Role of adipose mesenchymal stem cells and secretome in peripheral nerve regeneration

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Review

Role of adipose mesenchymal stem cells and secretome in peripheral nerve regeneration

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ABSTRACT

The use of stem cells is a breakthrough in medical biotechnology which brings regenerative therapy into a new era. Over the past several decades, stem cells had been widely used as regenerative therapy and Mesenchymal Stem Cells (MSCs) had emerged as a promising therapeutic option. Currently stem cells are effective therapeutic agents againts several diseases due to their tissue protective and repair mechanisms. This therapeutic effect is largely due to the biomolecular properties including secretomes.

Injury to peripheral nerves has significant health and economic consequences, and no surgical procedure can completely restore sensory and motor function. Stem cell therapy in peripheral nerve injury is an important future intervention to achieve the best clinical outcome improvement. Adipose mesenchymal stem cells (AdMSCs) are multipotent mesenchymal stem cells which are similar to bone marrow-derived mesenchymal stem cells (BM-MSCs). The following review aims to provide an overview of the use of AdMSCs and their secretomes in regenerating peripheral nerves.

1. Peripheral nerve injury

Peripheral nerve injury is a health problem which can cause significant disability. Peripheral nerve injury is defined as injury to the major peripheral nerves on the distal side of the nerve root [1]. Peripheral nerve injury can result in severe morbidity for those suffering from sensory loss, motor loss, chronic pain or a combination of those symptoms [2].

2. Epidemiology

In the United States, as many as 1.4 million injuries occur annually, and these injuries usually cause significant functional impairment.

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Abbreviations

AdMSCs	Adipose derived Mesenchymal Stem Cells
BDNF	Brain derived neurotrophic factor
BM-MSCs	Bone Marrow Mesenchymal Stem Cells
CM	Conditioned Media
DFX	Deferoxamine
ECM	Extra Cellular matrix
EGR2	Early Growth Response 2
EVs	Extracellular Vesicles
GDNF	Glial-cell line Derived Neurotrophic Factor
GFAP	Glial Fibrilar Acid Protein
HIF-1α	Hypoxia Inducible Factor 1 alpha
LIF	Leukemia Inhibitory Factor
MBP	Myelin Basic Protein
MPZ	Myelin Protein Zero
MSCs	Mesenchymal Stem Cells
PNI	Peripheral Nerve Injury
PNS	Peripheral Nervous System
SCs	Schwann Cells
SVF	Stromal Vascular Fraction
TGF-β:	Transforming Growth Factor-β
VEGF-A:	Vascular Endothelial Growth Factor-A

Based on several studies, trauma is the most common cause of these injuries. It is estimated that 2.8–5% of all trauma patients have peripheral nerve injury [3].

The most common pathophysiology of peripheral nerve injury is traction injury. The natural elasticity of the endoneurium and perineurium of the peripheral nerves allows the nerve to be stretched within the collagen fibers. If a heavy traction is applied to the nerves, the avulsion can cause anatomic disturbances and complete loss of function. Perineurium has greater elastic strength than endoneurium. Therefore, elasticity is maintained within the stretch-injured nerve until the perineurium is devitalized. Peripheral nerve lacerations resulting from penetrating trauma from the knife and glass account for up to 7% of all brachial plexus lesions. These injuries are usually partial, with the injured nerve segment still present. Another common cause of peripheral nerve injury is direct compression on the nerve. Pressure on this nerve causes mechanical compression and ischemia. Early microvascular damage to nerves can usually be reversed if the adverse mechanism is stopped within 8 h of the initial injury [4].

3. Pathophysiology

There are 3 main cells in the peripheral nervous system (PNS): axonal, glial and stromal cells, arranged in long efferent (motor) and afferent (sensory) fibers that convey information to and from the central nervous system. Nerve fibers in the peripheral nervous system, which convey sensory and motor information between the brain, spinal cord, and other parts of the body, regenerate more easily than nerve fibers in the central nervous system. Unlike central nervous system, neurons in the peripheral nervous system have full regenerative potential after injury. After injury, recovery is controlled by Schwann cells which replicate and modulate the subsequent immune response [4,5].

The peripheral nervous system transmits sensory and motor impulses from the central nervous system to targets throughout the body. This nervous system consists of neurons, glial cells (including Schwann cells), and the supporting stroma. After injury, neurons undergo altered genetic expression leading to release of neurotrophic factors and upregulation of their corresponding receptors. These factors support the axonal lengthening of the injured nerve from its proximal fragment. The damaged axons in the distal nerve fragments undergo degeneration, a process called Wallerian degeneration. Schwann cells (SC) and infiltrating macrophages support this process by clearing myelin debris and secreting neurotrophic factors. In addition, macrophages support the angiogenesis process and form connective tissue bridges in the nerve clefts. Schwann cells form an endoneurial tube called the Büngner band, which serves as a guide for the axonal regeneration process which starts from a growth cone, usually located at the Ranvier's node (Fig. 1). The rate of recovery is most likely directly related to the level of injury [3].

When the axons regenerate, they often get misdirected and do not reach the desired target. This condition leading to the formation of a benign tumor, known as neuroma, due to a disorganized growth of cells associated with peripheral nerves when there is an injury, such as crush, stretch or transection. Neuroma may often cause increasing response of nerves and pain sensitization (allodynia), a pain response from stimuli that normally do not provoke pain [6].

