Potential Applications for Using Stem Cells in Spine Surgery

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Abstract: While the use of biologics as adjuncts for spine surgery is growing annually stem cells have yet to be approved for this clinical application. Stem cells have the unique ability to differentiate into a variety of musculoskeletal tissues including bone or cartilage. Moreover they have been shown to secrete growth factors that promote matrix repair and regeneration and can down regulate inflammation and immune cell functions. It is these combined activities that make stem cells attractive candidates for advancing current techniques in spine surgery and possibly mitigating those pathologies responsible for tissue degeneration and failure thereby minimising the need for surgical intervention at a later date. This review focuses on the characteristics of progenitor cells from different sources and explores their potential as adjuncts for both current and future applications in spine surgery. Where possible we draw on the experimental outcomes from our own preclinical studies using adult mesenchymal progenitor stem cells, as well as related studies by others to support our contention that stem cell based therapies will play a significant role in spine surgery in the future.

Keywords: Stem Cell; Spine Surgery; Mesenchymal Stem Cell; Intervertebral Disc; Spine Fusion.

INTRODUCTION

Spinal surgery is concerned with the bone-cartilage-neural interface. It is a field of surgery that is rapidly changing and evolving; not only with the development of novel techniques, approaches and devices but also with regularly emerging evidence from large clinical trials assessing its indications, efficacy and outcomes. The use of biologics in spine surgery has become widespread and, whilst stem cells are not yet in routine clinical use in spine surgery, it is likely that they will have a significant role in the future.

Stem cell science encompasses a wide range of different multipotential and progenitor cell types. Cells which may have potential application in spine surgery, and broadly classified as stem cells, have the ability to differentiate into tissues such as bone or cartilage and to secrete factors that promote matrix repair and regeneration. Furthermore, laboratory studies have shown that some such stem cells exhibit anti-inflammatory and/or immune modulatory properties. It is these combined characteristics that make stem cells prime candidates for advancing current techniques in spine surgery and for providing new strategies directed at targeting the underlying causes of spinal diseases and disorders.

This review will explore the characteristics of progenitor cells from different sources and focus on their application to both current and potentially future areas of spine surgery. In particular, different stem cell characteristics and results of their use in preclinical experiments will be discussed in relation to their potential for clinical translation in spine surgery. This review will not address spinal cord injury.

STEM CELLS

Stem cells have two essential fundamental characteristics, the ability for self renewal, and the ability to differentiate into a variety of cell phenotypes [1]. Stem cells are loosely categorised as being either adult or embryonic depending on their origin.

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EMBRYONIC STEM CELLS

Human embryonic stem cell (ESC) lines were first derived from the blastocyst inner cell mass by Thomson [2]. Embryonic stem cells have a very strong capacity for self renewal and maintenance of viability in culture as well as the ability to differentiate into all three germ layer lineages; namely mesoderm, endoderm and ectoderm. Thus, they can differentiate into all cell types [3] but the former lineage is most relevant to spine surgery. Significantly, ESCs, by definition, have the potential to form teratomas [3] and there are moral and ethical dilemmas associated with their derivation from embryos [4]. We consider that ESCs will have a limited role in spine surgery in the foreseeable future, but may have a role in treating spinal cord injury [5].

MESENCHYMAL STEM CELLS

Adult or somatic stem cells have been isolated from virtually all tissues in the body [6], however those most relevant to spine surgery are of mesenchymal origin. These cells do not share the same ethical dilemmas as ESCs as they are sourced from a range of tissues which themselves are not capable of embryogenesis. The bone marrow contains both mesenchymal stem cells (MSCs) and haemopoetic stem cells, the later have been used clinically for many years, predominantly in the treatment of haematological malignancy [7]. MSCs, as they are generally now called, are a clonogenic population of cells originally termed fibroblast colony forming unit (CFU-f) [8, 9]. Their discovery is often attributed to Friedenstein in the 1970s yet reports of the osteogenic potential of bone marrow cells can be found from the late nineteenth century [10].

Bone marrow is not the only source of MSCs, as they have also been isolated from a range of tissues including adipose tissue [11], synovium [12], muscle [13] and dental pulp [14]. Mesenchymal stem cells have a more limited ability for differentiation than ESCs [15]. Bone, cartilage, muscle and fat being the predominant end points of MSC differentiation [1], though recent reports have documented neural differentiation [16]. Mesenchymal stem cells have been defined by the International Society of Cellular Therapy by their characteristic plastic adherence, fibroblastic morphology and by cell marker expression of CD105, CD73, CD90 while lacking expression of CD45, CD34, CD14, CD11b, CD79a, CD19, HLA-DR [17].

