Gingival mesenchymal stem cells, concentrated growth factors and silk-fibroin scaffold to alleviate peripheral nerve regeneration

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GINGIVAL MESENCHYMAL STEM CELLS, CONCENTRATED GROWTH FACTORS AND SILK-FIBROIN SCAFFOLD TO ALLEVIATE PERIPHERAL NERVE REGENERATION : A REVIEW

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Abstract : Peripheral nerve injury in the orofacial region often occurs due to dental procedure, trauma, or pathological obstruction. It can lead to loss of sensation and muscle innervation problems which decrease a patient's quality of life. Some medical approaches to achieve peripheral nerve regeneration such as surgical still have side effects. Tissue engineering approach with combination of Gingival Mesenchymal Stem Cells (GMSC), Concentrated Growth Factor (CGF) and Silk-Fibroin (SF) scaffold have potential to accelerate peripheral nerve regeneration. Peripheral nerve injury leads to activation of Wallerian degeneration as a complex mechanism that can maintain repair Schwann cell differentiation by induced signaling response. In peripheral nerve regeneration, neuropathic factors are needed to assist nerve cell proliferation and differentiation. However, functional recovery failure often occurs because of insufficient axonal regeneration. Thus, tissue engineering has potential properties to alleviate peripheral nerve generation because GMSC has the ability to differentiate into neuron cells expressed neurogenic-associated markers which are βIII-tubulin and glial fibrillary acidic protein (GFAP); CGF is one of growth factors that is able to hasten nerve regeneration by increasing Schwann cells proliferation and neurotrophic factors (NGF and GDNF) to achieve nerve recovery; and SF is a scaffold and nerve conduit that is biocompatible, biodegradable, and not immunogenic. All those components fulfil the principle of triad tissue engineering to alleviate peripheral nerve regeneration. GMSC, CGF and SF scaffold may have promising properties to alleviate peripheral nerve regeneration.

Key words : Gingival mesenchymal stem cells, concentrated growth factor, medicine, nerve injury, nerve regeneration.

INTRODUCTION

Peripheral nerve injury can bring an issue to loss of sensation and muscle innervation problems with the symptoms are such as paresthesia, neuropathic pain, paralysis as results of defect in the motor or sensory nerve (Grinsell and Keating, 2014). Major traumatic nerve injuries need surgical approach to achieve the reinnervation of the objective organs. Thus, non-invasive and fast procedure is needed. Biomaterials for nerve channel designing are often chosen to reflect the microarchitecture found along nerve sheaths. In spite of the fact that cells are micron-sized, nerves contain significantly littler nanometer scale sensory machinery which has impact cell motility and orientation, thus has been utilized to upgrade neurite augmentation and axon regrowth through impersonating local ECM (Mozafari, *et al*, 2019).

MATERIALS AND METHODS

This review article was searching from different databases, which are ScienceDirect, NCBI, Scopus and ResearchGate. The keywords for this independent literature research are Schwann cells, wallerian degeneration, neurotrophic factors, nerve regeneration, axonal sprouting failure, stem cells, mesenchymal stem cells, gingival mesenchymal stem cells, concentrated growth factors, nerve conduit, scaffold and silk fibroin hydrogel. Authors use several criteria to compile the data which are (1) All the journal and/or book in English; (2) Basic theories, clinical trials, observational study; (3) Books from the past 10 years (2010-2020) and journals from the past 5 years (2015-2020). Any related investigations were likewise looked to advance primary

study.