3.1. Classification

The classification of peripheral nerve injury was first described by Seddon and subsequently defined by Sunderland, based on the degree of injury. According to Sunderland, first degree injury is the result of conduction block and is also referred to as neuropraxia. Recovery is complete and usually lasts from a few days to months. Second-degree injuries result from axonal disturbances and are called axonotmesis in the Seddon classification, whereas third-degree injuries affect the axons and endoneurium. Recovery occurs spontaneously and the nerve regenerates at about 1 inch/month, with second degree injuries fully recovered, but only partial recovery can be expected in third degree injuries. Sunderland's fourth and fifth degree injuries (neurotmesis in Seddon's classification) have disturbances in the perineurium, and both perineurium and epineurium. This category includes nerve avulsions and transection, which require surgical intervention [3].

3.2. Regenerative process

Schwann cells have regenerative abilities after peripheral nerve injury. Myelinated Schwann cells and those which are not myelinated are reprogrammed to become Schwann cell progenitors which proliferate and promote the whole regeneration processes [7–9]. This reprogramming process under physiopathological conditions is defined as dedifferentiation or transdifferentiation (Fig. 2), because in addition to re-expressing immature Schwann cell markers, Schwann cell repair exhibits completely different features [10]. Injury that induces conversion to mature Schwann cells in cells that are promoted to regenerate is an active phenomenon. This involves downregulation of pro-myelinating genes including Early Growth Response-2 (EGR-2) which is more commonly called Krox-20, POU domain class 3 transcription factor 1 (Pou3f1 or Oct-6), Myelin Zero Protein (Myelin Protein Zero)/MPZ) or Myelin Basic Protein (MBP), as well as upregulation of markers for immature and differentiated Schwann cells such as c-Jun, low affinity neurotropin receptor (P75NTR) or Glial Fibrilar Acid Protein (GFAP) and it is also supported by gene-specific repair [11]. After damage, the neural network undergoes a complex series of multicellular and molecular events played by Schwann's cells as orchestrators.

Immediately after a nerve injury, the damaged axon on the distal side degenerates in an active process called Wallerian degeneration. An unidentified signal from the damaged nerve causes reprogramming of Schwann cells. These regulating pro-myelin genes begin to clear their myelin sheath via an autophagic mechanism called myelinophagia [12,13]. Axonal and myelin debris are also cleared by resident macrophages and blood-derived-macrophages recruited by Schwann cells [14–16]. An

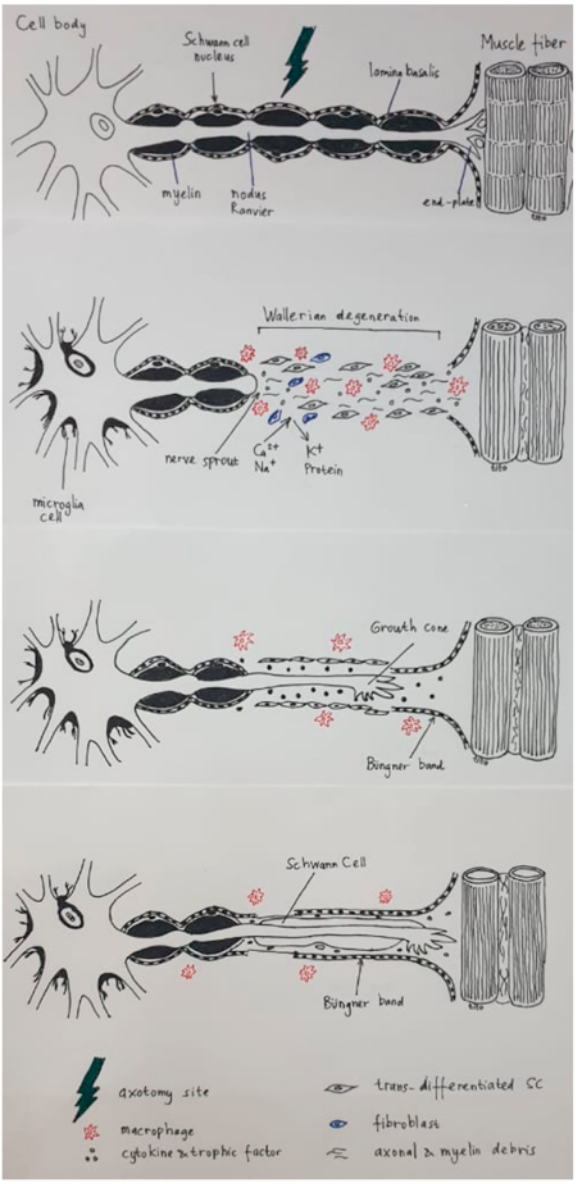

Fig. 1. Degeneration and regeneration of peripheral nerves after injury.

inflammatory reaction occurs, many blood cells migrate to the area of the lesion and secrete many cytokines and chemokines [17–19]. After nerve axotomy, the basal lamina of Schwann cells and connective tissue is severed [20]. A tissue bridge is formed between the two nerve endings over the site of the lesion. Fibroblasts play a major role in building this bridge by interacting with Schwann cells [21]. The newly formed blood vessels play an important role in guiding the growing Schwann cells and axons through the lesion site [22]. Many chemical and physical interactions occur in the injured nerve, creating a permissive and beneficial environment for regeneration [23].

