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Mini Review

Stem Cell Mediated Neural Regeneration in Diabetic Neuropathy

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Abstract

Diabetes is one of the leading health problems of today. It may cause major complications such as cardiovascular disease, renal disease, retinopathy and neuropathy, the most common being Peripheral Diabetic Neuropathy. Peripheral nerve damage can be categorized based on the type and extent of damage to both nerves and surrounding connective tissue. This condition usually gives rise to loss of protective limb sensations and traumatic ulceration that often result in amputations. Most cases have myelin degeneration as a common factor along with declining microvascularity in the peripheral nerves causing hindered impulse conduction. Mesenchymal stem cell (MSC) therapy has the ability to target and treat neural and vascular elements of the Peripheral Nervous System by myelin regeneration through stimulation of Schwann cells. MSCs can be isolated and harvested from prospective sources like adipose tissues, bone marrow, amniotic fluid, tonsils, umbilical cord and nervous tissue. The MSCs secrete biologically active factors which help in angiogenesis and also combat cell apoptosis. Once cultured and induced into Schwann cells *In vitro,* they are subcutaneously transplanted at the target site via biological scaffolds. These differentiated cells induce the secretion of components needed for regeneration of damaged tissue, which results in reducing nociceptive precursor effects and enhancing regeneration of nerve fibers by stimulating the living being's very own self-regenerating phenomenon.

Keywords: Peripheral Diabetic Neuropathy; Myelin Degeneration; Mesenchymal Stem Cells; Schwann Cells; Biological Scaffolds

Introduction

Neuropathy

Neuropathy, in general, is described as damage to or a disease condition affecting nerves. A condition that develops as a result of damage to the peripheral nervous system (the vast communications network that transmits information between the central nervous system, brain and spinal cord). Neuropathy may be hereditary or acquired, and is a disease affecting the cell body of peripheral sensory or motor neurons, their axon, or the myelin. It can be broadly classified into mononeuropathy and polyneuropathy. Mononeuropathies affect the peripheral nervous system at a particular site – usually a limb – and then spread to a different site in an asymmetrical pattern. Polyneuropathies affect all the peripheral nerves and heralds the feet where the fibers are the longest [1].

Specifically, Diabetic neuropathy (DN) is the most common of them all and is classified under distal peripheral neuropathy. DN is a family of nerve disorders caused by a condition that develops as a result of damage to the peripheral nervous system due to hyperglycemia. Elevated levels of glucose within cells cause non-enzymatic covalent bonding with proteins which alter their structures and inhibit their functions. Symptoms can range from numbness or tingling, to pricking sensations (paresthesia), or muscle weakness. Areas of the body may become abnormally sensitive leading to an exaggeratedly intense or distorted experience of touch (allodynia). In such cases, pain may occur in response to a stimulus that does not normally provoke pain. Severe symptoms may include burning pain (especially at night), muscle wasting, paralysis, and organ or gland dysfunction. Damage to nerves that supply internal organs may impair digestion, sweating, sexual function, and urination. In extreme cases, breathing may become difficult, or organ failure may occur [2].

Clinical data on the earliest signs and symptoms on diabetic rats showed slowing of sensory and motor nerve conduction velocity (NCV) as well as manifestations of evoked pain within the

first month of onset of hyperglycemia. When the condition was prolonged in rats, signs of axonopathy, demyelination and hindered nerve regeneration were detected [3]. Various other data on pathways activated by hyperglycemia converge in the generation of reactive oxygen species (ROS). The ROS overwhelms the intrinsic antioxidant mechanisms of the cell and induces oxidative stress and pro–inflammatory conditions in the tissues. This inflammation causes glial cell (responsible for nerve support) injury, which is responsible for the demyelination of the neuron and explains the decrease in the NCV and results in painful manifestations of the disease. Glial cell injury will affect the nerve neurotropism which adds to the progression of neuronal defects [4]. Oxidative stress and impaired nitric oxide production in the endothelium of epineurial and endoneurial circulation causes impairment of circulation which exaggerates the direct effects of hyperglycemic conditions on glial cells and neurons. The oxidative stress also affects the production of cytokines by glial cells and provokes the recruitment of immune response cells into the affected cells [5].