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Reports comparing stem cells derived from bone marrow with those derived from adipose tissue have found differences in cell marker expression, such as CD49d and CD54 being present only in the latter [18]. Other studies have also documented large variability in marker expression of MSCs [19]. Cell surface marker expression also varies between passages of cells from the same isolate and a significant proportion of cells are quiescent [20]. The very nature of isolating cells by density gradient centrifugation and plastic adherence yields a heterogeneous population of cells even from isolates of the same source [21, 22]. It should be emphasised that the term MSCs refers to a loosely defined population of cells with variable characteristics [23]; the term MSC should be therefore be used with a degree of caution. Moreover there are differences in growth rates and differentiation potentials in cell populations harvested from different sources or by different methods [23, 24]. An example is that the growth factors required for a bone marrow derived MSC to differentiate into cartilage differ from the growth factors required for chondrogenic differentiation of an adipose derived MSC [25, 26]. It has also been shown that chondrogenic differentiation of adipose versus bone marrow derived MSCs occurs along different differentiation pathways [21] which is perhaps a reason why some believe adipose MSCs have an inferior chondrogenic potential compared with bone marrow derive MSCs [19, 27]. Thus, this issue of heterogeneity, in cell characterisation and differentiation, becomes significant if these cells are to be used clinically [28] in spine surgery, particularly in an allogeneic setting.

The fact that MSCs have been isolated from most tissues in the body begs an etymological question as to their origin and purpose. One hypothesis is that MSCs either originated from, or are synonymous with, endothelial progenitor cells lining blood vessels called pericytes and which have a vital role in tissue homeostasis and repair [25, 29]. However, the avascular nucleus pulposus of the intervertebral disc challenges the validity of this theory since it is devoid of blood vessels and thus pericytes, and yet it has been shown to contain so called, progenitor cells [30, 31]. These cells exhibit characteristics similar to MSCs, however small subsets were positive for the haematopoeitc marker CD133. Interestingly, these CD133 positive cells were able to differentiate into bone and cartilage as were their CD133 negative counterparts. Intervertebral disc cells are also unique as they exhibit additional non-MSC characteristics such as the ability for phagocytosis [32], which suggests that the progenitors were laid down during ontogeny and are perhaps remnants from the embryonic origin of the intervertebral disc. Other progenitors cells which exhibit certain embryonic cell characteristics have also been isolated from adult body organs [33].

MESENCHYMAL PROGENITOR CELLS

A population of stromal stem cells isolated from bone marrow [34] and adipose tissue [24] have been designated as Mesenchymal Progenitor Cells (MPCs). These are a purified monoclonal population of cells derived by immunoselection employing beads coupled to STRO-1 Mab (and other antibodies) to capture these precursor stem cells [35]. These MPCs contrast with the typical MSC populations derived using density gradient centrifugation followed by plastic adherence in culture which are a mixed cell population with limited potential for self renewal. The MPC are a richer source of CFU-F, not only with the potential for differentiation into the tissues of the mesenchymal lineage but also are more potent with respect to ability for self-renewal [34]. It is possible that those cells, which demonstrate differential potential within a typical MSC colony, are in fact MSCs.

AMNION EPITHELIAL CELLS

Between the extremes of ESCs on one hand, and adult stem cells on the other are a diverse range of other pluripotent stem cells. These are mainly derived from pregnancy tissue such as the fetus [36], amniotic fluid [37], placenta [38], fetal membrane [39] and umbilical cord [40]. There is great interest in cells from placenta and fetal membrane as, like the MSC and in contra-distinction to the ESC they do not incite ethical dilemmas; being derived from tissue that is usually discarded after birth. They share with ESCs the ability to differentiate into all three lineages but, unlike ESCs, do not form teratomas [39, 41]. There are also MSCs present in afterbirth tissue such as in the chorion and Wharton's jelly [42, 43]. These MSCs, together with the other placental pluripotent cells, also have the advantage of being obtained without the need for an invasive procedure such as bone marrow biopsy required for harvesting bone marrow derived MSCs. Cells of these origins are already used clinically for treating a range of haematological conditions such as malignancy [44].

Our group has an interest in cells derived from the amniotic membrane obtained from term deliveries, which have been termed amnion epithelial cells (AECs). These cells are originally derived from epiblast cells prior to gastrulation which migrate along the walls of the amniotic cavity to form the amnion epithelium [39]. Thus they possess pluripotent characteristics similar to ESCs. Amnion epithelial cells can differentiate down all three lineages [41] and the ability to evade an immune response with allogeneic or xenogeneic transplantation due to minimal MHC class one and two expressivity [45]. Moreover, such cells have been shown to have anti-inflammatory properties [46]. Although, amnion has been used clinically for the treatment of burns and ocular injury [47-49], AECs have not been used clinically in spine surgery. Our group are currently studying their effectiveness in spinal fusion in preclinical trials [50].

