertebral

Palabras clave:
Disco intervertebral
Biología del disco intervertebral
Mecanobiología del disco intervertebral
Mecanoproteínas en el disco intervertebral

RESUMEN

El disco intervertebral (DIV) se caracteriza por su escasa celularidad y por constituir la estructura avascular más grande del cuerpo humano. Las escasas células del disco tienen que adaptarse a un metabolismo anaerobio con baja tensión de O_2 y pH ácido. Además de sobrevivir a un microambiente adverso, están expuestas a un elevado estrés mecánico. La adaptación biológica de las células a las condiciones de acidosis e hiperosmolaridad está

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* *Corresponding author.*
E-mail address: jcosamalon@smonica.com (J. García-Cosamalón).

regulada por mecanoproteínas responsables de convertir una señal mecánica en respuesta celular, modificando su expresión génica. La mecanobiología nos ayuda a entender mejor la biopatología del DIV y su potencial reparación biológica.

Cells and cell function

The embryonic origin of intervertebral disc (IVD) cells depends on the structure that they comprise. Embryologically, the annulus fibrosus (AF) derives from the mesenchyma, while the nucleus pulposus (NP) develops from the notochord. Notochord cells, notochord remnants and chondrocytes coexist in the NP of the foetus.[1] Notochord cells are present in childhood, disappear between 4 and 10 years of age and are replaced by cells reminiscent of articular cartilage chondrocytes. However, outer AF cells resemble fibroblasts.[2] Cartilaginous endplate (CE) chondrocytes are closely related to articular cartilage chondrocytes, and inner AF chondrocytes are closely related to fibrochondrocytes, while NP chondrocytes are considered to be somewhere between the two. Immunohistochemical studies have observed that some of these chondrocytes may undergo a change in their specific phenotype towards phagocytes during the degenerative process of the IVD.[3]

The IVD has a very limited number of cells. Mean cell density in an adult is 5500 cells/mm^2. Cells are not uniformly distributed throughout disc tissue. Cell density is higher close to the CE and on the periphery of the AF. These are the regions closest to the limited vascular supply.[4] The cell density of the IVD decreases throughout life due to necrosis, apoptosis and senescence.[5–7] Necrotic cells amount to 2% in the foetus, 50% in the adult population and 80% in the elderly.[8,9] Programmed cell death, which is essential in many states of normal tissue development and homeostasis, has been found to be one cause of the gradual decrease in the number of cells in the IVD. Apoptosis would be induced by endogenous and exogenous stimuli, which would activate a series of events culminating in cell death.[10] This process has been observed from childhood, and so together with the loss of notochord cells it is considered to be one of the earliest signs of "ageing" and degeneration.[11,12] Given that apoptosis is regulated by cytokines and growth factors, several studies have suggested alternatives through which growth factors, cytokines, hormones and even specific gene therapy may be manipulated to inhibit programmed cell death.[10,13,14] The gradual disappearance of the cells is also attributed to the chronic hypoxia and lack of glucose to which the NP cells are subjected.[1] The factors described above render the mature IVD one of the least cellular tissues in the human body. Therefore, it is not surprising that the cells have trouble maintaining the integrity of the extracellular matrix (ECM) throughout life.[15]

IVD cells are biologically active and are involved in producing proteoglycans (PGs), collagen and enzymes that influence ECM formation and remodelling.[12] The IVD remains healthy as long as the proportion of macromolecular synthesis and degradation is in equilibrium. However, if degradation predominates over synthesis, then the ECM starts to disintegrate. From a biochemical point of view, degeneration results from the failure of the cells to produce, maintain and repair the ECM.[16]

Modulation of cell function

The cells regulate the homeostasis of the tissue of the IVD by maintaining a balance between anabolism and catabolism measured at once through a variety of substances including cytokines, enzymes, enzyme inhibitors and growth factors in an autocrine or paracrine form. Anabolic factors include growth factors (IGF, TGF-beta and BMP). The catabolic process is also regulated by several enzymes such as ECM metalloproteases, aggrecanases and cytokines.[3,14] An imbalance between the anabolic process and the catabolic process may be the start of the degenerative process.

Under physiological conditions, IVD cells are subjected to multiple complex stimuli of compression, tension, shear, fluid flow, osmotic and hydrostatic pressures, and electrokinetics. The response of the cells to these different biophysical stimuli depends on their anatomical region and cell origin[17,18] (Fig. 1). IVD cells are sensitive to mechanical signals and may be negatively affected by mechanical stress throughout life, thereby leading to quantitative and qualitative modulation of ECM metalloproteases.[19] The cells of the NP and inner AF respond to changes in their mechanical environment like articular cartilage chondrocytes by increasing or decreasing their biosynthesis of PGs. Extreme hydrostatic pressure decreases synthesis, while moderate loads increase synthesis.[18] Pressures that exceed 3 MPa (equivalent to moderate manual activity) increase the synthesis of degradative metalloproteases of the ECM. The NP cells respond to compression cycles by producing more collagen. This suggests that the cells may be capable of behaving like fibroblasts or chondrocytes depending on the prevalent mechanical environment.[2]

Nutrition of the intervertebral disc

From the embryonic state, the IVD essentially receives its nutritional supply from 2 sources: a network of blood vessels that penetrate up to the outer third of the AF (marginal vessels) and other axial vessels that penetrate the cartilage of the CE from the vicinity of the vertebral bodies.[15] The cells receive their supply of glucose and oxygen, essential for their survival, through this vascularisation.[16] Histological studies have demonstrated that the vascular supply of the disc starts to decrease in the first few years of life and disappears at