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Prospects of cell replacement therapy for the treatment of degenerative cervical myelopathy

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Abstract: Degenerative cervical myelopathy (DCM) presents insidiously during middle-age with deterioration in neurological function. It accounts for the most common cause of non-traumatic spinal cord injury in developed countries and disease prevalence is expected to rise with the aging population. Whilst surgery can prevent further deterioration, biological therapies may be required to restore neurological function in advanced disease. Cell replacement therapy has been inordinately focused on treatment of traumatic spinal cord injury yet holds immense promise in DCM. We build upon this thesis by reviewing the pathophysiology of DCM as revealed by cadaveric and molecular studies. Loss of oligodendrocytes and neurons occurs via apoptosis. The tissue microenvironment in DCM prior to end-stage disease is distinct from that following acute trauma, and in many ways more favourable to receiving exogenous cells. We highlight clinical considerations for cell replacement in DCM such as selection of cell type, timing and method of delivery, as well as biological treatment adjuncts. Critically, disease models often fail to mimic features of human pathology. We discuss directions for translational research towards clinical application.

Keywords: cell therapy; cervical myelopathy; gliosis; inflammation; ischemia; regenerative medicine; remyelination.

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Introduction: current status in the management of degenerative cervical myelopathy (DCM)

An increase in disease prevalence amongst the aging population

Degenerative cervical myelopathy (DCM) represents the most common cause of spinal cord impairment in the middle-aged and elderly (Nouri et al. 2015). Disease prevalence is estimated to be as high as 5% in people over the age of 40(The Lancet 2019). In reviewing the global epidemiology of non-traumatic spinal cord injury, DCM accounts for 54% of cases in the United States, 59% in Japan, and 41% in Israel (New et al. 2014). Strikingly, cross-sectional studies have demonstrated the presence of radiological cervical cord compression in over 30% of patients by the fifth decade, representing the proportion of patients at risk of developing symptoms. The prevalence of both asymptomatic cord compression as well as patients presenting with neurological impairment is projected to rise with the aging population (Davies et al. 2018).

Delayed diagnosis contributes to disease morbidity

Clarke and Robinson described in 1950s that most patients with DCM progressed in a step-wise manner with stable intervening periods, whilst others demonstrated a slow and steady decline. This observation has withstood the test of time (Paul et al. 2009b). Neurological deterioration classically occurs over years to decades, with patients complaining of increasing motor, sensory and sphincter disturbances (Badhiwala et al. 2020). In 20–62% of patients, Japanese Orthopaedic Association (JOA) functional scores decreased by at least 1 point in the 3–6 years after diagnosis (Karadimas et al. 2015a). Similarly, the proportion of symptomatic patients requiring surgical decompression increased over time. Diagnosis of DCM is often delayed because of the overlap of symptoms and signs with other neurological disorders, as well as a low awareness of disease amongst primary care physicians

(Behrbalk et al. 2013). This presents a clinical dilemma as delayed decompression is associated with limited functional improvement (The Lancet 2019). Conservative management is indicated when there are mild symptoms, but has limited efficacy in advanced disease.

Neurological recovery remains incomplete following surgical decompression in advanced disease

Following surgical decompression of the cervical spine in patients suffering from DCM, improvement in upper limb function is demonstrable in 65% of patients, followed by improved lower limb function in 44% of patients, whilst less than 20% reported improvement in sphincter function (Cheung et al. 2008). Increasing patient age, duration of symptoms, severity of cord compression and radiological evidence of cord atrophy have all been correlated with poorer outcomes subsequent to surgery (Kohno et al. 1997). In view of this, the primary objective of surgical decompression is to prevent further neurological deterioration. Although early diagnosis amongst patients suffering from DCM by raising awareness amongst the public and health care professionals will undoubtedly be of benefit, it is important to understand why the chronically compressed cord fails to fully recover, and occasionally deteriorates subsequent to decompression. Research on DCM (Figure 1) has been focused on surgical management (Mowforth et al. 2019). As the disease burden from late presenters with significant compression increases, a thorough understanding of the underlying pathophysiology is required to direct research initiatives on novel treatment modalities. Surgical decompression has the capacity to attenuate further injury to the cervical spinal cord, yet

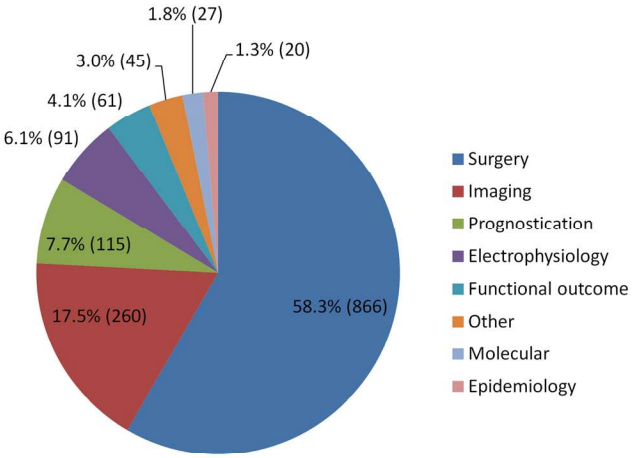

Figure 1: Research theme for published studies on DCM, 1995–2015. Adapted from data published by Mowforth et al. (2019).

biological means of promoting regeneration should be sought. Individual pathological aspects of DCM relating to cell loss and the altered tissue microenvironment are subsequently reviewed in depth, with an emphasis on their translational implications for cell replacement therapy. We shall see how cell transplantation is a logical treatment approach that possesses significant unchartered potential.