OTHER STEM CELLS

Historically, differentiation was thought to be an irreversible unidirectional process such that an MSC was the progeny of an embryonic cell that had differentiated and was now committed to the mesenchymal lineage. This edict, however, has now been discarded since *in vitro* studies have shown that MSCs in culture induced to differentiate into adipocytes, osteoblasts or chondrocytes can be trans-differentiated to an alternate cell type simply by changing the culture media and constituent growth factor conditions [51]. The demise of the unidirectional hypothesis was also confirmed by studies on induced pluripotent stem cells (iPS). These studies demonstrated that fully differentiated somatic cells, such as dermal fibroblasts, could be re-programmed into cells with morphological, antigenic and epigenentic characteristics of an embryonic stem cell with pluripotent potential [52]. Currently, however, there is limited clinical utility of this finding as, like ESCs, iPS cells have the ability to form teratomas and the potential for oncogenesis [33, 52-55]. An alternate approach may be using partially differentiated iPS cells. In a murine model of hindlimb ischaemia iPS-derived MSCs had superior effects compared with bone marrow derived MSCs and no tumour formation was evident at four months [56].

Other adult stem cells that have been recently described include marrow isolated adult multineage inducible stem cells (MIAMI cells) [57], and multi-potent adult progenitor cells (MAPC) [58]. These cells are thought to be a precursor to bone marrow cells including the hematopoetic and mesechnymal stem cells and thus have a differentiative potential compared to classical MSCs [59, 60]. Another progenitor cell, termed Very Small Embryonic-Like Cells (VSEL) have been isolated from a range of tissues [33]. Of great interest is that VSEL cells have been found to be circulating in patients following significant biological insults such as myocardial infraction and stroke [33, 61]. To our knowledge none of these cell types have not been tested in spine surgery.

CLINICAL APPLICATION OF STEM CELLS

Of the cells discussed thus far, we believe the MSC class of cells, and in particular MPCs, due to their well-characterised and

tested monoclonal population, are currently closest of all stem cell types to mainstream clinical use in augmenting spine surgery.

The mode of action by which a stem cell may augment spinal surgery is threefold. Firstly, as already discussed, they possess the ability to differentiate into bone and cartilage, which is an important attribute for fusion surgery and disc regenerative therapies respectively. Secondly, they secrete multiple bioactive factors such as multiple bone morphogenetic proteins (BMPs)[1]. Bone morphogenetic proteins have been used clinically to promote osteogenesis [62, 63] and preserve disc integrity [64]. Thirdly, MSCs possess immune modulatory, anti-inflammatory and anti fibrotic activities. The expression of these effects in-situ would have enormous potential in the treatment of both myelopathy and radiculopathy. This being said, it is highly likely that a multimodal approach may be adopted in the future where two or more cell types with different characteristics and potentials may be used in combination to achieve different effects. An example may be to promoting fusion using the osteogenic properties of cell A together with treating radiculopathy using the anti-inflammatory properties of cell B.

MESENCHYMAL CELL TRANSPLANTATION

Spine surgery has been utilising autologous mesenchymal cell transplantation for many years. Iliac crest autograft is still considered the gold-standard source of bone graft by many as it is a) osteogenic (cells within the graft can directly differentiate into osteogenic cells), b) osteoinductive (factors and cells within the graft can signal endogenous local cells to differentiate into osteogenic cells) and c) osteoconductive (the graft itself can act as a scaffold for bony in-growth) [65]. The bone marrow stroma that is transplanted during these procedures is responsible for its osteoinductive properties presumably due to the presence, albeit in low numbers, of stromal progenitor cells. Despite this, alternatives to autograft have been sought to minimise potential donor site morbidity [66]. Autologous mesenchymal cell transplantation has a similar potential for donor site morbidity, but the bigger issue is that, following harvest, the cells require culture expansion. This introduces cost of individual culture expansion and logistical impediments, as surgery using these cells is delayed by several weeks from the time they are harvested. Furthermore autologous cells are of variable quality depending on the protoplasm of the patient.

Allogeneic cell transplantation overcomes these problems as an 'off the shelf' product with batch to batch consistency and can be used as needed. The potential for transmission of infection and rejection are the obvious concerns of an allogeneic approach. Donor screening and extensive testing of the cells, in a similar manner employed for blood transfusions minimises the infection risk. The rejection risk is minimal as mesenchymal cells are of low immunogenicity. They exhibit low levels of cell surface markers such as the MHC class and lack surface expression of immune co-stimulatory molecules [67]. MSCs also lack the ability to induce an allogeneic Mixed Lymphocyte Reaction (MLR) [68, 69] and secrete multiple anti-inflammatory and immunosuppressive cytokines, e.g. IL-10 [68]. They actively suppress ongoing immune reactions by modulating dendritic cells and preventing monocyte and macrophage differentiation and activation [69, 70]. Allogeneic transplantation of the MSC class of cells is therefore an attractive prospect for spine surgery, with the potential to revolutionise this field.

