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Role of Umbilical Cord-Derived from Mesenchymal Stem Cells and Adipose Tissue on Nerve Growth Factor (NGF) in Peripheral Nerve Injury

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Abstract

Peripheral nerve injury is the predominant cause of disability in individuals of working age. To date, the only treatment for peripheral nerve injury is surgical intervention; nevertheless, postoperative outcomes frequently fail to meet expectations. This review provided a comprehensive role of umbilical cord derived from Mesenchymal Stem Cell (MSC) and adipose tissue on nerve growth factor in peripheral nerve injury. A literature search was conducted in the form of periodicals related to the theme raised during the preparation of the paper. The search for 1,834 articles through PubMed was conducted using the keywords peripheral nerve injury, umbilical cord stem cell, adipose-derived stem cell, nerve growth factor, and nerve regeneration. Data were analysed and presented descriptively in the form of text and figure. Mesenchymal stem cells facilitate axonal regeneration in peripheral nerve injury, notably through the synthesis of Nerve Growth Factor (NGF). Mesenchymal stem cells derived from both umbilical cord and adipose tissue contribute to the synthesis of NGF.

Introduction

Patients with extremity trauma may sustain peripheral nerve injury. Huckhagel et al. discovered that 1.8% of patients with leg trauma had peripheral nerve injury in the TraumaRegister DGU between 2002 and 2015. They evaluated 60,422 patients with leg trauma over this period. The average age of patients with peripheral nerve injury was 38.1 years, and 80% of them were male. Motorcycle accidents (31.2%) and auto accidents (30.7%) were the most prevalent causes [1]. Peripheral nerve injury is a significant cause of disability worldwide, despite its modest frequency of occurrence. In 2011, the World Health Organization (WHO) reported that approximately 35,400,000 individuals under the age of 60 in developing countries had disabilities as a result of accidents [2]. Subsequently, the Ministry of Health of the Republic of Indonesia reported that leg injuries were experienced by 67.9% of the total population who were involved in accidents in 2018 [3].

There are numerous causes of peripheral nerve injury. Specifically, due to the existence of a mass in the spine, such as a tumor or intervertebral disc prolapse. It may also result from direct injury to the nerves, such as pressure or straining. Symptoms such as persistent pain, neurological deficits (paraesthesia and paralysis), or muscle atrophy may manifest following the injury. Immediate treatment is necessary for this condition, as delayed treatment may result in complete paralysis. Currently, the primary treatment option for brief nerve injuries (<5mm)

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is nerve repair through surgical methods. Nevertheless, most of the time, the functional enhancement of the injured nerve is not as significant following surgery. Numerous researchers have initiated the search for alternative therapies, including the utilization of stem cells, as a result of the fact that numerous patients are unable to regain their former levels of bodily function following an injury.

Currently, stem cells are a highly developed non-operative therapy, particularly for the regeneration of nerve cells. It is possible for stem cells to develop in a manner similar to Schwann cells and to activate neurotrophic factors, which are instrumental in the regeneration of nerve cells. Mesenchymal stem cells are currently being utilized more frequently due to their multipotent nature and their lack of controversy with regard to ethics. Mesenchymal stem cells can be derived from a variety of sources, such as subcutaneous adipose tissue and the umbilical cord. The objective of this paper is to evaluate the impact of Nerve Growth Factor (NGF) regulation in peripheral nerve regeneration by contrasting the effects of stem cells from the umbilical cord and adipose tissue.

Mesenchymal stem cells

Stem cells are pluripotent cells that have the capacity to proliferate indefinitely and differentiate into either identical or dissimilar cells. In general, stem cells are classified into two categories according to their origin: adult stem cells and embryonic stem cells [4].

Mesenchymal Stem Cells (MSCs) are of interest to researchers due to their lack of conflict with ethical standards. Friedenstein initially isolated and characterized these cells in 1974. MSCs are multipotent adult stem cells that are derived from the mesoderm and are non-hematopoietic. This means that they have the capacity to differentiate into a variety of distinct cell types. MSCs can be isolated from bone marrow, umbilical cord, adipose tissue, fetal liver, muscle, and lungs [5].

