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Review

The lumbar intervertebral disc: From embryonic development to degeneration

Pauline Colombier[a,b], Johann Clouet[a,b,c,f], Olivier Hamel[a,b,d,g], Laurent Lescaudron[a,b,e], Jérôme Guicheux[a,b,h,*]

[a] *INSERM UMRS 791, LIOAD, Groupe Skeletal Tissue Engineering and Physiopathology (STEP), 1, place Alexis-Ricordeau, 44042 Nantes, France*
[b] *Université de Nantes, UFR Odontologie, 1, place Alexis-Ricordeau, 44042 Nantes, France*
[c] *Université de Nantes, UFR Sciences Biologiques et Pharmaceutiques, 9, rue Bias, 44035 Nantes, France*
[d] *Université de Nantes, UFR Médecine, 1, rue Gaston-Veil, 44035 Nantes, France*
[e] *Université de Nantes, UFR Sciences et Techniques, 2, chemin de la Houssinière, 44300 Nantes, France*
[f] *CHU de Nantes, Pharmacie Centrale, 85, rue Saint-Jacques, 44093 Nantes, France*
[g] *CHU de Nantes, Service de Neurotraumatologie, 1, place Alexis-Ricordeau, 44000 Nantes, France*
[h] *CHU de Nantes, Pôle Hospitalo-Universitaire 4 OTONN, 1, place Alexis-Ricordeau, 44000 Nantes, France*

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ABSTRACT

Lumbar intervertebral discs (IVDs) are prone to degeneration upon skeletal maturity. In fact, this process could explain approximately 40% of the cases of low back pain in humans. Despite the efficiency of pain-relieving treatments, the scientific community seeks to develop innovative therapeutic approaches that might limit the use of invasive surgical procedures (e.g., spine fusion and arthroplasty). As a prerequisite to the development of these strategies, we must improve our fundamental knowledge regarding IVD pathophysiology. Recently, several studies have demonstrated that there is a singular phenotype associated with *Nucleus pulposus* (NP) cells, which is distinct from that of articular chondrocytes. In parallel, recent studies concerning the origin and development of NP cells, as well as their role in intervertebral tissue homeostasis, have yielded new insights into the complex mechanisms involved in disc degeneration. This review summarizes our current understanding of IVD physiology and the complex cell-mediated processes that contribute to IVD degeneration. Collectively, these recent advances could inspire the scientific community to explore new biotherapeutic strategies.

1. Introduction

Lumbar intervertebral discs (IVDs) are complex anatomical structures that are essential for the mobility of intervertebral joints. They also participate in anchoring vertebrae together and distributing the pressure that results from movement of the entire trunk. Notably, the functional roles of IVDs in absorption and load distribution are directly related to their unique structure (Fig. 1).

In most mammals, the first signs of IVD degeneration begin to appear upon skeletal maturity in the *Nucleus pulposus* (NP) [1]. Up until this time, two cell types populate the NP: chondrocyte-like cells and notochordal cells. It is now accepted that notochordal cells are largely responsible for maintaining homeostasis [2–5]. Thus, the loss of these cells during skeletal maturation might constitute one of the first changes that occur in the cascade of degenerative events. Although this degeneration arises during the natural aging process, pathological degeneration can also occur, which progresses in an accelerated and brutal manner. Nevertheless, in this review, we only focus on the mechanisms of development, maturation, and degeneration associated with normal aging.

2. Intervertebral disc physiology

2.1. Embryonic development

In humans, the formation of the three embryonic layers occurs in the third week of gestation. During this phenomenon, called gastrulation, epiblast cells (future ectoderm) invaginate at the Hensen's node and colonize the mesoblastic space to form the notochord (chordal mesoderm). The development of the notochord is dependent on the expression of several genes, including Forkhead box A2 (Foxa2), Brachyury (T), and Notochord homolog (Noto). In addition, a part of maturing somites known as the sclerotome gives rise to the vertebrae, endplates, and *Annulus fibrosus* (AF) under the action of the Sonic hedgehog (Shh) factor and members of transforming growth factor (TGF) family (Fig. 2). The Shh-dependent expression of Paired box 1 and 9 (Pax1/9) controls the vertebral endochondral ossification process [6], whereas TGF-β is involved in the differentiation of the sclerotome into AF cells [7].