SPINE SURGERY:

Current Indications

The indications for a spinal operation are invariably pain and/or disability for which conservative measures have been exhausted. Degenerative disease is the most common underlying aetiology but congenital and traumatic conditions also play a causative role.

The most common degenerative conditions are disc herniations and spondylosis, both of which occur predominantly in the cervical and lumbar spine [71]. Both of these conditions usually manifest clinically as they cause neural compression. This may be central compression, which affects the spinal cord in the cervical region or the cauda equina in the lumbar region and/or nerve root compression. Nerve root compression generates radicular pain and may be associated with other features including weakness and sensory disturbance, collectively termed radiculopathy. The term compression, which is often used to describe the cause of radiculopathy, implies a mechanical aetiology, however, it is well accepted that a chemical or inflammatory component plays an important role in nerve root irritation and hence the causation of radiculopathy [72, 73].

The pain caused by gradual compression of the cauda equina is termed neurogenic claudication. This is a dynamic phenomenon of pain on walking or standing that is relieved by flexion [74]. Compression of the spinal cord in the cervical region causes cervical myelopathy which, unlike in the lumbar region, may not produce pain at all [75]. Cervical myelopathy causes progressive neurological symptoms such as disturbance of gait or hand dexterity [76] which are the most devastating sequelae of degenerative disc disease [77].

Pain frequently occurs without neural compression as the degenerate disc may itself be a pain generator causing what has been termed 'discogenic pain' [78, 79]. Discogenic pain is more difficult to diagnose than radicular pain as the imaging features of an ageing compared with a degenerate or painful disc are often indistinguishable [79-82]. Facet arthropathy, deformity and segmental instability arising from congenital or traumatic causes may also precipitate pain either themselves or through neural compression. Back pain may also arise from other extra axial sources arising from dysfunction in other joints such as the hip [83].

Surgery to the spine generally aims to fulfil one or more of the following goals: neural decompression, stabilisation or restoration of the deformity and removal of the pain generator. A summary of the current surgical approaches and where we believe stem cells may augment these approaches or ob*via*te the need for surgery are shown in Fig. (**1**).

LUMBAR VERSUS CERVICAL

The operative treatment of discopathies in the cervical and lumbar spine is significantly different and this impacts on the choice of stem cell to be used for each region. Whilst there is some controversy regarding the surgical approach [84] and the amount of disc to be removed [85], a subtotal discectomy *via* a posterior approach is the most commonly employed technique for a lumbar disc herniation [85, 86] Fig. (**2**), whereas the majority of spine surgeons would perform a total discectomy *via* an anterior approach for treatment of cervical radiculopathy and this is often followed by interbody fusion, hence anterior cervical discectomy and fusion (ACDF) [87-89] (Fig. **3**). This distinction is largely due to anatomical differences and, although surgery always aims to minimise neural retraction, the spinal cord has much less tolerance to retraction in the cervical region compared with retraction of the nerve roots in the lumbar region; consequently the posterior approach in the lumbar region which invariably requires a degree of neural retraction. A subtotal lumbar discectomy in the current era is typically performed with operative magnification hence the term lumbar microdiscectomy, which will be discussed later [90]. Total discectomy and interbody fusion in the lumbar spine is reserved for patients with instability or deformity and most commonly for patients suffering chronic axial low back pain [91, 92] as the discectomy removes the pain generator [93]. This may be approached through an anterior lumbar interbody fusion (ALIF), posterior lumbar interbody fusion (PLIF), transforminal lumbar interbody fusion (TLIF) or extreme