Various neurotrophic factors, growth factors, and cytokines are produced by MSCs, which are involved in axonal regeneration. Mesenchymal stem cells have been demonstrated to generate a variety of neurotrophic factors in numerous in vitro and in vivo studies [6].

Additionally, umbilical cord stem cells are fetal stem cells that possess advantages over other adult stem cells. The first reason is that it can be extracted in large quantities without causing harm to the donor, as it is extracted from the umbilical cord tissue after the infant is born. Furthermore, umbilical cord stem cells are younger than other adult stem cells, which allows them to endure a greater number of mitoses. Consequently, the immune response they generate is less robust than that of other adult stem cells [7]. Mesenchymal stem cells are derived from two sources in the umbilical cord: Wharton's fluid and umbilical cord blood [8].

Umbilical cord stem cells were cultured to produce a variety of neurotrophic factors that are beneficial in the field of regeneration [9]. Subsequently, numerous investigations utilizing umbilical cord stem cells on model rodents with peripheral nerve injuries yielded favourable outcomes. Schwann cells can be promoted to proliferate and myelinate by umbilical cord stem cells, which can differentiate to resemble them [7]. In order to demonstrate the paracrine activity of umbilical cord stem cells with conditioned media, a study evaluated proteins that are involved in angiogenesis and neurogenesis during the development and regeneration phases of nerve cells. The findings of the investigation demonstrated that umbilical cord stem cells have the capacity to generate a significant quantity of neurotrophic factors, including Nerve Growth Factor (NGF 10). Furthermore, a study was conducted to create umbilical cord stem cells that contain an extracellular matrix. Consequently, stem cells have the ability to promote the production of neurotrophic factors, such as NGF, by endogenous Schwann cells. This suggests that the paracrine function of endogenous Schwann cells can be stimulated by the extracellular matrix of umbilical cord stem cells [11]. In addition to their function in paracrine activity, umbilical cord stem cells have the ability to increase the number of neurotrophic factor receptors. TrkA is a specific receptor for NGF [12,13].

Furthermore, mesenchymal stem cells from adipose tissue can be isolated through a minor surgical procedure, specifically liposuction from subcutaneous adipose tissue. These cells exhibit a higher proliferation rate than bone marrow stem cells [14].

Adipocytes, pre-adipocytes, blood cells, fibroblasts, smooth muscles, and stem cells are present in adipose tissue. Stem cells that are derived from adipose tissue possess significant characteristics, including the ability to differentiate into a variety of cell lines and a high division capacity [15].

A study was conducted to compare stem cells that were derived from adipose tissue from superficial and deep adipose. The layer situated between the epidermis and superficial fibrous connective tissue was harvested for superficial adipose tissue. Deep adipose was extracted from the layer that lies beneath the fascial connective tissue and above the muscular fascia. This investigation demonstrated that there was no discernible distinction between the NGF produced by superficial and deep adipose [16]. The science of regeneration has the potential to employ stem cells derived from adipose tissue in peripheral nerve injury therapy, both undifferentiated and differentiated to resemble Schwann cells. Undifferentiated stem cells are involved in the axonal regeneration process, particularly in paracrine activity, which involves the production of neurotrophic factors. While endogenous Schwann cells and progenitor cells that have differentiated into Schwann cells are involved in the myelination and proliferation process [15].

The secretion of neuroprotective/neuroregenerative factors is the cause of rapid nerve cell growth in adipose tissue stem cell transplantation. NGF is one of the neurotrophic factors that is produced in significant quantities [16,17]. Adipose tissue stem cells have been employed as a therapy for peripheral nerve injury model mice in numerous investigations. The study's findings demonstrated that the stem cell culture has the capacity to directly synthesize and release NGF, as well as to modify the phenotype of Schwann cells [18,19].

Regeneration of peripheral nerve injury

Wallerian degeneration is concurrently accompanied by axonal regeneration. Schwann cells are crucial in this process, as they are responsible for the activation of neurotrophic factors and the regulation of axon growth. Depending on the severity of the injury, the regeneration of nerve cells can take anywhere from months to years. In neuropraxia, the morphological and physiological alterations that have resulted from injury can be restored to their original state. At the same time, the regeneration process is slowed down during axonomtesis, and the

endoneurium, which has formed scar tissue, impedes axonal regeneration. In neurotmesis, the tissue surrounding the axon is also injured, resulting in the axon's uncontrolled growth and the failure of nerve cells to connect to the end organ. In general, nerves must undergo three processes in order to attain a state of repair: axonal regeneration, Wallerian degeneration, and end organ reinnervation [20]. Bungner's bands are formed when Schwann cells proliferate, migrate, and align during axonal regeneration. Following this, Schwann cells will generate neurotrophic factors that serve to direct the growth, proliferation, and resistance of these nerve cells [21].