* Corresponding author. INSERM U791, 1, place Alexis-Ricordeau, 44042 Nantes cedex 1, France.Tel.: +33 2 40 41 29 82; fax: +33 2 40 08 37 12.
E-mail address: jerome.guicheux@inserm.fr (J. Guicheux).

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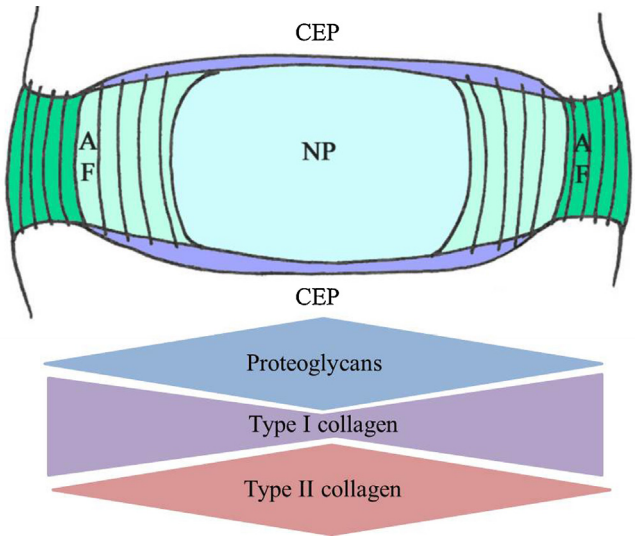

Fig. 1. Schematic representation of the structure and composition of the IVD, indicating proteoglycan content as well as type I and II collagen in the NP and AF. AF: *Annulus fibrosus*; CEP: cartilage endplate; NP: *Nucleus pulposus*.

Notochordal cells die by apoptosis when the sclerotome condenses and proliferates to form vertebral bodies. However, the NP is generated by their proliferation at the intervertebral level. Recent studies have demonstrated that all of the NP cells arise from the notochord [8,9].

2.2. *The* endplates

Like articular cartilage, the endplates are composed of subchondral bone and a thin layer of hyaline cartilage (approximately 1 mm in humans) on which the fibers of the AF anchor. Notably, these cartilage endplates (CEPs) are composed of only chondrocytes, which synthesize an extracellular matrix (ECM) that is rich in type II collagen and proteoglycans (PGs). In these plates, the ratio of PG to type II collagen is approximately 2:1, which is similar to articular cartilage, and the water content is 50–60% [10]. PGs are macromolecules that are composed of a protein body covalently linked to sulfated polysaccharide chains, called glycosaminoglycans (GAGs). These sulfated GAGs carry an overall negative charge that is responsible for retention of water molecules, efficiently allowing hydration of the extracellular matrix (ECM).

CEPs are also the site of a microscopic network of blood vessels that are responsible for nutritional intake during development and growth of IVDs [11]. Metabolites diffuse through pores present in the growth plates based on their size and charge. Only positive ions (e.g., sodium, calcium) or neutral molecules, such as glucose and oxygen, can diffuse [12].