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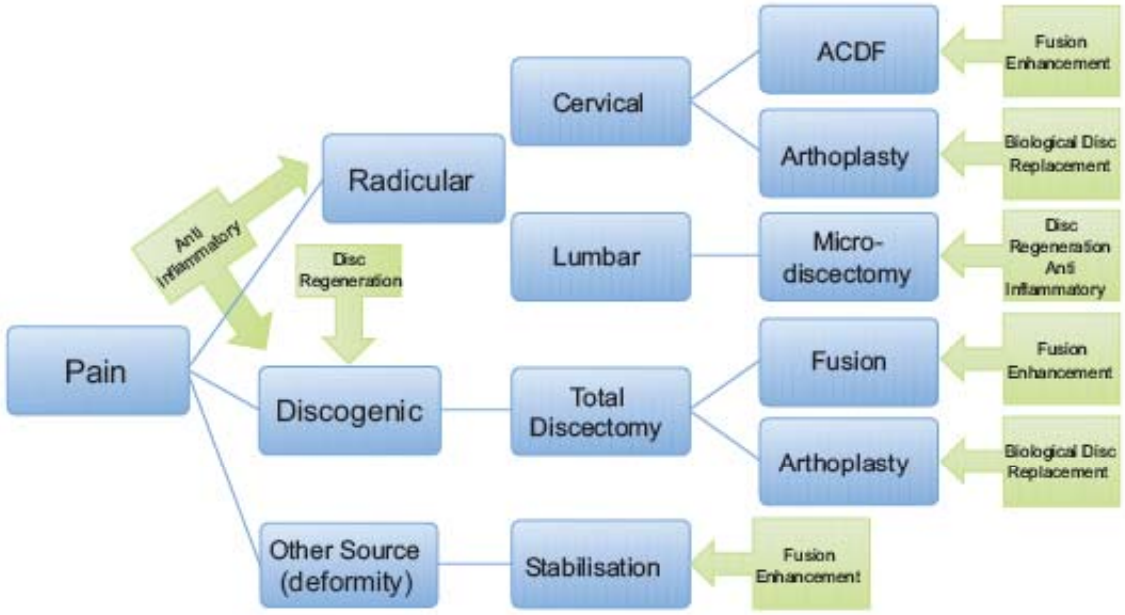

Fig. (1). Schema of current surgical indications and operations (blue boxes) and potential roles for stem cell based therapies (green boxes with arrows).

lateral interbody fusion (XLIF). There is strong evidence supporting surgery [92] for refractory back pain in carefully selected patients [91, 94].

INTERBODY FUSION

Following total discectomy the void in the interbody space needs to be stabilised. The current options include prosthetic disc arthoplasty or fusion. In the cervical region there are some who advocate discectomy alone [95-99] which usually results in fusion anyway but has the disadvatage of reducing foraminal height [98]. Systematic literature reviews have failed to identify the best approach from published trials [87, 100], and therefore an ongoing prospective trial is underway that aims to answer this question [101].

Disc replacement with a new tissue engineered disc, using stem cells, is certainly the Holy Grail in terms of future therapies and would likely provide the best option for occupation of the interbody space following discectomy. This being said, it is likely that for certain indications, such as in severe traumatic injuries, such treatment may not be feasible and spinal fusion will therefore likely always remain part of the surgical armamentarium. Regenerative therapies using stem cells may also not be possible in patients who have severe disc degeneration, in whom the aetiological factors such as nutritional impairment to the disc persist, such as is the case with severe calcification of the endplates [102]. The use of stem cells in such an interbody space would be futile as this is an extremely hostile environment, and without adequate nutrition they would not survive [103]. Fusion therefore, may be the only option for this group of patients.

There are various graft options currently available for both cervical and lumbar fusion surgery. Tricortical autograft bone, usually from the iliac crest was the first interbody implant used, achieving high fusion rates, for the reasons discussed above. Significant problems with autograft can occur; including donor site residual pain, infection and cosmetic problems [66]. Allograft of cadaver bone is therefore used to avoid donor site morbidity although with an inferior fusion rate compared with autograft [104]. Allograft has potential problems of its own including rejection, resorption, infection and logistic issues [105]. Alternative synthetic interbody products such as interbody cages (Fig. **3**) filled with bone substitutes such as tricalcium phosphate are widely available producing successful fusion without donor site morbidity [106, 107]. These bone substitutes are osteoconductive *per se* meaning they provide a matrix into which local cells including endogenous mesenchymal stem cells, blood borne cells and osteoblasts can integrate and produce bone. These substitutes lack the osteoinductive ability that autografts have to a small extent due to the presence of bone marrow stromal cells in the graft.

There has long been a need for factors that could be used to increase fusion rates in spinal surgery. This is particularly so for lumbar surgery and for ALIF where fusion rates are lower. The situation is exacerbated in patients with comorbidities such as rheumatoid arthritis [108], smoking [109, 110] or patients on anti-inflammatory medications [111] which can independently decrease fusion rates. Recombinant bone morphogenetic protein-2 (BMP-2) and recombinant BMP-7 have been widely used in a range of spinal and other orthopaedic surgeries as osteoinductive agents to promote fusion [112-115]. There are, however, reports of adverse effects of their use in the cervical spine where ectopic bone formation and soft tissue swelling have been reported [116, 117]. Recently, the Food and Drug Administration (FDA) issued a warning advising that rhBMP should only be used in an approved clinical trial in the cervical spine [104, 118].