Pathophysiology of DCM: the case for cell replacement therapy and biological adjuncts

Mechanical compression

The underlying pathophysiology of DCM is multifactorial, yet from a biomechanical standpoint the instigator to neurological dysfunction is chronic compression of the cervical spinal cord. It has long been recognized that the diameter of the spinal cord, bony canal, and subarachnoid space were associated with the onset of myelopathic symptoms (Bohlman and Emery 1988). All structures potentially encroaching into the spinal canal can cause compression, and include protruding intervertebral discs, degenerative uncovertebral joints, hypertrophied facet joints and ligamentum flavum, as well as an ossified posterior longitudinal ligament (Badhiwala et al. 2020). There is an additional dynamic aspect to compression as soft tissue and bony instability can result in further impingement upon neck movement (Nouri et al. 2015). Nevertheless, disease severity demonstrates poor correlation with the degree of mechanical compression alone. Cadaveric samples have been particularly revealing of clinicopathological correlates whilst recent basic research has elucidated molecular mechanisms of disease contributing to neurological decline.

Loss of tissue substance

DCM is histopathologically distinct from acute traumatic cord injury

Subsequent to acute traumatic spinal cord injury, the primary mechanical insult results in loss of neurons and glia via necrosis within minutes to hours of injury (Rust and Kaiser 2017). Secondary injury over the lesion site is caused by breakdown of the blood brain barrier and a cytotoxic neuroinflammatory response. Over time, a non-neural lesion

core abundant in microglia and macrophages is established and surrounded by a reactive astrocytic scar (O'Shea et al. 2017). In DCM, neurological decline is gradual with clinical features and cord pathology distinct from that following acute traumatic injury (Table 1). Loss of cord substance following chronic compression results from Fas-mediated apoptosis of neurons and glia, and is accompanied by progressive demyelination (Yu et al. 2011). Cell necrosis and reactive gliosis are minimal until late disease (Ogino et al. 1983), and the extent of disruption to the blood brain barrier (BBB) also increases with clinical severity (Blume et al. 2020). Changes to cord vasculature limit perfusion as well as regeneration, and contribute towards reperfusion injury following surgical decompression (Vidal et al. 2017). A schematic overview of the histological changes in DCM as compared to traumatic spinal cord injury is illustrated in Figure 2.

Neuronal apoptosis and loss of axonal tracts

Macroscopically, chronic compression results in significant atrophy of the cervical cord. In considering individual spinal tracts, the lateral white columns are sensitive to

Table 1: Comparison of clinical and histopathological features in patients with degenerative cervical myelopathy and traumatic spinal cord injury.

(A) Clinical features.

	Degenerative cervical myelopathy	Traumatic spinal cord injury
Age at presentation	Middle-aged/Elderly	Young adults most commonly affected
History of injury	None	Traumatic episode
Onset	Insidious	Sudden
Neurological deficit	Patients have motor, sensory, or sphincter-related complaints but are usually ambulatory and functionally independent until late disease	Variable; usually more severe than DCM and patients may be paraplegic or quadriplegic
Progression	Gradual neurological decline over years	Sudden loss of neurological function subsequent to acute injury
Recovery potential	Variable, but patients do have a potential to improve after timely surgical decompression	Limited; patients with complete cord injury fare the worst
Current standard of care	Observation if clinically asymptomatic, surgical decompression upon significant neurological impairment/decline	Surgical decompression and stabilization Maintenance of spinal cord perfusion Supportive medical management of associated complications Multidisciplinary rehabilitation

(B) Histopathological features.

Degenerative cervical myelopathy	Traumatic spinal cord injury
Mild to moderate compression	Acute phase (hours to days)
– Localized gray matter atrophy and neuronal loss (anterior horn, intermediate zone)	– Haemorrhage – Edema
– Demyelination of lateral corticospinal tracts	– Inflammation (neutrophil infiltration)
– Small cystic cavities	– Neuronal necrosis – Oligodendrocyte necrosis/apoptosis – Demyelination
Severe compression (< 20% AP compression ratio)	Intermediate phase (days to weeks)
– Diffuse gray matter atrophy and neuronal loss	– Inflammation (microglia activation)
– Demyelination of posterior column	– Astrocyte activation
	Late disease (weeks to months)
– Necrosis	– Wallerian degeneration
– Neuroinflammation	– Central cystic cavitation
– Reactive gliosis	– Fibroblast scar
– Central cystic cavitation	– Glial scar

Summarized from findings published by Ogino et al. (1983), Ito et al. (1996), Yu et al. (2011) and Blume et al. (2020).