Conventional methods of treatment that are available today are based primarily on treating the symptoms and mitigating pain but not treatment of the underlying cause of the disease. The treatments available focus on the use of some sort of physical aid, physiotherapy, regulation of blood glucose levels to avoid the disease condition entirely [6]. Pharmacological treatment of painful distal peripheral neuropathy (DPN) is not entirely satisfactory because, the currently available drugs are often ineffective and complicated by adverse events. Tricyclic compounds (TCAs) have been used as first-line agents for many years, but their use is limited by frequent side effects that may be central or anticholinergic, including dry mouth, constipation, sweating, blurred vision, sedation, and orthostatic hypotension (with the risk of falls particularly high in elderly patients). The selective serotonin noradrenalin reuptake inhibitors (SNRI) duloxetine and venlafaxine have been used to relieve pain by increasing synaptic availability of 5-hydroxytryptamine and nor-adrenaline in the descending pathways that inhibit pain impulses. However, the main side effects include nausea, somnolence, dizziness, constipation, dry mouth, and reduced appetite, although these tend to be mild to moderate and are transient [7]. Other effective but generally considered second line drugs for painful DPN include other anticonvulsants, like carbamazepine, although it has troublesome side effects including dizziness, somnolence and gait disturbance [8].

However, these drugs have their own complications as the development of these drugs is based on a general population, rather than being tailor made for individual patients who may have multiple disease conditions. The initial selection of a particular first-line treatment will be influenced by the assessment of contraindications, evaluation of comorbidities (including sleep disturbance, mood disorders, and other chronic medical/diabetes complications). For example, in patients with liver disease, duloxetine should not be prescribed, and in those with peripheral edema, pregabalin or gabapentin should be avoided. Moreover, although pharmaceutical companies may recommend a particular starting dose for their drugs based on their clinical trials, one has to appreciate that the clinical practice scenario is quite different from the clinical trial scenario because elderly patients with multiple comorbidities would have been excluded from trials [9]. Therefore, treatment has to be individualized to improve the current treatment methods, to effectively improve treatment procedures.

Tissue regeneration

Tissue regeneration is a fundamental characteristic involved in helping the body sustain itself. Regeneration occurs when cell proliferation proceeds via growth factors which are dependent on the integrity of the extracellular matrix and development of mature cells from the stem cells. A combination of signal and control mechanisms result in the proliferation of several types of cells during the period in which tissue repair takes place [10]. These are remnants of injured tissue which attempt to restore normal structure, vascular endothelial cells which create new vessels that provide nutrients needed for tissue repair and fibroblasts which is the source of fibrous tissue used in scar formation.

Any cell or tissue that is damaged has to be replaced or repaired following an injury, to ensure regeneration. This particular process is very efficient in some living beings, such as lizards, star fish and so on. This involves reprogramming of cells at the injury site back to a multi-potent progenitor state with encoded positional information that allows the recapitulation of developmental processes to regenerate the lost cellular structures (Poss, 2010) [11]. But the same case does not apply to humans. Human cells can only replicate or regenerate to a certain extent and the adult stem cells, they differentiate to a far lesser extent. Adult somatic cells develop gradually, quicker at the start of development and slower at the later stages, all the while replacing lost cells wherever possible, but confined to the boundaries of tissue organization and rarely, organ systems.

Peripheral nerves, unlike those in the CNS have comparatively more regenerative capacity in mammalian systems. This does not, however, involve regeneration of entire nerve fibers in the damaged area. The damaged area, around the distal end, remains intact

and later joins with the proximal end via a connecting "bridge" that regains vasculature and nerve function with the help of Schwann cells, macrophages and their combined secretions, all in a chemotactic nature. The Schwann cells (SC) envelop and associate with the axons, myelinating the larger diameter axons and making bundles of the smaller ones (Remak bundles). This occurs even in complete transections, where the nerves end up slowly connecting back with their parent sources.

In addition to the types of cells that proliferate during tissue repair, depending on the intrinsic proliferative capacity, three types of tissue are formed. First is Labile tissue, which continuously replaces damage cells at a high rate in a continuous process and is found in bone marrow and surface epithelia like skin, oral, vaginal cavity. The next tissue type is Stable tissue which performs tissue regeneration at a lower rate but predominantly in liver, kidney, pancreas, fibroblasts, endothelial and smooth muscle cells. The last type of tissue is Permanent tissue, which has no regenerative capacity and makes up the neural cells, skeletal muscles and cardiac muscles.

