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REVIEW ARTICLE

Bedside to bench and back to bedside: Translational implications of targeted intervertebral disc therapeutics

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Summary Spinal pain and associated disability is a leading cause of morbidity worldwide that has a strong association with degenerative disc disease (DDD). DDD can begin in early—late adolescence and has a variable course. Biologically based therapies to treat DDD face significant challenges posed by the unique milieu of the environment within the intervertebral discs. Many potential promising therapies are still in the early stages of development with a hostile microenvironment within the disc presenting unique challenges.

The translational potential of this article: Patient selection, reasonable therapeutic goals, approach, and timing will need to be discerned in order to successfully translate potential therapeutics.

Introduction

Low back pain is a leading worldwide cause of disability with degenerative disc disease (DDD) being the most common source of low back pain [1]. In fact, evidence of DDD has been found in 40% of volunteers aged younger than 30 years, and this rises to more than 90% by age 55 years [2]. A recent systematic review of chronic back pain reported a prevalence of 4.2% between 24 years and 39 years of age, and amongst those between 20 years and 59 years old the prevalence increased to 19.6% [3]. Other studies involving persons aged older than 18 years reported chronic back pain to a similar to a similar degree at between 3.9% and 10.2%, with several others reporting between 13.1% and 20.3% [3]. A cross-sectional study of 876 family health clinic patients

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found that risk factors for chronic back pain included female sex, age 30 years or older, lower education status (4 years or less), anxiety, and an occupation requiring high exertion. Furthermore, quality of life and self-rated health scores were significantly worse among individuals with chronic spinal pain [4]. Furthermore, it has been demonstrated that sexual dimorphism exists with respect to DDD and that postmenopausal women are at an increased risk of disc degeneration perhaps because of the impact of the oestrogen receptor on collagen metabolism [5,6]. Back pain has been reported to be the most common reason for healthcare visits among those with musculoskeletal disorders (more so than hypertension and arthritis) and has the greatest impact and resource use [7]. Back pain is also costly, with 5% of the American workforce missing at least 1 day of work per year, with direct and indirect costs estimated to range between $19.6 billion and $118.8 billion in the USA [1,7,8]. Like the lumbar spine, DDD affecting the cervical spine can be painful and disabling; moreover, it is also the main cause of cervical spondylotic myelopathy—the leading cause of spinal neurological impairment in persons aged older than 65 years [9]. DDD may overload segmental muscles, facet joints, and capsules, leading to pain arising from these spinal joints and soft tissues that might otherwise be classified as "muscular" or ill-defined soft tissue pain, perhaps underestimating the impact of DDD and spinal pain [10]. Treatment of spinal pain secondary to DDD is largely afforded by various modes of physical and cognitive behavioural therapy that achieve similar benefits as spinal fusion surgery, leaving the field with no effective disease-modifying therapy [11]. Therefore, new interventions including biologics and/or tissue engineering approaches are currently under intense investigation with a view to being able to influence the course of the disorder [12].

Intervertebral disc degeneration

Homeostatic regulation

The intervertebral disc (IVD) complex is composed of specialised cells and extracellular matrix (ECM) that are able to withstand high tensile strength as well as compressive and off-axis loading that affords the spinal column with strength, flexibility and protection of the spinal cord. In youth, the nucleus pulposus (NP) is gelatinous with a proteoglycan (PG) network rich in aggrecan and collagen type 2. PGs within the IVD NP ECM (principally aggrecan) are highly negatively charged; they bind water molecules and are responsible for the high net swelling pressure unique to the IVD NP. The healthy IVD NP is capable of resisting compression and deformation principally owing to the hydrophilic NP rich in highly negatively charged PGs that strongly bind water molecules. Homeostatic regulation of the healthy NP ECM involves a balance between anabolic and catabolic activity. However, in DDD this normally tightly regulated process becomes dysfunctional, such that ECM-degrading enzymes and proinflammatory molecules lead to progressive degeneration, loss of viable cells, and a fibrocartilaginous degenerative phenotype [13—15].

Apart from a limited vascular supply to the periphery of the annulus, the inner annulus and NP is hypoxic, ischaemic, aneural, and isolated from the immune system, and represents a unique tissue compartment. The cells within the NP have adapted to this harsh environment by relying upon glycolytic metabolism and diffusion of nutrients and waste products into and out of the NP via the vertebral endplates [16]. With maturity and DDD, the cellular and extracellular phenotype within the IVD NP changes from the youthful highly notochordal composition to one where small, chondrocyte-like cells predominate, where there is a gradual replacement of collagen type 1 and relative loss in collagen type 2 leading to the development of a fibrocartilaginous IVD NP [17]. The vertebral endplates form the superior and inferior boundaries of the IVD and act as diffusible barriers between the bone marrow of the vertebral body and the disc itself. With progressive DDD, the small pores within the endplates calcify, thus compromising their diffusion capacity and further compromising the already delicate molecular exchange within the IVD NP [18,19].

Genetic and epigenetic influences

Some patients develop DDD to a greater degree than others, and it has been demonstrated that certain genes and/or small nucleotide polymorphisms such as collagen IX, the vitamin D receptor, collagen type 1, aggrecan, matrix metalloproteinase-3, and the interleukin (IL)-1 receptor can influence a patient's predisposition to DDD [20,21]. Data concerning the precise mechanisms whereby these genetic anomalies may influence the development and progression are not yet fully understood. However, many of the candidate genes involved with DDD (*collagen 1*, *IX*, *XI*, *aggrecan*, *matrix metalloproteinase-3*, and the *vitamin D receptor*) likely result in the deposition of flawed ECM proteins. In the case of IL-1 and its receptor, it is likely that impaired regulation of inflammation and/or even pain could be candidate targets [22]. All the factors listed above plus activities of daily living, trauma, and occupational demands lead to a net decrease in the main PG aggrecan, a decrease in type 2 collagen, an increase in the degradation of collagen type 2, and an increase in type 1 collagen within the NP [23]. The loss of functional aggrecan leads to a progressive inability of the NP ECM to bind water that, in turn, leads to a decrease in intradiscal pressure. The accumulated loss of ECM integrity such as enzymatic cleavage of PG core proteins (such as biglycan, decorin, and fibromodulin) further contribute to DDD, loss of disc height, and a reduced ability of the IVD to resist compressive/shear forces. With respect to epigenetic influences, Matsui et al [24] demonstrated a higher likelihood of DDD in patients with a relative who underwent herniated disc surgery. Furthermore, smokers and patients living with diabetes also have elevated risk of developing DDD [25]. It is therefore likely that certain mutated genes impair cell viability and the deposition and regulation of cellular—ECM interaction that along with multiple processes such as inflammation, leads to progressive DDD [26,27].

For more details with respect to the complexities and changes in cellularity and ECM, the reader is referred to several published reviews such as those by Feng et al [28] and Adams and Roughley [29].