

The promise of mesenchymal stem cells for intervertebral disc repair

Abstract

The Intervertebral disc (IVD) is a major weight bearing structure which undergoes degenerative changes with ageing limiting its ability to dissipate axial spinal loading in an efficient manner resulting in the generation of low back pain (LBP). LBP is a number one global musculoskeletal disorder with massive socioeconomic impact. The WHO has nominated development of mesenchymal stem cells (MSCs) and bioscaffolds to promote IVD repair as primary research objectives. There is a clear imperative for the development of strategies for the treatment of IVD degeneration and LBP. Early pre-clinical and animal model studies, and preliminary phase I and II clinical trials with MSCs have yielded impressive results in IVD repair. Combinatorial therapeutic approaches encompassing biomaterial and cell-based therapies promise significant breakthroughs in IVD repair in the near future.

Keywords: mesenchymal stem cells, intervertebral disc repair, low back pain, cellular proliferation, matrix production

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Abbreviations: DD, disc degeneration; LBP, low back pain; MMP, matrix metallo protease; TIMP, tissue inhibitor of metallo protease; IVD, inter vertebral disc; NP, nucleus pulposus; WHO, world health organization; DALYs, disability adjusted life years; MSCs, mesenchymal stem cells

Introduction

Disc degeneration (DD) is a major musculoskeletal condition affecting 80% of the general global population.¹ The associated low back pain (LBP) has major socioeconomic impact reviewed in.² In the past 25 years a number of promising biological therapies have been investigated for the treatment of degenerative Disc Disease (DDD) and these have identified many potential molecular targets for biologic intervention.³⁻⁵ These include agents which induce cellular proliferation, matrix production, regulate matrix metallo protease (MMP) and tissue inhibitor of metallo protease (TIMP) production, inflammation, vascular in-growth and cell viability.⁶ The cell density in the IVD is low⁷ and disc cells are exposed to a hostile environment of low oxygen tension, high lactic acid levels, low nutrition and a high hydrostatic pressure leading to cell death and a diminution in cell numbers over time due to cellular senescence,^{8,9} apoptosis^{10,11} and autophagy.^{12,13} The resultant decline in cell number with DD places severe demands on any therapeutic measures to alleviate this condition.

Matricryptins have found application as therapeutic agents in inter vertebral disc (IVD) repair. Hyaluronan oligosaccharides (10-12 mer, HA oligos) stimulate anabolic gene expression, up-regulate MMP-2 and 9 synthesis and activation *in-vitro*. MMP-1, 13, ADAMTS1, ACAN, COL1A1 and COL2A1 gene expression are also up-regulated by HA oligos and annular repair promoted in an annular lesion experimental model of DD.¹⁴ A small link protein derived peptide (DHLSDNYTLHDRAIH), link N has cell proliferative properties and the ability to promote and direct matrix synthesis by the resident disc cells.¹⁵⁻¹⁸ Link N also promotes Mesenchymal stem cell (MSC) proliferation and differentiation and stimulates IVD repair.^{19,20} Peniel

2000, an en-silico developed biglycan peptide with TGF- β 1 inhibitory activity has also been used to treat disc degeneration.²¹

Several natural compounds have displayed potential as therapeutic agents in IVD repair. Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene), a plant phenolic compound found in the skins of grapes, blueberries and raspberries provides beneficial effects in the treatment of DD.^{5,22,23} The lipid lowering medications simvastatin,^{4,24,25} ortovastatin, and lovastatin²⁶⁻²⁸ all display protective effects on the IVD which may be of application in therapeutic repair strategies. Naringin, a grapefruit flavonoid and component of the Chinese medicinal herb *Rhizoma Drynariae* has potent anti-inflammatory and anti-oxidant properties,²⁹ enhances nucleus pulposus (NP) cell proliferation and down-regulates the effects of tumour necrosis factor (TNF)- β on NP cells *in-vitro* and elevates BMP-2, aggrecan and type II collagen protein production.³⁰ Naringin also upregulates ACAN and SOX6 and decreases MMP3 gene expression suggesting that it might be a useful therapeutic agent in the treatment of disc degeneration. Despite their promise as therapeutic agents for IVD repair these molecules have yet to enter the clinic in single or in combination therapies.