Schwann cells at the distal end proliferate, secreting several trophic factors that support glial and neuronal survival and regrowth including artemin, Brain-Derived Neurotrophic Factor (BDNF) or Glial cell line-Derived Neurotrophic Factor (GDNF) [24–26]. They also form a band called the Büngner band and provide trophic and physical support for the axons to properly regrow and re-energize their targets [12,27]. In the neuromuscular junction, specialized terminal Schwann cells direct reinnervation by helping axons find their way to the appropriate site [28]. After axonal regeneration, Schwann cells immediately exit the cell cycle and redifferentiate into myelinated and unmyelinated Schwann cells to support complete functional recovery. However the newly formed myelin sheath is shorter and thinner than expected based on the axonal diameter [12].

The regenerative process can also be observed in the conduit which consists of five phases: (1) fluid phase, (2) matrix phase, (3) cellular migration phase, (4) axonal phase, and (5) myelination phase.

In the first phase, there is an inflow of plasma, which contains neurotrophic factors and an extracellular matrix, from both the proximal and distal nerve fragments which peak at 3–6 h. Next, acellular fibrin cords are formed between the nerve fragments, starting within 1 week. In the third phase, Schwann cells migrate along the fibrin cord of the nerve fragments to form Bünger bands. During the axonal phase, nerve sprouting is guided by the Bünger band from the proximal to distal nerve fragment and reaches its target after approximately 2–4 weeks. Finally, in the fifth phase, Schwann cells transform into a myelinated phenotype to form myelinated axons 6–16 weeks after repair initiation. When the fibrin cord decreases about 2 weeks after repair, any gaps that Schwann's cells cannot pass within this period will remain, resulting in a critical limit of 3–4 cm [3].

3.3. Mesenchymal stem cells/MSCs

Mesenchymal stem cells/MSCs are unspecified cells that can be isolated from various tissues in the body including bone marrow, adipose tissue, dermal tissue, umbilical cord blood, and synovial fluid [29]. MSCs are currently effective agents for the treatment of many diseases, due to their tissue protective and reparative mechanisms. The therapeutic effectiveness of MSC has been demonstrated by many clinical trials worldwide, with most diseases being treated [30].

3.4. Adipose-derived mesenchymal stem cells (AdMSCs)

Adipose-derived Mesenchymal Stem Cells/AdMSCs, have been shown to have broadly the same biological capabilities as Bone Marrow Mesenchymal Stem Cells (BM-MSCs). The advantages of AdMSCs over BM-MSCs and other types of adult stem cells are relatively easy to obtain from liposuction performed under local anesthesia, can be obtained in large quantities, able to maintain long-term phenotype and plasticity in vitro culture and have low immunogenicity. Thus AdMSCs are attractive and are the most preferred cell type for tissue engineering and regenerative medicine [31–33].

There are more stem cells from adipose tissue than stem cells from bone marrow. One gram of aspirated adipose tissue yielded approximately 3.5×10^5 to 1×10^6 AdMSCs, whereas isolation from 1 g of aspirated bone marrow resulted in 5×10^2 to 5×10^4 bone marrow-derived MSCs (BM-MSCs). In addition, AdMSCs have advantages in terms of proliferation and differentiation as well as age and location of origin which do not have major difference in its therapeutic effect [34].

AdMSCs are considered ideal for applications in regenerative therapy. Their main advantage over mesenchymal stem cells derived from other sources, is that they can be easily and repeatedly harvested using minimally invasive techniques with low morbidity. These cells are multipotent and can differentiate into various cell types from the trigerm lineage, including for example osteocytes, adipocytes, nerve cells, vascular endothelial cells, cardiomyocytes, pancreatic cells, and hepatocytes. Interestingly, AdMSCs are characterized by immunosuppressive properties and low immunogenicity. Their secretion of trophic factors strengthens the therapeutic and regenerative results in a variety of applications. Taken together, the secretion of these trophic factors makes AdMSCs highly relevant for clinical applications [35].

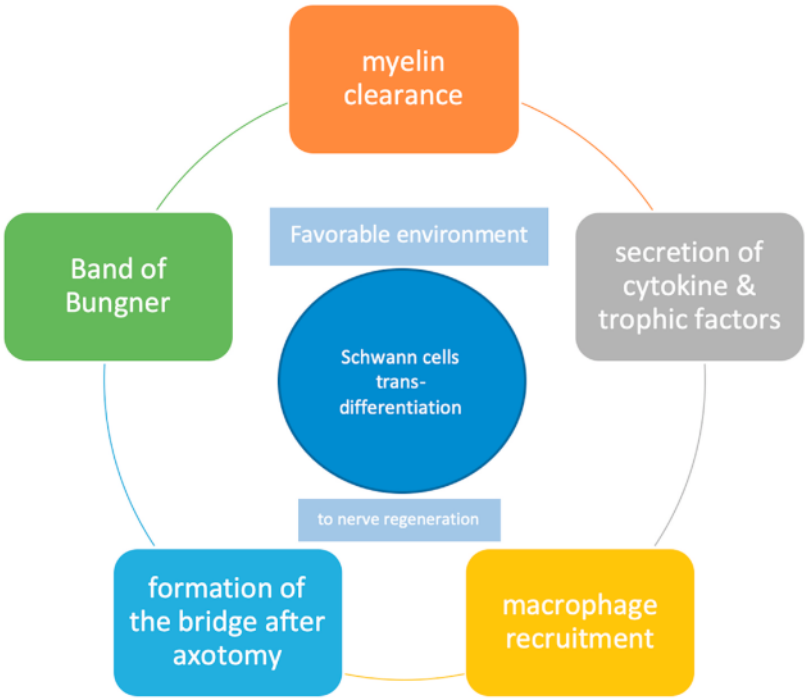

Fig. 2. Schwann cells response to nerve injury.