Mechanism of Tissue regeneration

The mechanism of tissue regeneration in the human body is accompanied by the deposition of connective tissue. The replacement of injured cells by the connective tissue leads to scar formation by the regeneration of residual cells and replacement of non-regenerative parts by connective tissue. The four major steps involved are (i) Angiogenesis, where neovascularization takes place in the presence of factors like basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and Proteoglycans. The receptor involved is intrinsic kinase on the surface endothelial cells. Angiogenesis is followed by (ii) migration and proliferation of fibroblasts. This involves the migration of Fibroblasts to the injury site and their subsequent proliferation. The factors involved in this process are, Interleukins (IL) and Macrophage chemo attractant protein (MCP). (iii) Deposition of extracellular matrix (ECM). As the regeneration progresses, the number of proliferative fibroblasts and new vessels decreases, which gives the site a synthetic phenotype resulting in the increased deposition of ECM accompanied by Collagen synthesis. The factors involved in this synthesis are Platelet derived growth factor (PDGF), (bFGF), Transforming Growth factorβ (TGFβ), Cytokines (interleukine 1) and Tumor necrosis factor (TNF). Finally, (iv) remodeling of fibrous tissue takes place which is the degradation of extra collagen and other ECM components. The factors are Metalloproteinases dependent on zinc ions, Neutrophil elastase, Cathepsin G plasmin and Serine Proteinases [12].

The major growth factors involved in tissue regeneration

Epidermal growth Factor (EGF), Platelet derived growth factor (PDGF), Fibroblast growth factors (FGF), Transforming growth factor β(TGFβ, given in low concentrations to avoid it's inhibition), Vascular endothelial growth factor (VEGF), Cytokines (Interleukins), Tumor necrosis factor (TNF) [13].

Stem cells

Stem cells are undifferentiated or unspecialized cells that are characteristically of the same lineage (same family type) [14]. Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In many tissues, they serve as an internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. During cell division, stem cells have the potential either to remain as a stem cell or become another type of stem cell with a more specialized function. Stem cells stand out from other cell types by two of their important characteristics: 1) they are unspecialized cells capable of renewing themselves through cell division even after long periods of inactivity, 2) Under certain physiologic or experimental conditions they can be induced to become tissues, or organs, or specific cells with special functions.

Stem cells are broadly classified into two types: Embryonic stem cells and Adult stem cells. Embryonic stem cells are derived from embryos that develop from eggs that are been fertilized. Adult stem cells are undifferentiated cells found among various organs and tissues including brain, bone marrow, peripheral blood, blood vessels, skeletal muscles, skin, teeth, tonsils, heart, gut, liver, ovarian epithelium and testis. Adult stem cells are also called somatic stem cells where somatic refers to the cells of the body [15].

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are examples of adult stem cells. MSCs are widely used in tissue engineering (TE). MSCs are a highly interesting stem cell source for TE as they have the potential to be expanded in culture and exhibit multilineage differentiation. The other properties of MSCs include their ability to self-renew, modulate immune response and their relatively easier bioavailability (they can be obtained from a small scale aspirate of bone marrow or adipose tissue). MSCs can be isolated from adults; therefore, allogenic transplant of these cells would eliminate raising ethical issues in regards to their use in TE and regenerative medicine [16]. Mesenchymal stem cells (MSCs) are multipotent stem cells derived from various tissues, which have the capacity to differentiate into several mesodermal lineages, including osteoblasts, chondroblasts,

and adipocytes [17]. These diverse multipotent MSCs can also be differentiated into cells of the ectodermal lineage including neurons and glial cells. Various studies using skin-derived MSCs, adipose tissue-derived MSCs (AMSCs), bone marrow-derived MSCs, and umbilical cord-derived MSCs have been performed in attempts to differentiate them into SCs under diverse conditions [18-21]. Bone marrow stem cells (BMSC) are interesting cell sources, because they are able to self-renew with a high growth rate, possess multi-potent differentiation properties and are easy accessible. BMSC have the potential to transdifferentiate into neuron like cells with various neuronal markers and functional neuronal activity [22]. Due to their high plasticity and low immunogenicity, application of mesenchymal stem cells (MSC) is considered as an attractive form of cell therapy for the injured nervous system [23]. Previous studies have demonstrated that differentiated Schwann cells help neurite outgrowth [24] and provide trophic support for surviving axons as well as remyelinating injured axons *In vivo* [25,26]. However, bone marrow-derived MSCs have their fair share of limitations because of their low yields and the need for major invasive procedures for isolation.

