

EDITORIAL

The enigma that is the nucleus pulposus cell: the search goes on

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See related research by Gilson *et al.*, <http://arthritis-research.com/content/12/1/R24>

Abstract

The development of an effective treatment for degenerative disc disease has been hampered for many years by what seems a fundamental problem; what exactly defines a nucleus pulposus (NP) cell? The paper by Gilson and colleagues elegantly re-opens the debate concerning the lineage and identity of NP cells that are alike yet different from chondrocytes. As we pursue novel investigations and treatment strategies for degenerative disc disease, how do we isolate these unique cells and what is the role of the primordial notochordal cell that may well linger within the NP far longer and perhaps in a different phenotypic appearance than previously thought? The paper by Gilson and colleagues that is the subject of the present editorial presents compelling data concerning the heterogeneity of the cells of the NP, and their origin, development, maturation and function.

A recent issue of *Arthritis Research and Therapy* contains a report by Gilson and colleagues describing their investigation of the differential cell surface marker expression found in samples of bovine intervertebral disc (IVD) and articular chondrocytes [1]. This report raises interesting questions about the identity of the residents within the nucleus pulposus (NP) and has broad implications with respect to regenerative medicine and tissue engineering of the IVD.

A recent search of PubMed using the search term 'tissue engineering and intervertebral disc' returned 263 hits, with the oldest publication dating to 1989. Although investigators have clearly been interested in developing a biological treatment for degenerative disc disease for

over 30 years, we must be in the early days since we have yet to characterize the ubiquitous NP cell or to really understand the composition of the NP cellular milieu.

The flexible model of cell and tissue classification whereby expression patterns reflect a functional approach rather than strict germ layer derivation suggests that, with respect to the identity of NP cells, there may be more than meets the eye [2].

The notochord derives from all three germ layers as it originates in a blended fashion from primitive ectoderm, sharing mesodermal and endodermal attributes as it develops as an outgrowth from Hensen's node between the ectoderm and endoderm [3]. This co-joined origin is particularly poignant in human and other mammals, as distinct from lower animals, because in higher mammals the developing notochord provides a pathway for migration of ectoderm to endoderm [3]. The presence of vimentin in NP cells suggests that motility may play a role in the development of the NP cellular composition; perhaps including cells that migrate inwards from the vertebral endplates [4]. As Gilson and colleagues have reported, however, the cells occupying the NP may change their appearance over time, masking their original phenotype but perhaps retaining some of their original capacity. Have these cells altered their phenotype as a consequence of maturation or pathological events, or as an adaptive response to life in the disc over time?

The IVD is a hypoxic, isolated, immune-privileged compartment, the cells of which must necessarily be highly specialized in order to survive. Classically it has been thought that once the NP has been formed the notochordal cells disappear, leaving behind the fibrocartilagenous NP cell. But then along come Gilson and colleagues – who find that within adult bovine caudal discs (a tissue compartment formerly thought to be fairly homogeneous) there exists a small percentage of notochordal holdouts that continue to express their notochordal lineage markers. Is it that a small, primordial notochordal cell reservoir may linger longer than was previously thought within the mature NP?

These observations raise a number of questions – notably, is the protection from degenerative disc disease

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seen in species that retain their notochordal cell-rich appearance, such as the nonchondrodystrophic canine and rabbit, due to the differential extracellular matrix synthesized by these cells as compared with the NP cell? [5]. Is it a dose–response issue whereby the discs that are relatively deficient in notochordal cells are therefore lacking in the necessary and sufficient molecules synthesized by these cells that may act upon the NP cell [6,7]? It is thought that the notochordal cell-rich disc NP phenotype confers superior biomechanical properties [5,8]. Do notochordal cell-deficient discs therefore fail to resist the loads imposed by daily life over time due to biomechanical or biochemical reasons – or both? Also, and importantly from the perspective of evaluating putative therapies, which cells are the best to use for *in vitro* assays? Should future NP cell experiments exclude cytokeratin-8⁺ cells or does this matter when evaluating the mechanisms of the IVD NP as an organ?

In terms of the progression of degenerative disc disease, the NP could arguably represent the lynchpin in the degenerative cascade since many investigators consider the NP as the area demonstrating the earliest degenerative changes [9-11]. We may therefore need to look ever closer at the question of what really defines the cells within the disc. Are the current models of events leading to failure of the disc as an organ correct? What role(s) do the cells play within the NP that may mitigate or contribute to the progression of organ failure?

As we look to the future and contemplate cell-based therapeutics for the treatment of degenerative disc disease, one must wonder what might be the most appropriate source of cells. Bone marrow-derived stem cells originate within an entirely different niche to cells that have adapted to survive within the NP with its tenuous nutrient supply and hypoxic environment. Along which lineage should stem cells or progenitor cells therefore be directed in order to potentially repopulate the disc and how would they best be able to restore homeostasis? For now, given that the mature disc nucleus contains holdouts of the primitive notochordal cell,

perhaps the best perspective from which to answer these questions is one where we take a fresh look back at the origin, development and maturation of the IVD.

Abbreviations

IVD, intervertebral disc; NP, nucleus pulposus.

Competing interests

The author declares that he has no competing interests.

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