Zuk and colleagues were the first team to investigate whether human adipose could be an alternative source of Mesenchymal stem cells (MSC). These authors obtained human adipose from aspiration of liposuction and used the collagenase enzyme to release stromal cells from extracellular matrix by processing the stromal vascular fraction (SVF), which contains various types of cells including AdMSCs. The isolated adipose stromal cells were cultured with specified media to induce adipogenic, osteogenic, or chondrogenic differentiation. Adipose stromal cells are capable of developing intracellular lipid stores, alkaline phosphatase expression, or proteoglycan expression, markers that indicate adipose tissue, bone, and cartilage, respectively [36].

To determine whether isolated adipose stromal cells are indeed stem cells, Zuk et al., examined antigen expression as well as surface and differentiation capacity of clonogenic cultures. Using flow cytometry, it was shown that clonogenic cells express surface antigens similar to bone marrow mesenchymal stem cells. In addition to differentiation of the mesenchymal lineage, clonal cells are capable of differentiating into neuron-like cells, as judged by morphology and expression of phenotypic markers. AdMSCs also tend to stimulate angiogenesis, an important feature for regenerative purposes [37–39].

Neurotrophic and angiogenic properties are due to the secretion of Nerve Growth Factor (NGF), Brain-derived Neurotropic Factor (BDNF), Glial Cell-derived Neurotrophic Factor (GDNF), Vascular Endothelial Growth Factor-A (VEGF-A) and angiopoietin-1 [40]. The secretome of AdMSCs is complex, AdMSCs have the ability to secrete proteins involved in angiogenesis, wound healing, tissue regeneration and immunomodulation [41]. AdMSCs have the capacity to differentiate into Schwann cells. Thus, AdMSCs have properties, important for injury healing and can be an attractive source of stem cells for tissue engineering as well as regenerative therapy [42].

Determining whether adipose tissue is a source of MSCs comparable to bone marrow, a comparison of the yield and differentiation capacity of cells isolated from each tissue was performed. de Ugarte et al., found no significant difference in the number of cultured adherent cells per gram of stromal cells obtained from bone marrow or adipose tissue. However more than double the mean mass of adipose tissue (17 gr) could easily be isolated from each patient compared to bone marrow (7gr). There was no difference in the number of cells that developed lipid droplets (adipogenic cells) or osteogenic cells phosphate alkaline activity at cultured isolated cells in various differentiation media. When induced to differentiate into cartilage, adipose derived cells were stained positive for chondrogenesis but absent for bone marrow derived cells [43].

Several other studies have compared the ability of bone marrow and adipose cells to differentiate along this lineage using a similar method, and demonstrated that cells from both tissues have the same capacity to become adipose, bone and cartilage [44–46].

Carbone et al., demonstrated that AdMSCs cultured in conditioned media from chondrocytes and osteocytes were capable of producing glycosaminoglycans and mineralized matrix. These results suggest that AdMSCs require growth factor supplementation from the tissue environment in order to properly differentiate with mesodermic lineages. This evidence suggest that compared to bone marrow, a large number of MSCs capable of differentiating multiple lineages could also be obtained from adipose tissue [47].

3.5. Secretome of adipose derived mesenchymal stem cell (AdMSCs)

Initially, it was believed that the therapeutic effect of AdMSCs came from the migration of these cells to damaged tissue and subsequent homing, proliferation and differentiation to replace damaged or dead host cells. This mechanism of action was redefined in the early twenty-first century when for the first time, Gnecchi and colleagues demonstrated that MSCs mediate their therapeutic effect by releasing a paracrine factor, known as secretome [30]. The MSC secretome is a complex mixture of dissolved products consisting of a soluble protein fraction (formed by growth factors and cytokines), and a vesicular fraction consisting of microvesicles and exosomes, which are involved in the

transfer of protein and genetic material (e.g. microRNA) to other cells, with promising therapeutic effects [48].

Recently there has been a renewed debate about the regenerative effect of these cells. It remains unclear whether AdMSCs exhibit their main effect directly by differentiating into mature cells at the implantation site, or by their paracrine effect of multiple growth factors prominently to promote regeneration/remodeling and modulate inflammation in tissue [49].

The regeneration potential of AdMSCs and therapeutic value also lie in their secretome, which is rich in extracellular proteins and growth factors (Fig. 3) [50].

A number of studies have shown that secretomes contain immunomodulatory, anti-inflammatory, anti-apoptotic, anti-oxidant, anti-fibrotic, anti-bacterial, and neuroprotective properties. Therefore, it can be used in various diseases and represents a ready-made therapeutic agent [51].