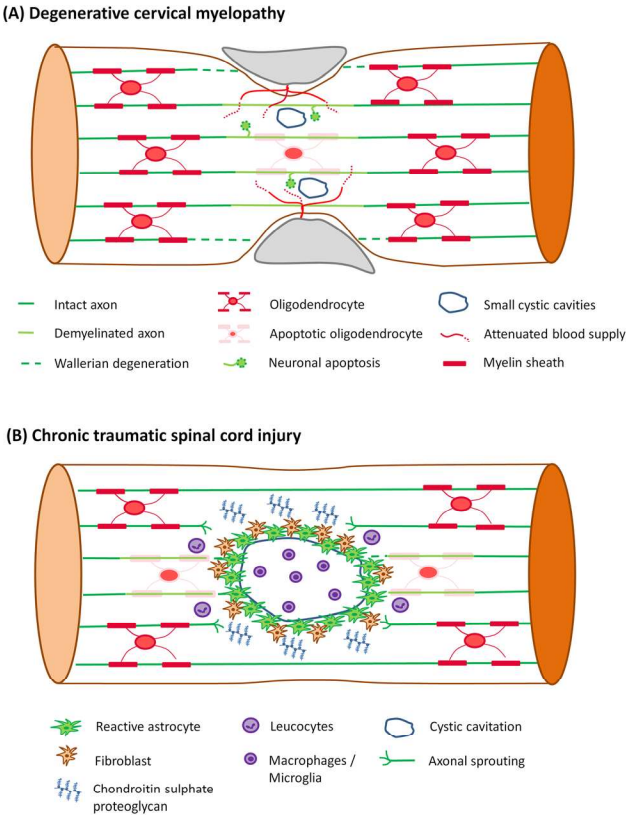

Figure 2: Schematic illustration on the barriers to regeneration in degenerative cervical myelopathy and chronic traumatic spinal cord injury.
In degenerative cervical myelopathy (A), the compressed cord is atrophic and tapered. Oligodendendrocyte apoptosis results in demyelination, and is accompanied by axonal degeneration. There is minimal reactive gliosis and inflammatory cellular infiltrate until end-stage disease. (B) In chronic spinal cord injury, the lesion core contains a fluid-filled cystic cavity rich in activated microglia and macrophages. This is bordered by reactive astrocytes forming a glial scar, as well as fibroblasts. Reactive astrocytes secrete chondroitin sulphate proteoglycans (CSPGs) into the extracellular matrix, which inhibit axonal regeneration.

minor compression as evidenced by localized demyelination. Anterior horn cells and intermediate gray matter are affected as compression increases, resulting in neuronal loss (Ogino et al. 1983). The posterior white column is spared until late disease upon significant canal narrowing (Ito et al. 1996). This provides the pathophysiological basis for progression in clinical symptoms and signs as impaired balance and proprioception occurs in late disease (Dhillon et al. 2016). The loss of neurons and axonal fibres is largely irreversible and persists subsequent to decompression (Someya et al. 2011).

As *de novo* neurogenesis is limited in the adult spinal cord (Martínez-Cerdeño and Noctor 2018), neurological improvement subsequent to timely surgical decompression results from other means. Dormant spinal interneurons within gray matter may be activated to form relays circuits (Chen et al. 2018). Such circuitry reorganization in DCM is evidenced by increased synaptic marker expression within the spinal cord subsequent to decompression (Dhillon et al. 2016) as well as reweighting of proprioceptive, visual, and vestibular inputs (Lin et al. 2019) for postural control. Over the higher centres, expansion of motor cortical representation occurs in DCM (Green et al. 2015), and upon decompression there is further reorganization resulting in increased recruitment of supplementary motor areas during task performance (Bhagavatula et al. 2016). Despite these compensatory mechanisms, motor and sensory deficits often persist despite surgery. The absolute reduction in cell numbers beyond a "point of no return" likely limits the extent of recovery despite evidence of neuroplasticity at multiple anatomical levels.

Oligodendrocyte apoptosis and demyelination

Oligodendrocytes form myelin sheathes to accelerate nerve conduction, and are also metabolically coupled with neurons to maintain homeostasis (Philips and Rothstein 2017). Cadaveric specimens of patients suffering from DCM demonstrate reduced numbers of oligodendrocytes, a reduction in myelin thickness, and evidence of remyelination (Fujiwara et al. 1988). Loss of oligodendrocytes is predominantly mediated by apoptosis (Yamaura et al. 2002) as opposed to necrosis following traumatic injury (Gaudet and Fonken 2018).