Schwann cells and its plasticity

Schwann cells are widely known as one of the most important neurogenic cells that plays big roles in the peripheral nervous tissue regeneration ability, which is not found in the central nervous tissue. The immature Schwann cells could develop into various phenotypes of Schwann cells, namely myelinating Schwann cells, non-myelinating (Remak) Schwann cells or repair Schwann cells according through various signaling and tissue conditions. Myelinating Schwann cells mainly found in larger axons meanwhile non-myelinating axons mainly found in smaller axons. Injured nerve tissue caused an elevating c-Jun signaling response to activate repair program by dedifferentiating Schwann cells to repair cell phenotype and inhibit myelin gene expression. These repair cells act an important role to autophagocyte myelin debris, secreting pro-inflammatory cytokines and neurotrophic factors. These cells also proliferate in a big number to form a tract named Bands of Bungner to connect proximal stump and distal stump to guide axonal elongation and sprouting towards target tissue. Repair Schwann cells could phenotypically transform back into myelinating or non-myelinating Schwann cells on fully regenerated axons (Mirsky and Lloyd, 2015; Jessen and Mirsky, 2016; Boerboom *et al*, 2017; Castelnovo *et al*, 2017; Quintes and Brinkmann, 2017).

Wallerian degeneration: neuronal inflammation and its resolution

Peripheral nerve tissue responds to nerve injury through a complex process called Wallerian degeneration. Wallerian degeneration occurs from the injury site to the target tissue and it needs 24–48 hours after injury to degenerate myelin debris followed with axonal regeneration rate 1 mm/day (Grinsell and Keating, 2014). The degeneration aims to clear the nerve tissue from myelin and axon debris through various neuro-inflammation mechanisms. Clearance of the debris might be important to eliminate the axon growth inhibiting characteristic that found in myelin-associated glycoprotein (MAG) molecules in injured matured myelin. Free MAG molecules were found to bind to $p75^{NTR}$ and induced neurite colapse (McGregor and English, 2019; Rotshenker, 2015).

Wallerian degeneration in injured nerve tissue started with disrupted calcium influx and induced various signaling responses such as c-Jun to transform repair Schwann cells and STAT3 to maintain repair Schwann cells's differentiation and survival in long-term (Benito *et al*, 2017). This process further leads to demyelination from its respective axon and starts to autophagy to initiate debris clearance. An axonal breakdown occurs along with the demyelination process retrogradely at the distal stump (Jang *et al*, 2016; Wong, Babetto and Beirowski, 2017). These debris might lead to damage-associated molecular patterns (DAMPs) release that will activate neuro-inflammation through various signaling. Previous studies elaborate the involvement of toll-like receptors (TLR) 1, 3, 4 and 7 signaling in Schwann cells in inflammation activation and initiation (Lee, Min and Cho, 2016; Boerboom *et al*, 2017). The signaling lead to expression and secretion of various inflammatory cytokines by Schwann cells in large number, such as chemokine chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), interleukins (ILs)-1, IL-6, granulocyte colony-stimulating factor (GM-CSF) and Galectin-3 to induce resident macrophages activation and monocytes recruitment in the process of large-scale phagocytosis. At this phase, Schwann cells and macrophages only secrete a small amount of IL-10, indicating an importance of the pro-inflammatory phase in Wallerian degeneration (Rotshenker, 2015).

Wallerian degeneration occurs as long as myelin and axon debris still exist, as remyelination can only occur in a fully cleared tissue environment. Duration needed might be different in each study according to its injury severity and length. This states the importance of neuroinflammation acceleration and activity to reach its resolution faster (Grinsell and Keating, 2014).

Neurotrophic factors

Neurotrophic factors are important in the process of peripheral nerve development, maintenance and regeneration. Various neurotrophic factor were reported before, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), glial cell derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF) which are secreted by Schwann cells. These neurotrophic factors, mainly BDNF and NGF are involved in neuronal survival, growth and regeneration through each respective receptor and signaling pathway (Önger *et al*, 2017).

BDNF mainly secreted through Ca^{2+} dependent secretory pathway and its mature molecule protein mainly binds with tropomyosin receptor kinase B (TrkB) under pathologic condition. Their binding results into the activation of 3 signaling pathway: phospholipase C gamma (PLCγ), phosphotidyl-inositol-3 kinase (PI3K) and mitogen activated protein kinase/extracellular receptor kinase (MAPK/ERK). PI3K signaling pathway known to induce actin transport towards growth cones and

elevates its growth rate. Meanwhile, MAPK is known to induce cAMP production and stability by inhibiting phosphodiesterase (PDE), which play a big role in transcription factors activity and remyelination initiation. Whereas PLCγ signaling pathway activates protein kinase C (PKC) through diacylglycerol (DAG) production (Benarroch, 2015; Sasi *et al*, 2017; McGregor and English, 2019).