Secretomes are hypothesized to enhance endogenous repair and immunomodulating mechanisms. It has even now been proposed that

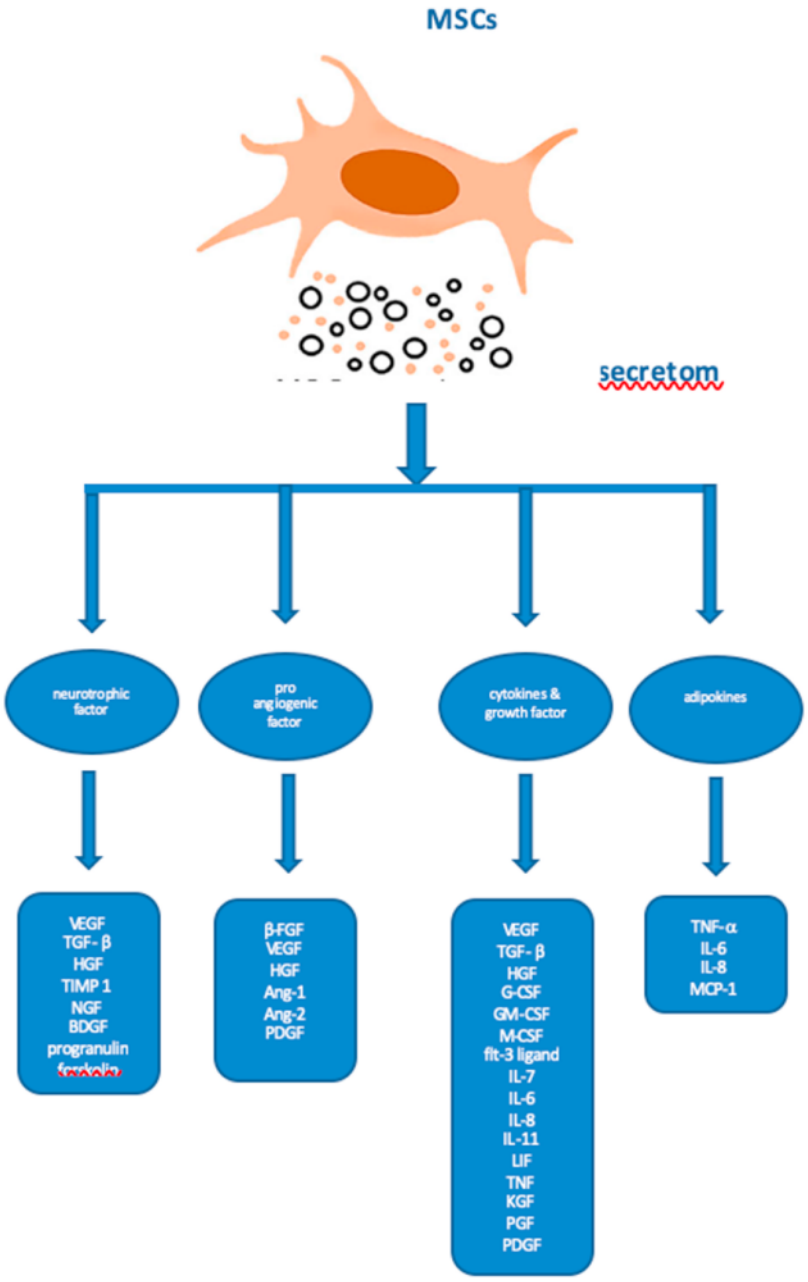

Fig. 3. Secretome of AdMSCs, contain cytokines, growth factors, angiogenic factors, adipokines and neurotrophic factors, so AdMSCs have ability to regenerate and repair the injured tissue.

MSCs are medicinal signaling cells to reflect their mechanism of action more accurately. This increases the likelihood of administering MSCs-derived products as therapy rather than implanting the cells themselves, which would overcome some of the major clinical challenges of MSCs-based therapy [29].

Caplan in 2017 has proposed changing the name of MSCs from Mesenchymal Stem Cells to Medicinal Signaling Cells in order to more accurately demonstrate the fact that these cells are at the site of injury or disease sites and secrete bioactive factors, immunomodulators and regenerative trophic factors, meaning that these cells make in situ therapeutic agents of a medical nature. And the presence of bioactive factors secreted by MSCs after being supplied exogenously, is able to stimulate site-specific resident stem cells and patient-specific tissue to build new tissue for the regeneration process [52].

3.6. The advantages of secretomes

Using a free cell therapy strategy such as the administration of MSCs secretomes provides a major advantage over stem cell transplantation (Fig. 4). First, secretomal strategies address cell survival after transplantation; second, secretome compounds fewer cell surface protein expression giving lower immunogenicity when compared to living cells and proliferative cells [53]; third, using the secretome as a ready-to-use product greatly reduces the immensely high cell counts for transplantation (7×10 [6] cells/kg), as well as the possible phenotypic changes and therapeutic potential due to the expansion of in vitro MSCs long before transplantation; fourth, higher rates of production are possible through the use of dynamically controlled laboratory conditions (eg bioreactors) [48], providing a suitable source of bioactive factors; fifth, in the form of conditioned media, the use of MSCs secretome is more economical and practical for clinical applications because it avoids invasive cell collection procedures; sixth, the MSCs secretome obtained for therapeutic applications can be modified as desired; seventh, the time and costs of developing and maintaining cultured stem cells can be greatly reduced and ready-to-use secretory therapies are readily available for therapy; eighth, MSCs secretomes can be evaluated for safety, dosage and potency in a manner similar to conventional pharmaceutical compounds; and lastly, the MSCs secretome can be stored safely without loss of its potency, regardless of the use of potentially toxic cryoprotectant agents [53].