A recent preclinical study by our group designed to assess the safety and efficacy of MPC facilitated cervical interbody fusion [119] showed no cell related adverse events, including absence of swelling, airway compromise or neural compression [120]. MPCs were added to a commercially available tricalcium phosphate and hydrodxyapetite carrier and were demonstrated to promote a faster and more robust fusion than current clinical treatments using autograft or carrier alone [120-122]. Biologically there is an interplay between the 14 naturally occurring BMPs involved in osteogenesis [123] and MPCs have been shown to secrete many of these growth factors[2]. This paracrine effect of MPCs, in addition to a direct effect of osteogenic differentiation at the fusion site, could account for the beneficial effects mediated by these cells in our animal model [120]. These observations support our contention that stem cells, such as MPCs, are likely to play an important role in fusion surgery

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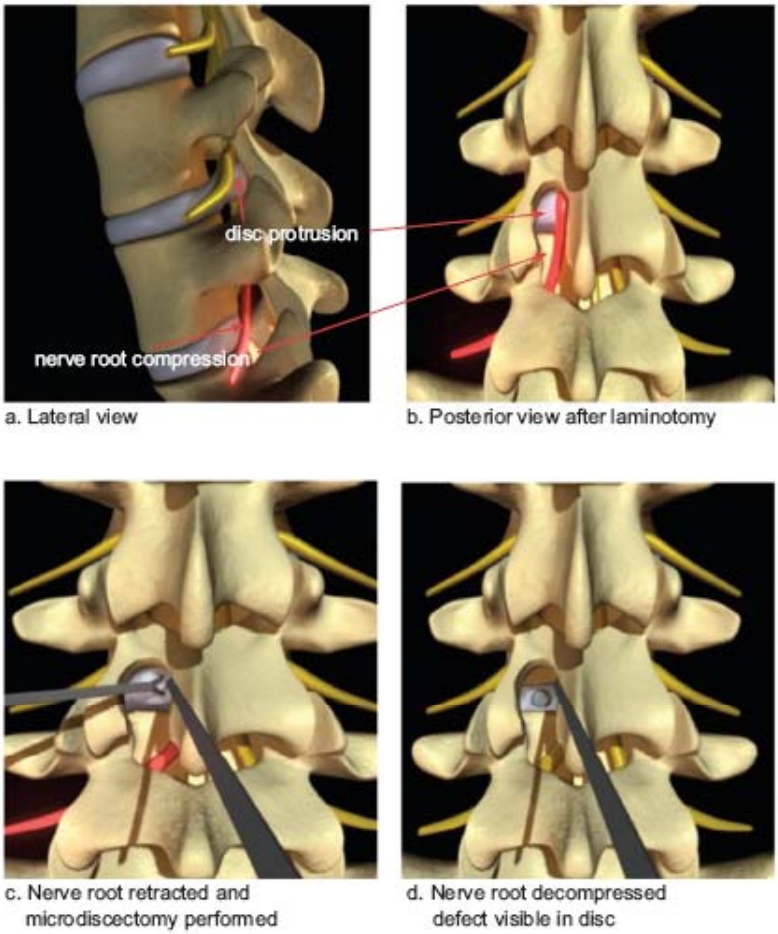

Fig. (2). Lumbar disc pathology.

in the future, particularly in the cervical spine where there is currently no satisfactory alternative. Clinical trials to assess the safety and efficacy of MPCs for cervical and lumbar interbody fusion are presently underway [124, 125].

POSTEROLATERAL LUMBAR FUSION

A lumbar interbody fusion, when performed from the posterior or transforaminal approach, is invariably accompanied with posterolateral-instrumented fusion. This is a bony fusion in the posterolateral gutters, typically undertaken in conjunction with instrumentation such as a screw-rod construct inserted trans-pedicularly. A posterolateral fusion may also be performed without an inter-body fusion for trauma or deformity correction such as in cases of scoliosis or spondylolisthesis. Bone grafts, graft substitutes and osteoinductive agents are used widely posterolaterally in the lumbar spine [126, 127]. The graft volume required in posterolateral fusion is substantially larger than the volume required for interbody fusion and the distance for bony bridging to achieve fusion is also larger. Mixed results have been reported using BMPs in posterolateral fusion [63, 128, 129], however, the limited number of clinical trials undertaken to assess the efficacy of MSCs and MPCs for posterolateral lumbar fusion have shown promising outcomes to date [130, 131].