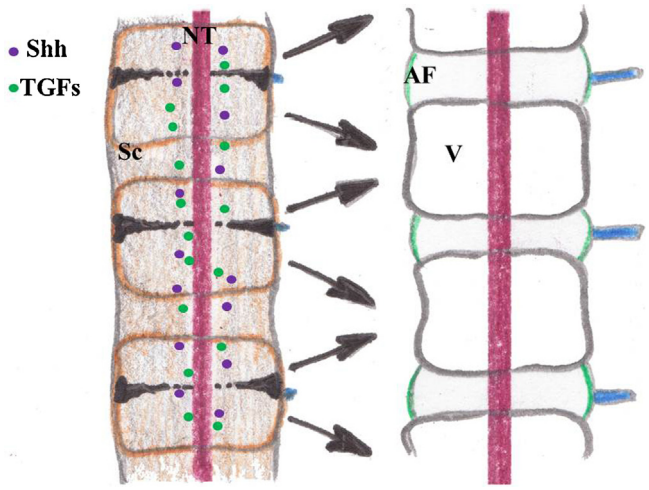

Fig. 2. Schematic representation of the resegmentation phenomenon of the sclerotome during the formation of the V and AF. AF: *Annulus fibrosus*; NT: notochord; SC: sclerotome; Shh: sonic hedgehog; TGFs: transforming growth factors; V: vertebra.

2.3. *The* Annulus fibrosus

The AF is composed of fibroblasts (approximately 9000 cells/mm^3), which mainly synthesize type I collagen fibers. The ECM of the AF is organized into 15–25 concentric lamellae oriented at 65° relative to the vertical plane. These lamellae are interconnected by PG aggregates and lubricin, as well as type VI collagen fibers [13,14]. Lubricin, known for its lubricant role within diarthrodial joints, is probably involved in the reduction of friction between adjacent lamellae of the AF [14].

The AF can be divided into two distinct areas: the outer AF and inner AF. The inner AF, which is also known as the transition zone, contains poorly organized ECM that is composed of type II collagen, PGs, and water. In contrast, the outer AF is highly organized and is rich in type I collagen, whereas type II collagen and PGs are virtually undetectable in this region [15]. Moreover, the outer AF has a higher resistance to tension than the inner AF. Collectively, the fibrous structure of the AF yields important mechanical properties that limit NP protrusion.

2.4. *The* Nucleus pulposus

The NP contains approximately 3000 cells/mm^3 and is composed of several cell types embedded in a matrix that is rich in both type II collagen and PGs (PG to type II collagen ratio is 27:1). The main PG within the NP is aggrecan, which contains ~30 chains of sulfated GAGs, contributing to a negative charge that fosters the hyper-hydrated state of the NP. Notably, this water content, along with type II collagen fibers, allows the NP to be elastic and deform under stress. Notochordal and chondrocyte-like cells synthesize the matrix components of the NP. It is now accepted that these chondrocyte-like cells have a phenotype distinct from that of articular chondrocytes [16,17]. Moreover, the presence of a third cell type, displaying progenitor properties similar to those of mesenchymal stem cells (MSCs), was recently described by Sakai et al. [18]. However, considering the characteristics of notochordal cells, it is likely that these progenitor cells are actually notochordal cells. Cells of the NP are highly specialized and survive in a very hypoxic environment (1% of O_2). For this reason, the hypoxia inducible transcription factors-1 and -2 (HIF-1 and HIF-2), which are key cellular regulators of the hypoxic response, were found to be constitutively active in NP cells [19]. Indeed, Agrawal et al. have demonstrated that the promoter of the aggrecan gene responds to HIF-1. Thus, constitutive activity of HIF-1 might be partly responsible for the large production of aggrecan by NP-resident cells, independently of oxygen conditions. They also demonstrated that the expression of some glucose transporters (GLUT1 and 2) were under the control of HIF-1 [20]. Therefore, NP cells possess a unique metabolism that allows them to be functionally and constitutively adapted to their environment, which is low in oxygen and nutrients.

Recent studies have shown the importance of notochordal cells in the synthesis of functional ECM and in the survival of chondrocyte-like cells. Erwin et al. have demonstrated that notochordal cells synthesize growth factors, such as connective tissue growth factor (CTGF/CCN2), stimulating the proliferation of chondrocyte-like cells and the synthesis of type II collagen and aggrecan [4]. It was also found that the secretome of notochordal