NGF is one of the neurotrophins secreted by Schwann cells through constitutive secretory pathways. NGF was found mainly secreted in sensory nerve tissue (McGregor and English, 2019). It is involved with peripheral nerve cell maintanance, innervation, axonal growth and neurotransmitter induction. NGF functions by binding to TrkA and activating PI3K results in the activation of its downstream pathway, such as mammalian target of rapamycin (mTOR) and glycogen synthase kinase 3β (GSK3β). The activation enhances neurogenic cells proliferation and differentiation. NGF also enhances MAPK signaling to inducing myelination further and its compactivity (Li, 2020).

Nerve regeneration: axonal sprouting failure and its guidance importance

Axon regrowth is an important aspect in the nerve tissue regeneration process where its success mainly affects the nerve fiber functional recovery. Various studies state the finding of functional recovery failure caused by inadequate axonal regeneration. The failure can be caused by the lack of repair Schwann cells, especially in chronic transect injury. Low number of Schwann cells might alter the Bands of Bungner formation which acts important as a guidance of axonal elongation to target tissue. This condition might lead to misdirection of the axon sprouting causing functional recovery failure. The lack of Schwann cells also lead to deficit number of neurotrophic factors secretion to maintain neuronal regeneration. It also lead to reduced Wallerian degeneration response causing an prolonged and inadequate inflammation at surrounding nerve tissue leading to inefficient debris clearance and presence of growth-inhibiting molecules. Slow rate growth of axon make the condition worse, especially in transectly injured motor nerves where it possibly lead to muscle atrophy (Mietto *et al*, 2015; Jessen and Mirsky, 2019). Hence, an Schwann cells proliferation and differentiation acceleration might be an efficient target for further study.

Gingival mesenchymal stem cell

Gingival mesenchymal stem cells (GMSC) is potential sources of nerve regeneration, due to limited sources of human neural stem cell (Li *et al*, 2018). GMSC was chosen because it is homogeneous, nontumorigenic, easily separated and phenotypically stable (Nugraha *et al*, 2018a; Nugraha *et al*, 2019a). GMSCs can differentiate into mesenchymal lineage such as osteogenic differentiation that expressed RUNX2, osteocalcin, osteopontin, osteonectin, Alkaline phosphatase, and express chondrogenic differentiation such as sox9 and aggrecan (Nugraha *et al*, 2018b-d; Nugraha *et al*, 2019b-c). Several study have been proved that GMSC has neurogenic potential for neural regeneration. Zhang *et al* (2016) stated that GMSC can directly induced neural progenitor like cells (iNPC), these cells increased neurotrophic factor GDNF and pro-angiogenic factor VEGF. iNPC can differentiate into neuronal and Schwann cell and showed potential effect to axonal regeneration.

The mechanism of GMSC to regenerate peripheral nerves is to differentiate directly into neural progenitor like cells which later differentiate into neuronal cells and Schwann cells. GMSC have autocrine and paracrine effects to trigger of nerve regeneration processes and increase cell survivability by expressing growth factors such as FGF, NGF, CNTF, BDNF, GDNF and VEGF. These factors also trigger the migration of endogenous Schwann cells towards the damaged part. VEGF expressed also triggers angiogenesis in nerve tissue, which helps to transport nutrients and signaling to damaged nerve parts. GMSC also has an immunomodulatory ability to reduce the inflammatory response that occurs by inhibiting the formation of excess proinflammatory cytokines so prevent over-activation of lymphocyte T cells and NK cells that prolonged inflammation process (Zhang *et al*, 2016; Hu *et al*, 2017; Mathot, Shin and Van Wijnen, 2019; Rao *et al*, 2019).