MICRODISCECTOMY

Lumbar microdiscectomy involves partial discectomy or removal of the offending disc fragment from the peri-discal space [85, 132]. In this procedure the majority of the disc remains in place after surgery since at the onset of the disc herniation it is generally part of the nucleus pulposus and some annular fragments that are sequestered extradiscally [133]. Whilst microdiscectomy normally resolves the patient's pain in the short-term there is nevertheless a significant incidence of recurrent disc prolapse or discogenic back pain arising from the damaged disc structure, which does not undergo spontaneous healing [134-136].

The long-term problems associated with microdiscectomy, together with a more conservative approach to spinal surgery in recent years, has stimulated increased interest and research into methods that might be harnessed to promote the repair and regeneration of the injured disc. Mesenchymal stem cells have played and will continue to play a pivotal role in these endeavours.

Cells from the annulus fibrosis [137] (AF) and nucleus pulposus [138] (NP) have been isolated from explanted discs and cultured both *in vitro* [139, 140] and *in vivo* [141] within a variety of scaffolds. Stimulation in the form of growth factors or mechanical strain [142] have been tested for their ability to facilitate cell proliferation and even cells from severely degenerated discs showed some positive response in culture [143, 144]. Other experiments have resulted in differentiated disc like cells from MSCs [145] or from co-cultures of MSCs with disc cells [146]. These reports demonstrate that, even in the diseased state, AF and NP cells retain the ability to be activated and that regeneration of extracellular matrix constituents is possible. Moreover, MSCs have been co-cultured with whole disc tissue explants, rather than with isolated cells and this produces functional disc-like cells and extracellular matrix [147].

The Eurodisc study specifically investigated regenerating the disc following microdicectomy in a clinical trial [148-150]. It

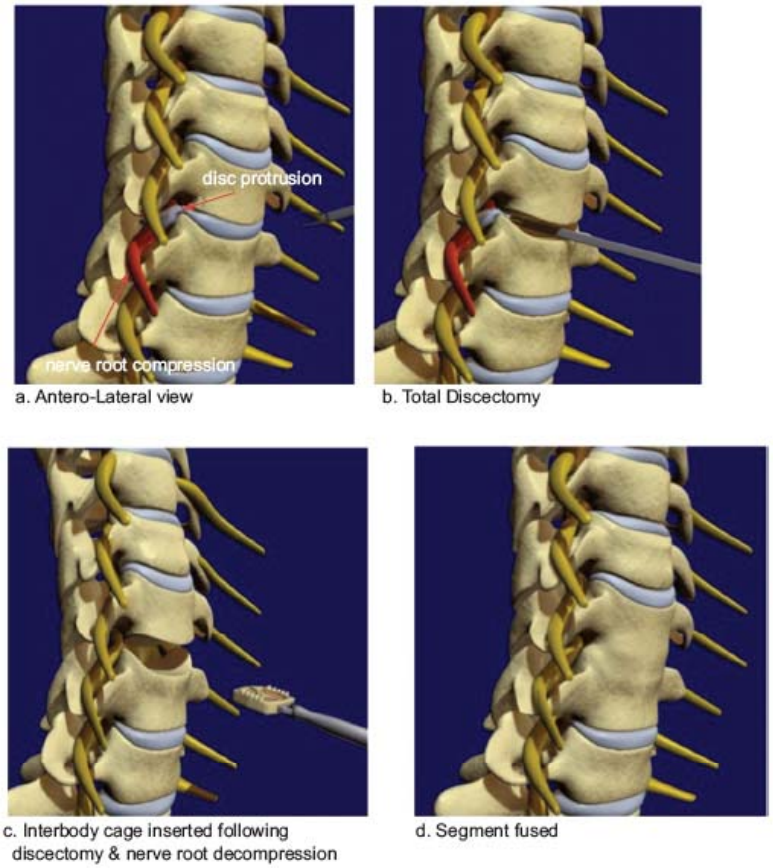

Fig. (3). Cervical disc pathology.

showed a decrease in back pain using autologous chondrocyte harvested during microdiscectomy and later transplanted following expansion. The limitation of this technique is the need for culture expansion of explanted cells and their injection into the damaged disc as an additional procedure. An alternative approach aimed at injection of regenerative stem cells into the disc during a microdiscectomy procedure would be beneficial and preferable to an approach requiring metachranous procedures. Preclinical studies using autologous adipose derived mesenchymal cells [151] or allogeneic MPCs [152] have demonstrated the regenerative potential of this approach but the former required an additional harvesting procedure pre-microdiscectomy highlighting the potential advantage of using allogeneic MPC for such therapies.