Remyelination is a dynamic physiological process that persists in the adult CNS yet declines in middle age (Sampaio-Baptista and Johansen-Berg 2017). In response to injury, oligodendrocyte precursor cells (OPCs) switch on a repair programme and contribute to recovery by proliferating, migrating to demyelinated regions, and remyelinating denuded axons (Totoiu and Keirstead 2005). Insufficient numbers of endogenous OPCs as well as failed recruitment contribute to remyelination failure (Franklin and Goldman 2015). Potential treatment strategies in DCM thus include enhancing OPC proliferation, recruitment, and remyelination, as well as transplantation of exogenous glia (Duncan et al. 2020).

Changes in the spinal cord microenvironment

Local ischaemia as a hurdle to regeneration

Extrinsic arterial supply to the spinal cord is derived from the anterior spinal artery located over the ventral midline, and paired posterior spinal arteries located just medial to the dorsal roots (Sliwa and Maclean 1992). These form a vascular ring upon the cord surface and give rise to feeding vessels penetrating into the cord interior, the largest of which is the central artery located over the anterior median fissure. Dynamically, cervical flexion causes mechanical distortion of extrinsic spinal arteries (Breig et al. 1966). Furthermore, persistent extrinsic compression of spinal arteries was sufficient to induce histological changes (Ito et al. 1996) and clinical signs (Hukuda and Wilson 1972) compatible with long-standing cervical myelopathy. Cadaveric specimens in elderly patients diagnosed with DCM demonstrate abnormal vessels (Someya et al. 2011). The anterior spinal artery is most commonly affected by arteriosclerotic changes, which are well correlated with aging, hypertension, and coronary/cerebral atheromatosis (Jellinger 1967). Adequate perfusion is critical for regeneration, as both neurons and oligodendrocytes are hypersensitive to hypoxic-ischemic damage (Petito et al. 1998).

Surgical decompression improves spinal cord perfusion and cellular metabolism (Dhillon et al. 2016). Nevertheless pathological changes to cord vasculature persist in spite of mechanical decompression (Someya et al. 2011). Additionally, reperfusion injury subsequent to decompression has been demonstrated in animal models to initiate a cytotoxic inflammatory response as well as reactive gliosis (Vidal et al. 2017). When considering the local and systemic vascular status of a typical middle-aged surgical candidate suffering from DCM, means of promoting neovascularization of the cord as well as to protect against reperfusion injury may be essential (Karadimas et al. 2015b).

Reduced inflammation and neurotoxicity in comparison to traumatic injury

Inflammation is understood to be a significant contributor to secondary injury following acute spinal cord trauma (Beattie and Manley 2011). Release of damage-associated molecular proteins (DAMPs) as well as upregulation in cytokines activate resident microglia to participate in phagocytosis and to orchestrate a massive inflammatory response (Gaudet and Fonken 2018). Breakdown of the blood brain barrier increases infiltration of peripheral monocyte-derived macrophages (Didangelos et al. 2014). Over time, polarization of activated macrophage to the cytotoxic M1 phenotype predominates, which inhibits endogenous repair processes as well as the capacity to receive transplanted cells (Allison and Ditor 2015). In the context of traumatic spinal cord injury, therapeutic strategies must be targeted to attenuate this destructive inflammatory response (O'Shea et al. 2017).

In DCM, physical encroachment increases gradually over years and cell loss is predominantly mediated via apoptosis (Hirai et al. 2013). Infiltration of microglia and macrophages into the cord epicenter in post-mortem studies performed shortly after decompression for DCM represents evidence of neuroinflammation (Yu et al. 2011), but a caveat is that this may have been consequent to surgical manipulation, reperfusion injury, and a systemic inflammatory response preceding the patients' demise. In contrast, only a limited number of inflammatory cells are present upon cadaveric specimens of patients suffering from DCM and managed conservatively (Ito et al. 1996), and when several years have elapsed since surgery (Someya et al. 2011). More recently, FDG-MRI imaging has classified patients pre-operatively along a metabolic spectrum attributable to a compression-induced inflammatory response (Floeth et al. 2013). Patients with "type 1" myelopathy demonstrate hypermetabolism and exhibit significant recovery following surgical decompression. Those with "type 2" myelopathy do not have metabolically active cords, and surgery leads to minimal improvement. The clinical implication of this is that the onset of inflammation in DCM heralds poor recovery potential and the need for early decompression. For patients with a hypermetabolic cord, use of neuroprotective/immunomodulatory agents during the perioperative period such as riluzole (Karadimas et al. 2015b) and methylprednisolone (Vidal et al. 2018) may be particularly warranted. Conversely those with hypometabolic, atrophic cords would require biological stimulation.

