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Delivery systems for the treatment of degenerated intervertebral discs ☆

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ABSTRACT

The intervertebral disc (IVD) is the most avascular and acellular tissue in the body and therefore prone to degeneration. During IVD degeneration, the balance between anabolic and catabolic processes in the disc is deregulated, amongst others leading to alteration of extracellular matrix production, abnormal enzyme activities and production of pro-inflammatory substances like cytokines. The established treatment strategy for IVD degeneration consists of physiotherapy, pain medication by drug therapy and if necessary surgery. This approach, however, has shown limited success. Alternative strategies to increase and prolong the effects of bioactive agents and to reverse the process of IVD degeneration include the use of delivery systems for drugs, proteins, cells and genes. In view of the specific anatomy and physiology of the IVD and depending on the strategy of the therapy, different delivery systems have been developed which are reviewed in this article.

Contents

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1. Introduction

Around 70–80% of the people are suffering from back pain at a certain stage of their life, of whom 15–20% experience protracted pain and approximately 7–8% develop constant chronic pain [1]. Back pain is generally related to pathologies like intervertebral disc (IVD) herniation, spine stenosis, radiculopathy or sciatica [2,3], leading to pain caused by compression and/or inflammation of nerves in the cervical or lumbosacral area where the spine forms the lordotic curve.

In many cases, back pain can be linked to multifactorial parameters like physical characteristics, lifestyle factors, employment conditions, social factors, heredity and ageing [4–7]. It has been demonstrated that back pain is most-often caused by degenerative conditions of the spine, especially degeneration of the IVD [2,8,9].

The IVD is a heterogeneous, fibrocartilaginous tissue located between each of the 24 vertebrae of the spine, which are subdivided in 7 cervical, 12 thoracic and 5 lumbar vertebrae [10]. An illustration of the human IVD is shown in Fig. 1. The function of the IVD is to absorb and transmit shocks and stresses subjected to the spine, as well as to confer flexibility to the backbone [11,12]. The IVD is structurally and biologically diverse, as it consists of three distinct parts. The centre of the disc, the nucleus pulposus (NP), is a highly hydrated gelatinous tissue mainly composed of aggrecan proteoglycan and collagen type II [13]. Except the upper and lower surface, the NP is completely surrounded by the annulus fibrosus (AF), which is mainly composed of organized and oriented collagen type I fibres [14]. The cartilaginous end-plates of the two adjacent vertebrae are in contact with the upper and lower surface of the IVD and allow the transfer of nutrients, oxygen, metabolic products and water [15]. The cell populations present in the IVD correspond to 1% of the total disc volume, and this limited number of cells impedes the synthesis of extracellular matrix (ECM) [16]. The lack of vascularization of the IVD, with capillaries only supplying the outside of the AF and the upper and lower surface of the disc through the end-plates, makes it the largest avascular structure in the body [17]. In addition, the IVD is largely aneural, with nerve endings only reaching the periphery of the AF [10]. Consequently, the nutritional process is strongly impaired which may explain why the IVD is prone to degeneration [18–20].

Disc degeneration is associated with morphological (decrease of disc height, bulging, ingrowth of blood vessels and nerves) [21–23], physical (decrease of water content inside the disc) [24] and mechanical (loss of flexibility and elasticity) [25,26] changes leading to disc pathology. The loss of IVD function is essentially the consequence of deregulation of the physiology of the disc, which affects the balance between anabolic and catabolic processes [27–29]. This results in down-regulation of ECM synthesis in the degenerating disc [30], with a drastic drop of proteoglycan production in the NP which induces a fall in osmotic pressure of the disc matrix resulting in loss of hydration [13,31]. In addition, alteration and denaturation of collagen in the AF make the tissue less elastic and less tough [32,33]. Moreover, pro-inflammatory substances such as cytokines are produced which trigger an inflammatory cascade (interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor-α (TNF-α)) [34–37] and an augmentation of enzyme activity which is the main cause of ECM degradation (matrix metalloproteinases (MMPs), aggrecanase, cathepsin) [38–41]. Finally, chemical factors are also involved such as an increasing acidity due to the lack of cell nutrition, which compromises cell function and may cause cell death [42,43].

Established protocols to treat back pain consist of physiotherapy and pain medication by drug therapy, which show limited success in the case of chronic back pain. Surgical treatments are the current alternative [44]. Spinal fusion [45], total discectomy [46] and partial nucleotomy [47] are the most common surgical procedures performed to reduce the pain. However, these interventions do not allow restoration of disc function and are associated with drawbacks such as high invasiveness, high risk of recurrence, loss of mechanical properties and degeneration of adjacent IVDs [48,49]. As both non-surgical and surgical therapies are sub-optimal, it is very important to find more-effective therapeutic strategies for the treatment of back pain.

Taking into account the different mechanisms related to IVD degeneration, current research is focused on different approaches for pain treatment and/or reversal of disc degeneration. A common aspect of all strategies is the use of a therapeutic delivery system, either for drugs, proteins, cells or genes. Although many reviews have been published on delivery systems for the treatment of bone and cartilage defects [50–53], delivery systems to treat IVD degeneration have not been reviewed. In this article, we will discuss the non-sustained delivery of bioactive agents and cells, after which an overview will be given on the development and optimization of specific carrier systems for the (sustained) delivery of bioactive agents, cells and genes, in the context of the treatment of IVD degeneration.

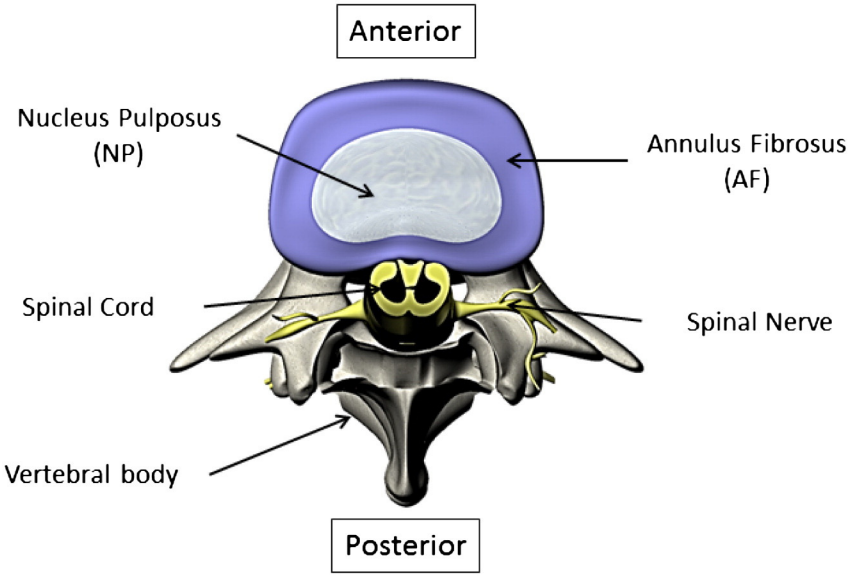

Fig. 1. Illustration of the human IVD anatomy and location.

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