DISC ARTHOPLASTY

Whilst the success rate of surgically relieving discogenic pain is high in the correctly selected patient, discectomy (or removal of the 'pain generator') and fusion of this segment may exacerbate degeneration at adjacent levels, a problem known as adjacent segment disease [153]. Motion preservation techniques or disc arthroplasty using a variety of implantable devices are already used in selected patients in an attempt to reduce the incidence of adjacent segment disease. Whether there is a long term benefit of disc arthoplasty presently remain unclear [101, 154-158]. Although lumbar disc arthoplasty has perhaps more supportive evidence than cervical, in general, longer term studies are needed. Nevertheless, disc arthoplasty prostheses are expensive and non-biological. The capacity to insert a new tissue engineered disc following discectomy, if this were possible, could provide a superior approach to the use of existing fusion or prosthetic procedures.

Despite all the recent progress in the use of tissue engineering in surgical spinal disc repair, the ability to tissue engineer a new disc is still some way off, in particular, engineering a biomimetic annulus fibrosis presents the greatest challenge [77]. An alternate approach that has been used is allograft disc transplantation [159]. In one report cervical discs together with the endplates and uncovertebral joints were removed from donors and frozen and then subsequently transplanted into patients. In this series of five patients with a five-year follow up, there was radiological evidence of fusion over the transplanted disc space in some cases [159]. As no explants of the transplanted discs were available, disc analysis could not be performed, but it is possible that a fibrous non-union was achieved over the interbody space [159]. The authors themselves conceded that there was no way of establishing whether the annulus and nucleus cells in the transplanted discs survived the transplantation [159]. Motion preservation however was maintained to some extent in all patients and there was no evidence of adjacent segment disease in the interim results reported.

The use of stem cells together with an appropriate chondrogenic stimulus and an appropriate bio-scaffold to replace a damage or degenerated disc could be implanted to provide a fibrous or cartilaginous joint similar to that achieved in the transplantation study above. The tissue generated by such a procedure would not, of course, reproduce the complex integrated matrix of the disc but could provide a cartilaginous structure, which would provide articulation of the adjacent vertebral bodies to achieve similar results. Our group is currently exploring such an approach *in vivo* [160, 161].

PAIN AND INFLAMMATION

Pain is the most common underlying reason and presenting feature for spine surgery and the goal of the above mentioned procedures is to alleviate pain through neural decompression or re-

moval of the pain generator [162]. Since inflammation is a causative factor of this pain [72, 73], the anti-inflammatory properties of MSCs have the potential to directly reduce pain in addition to their other applications in the surgical procedure. MSCs act through various anti-inflammatory mechanisms. They do not induce an allogeneic Mixed Lymphocyte Reaction (MLR) [45, 68, 69], they secrete multiple anti-inflammatory and immunosuppressive cytokines, such as interleukin-10 [68] and they actively suppress ongoing immune reactions by modulating dendritic cells and preventing monocyte and macrophage differentiation and activation [69, 70].

FUTURE TREATMENTS

The biologic approaches discussed in this review using stem cells, if successful, would provide alternative options and improvements to current techniques used in spinal surgery. Moreover, we consider that the use of stem cell to treat spinal disorders offer a far more exciting and diverse role than do growth factors which have short half-lives and can induce untoward effects in sites adjacent to their application. Stem cells offer the opportunity to treat the pathological defects at an earlier time point than is currently possible, halting or reversing further degeneration consequently obviating the need for surgery all together. In this respect, our own research has generated histological and biochemical evidence of tissue regeneration, with corollary imaging improvement, following injection of stem cells into degenerative lumbar discs in an ovine model [163]. Others too have provided *in vivo* evidence of disc regeneration using stem cells in other models [151].

These promising experimental studies in laboratory animals are still in the process of translation to human clinical trials. The major clinical challenge will be the ability to diagnose the 'pain generator' in the patient presenting with back pain. Notwithstanding the use of multiple modalities [164], including clinical examination, imaging (usually MRI) and discography [165, 166], distinguishing the ageing versus the degenerate disc is still difficult [80, 167]. The pain can arise from a source other than the disc [83] and, if it is from the disc, its causation may be from pathological in-growth of nerve fibres [78, 168], which is not something that was specifically tested in the disc regeneration animal models. The known anti-inflammatory/immunosuppressive effects of some stem cells are likely to have a positive effect in spinal application and although there is evidence in animals of pathological ingrowth of nerve fibres [163], the true analgesic effect of stem cell therapy can only be truly tested in human clinical trials.

CONCLUSION

In summary, stem cell science holds much promise in complimenting, improving and augmenting current techniques in spinal surgery. However, cell based treatments which intervene and attenuate discopathies and radiculopathies at an earlier time point, providing regenerative and anti-inflammatory treatments could potentially minimize the need of invasive surgery altogether in a select patient population. Research and innovations in the areas of imaging and diagnosis along side of regenerative medicine using stem cells and appropriate biomatrices are essential if progress is to be made in this important field of spinal surgery.

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