Limited gliosis until advanced disease

A glial scar forms in response to traumatic spinal cord injury and surrounds the lesion core to limit spread of the cytotoxic inflammatory response to viable surrounding neural tissues (O'Shea et al. 2017). This is achieved as

reactive astrocytes within the scar proliferate, hypertrophy, secrete chondroitin sulphate proteoglycans (CSPGs), and form tight gap junctions (Horng et al. 2017). The glial scar has long been viewed as a physical and biochemical barrier to neural regeneration, although recent work has challenged this dogma as astrocytes have been shown to be essential for facilitating axonal regeneration in the presence of growth factors (Anderson et al. 2016). As with necrosis, glial scarring appears to be a late event in DCM, being demonstrable upon cadaveric specimens at an anteroposterior compression ratio of <20% relative to the transverse diameter at the most damaged segment (Ogino et al. 1983). This is inconsistent with the ubiquitous histological findings of gliosis and neuroinflammation in the mouse model (Yu et al. 2011), with a contributory factor likely being the increased rate at which compression develops in comparison to human pathology (Long et al. 2013). Ancillary disease processes such as gliosis and neuroinflammation are terminal events in DCM causing overlap in pathological findings when compared to traumatic injury (Figure 3).

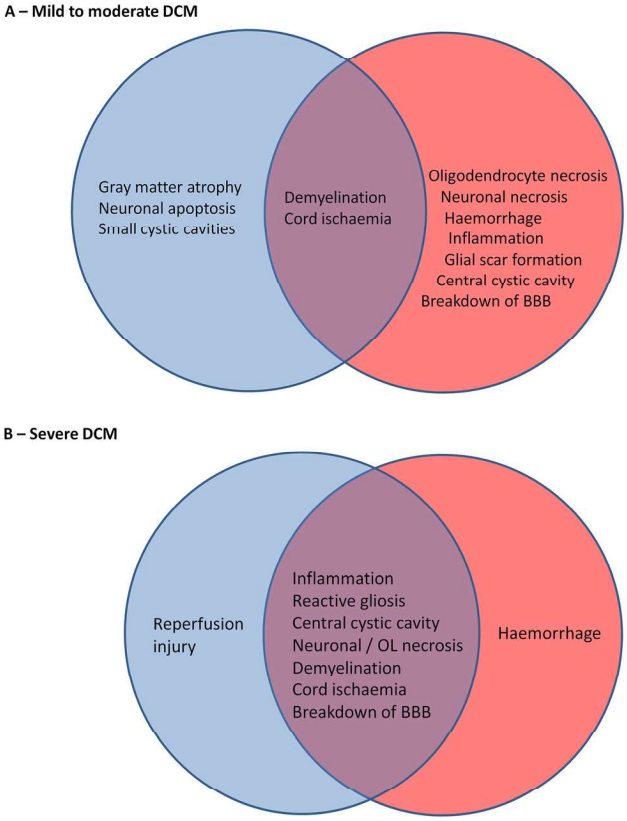

Figure 3: Venn diagram comparing stages of DCM with traumatic cord injury. Processes distinct to DCM are highlighted in blue, and those to traumatic injury in red. There is an increasing overlap in pathological processes upon progression to severe DCM.

Clinical considerations for cell replacement therapy in DCM

Selection of an appropriate cell source

Candidate stem/progenitor cells for replacement therapy may be obtained from embryonic, foetal, and adult sources. iPSCs in particular have been a revolutionary breakthrough in presenting an autologous, immunocompatible cell source with unlimited potential for self-renewal and differentiation. Nevertheless, expectations on clinical application need to be tempered by reports of genomic instability subsequent to cellular reprogramming (Yoshihara et al. 2017). Other sources include embryonic stem (ES) cells, umbilical cord stem cells, foetal-derived progenitors and bone marrow stromal cells (BMSCs), which have been reviewed in-depth elsewhere (Assinck et al. 2017). Transplantation of stem/progenitor cells poses an inherent safety hazard from their potential to proliferate and form tumours as well as a lack of direction regarding cell fate (Trawczynski et al. 2019). Tumour formation would be catastrophic within the cervical cord of patients with DCM, in forming a space-occupying lesion capable of causing recurrent compression and even quadriparesis (Steward et al. 2014). Towards replacement of lost cells in DCM, stem/progenitor cells may instead be directed by defined *ex vivo* culture conditions into lineage-restricted glial/neuronal precursors or terminally differentiated cell types prior to delivery. It is therefore essential to determine extrinsic growth factors and signalling pathways that are essential for inducing lineage commitment, and to prepare a defined, homogenous cell population prior to transplantation (Cai et al. 2017; Shea et al. 2010; Shea et al. 2020). Alternatively, precursors and differentiated cell types may be harvested autologously with examples being olfactory ensheathing cells (OECs) from the nasal mucosa (Gilmour et al. 2020) and Schwann cells from the sural nerve (Anderson et al. 2017). We next consider the rationale towards transplanting specific cell types.