The MSCs secretomes contain many cell signaling molecules, including growth factors and cytokines that modulate cell behavior such as proliferation, differentiation, and extracellular matrix production or exert pro-inflammatory and anti-inflammatory effects.

Recent study has provided evidence that MSCs also secrete small membrane-bound extracellular vesicles (EV) inviting a number of biomolecules, including not only growth factors and cytokines but also various forms of RNA capable of triggering various biological responses throughout the organism [29].

4. Adipose derived mesenchymal stem cells and its secretome in peripheral nerve injuries

Over the last decade, a number of studies have emerged supporting the neuroprotective and neurotrophic effects of secretory MSCs (Fig. 5). In fact, it is known that the MSCs conditioned media contains a number of neurotrophic factors. Several studies have reported the beneficial effects of MSCs-based approaches in neuronal injury models. These effects include modulation of the environment at the site of inflammation, increased vascularization at the site of regeneration, increased thickness

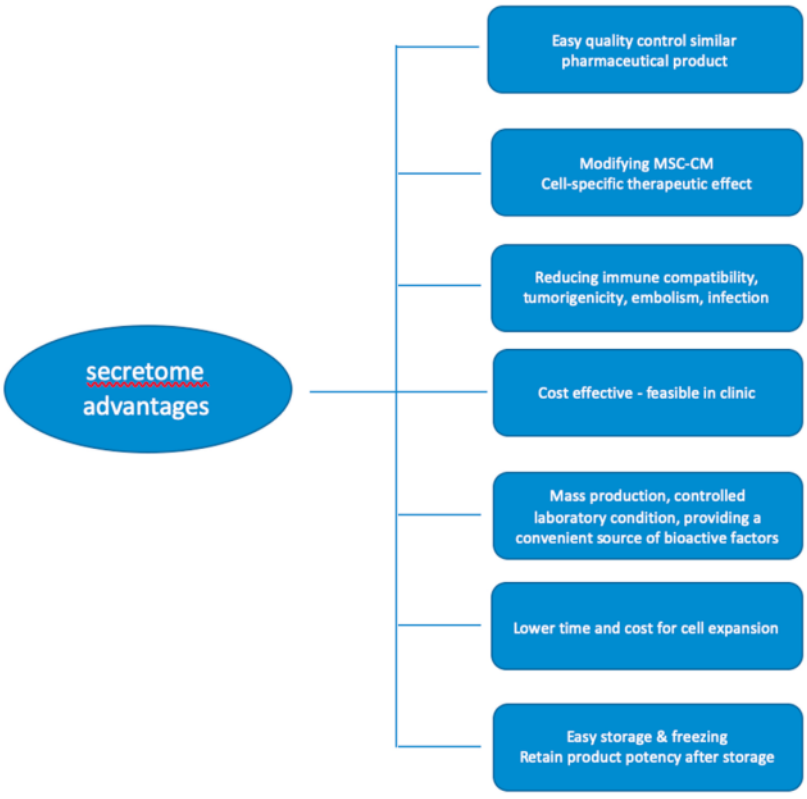

Fig. 4. The advantages of the secretome.

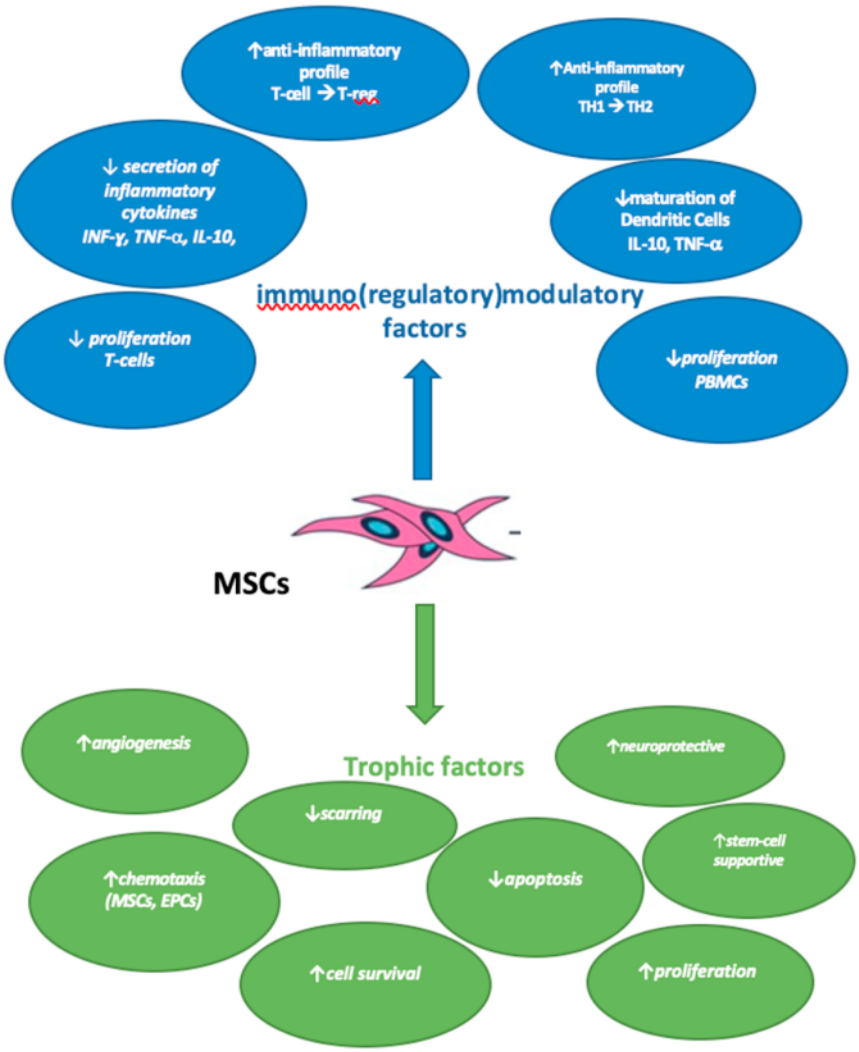

Fig. 5. Immunomodulatory and trophic effects on mesenchymal stem cells.