Isolation of tonsil-derived MSCS and the preparation of Bioscaffolds containing MSCS differentiated into Schwann cells

Tonsil-derived MSCs (T-MSCs) are harvested from tonsils, during tonsillectomy procedures. The isolated tonsillar tissues are then washed with buffered saline solutions and incubated in DNase, Collagenase and cultured in a Dulbecco's modified Eagle's medium (DMEM). After sufficient stirring, the digested tissues are filtered and centrifuged. After centrifugation, the adherent cells are isolated and further supplemented in DMEM, with subsequent sub-culturing twice a week. The isolated cells are then checked for several basic characteristics, like MSC-specific surface antigen profiles, colony-forming unit-fibroblast features and so on. *In vitro* mesodermal differentiation converts the isolates to adipocytes, osteocytes and chondrocytes. This may be detected by staining with either cell-specific dyes or antibodies after incubation with each appropriate differentiation medium. Expression of mesoderm-specific genes will be quantified by real-time polymerase chain reaction (PCR) assay. Expression profiles of endoderm-specific genes will then be identified by reverse transcription PCR assay. The feasibility of T-MSC in future engraftment is tested by short tandem repeat (STR) analysis using genomic DNA isolated randomly from three independent subjects. These isolates, after being quantified and analyzed qualitatively, are then cryopreserved if deemed to have differentiated into Schwann cells showing all the necessary surface markers and superficial structural composition [27].

These differentiated T-MSCs are then used in conjunction with collagen scaffolds to produce engineered tissues. These approaches include seeding such scaffolds with neural stem cells (Ma *et al.*, 2004; O'Connor *et al*., 2000; Watanabe *et al.*, 2007). These cells differentiate and form functional circuits inside of the scaffolds (Ma *et al*., 2004).

A study showed that porous 3-dimensional collagen scaffold material supports capillary formation *In vitro* and promotes vascularization when implanted *In vivo*. Collagen scaffolds were synthesized from type I bovine collagen and have a uniform pore size of 80 µm. *In vitro*, scaffolds seeded with primary human microvascular endothelial cells suspended in human fibrin gel formed CD31 positive capillary-like structures with clear lumens. *In vivo*, after subcutaneous implantation in mice, cell-free collagen scaffolds were vascularized by host neovessels, whilst a gradual degradation of the scaffold material occurred over 8 weeks. Collagen scaffolds, impregnated with human fibrinogen gel, were implanted subcutaneously inside a chamber enclosing the femoral vessels in rats. Angiogenic sprouts from the femoral vessels invaded throughout the scaffolds and these degraded completely after 4 weeks [28].

Mechanism of action

Role of differentiated T-MSCs and Macrophages in neural regeneration

Following an injury, the Schwann cells (SCs) in both the proximal stump and throughout the nerve downstream of the cut dedifferentiate to a progenitor-like cell, which proliferate, orchestrate an inflammatory response that clears the debris and remodels the environment [29]. The administered MSCs that have differentiated into Schwann cells *In vitro*, move along to the damaged end of the bridge and use the vasculature as a temporary scaffold to hold all the progenitor cells. This makeshift scaffold holds the migrating SCs, macrophages, VEGF-A and other Schwann cell secretions in one place. As the angiogenesis progresses, the differentiated SCs will guide the regrowing axons towards the damaged site, which results in the effective regeneration of peripheral nerves.

This entire process occurs by the initiation a complex cascade of signals involving neurons, glia, and cells of the immune system that leads to Wallerian degeneration inducing the invasion of macrophages [30]. The macrophages from various other systems come up to the injury site and cause phagocytosis that will ensure further clearance of debris around the damaged/transected area. While the macrophages help in efficient degeneration of the damaged nerve fibers, they also secrete components like VEGF-A, which starts up a series of reactions leading to angiogenesis. This process of angiogenesis, by triggering polarized vasculature across the

bridge between the distal and proximal stumps, normally occurs in conditions of hypoxia (decreased oxygen levels). Upon hypoxia, the transcription factor HIF-1α is stabilized and initiates a transcriptional response that induces angiogenesis by up-regulating pro-angiogenic factors such as VEGF (Krock et al., 2011, Pugh and Ratcliffe, 2003). The Schwann cells then start to interact with the polarized blood vessels, and these newly formed capillaries attract RBCs and SCs to migrate within them.