A number of studies have used replacement therapy of other connective tissue cells or pluripotent mesenchymal stem cells (MSCs) to treat IVD,³¹⁻³⁴ several reviews have extensively documented this area of repair biology.³⁵⁻³⁸ The mode of action whereby MSCs illicit their therapeutic response *in-situ* however remains elusive. A recent study examined paracrine effects of MSCs isolated from vertebrae in co-cultures with annulus fibrosus (AF) and NP cells.³⁹ MSCs down-regulated the expression of pro-inflammatory cytokine genes in degenerate NP (IL-1 α , IL-1 β , IL-6, and TNF- α) and AF cells (IL-1 α and IL-6). These co-cultures also accumulated more extracellular matrix (ECM) than monocultures. In addition, growth factor mRNA expression was upregulated in MSC co-cultures with disc cells, EGF, IGF-1, OP-1, GDF-7 and TGF- β were all up-regulated in NP cell cultures and IGF-1, OP-1 and GDF-7 in AF cells. This therapeutic effect is in keeping with the use of these growth factors to effect biological repair of degenerate IVDs^{40,41} and also establishes a paracrine mode of

action for MSCs. The Euro DISC clinical trial for the treatment of DD⁴² investigated the transplantation of expanded autologous chondrocytes in patients undergoing single level discectomy. Interim analysis of 28 patients at 24 months showed chondrocyte transplantation produced greater pain reduction and increased IVD fluid content as shown MRI. Percutaneous injection of expanded autologous MSCs in two small non-controlled clinical trials improved MRI T2 signal and clinical improvement.^{43,44} Administration of autologous bone marrow MSCs in two small series of patients with IVDD resulted in clinical improvement in 9 of 10 patients compared to conservative treatment which failed.^{43,44} A phase II clinical trial has been conducted with adult bone marrow MSCs for the treatment of back pain.⁴⁵ A majority of the MSC treated patients achieved minimal levels of residual back pain and other indices of clinical improvement. A multi centre Phase III clinical trial is currently being conducted on the use of MSCs for the treatment of disc degeneration in 25 centres throughout the USA and the findings of these studies are eagerly awaited.

A recent ten-year global study which surveyed 291 major human diseases placed LBP as the number one musculoskeletal disorder.⁴⁶ Approximately 80% of the general populations in Western Societies are affected by LBP and its incidence increases with aging, peaking in the fifth and sixth decade.⁴⁶ In 1998 UK costings for the treatment of LBP were costed at £12.3billion,⁴⁷ in 2001 LBP cost \$9.17 billion in Australia.⁴⁸ In 2006 the American Academy of Pain Medicine published costs for chronic pain in the USA at \$560-635billion/annually, 53% of all chronic pain patients had LBP and 31million people were estimated to suffer from LBP at any one time.^{1,6,49} In 1999 the World Health Organization (WHO) published the IRIS low back pain initiative⁵⁰ which highlighted LBP as a priority area and designated the development of biomaterials for disc replacement and stem cell methodology to restore functional IVDs as high priority research areas.² LBP was also made a national research priority area by the National Health and Medical Research Council (NHMRC) and Australian Institute of Health and Welfare (AIHW) in 2009⁴⁹ but to date have failed to fund any innovative projects designed to alleviate or better understand this condition. This is a major deficiency given the major and ever-increasing impact LBP makes on the Australian community, affects which are mirrored in other global communities.^{48,51} Recent findings of the global burden of disease study 2010 [46] found that of the 289 major human diseases examined, LBP ranked highest in terms of overall disability in terms of disability adjusted life years (DALYs) confirming the impact of LBP on the daily life of all individuals.⁵²⁻⁵⁴

Conclusion

Information presented in this mini review shows that there is a clear need for the development of effective measures for the treatment of DD and LBP. MSCs represent one area of considerable potential in this area of repair biology and it is to be hoped that funding agencies understand the true therapeutic potential of MSCs and support such ventures accordingly.

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Conflict of interest

The author declares no conflict of interest.

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