Transplantation of myelinating glia

A pertinent question with regards to cell replacement in the context of DCM is whether the rate-limiting step to recovery is oligodendrocyte loss and demyelination, or neuronal

loss and axonal degeneration. Oligodendrocytes do not merely play a passive insulating role but are essential to maintaining neuronal homeostasis via the regulation of glutamate, nitric oxide, and calcium levels (Philips and Rothstein 2017). In turn, oligodendrocytes depend upon neuron-derived signals for survival, proliferation, and differentiation (Almad et al. 2011). Reasons in favour of glial replacement include oligodendrocyte apoptosis and demyelination preceding axonal loss upon cadaveric specimens (Ogino et al. 1983). Furthermore, animal experiments have demonstrated that <12% of intact axons are required for recovery of gait following spinal cord injury (Fehlings and Tator 1995b) thus signifying that glial loss has a more substantial impact on motor function.

Myelinating glia are able to contribute to regeneration predominantly by means of (i) neuroprotection, (ii) secretion of neurotrophic factors to enhance axonal growth and induce plasticity, and (iii) remyelination of denuded axons. Transplantation of oligodendrocyte precursor cells (OPCs) as opposed to mature oligodendrocytes has potential advantages in their capacity for proliferation and migration (Kuhn et al. 2019). Extensive pre-clinical studies following acute traumatic spinal cord injury have demonstrated that OPC transplantation improves upon the percentage of myelinated axonal fibres, latency of motor-evoked potentials (MEPs), and motor function scores (Fu et al. 2018). This has resulted in progression to Phase I/II clinical trials (Jin et al. 2019). Schwann cells are the counterpart of oligodendrocytes within the peripheral nervous system and possess similar reparative properties, and are also able to form aligned bands of Bugner to provide topographical guidance for axonal regeneration. Transplantation of sural nerve-derived autologous Schwann cells have been spearheaded by The Miami Project and progressed to clinical trials following thoracic spinal cord injury (Anderson et al. 2017). Olfactory ensheathing cells (OECs) are another type of glia similar to OPCs and Schwann cells that are conveniently obtained from the nasal cavity (Gilmour et al. 2020), and have also been reported to improve spinal cord vascularity following transplantation (López-Vales et al. 2004). Genetic modification of myelinating glia is a means towards enhancing their regenerative properties, for example via overexpression of neurotrophic factors, angiogenic factors, and promyelinating transcription factors.

Transplantation of neural progenitors/ differentiated neurons

In its strictest definition, regeneration of the spinal cord entails reconnection of descending and ascending neuronal fibres to their original targets (Katoh et al. 2019). As this is often impossible, the intrinsic capacity of the spinal cord to demonstrate recovery subsequent to injury has instead been attributed to the reorganization of local propriospinal relays (López-Vales et al. 2004). Formation of tissue bridges and relay circuits can replace and bypass disrupted axons over the lesion site (Assinck et al. 2017). The rationale for transplanting cells with neurogenic potential is to provide an exogenous supply of axons to restore connectivity, although secretion of neurotrophins is a recognized by-product that contributes to regeneration (Trawczynski et al. 2019). Neural stem/progenitor cells have the potential to not only provide neurons, but glia to facilitate recovery by means described above. Multiple pre-clinical studies on iPSC-derived neural progenitor cell transplantation following cord contusion have demonstrated migration, engraftment, and differentiation into cell types including motor neurons, astrocytes, and oligodendrocytes (Trawczynski et al. 2019). Directed differentiation of iPSCs to motor neuron progenitors, general motor neurons, and their subtypes has also been well established. Transplantation of neural precursors appears to be favoured within the hostile pro-inflammatory microenvironment following traumatic spinal cord injury, but mature cell types may be better received in DCM. Recent work on the capacity of spinal interneuron reactivation to restore stepping ability following cord hemisection (Chen et al. 2018) should also highlight the transplantation of derived interneurons (Butts et al. 2017) and /or pharmacological activation of such relays (Fehlings and Tator 1995a) as additional therapeutic strategies.

Transplantation of cells to promote neovascularization and immunomodulation

The therapeutic effect of cell transplantation for stroke should be regarded when targeting tissue ischaemia as a barrier to neurological recovery following DCM. Cell types able to promote neovascularization by means of secretion of angiogenic factors such as VEGF (vascular endothelial growth factor) and PDGF (platelet-derived growth factor) include neural stem cells, BMSCs, umbilical cord stem cells, and endothelial progenitor cells (Stonesifer et al. 2017).

Inflammation is a key contributor to secondary injury following traumatic spinal cord injury, and also contributes to impaired receptivity towards exogenous cells. Whilst inflammation is not ubiquitous in patients with DCM (Floeth et al. 2013), transplantation of BMSCs and neural stem cells may have a useful immunomodulatory

effect in certain patient subgroups. BMSCs exert their therapeutic effects by secreting anti-inflammatory and neuroprotective cytokines (Yang et al. 2020).