Factors involved in neural regeneration and immune response

Cytokines induced in Schwann cells after peripheral nerve injury play an important role in the interactions between Schwann cells and macrophages. The neuropoietic cytokines, leukemia inhibitory factor (LIF) and interleukin-6 (IL-6) are involved in the neuronal and immune responses to injury. Schwann cells in transected nerves subsequently increase the expression of LIF and IL-6. Another potential Schwann cell-derived macrophage attracting agent, monocyte chemoattractant protein-1 (MCP-1), attracts macrophages in other systems due to nerve transection. A recent paper pinpoints tumor necrosis factor- α (TNF-α) as an inducer of MCP-1 in Schwann cells after nerve injury upto four days after the nerve has been affected [31]. IL-6 rapidly induces LIF mRNA in primary Schwann cells, and LIF, in turn, results in MCP-1 mRNA expression. We find LIF and MCP-1 to be important components of the secreted signals that attract macrophages. Treatment of RN22 Schwannoma cells with IL-6 or LIF enhances the secretions of the chemotactic activity of these cells. These observations show that Schwann cells attract macrophages by secreting MCP-1 and LIF that bind to the surface receptors of macrophages. They also provide evidence for an autocrine-signaling torrent involving IL-6, LIF, and MCP-1, which amplifies the Schwann cell-derived chemotactic signals gradually, in agreement with the delayed entry of macrophages to injured nerves. MSCs are inherently loaded with a lot of cytokines and factors which are immunosuppressive, like prostaglandin E2 (PGE2), interleukin 10 (IL-10), IL-6, transforming growth factor-β (TGF-β), indoleamine-2,3-dioxygenase (IDO), and nitric oxide (NO). MSCs also express very low levels of major histocompatibility complex (MHC) class- I and II molecules on their surface which effectively cloaks them from immune soldiers.

Hypothesis

Figure 1

Although bone marrow-derived MSCs have so many advantages and are one of the most intensively studied types of MSC associated with SC differentiation, they are limited in terms of clinical applications because of their low yields and the need for invasive procedures to isolate them [32]. Moreover, their proliferation rates and differentiation potentials have been shown to decrease with donor age.

Tonsil-derived MSCs (T-MSCs), isolated from palatine tonsils during tonsillectomy, have been reported recently as a new class of MSC [33,34]. Human tonsils are lymphoepithelial tissues that act as immune organs until puberty and undergo atrophy during aging. As with other MSCs, T-MSCs also exhibit self-renewal capacity, multi-lineage differentiation properties, and immunosuppressive characteristics [34]. In particular, the high proliferation rate of T-MSCs is very important for quantitative recovery and for the establishment of dependable cell lines. Several studies have confirmed that T-MSCs express typical MSC cell surface markers and can differentiate into mesodermal lineages [33-35].

Normal neural regeneration takes place by the body's own mechanism of trying to treat the damaged neurons by first clearing out the affected area by phagocytosis and then, initiating series of steps by which the distal neural stump is reattached to the peripheral site, by a bridge formed by angiogenesis. This angiogenesis is caused by vasculature forming components secreted by macrophages, existing Schwann cells and other monocyte like cells. But due to the delayed entry of the macrophages to the target site, the existing Schwann cells repurpose themselves into clearing up the debris for total degeneration to occur. This process takes enough time to let the diabetic/hyperglycemic condition of the patient to recur and destroy more neural tissue.

The use of T-MSCs as an additional supplement to the damaged area, has a multi-fold action. They start attracting macrophages form various systems, due to their surface markers mirroring those of the Schwann cells, resulting in the relatively faster approach of the macrophages to the damaged site, for efficient Wallerian degeneration. The macrophages then, secrete factors like VEGF-A, which are responsible for the subsequent microvascular regeneration, followed by the chemotactic response of Schwann cells in re-myelinating the transected neural tissue.

Conclusion

Diabetes is one of the leading health problems of today. It may cause major complications such as cardiovascular disease, renal disease, retinopathy and neuropathy, the most common being Peripheral Diabetic Neuropathy. Peripheral nerve damage can be categorized based on the type and extent of damage to both nerves and surrounding connective tissue. This condition usually gives rise to loss of protective limb sensations and traumatic ulceration that often result in amputations. Most cases have myelin degeneration as a common factor along with declining microvascularity in the peripheral nerves causing hindered impulse conduction. Mesenchymal stem cell (MSC) therapy has the ability to target and treat neural and vascular elements of the Peripheral Nervous System by myelin regeneration through stimulation of Schwann cells. MSCs can be isolated and harvested from prospective sources like adipose tissues, bone marrow, amniotic fluid, tonsils, umbilical cord and nervous tissue. The MSCs secrete biologically active factors which help in angiogenesis and also combat cell apoptosis. Once cultured and induced into Schwann cells *In vitro*, they are subcutaneously transplanted at the target site via biological scaffolds. These differentiated cells induce the secretion of components needed for regeneration of damaged tissue, which results in reducing nociceptive precursor effects and enhancing regeneration of nerve fibers by stimulating the living being's very own self-regenerating phenomenon.

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