Role of neurotrophic factor:

Neurotrophic factors are proteins that are crucial for neural activity, particularly in the regeneration process following injury [7]. The isolation of Nerve Growth Factor (NGF) was the initial discovery of the ability of these proteins to stimulate nerve cell proliferation. Since that time, numerous additional neurotrophic factors have been identified, including Neurotrophin-3 (NT-3), Neurotrophin-4 (NT-4), and Brain-Derived Neurotrophic Factor (BDNF) [22]. In general, neurotrophic proteins possess two kinds of receptors: Tropomyosin-Related Kinase (Trk) and p75 neurotrophin receptor (p75NTR). These two receptor types can function independently or in conjunction to generate the biological effects of neurotrophins. Immature neurotrophins (proneurotrophins) exhibit a greater affinity for the p75NTR receptor, whereas mature neurotrophins more firmly bind to the Trk receptor [22].

Neurotrophins that bind to Trk receptors (Figure 1) will activate intracellular tyrosine through the phosphorylation process, allowing them to be identified by the adaptor protein, Shc. Shc protein then activates the MAPK/MEK/ERK cascade to stimulate cell growth and differentiation, and PI3K/PDPK1/AKT as a signal for defense. Meanwhile, neurotrophins that bind to the p75NTR receptor have the potential to induce apoptosis via the JNK/p53/Bax pathway [22].

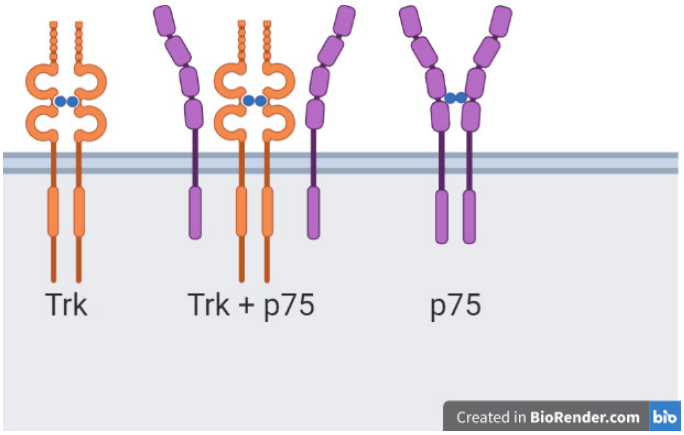

Figure 1: Neurotrophins receptors.

Nerve growth factor (NGF)

NGF is the first neurotrophins discovered and plays an important role in the development and regulation of the phenotype of nerve cells in the peripheral nervous system. The mature form of NGF plays an important role in development in adulthood, namely as a pro-apoptotic agent [23]. In addition, NGF also acts as a guide or chemotaxis of the growth tips of axons [24].

NGF is produced by nerve cells and target tissues innervated by sensory afferents and sympathetic efferent. In addition, it is also produced by microglia cells and several other cells such as immune cells and epithelial cells [25]. When an injury occurs, NGF expression increases in the distal part of the axon by 10 times in the first 12 hours after injury and will decrease to 5 times the normal amount within 72 hours after injury. After that, NGF levels will stabilize in this condition for about three weeks [24].

NGF binds specifically to Tropomyosin Kinase Receptor A (TrkA). Activation of this receptor will cause a series of intracellular changes and gene expression responsible for survival, growth and proliferation. NGF that binds to TrkA will activate Ras-Mitogen Activated Protein Kinase (MAPK), Phosphatidylinositol 3-Kinase (PI3K)-Akt, and Phospholipase C gamma (PLC-γ) (Figure 2) [22].