of the myelin sheath, modulation of the stage of Wallerian degeneration, accelerated regeneration of nerve fibers and increased number of nerve fibers, decreased scar fibrosis, and increased nerve fiber organization [53].

The analysis of substances examination showed that the secretome contains increased concentrations of FGF, VEGF-A, and NGF which play a role in the health of nerve tissue and blood vessels. In addition, AdMSCs are known as immunomodulators through the regulation of immune cells through mechanisms that include direct cellular contact and the release of dissolved factors such as TGF-β, IL-10, LIF and others [54].

In experimental mice model, Brini et al., demonstrated the effects of both human mesenchymal stromal cells of adipose tissue (hASC) and their conditioned media (hASC-CM) on neuropathic diabetes. Both restored the correct pro/anti-inflammatory cytokine balance and prevented the loss of innervation of the skin [54].

Many studies have shown the ability of AdMSCs to increase nerve regeneration in experimental animal models with peripheral nerve injury, but how to increase nerve regeneration remains unclear. An unanswered question that seems to have great relevance at present is "Is the tissue regeneration directed by AdMSCs a result of their differentiation into the desired cell type, or do AdMSCs initiate the healing process (regeneration) by influencing the surrounding tissue via a paracrine signaling mechanism ?" Regarding nerve regeneration, does the ability of AdMSCs as neurotrophic mediators trigger an intrinsic healing response that result in nerve regeneration ? A review of the current literature on the use of AdMSCs in peripheral nerve regeneration has been conducted and compared different approaches to transplantation, differentiation and utilization of these cells in models peripheral nerve injury. The answers to these questions will substantially assist the development of a comprehensive cell-based regenerative approach to the management of the peripheral nerve injury using the AdMSCs that accompany in vitro cell differentiation [33,55].

The function of paracrine AdMSCs in nerve regeneration is related to the role of dissolved growth factors. These growth factors can induce vascularity, protect tissue or suppress host inflammatory pathways to promote healing [33]. Like BM-MSCs that secrete several growth factors, namely insulin-like growth factor-1 (IGF-1), vascular endothelial growth

factor (VEGF), fibroblast growth factor 2 (FGF-2), platelet-derived growth factor (PDGF) and BDNF [56,57]; AdMSCs showed the same gene expression characteristics in the study by comparing the expression profiles of neurotrophic factors of the two sources of MSCs [58] and also express level of certain growth factors such as VEGF, CNTF and NGF [39,58,59]. The similar neutrophin secretion by these two sources of MSCs suggests that they could be promising MSCs as neurotrophic modulators of nerve regeneration. These paracrine factors are called secretomes and could be central to a new theory of tissue regeneration modulated by the secretion of specific solute factors [60].

The number of soluble growth factors secreted by AdMSCs includes VEGF, hepatocyte growth factor (HGF), NGF, BDNF and a number of interleukins [60]. VEGF is considered to be the most important secretome involved in the transformation of in vivo healing, through increased vascularity and neoangiogenesis which form the backbone of regenerative events [61–64]. Associated with this angiogenic-derived, hypoxia becomes a stimulus for VEGF-induced vascularization. The conditioned media, obtained from AdMSCs under hypoxic culture conditions, has been used to increase the production of HGF, VEGF and transforming growth factor-β (TGFβ), increase endothelial cell growth, and reduce apoptosis [65]. Currently, secretomes are thought to be involved in the regeneration of various types of tissue and in pathophysiological healing responses. In the context of nerve regeneration, VEGF, basic fibroblast growth factor (bFGF), HGF are important growth factors, as well specific growth factors/neurotrophins such as BDNF, NGF, GDNF, and neurotensin-1 (NT-1) relevant to this process [66].

Although AdMSCs have the ability for neurogenic transformation, most of the in vivo studies have not demonstrated direct differentiation of AdMSCs transplanted into neurons [33]. Many researchers now consider the regeneration capacity of AdMSCs to be more possible through paracrine factors than differentiation of AdMSCs [67–70]. This effect is due more to the secretion of neurotrophic factors by the AdMSCs. Several studies have shown that certain neurotrophic factors such as BDNF, NGF, and GDNF are increased in conditioned media from culture of AdMSCs [33,68,71–73]. AdMSCs were able to promote intrinsic healing using host cells under the orchestration of resident Schwann cells. In addition, there is a role for paracrine factors in the immunosuppressive effects of AdMSCs [33].