Adjuvant treatments to enhance the efficacy of cell transplantation

The objective of adjuvant treatment should be to modulate the spinal cord microenvironment in favour of repair (Gilmour et al. 2020). Neuroinflammation and gliosis subsequent to post-traumatic injury are aspects of the cord milieu that require attenuation in preparation to receive exogenous cells, and may similarly have to be addressed in severe DCM (Figure 3). Pharmacological strategies attenuating inflammation include inhibiting local activation of infiltrating immune cells, promoting M2 macrophage polarization, and provision of neuroprotective agents (Orr and Gensel 2018). CSPGs within the glial scar may be tackled by enzymatic inhibition to prevent formation, catabolism via ChABC delivery, as well as by blockade of CSPG receptors and downstream signalling pathways (Orr and Gensel 2018; Tran et al. 2018). An emerging perspective is that local infusion of neurotrophins promotes regeneration in the presence of a glial scar (Anderson et al. 2016), where the build up of astrocytes, previously thought to present a barrier to axonal outgrowth, has been paradoxically found to be beneficial. Changes in spinal cord perfusion subsequent to chronic compression may be another persistent impediment to recovery (Jellinger 1967). Apart from transplantation of exogenous cells capable of promoting angiogenesis, delivery of angiogenic factors such as VEGF holds promise (Povysheva et al. 2017). Preoperative workup via functional imaging and electrophysiological assessment should aim to identify such biological bottlenecks. Thereafter, appropriate cell types and treatment adjuncts attenuating underlying inhibitory disease processes may be co-administered (Rust and Kaiser 2017).

Timing of cell transplantation

Following traumatic spinal cord injury, there is a narrow therapeutic window lasting for weeks whereby the spinal cord microenvironment is relatively receptive to exogenous cells (Nori et al. 2018). A practical barrier to cell replacement therapy in this disease context is the lengthy duration required for cell preparation. Conversely, the slow and insidious onset of DCM (Ogino et al. 1983) may ensure for engraftment and integration of exogenous cells over a prolonged window period, allowing preparation and delivery of autologous cells, and preclinical models should establish as such.

Selection of cell type and adjuvant treatment should be considered with reference to chronicity and severity of compression. Decompression alone, potentially with delivery of myelinating glia such as OPCs, may suffice when the anteroposterior compression ratio exceeds 20% (Ogino et al. 1983). Patients in whom the AP compression ratio is less than 20%, or have had long-standing symptoms with significant neurological deficits, may benefit more from delivery of neural progenitor cells during decompression surgery to provide exogenous neurons. Local delivery of neurotrophins and VEGF can, respectively, stimulate axonal outgrowth in the presence of gliosis, and promote neovascularization. Perioperative riluzole (Vidal et al. 2017) may be an additional essential adjunct to prevent reperfusion injury.

Finally, cell replacement therapy can be applied as a rescue therapy in patients with persistent neurology following adequate mechanical decompression or upon clinical deterioration in the years subsequent to surgery and in the absence of recurrence in mechanical compression on reassessment imaging. There are presently no options in the physician's armamentarium to deal with such scenarios.

Method of cellular delivery to the lesion site

Studies on the method of cellular delivery are predominantly confined to the context of acute traumatic spinal cord injury. General considerations include accessibility to the lesion site, invasiveness of the procedure, and migrational competency of transplanted cells. Intravenous delivery of stem/progenitor cells is convenient and minimally invasive. Nevertheless, in order to reach the spinal cord, cells will be subject to significant first pass trapping in the lungs and thereafter are hindered in crossing the blood brain barrier (Kabat et al. 2020). Accordingly, few transplanted cells are demonstrable in the contused spinal cord subsequent to intravenous delivery, and engraftment is sensitive to timing with early infusion post-injury preferred (Osaka et al. 2010).

Intrathecal delivery of human BMSCs via lumbar puncture (LP) has been demonstrated to result in a dose-dependent improvement of function following contusion of the rat spinal cord (Pal et al. 2010). In comparison to intravenous delivery, LP injection of human bone marrow stromal cells into rats receiving cervical cord hemisection resulted in increased cell engraftment and tissue sparing (Paul et al. 2009a). Repeated dosing is a means to enhance engraftment and functional recovery (Cizkova et al. 2011). Clinical trials have demonstrated that

intrathecal delivery to a cohort of patients with cervical, thoracic, and lumbar spinal cord injuries was free from adverse events (Hur et al. 2016). Intrathecal injection via the exposed cervical cord dura may be offered at the time of surgical decompression. Should cells be able to engraft and migrate into the lesion, this approach would offer a good balance in circumventing the blood brain barrier and allowing for localized delivery without excessive procedural risk of damaging the spinal cord.