After two weeks of neuronal-differentiation, GMSCs have neural-like cells morphology and expressed neurogenic-associated markers which are βIII-tubulin and glial fibrillary acidic protein (GFAP) (Ansari *et al*, 2017). Previous study also found that GMSC-cultured Schwann cells shown significant increase in c-Jun, GFAP, STAT3 and Notch1, indicating the acceleration of Schwann cell transformation into repair cell type. It was also shown that GMSCs enhance Schwann cells proliferation rate by 52% by increasing Schwann cells marker S100β expression through paracrine action and further induced major myelin transcription factor Krox20 (Zhang *et al*, 2016; Mao *et al*, 2019). Increased Schwann cells proliferation might affect to increased neurotrophic factors secretion (Rao *et al*, 2019). It also elevate the Bands of Bungner forming ability of the Schwann cells, proved by Zhang *et al* (2016) states that a more organized and nearly similar to normal fiber was found on GMSCs-

induced iNPCs than in control group.

Concentrated growth factor acceleration

Concentrated growth factor (CGF) is the latest platelet concentrate containing abundant level of growth factors, such as transforming growth factor- β1 (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and insulin-like growth factor-1 (IGF-1) (Chen and Jiang, 2020). Administration of these exogenous growth factor elevate the activity of the already presence endogenous growth factor and giving various benefits towards nerve regeneration.

One of the most studied growth factor, TGF-β1 was reported to binding TGF-β receptor II (TGF-βRII) in Schwann cells and activating Smad2 further leading to AKT signaling. The process leads to elevated cell's proliferation and differentiation rate, meanwhile it also could attract hematogenous macrophages to injury site. These properties might affect Wallerian degeneration acceleration leading to more effective axonal elongation (Li, 2015; Sulaiman and Nguyen, 2016). Meanwhile, IGF-1 binds to its receptor IGF-1R in Schwann cells and enhance its proliferation, differentiation and survival through MAPK and PI3K signaling pathway (Bianchi, Locatelli and Rizzi, 2017). CGF also could enhance extraceluller matrix (ECM) formation which is important in neurotmesis injury regeneration where the epineurium was damaged (Chen and Jiang, 2020).

Utilization of CGF is assumed to give a huge benefit to peripheral nerve regeneration by regulating and stimulating cells activity and metabolism. Based on study conduct by Qin *et al* (2015), it was stated that CGF extracts can increase Schwann Cells proliferation with 100% CGF extracts as optimum dose; CGF-treated group have more glial GDNF and NGF mRNA expression compared to control; and functional nerve recovery in CGF-treated group are significantly higher than control group. It shows that CGF can accelerate nerve regeneration by increasing Schwann cells proliferation, neurotrophic factors (NGF and GDNF) secretion and nerve recovery.

Silk fibroin hydrogel as nerve conduit

Effective nerve recovery requires appropriate axon direction, crossing over of the injury site, reestablishing synaptic associations, and remyelination. Scaffold for facial nerve repair ought to imitate major physicochemical properties of the objective tissue's local ECM. Scaffold's physical properties (harshness and topography) and mechanical characteristics (solidness and versatility) impact cell morphology, with consequences for gene expression, expansion, relocation, and separation. Silk fibroin (SF) as scaffold offers high versatility, biocompatible, biodegradable, not immunogenic, facilitates angiogenesis, conveniently processed and purified in different 2D/3D shapes (Alessandrino *et al*, 2019; Mozafari, Sefat and Atala, 2019). Based on Teuschl *et al* (2015), SF has ability to be nerve conduit, from this study it showed that SF is not cytotoxic to Schwann cells; has resistant properties to external force; no inflammatory response or neuroma with partial integration between SF and nervous tissue in proximal and distal end (day 1 observation); and complete regenerated tissue and reconnection in both nerve end (day 3 observation). Encapsulated SF has correlation with secrotome activity as neurotherapeutic potency in mesenchymal stem cells (MSC). SF averts the negative regulation of TNF-α on BDNF, VEGF, SDF-1, but significantly expands the secretion of TGF-β1 (Martín-Martín *et al*, 2019). Triad tissue engineering (cells, growth, factors, scaffold) are required to enhance the quality and speed of axon growth and to improve nerve regeneration and repair.

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