Administration of AdMSCs to sciatic nerve injury has been shown to accelerate functional recovery in mice. This peripheral nerve regeneration mechanism involves the ability of AdMSCs to synthesize factors such as BDNF, bFGF, and IGF-1 in vitro and the ability of AdMSCs to induce GDNF production by Schwann cells in vivo. AdMSCs do not appear to produce GDNF in vitro. GDNF is an important trophic factor for neuronal survival, and the ability of AdMSCs to induce GDNF production by Schwann cells, despite the lack of GDNF production in cell culture, provides convincing evidence for the use of AdMSCs as a powerful neuromodulator in nerve repair [74].

The neuromodulatory effect of AdMSCs is very interesting, given the limited availability of Schwann cells and the difficulty in purifying them [75]. The effect of AdMSCs in injured mice was an increase in fiber growth and a decrease in inflammatory infiltrates. The results of the research by Marconi et al. (2012) led them to the conclusion that the effect of AdMSCs in the repair of sciatic nerve damage involves autocrine and paracrine mechanisms.

AdMSCs are reported to synthesize and release NGF, BDNF, GDNF; and secrete NGF, BDNF, neurotrophin-3 (NT-3), GDNF, CNTF, and leukemia inhibitory factors (LIF) [74,76,77]. In addition, Lopatina et al. (2011) demonstrated increased mRNA coding levels for some of these neurotrophins at the site of injury in animals transplanted with AdMSCs. The most commonly measured neurotrophic factors are NGF, BDNF and GDNF.

Factors secreted by mesenchymal stem cells can have an immunomodulatory effect or a regenerative/reparative (trophic) effect. Immunomodulatory factors (immunoregulation) provide an antiproliferative effect on T-cells, reduce the secretion of anti-inflammatory cytokines, change the inflammatory profile of T-helper 1 cells towards a more anti-inflammatory T-helper 2 profile, and increase the number of anti-inflammatory T-regulatory cells. Dendritic cell maturation decreases, which is accompanied by a change in secretion profile. Trophic factors secreted by mesenchymal stem cells induce angiogenesis, increase mobilization of stem cells and progenitors after injury, increase cell survival and proliferation, and support stem cells, and reduce scar tissue (fibrosis) and apoptosis [78].

There are several limitations of transplanting mesenchymal stem cells such as poor engraftment and low survival rates of these cells in areas of injury, so it is necessary to optimize the viability of mesenchymal stem cells by modifying the cells using some stimulation. Therefore, it is urgently needed to develop new strategies to increase the regenerative efficiency of mesenchymal stem cells. In vitro pretreatment (preconditioning) strategies can improve the survival, implantation and growth (engraftment), and paracrine effects of mesenchymal stem cells thereby optimizing their reparative and regenerative capacities [79].

Preconditioning human adipose tissue-derived MSCs with 150 μM or 400 μM iron chelator deferoxamine (DFX) for 48 h, increases the availability of Hypoxia Inducible Factor - 1α (HIF-1α) in a concentration-dependent manner, without affecting the morphology and viability of MSCs. This initial condition increases the expression of NGF, GDNF, and neurotrofin-3, and cytokines with anti-inflammatory activity such as IL-4 and IL-5. In addition, therapeutic useable molecules were also elevated in the secretomes of DFX-conditioned MSCs compared with the secretomes obtained from previously unconditioned cells. In addition DFX initial conditioning significantly increased the total anti-oxidant capacity of MSC secretions and they exhibited neuroprotective effects when evaluated in an in vitro neuropathic model of diabetes [80].

AdMSCs-CM reduces oxidative stress in stressed SH-SY5Y neuron-like cells and restores cell morphology, viability, and electrophysiological activity. This restructuring activity is associated with the presence of antioxidants and growth factors, such as BDNF, GDNF, and TGF-β1. Other studies have shown that VEGF-A and VEGF165b, derived from AdMSCs and AdMSCs-CM, are effective at reducing pain levels in oxaliplatin-treated neuropathic mice [50].

Based on the evidences above, AdMSCs and AdMSCs-Conditioned Media (Secretome) appear to be a potential agent for peripheral nerve regeneration.

Consent

Written informed consent was obtained from the all of the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the corresponding author of this journal on request.

Ethical approval

This is review article, no need ethical approval.

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The authors declare that this study had no funding resource.

Author contribution

Tito Sumarwoto, Heri Suroto, Ferdiansyah Mahyudin, Dwikora Novembri Utomo, Romaniyanto, Cita Rosita Sigit Prakoeswa, Fedik Abdul Rantam and Sholahuddin Rhatomy conceived the study. Sholahuddin Rhatomy, Tito Sumarwoto, Romaniyanto, and Heri suroto collected data. Sholahuddin Rhatomy, Dwikora Novembri Utomo, and Ferdiansyah Mahyudin analysed data. Sholahuddin Rhatomy, Tito Sumarwoto, Heri Suroto, Dwikora Novembri Utomo, Cita Rosita Sigit Prakoeswa, Fedik Abdul Rantam and Ferdiansyah Mahyudin prepared

and drafted the manuscript. Sholahuddin Rhatomy, Heri Suroto, Dwikora Novembri Utomo, and Ferdiansyah Mahyudin edited manuscript. Sholahuddin Rhatomy, Tito Sumarwoto and Dwikora Novembri Utomo reviewed the manuscript. Rhatomy and Sumarwoto, Sholahuddin Rhatomy, Tito Sumarwoto, Hari Basuki Notobroto and Damayanti Tinduh prepared, reviewed, edited and improved the final revision manuscript.

Registration of research studies

This is review article, no need registration of research studies.

Guarantor

Sholahuddin Rhatomy,MD.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10