Ras pathway: GTP protein that binds to Ras is activated through a series of adaptor proteins consisting of Shc (Src homology 2-containing protein), Grb2 (growth factor receptor-bound-protein), and Sos (Son of sevenless). After Shc is phosphorylated by TrkA, there will be a bond between these three proteins. This complex then converts GDP to GTP on Ras which causes activation of translocation on the cell membrane. Ras then activates the Raf protein (non-specific serine/threonine protein kinase) which then activates the MAPK (mitogen-activated protein kinases) cascade. This series then induces the transcription factors Elk-1 and CREB (cAMP response element binding protein) so that genes that regulate the defense system (survival) are activated [25].

PI3K pathway: Activation of TrkA kinase forms a complex with PI3K and induces phosphorylation, then converts PIP2 to PIP3 (phosphatidylinositol 3,4,5-trisphosphate). PIP3 plays a role in the activation of PDK-1 (3-phosphoinositide-dependent kinase 1) which then activates the serine/threonine kinase Akt. This causes transcription in genes that play a role in the defense and growth of nerve cells [25].

PLC-γ Pathway: The interaction between TrkA and NGF will activate PLC-γ (phospholipase C gamma) and convert PIP2 (inositol 4,5-bisphosphate) into IP3 (inositol triphosphate) and DAG (diacylglycerol). IP3 binding to specific receptors in the endoplasmic reticulum causes calcium release. Increased intracellular calcium causes DAG to activate PKC-δ (protein kinase C delta), which then makes several downstream effectors that play a role in nerve cell growth and differentiation activated [25]. NGF also binds weakly to the p75NTR receptor, which is one of the transmembrane glycoproteins [23]. Several studies have shown that p75NTR has a dual function, which functions as a signal for defense when working with TrkA and induces neuronal apoptosis when working alone [25].

NF-κB pathway: The binding of NGF to p75NTR causes activation of the NF-κB pathway through a complex formed between TRAF6 (TNF receptor associated factor-6) and IRAK (interleukin-1 receptor-associated kinase). This complex then recruits atypical protein kinase and activates IKK-β. This causes phosphorylation of IκB, so that NF-κB translocates to the nucleus and stimulates genes that play a role in dendritic growth and cell defense [25].

JNK pathway: The binding of NGF to p75NTR also stimulates the JNK apoptosis pathway through specific adaptor proteins recruited by p75NTR. JNK activation causes phosphorylation of

proteins that play a role in apoptosis such as p53, Bax, or Bad. Activation of this protein causes the release of Cytochrome c, and activation of caspase 3 and 9 which move to the nucleus and act as transcription factors in the regulation of apoptosis [25].

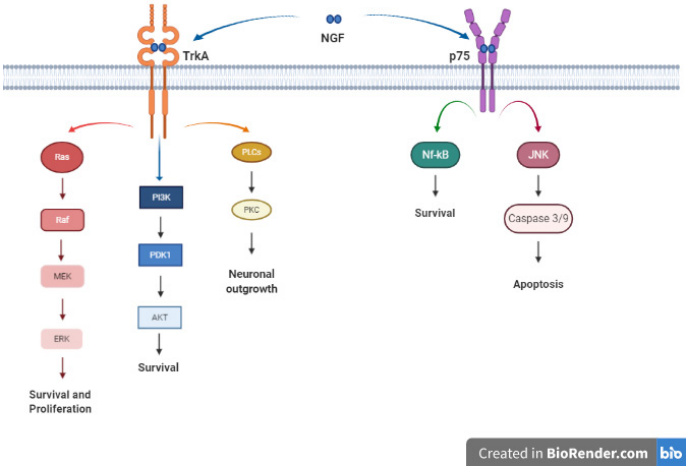

Figure 2: NGF signalling pathway in nerve cells.

Conclusion

In peripheral nerve injuries, both mesenchymal stem cells derived from adipose tissue and from the umbilical cord have the capacity to elevate NGF levels during the axonal regeneration process. Currently, it is recognized that umbilical cord stem cells have the capacity to directly express NGF, stimulate endogenous Schwann cells to produce NGF, and increase the number of specific NGF receptors, specifically TrkA, on nerve cells. In the interim, it is currently recognized that stem cells derived from adipose tissue have the capacity to directly synthesize and release NGF, as well as to stimulate endogenous Schwann cell activity.

Author declarations

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