Intramedullary injection into the lesion or perilesional tissues is the most invasive means of delivery but allows for a measured population of cells to be delivered to specific regions of interest. Ultrasound can be utilized to select transplantation site (Levi et al. 2018), and enable for topology-specific transplantation for example of motor neuron progenitors into the atrophied corticospinal tract, and provision of OPCs to the demyelinated posterior column. Clinical trials have reported this mode of delivery to be safe (Anderson et al. 2017) albeit in patients with complete spinal cord injury. In patients with DCM, iatrogenic injury to axonal tracts and/or bleeding could be expected occur, and result in neurological decline.

Translational research directions towards clinical application

Improving validity of disease models

Animal models of DCM most commonly utilize rodents. Local compression may be generated via surgical implantation of expandable polymers posterior to the cord. The rates of expansion as well as thickness of the implant are sensitive parameters that determine the loss of anterior horn cells as well as extent of demyelination within gray matter (Long et al. 2013). Cervical cord sections subsequent to compression are seen to be dumbbell-shaped as opposed to “triangular” or “boomerang” shaped in humans (Shimomura et al. 2007). Alternatively, the hyperostotic twy/twy (tiptoe walking) mouse model spontaneously develops cervical cord compression due to ossification of the posterior longitudinal ligament, and become quadriplegic 4–8 months after birth (Yamaura et al. 2002). The severity of neurological compromise and site of maximal compression (over the C1 – C3 vertebra) differ from human pathology. Significant gliosis and inflammation is observed in rodent models (Yu et al. 2011) which are unable to mimic the slowly progressive nature of human disease (Dhillon et al. 2016). A posterior screw-based chronic compression device is a step towards measured compression in rats (Lee et al. 2012). Another approach is to use larger animals with more spacious spinal canals. Canine models for example (Hukuda and Wilson 1972), do not demonstrate marked gliosis, and larger canal dimensions would facilitate experiments involving intrathecal delivery of cells. Accurate pre-clinical models enabling for (i) studies on the pathophysiological basis of disease, and (ii) assessment of safety and efficacy following cell transplantation are necessary to justify translation to the bedside.

Establishing efficacy of biological therapies

Over the period from 1995 to 2015, 60% of publications related to DCM concerned surgical technique, approach or strategy as compared to 2% relating to molecular and genetic aspects of disease (Figure 1) (Mowforth et al. 2019). An impetus should be placed upon proof-of-concept studies demonstrating the efficacy of cell transplantation. Pharmacological means of attenuating inflammation, gliosis, and ischaemia as secondary disease processes in advanced disease that hinder endogenous repair and receptivity towards transplanted cells has been discussed, and similar warrants further investigation. DCM has been reported to be present in twins (Mukerji and Sinar 2007) and demonstrates familial clustering (Patel et al. 2012). Determination of at –risk genotypes may yield novel therapeutic targets as well as identify those prone to early and rapid clinical deterioration requiring prompt surgical decompression.

Assessment tools for disease prognostication

As much as cadaveric specimens have furthered our understanding on the pathophysiology of DCM, non-invasive assessment indices need to be refined towards prognosticating for clinical deterioration and the potential for recovery following decompression alone. The objective of multimodal assessment should be (i) to determine the optimal timing for surgical decompression in order to prevent irreversible neurological deterioration past “the point of no return”, and (ii) to identify patients with poor prognosis in whom biological therapies such as cell transplantation would be of benefit. Means of assessing the cord microenvironment are essential as ultimately, transplanted cells will fail to survive, engraft, and provide functional benefit within a hostile niche.

Increasingly sophisticated MRI techniques have been developed to reflect upon spinal cord histopathology and function. These include diffusion tensor imaging (DTI), myelin water fraction (MWI), and MR spectroscopy (MRS) as has have been reviewed elsewhere (David et al. 2019). Elucidation of cord perfusion status, neuroinflammation, and gliosis via imaging would supplement the determination of management (Wen et al. 2014). Metabolic scans have allowed not only for the stratification of cord inflammation (Floeth et al. 2013), but also assessment of tract integrity as well (Bedenk et al. 2018). Electrophysiological studies offer an alternative dimension to assess for motor and sensory function, extent of demyelination, and recovery potential subsequent to decompression (Hu et al. 2008). Biomarkers harvested from the cerebrospinal fluid hold promise as a minimally invasive means to evaluate for neuroinflammation and apoptosis (Albayar et al. 2019) as late events in DCM.

Conclusion

The prevalence of degenerative cervical myelopathy (DCM) is expected to rise with the aging population to cause significant morbidity despite the best available care. Cell therapy with myelinating glia and neural cell types holds immense promise yet remains unexplored. A barrier to translational research is that animal models do not reflect slowly progressive mechanical compression as a hallmark of DCM. In considering clinical application, multimodal pre-operative assessment will be essential to identify suitable treatment candidates that are not amenable to spontaneous neurological recovery following surgical decompression, as well as to detect secondary disease processes such as gliosis, inflammation, and ischaemia that require attenuation.

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