Therapeutic techniques for Neural Regeneration in the Central Nervous System

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Scientists have studied multiple approaches that have been thought to enhance neural regeneration. These approaches have led to the development of groundbreaking treatment for age-related diseases and nerve injuries. The development and use of these treatments are vital because spinal cord injuries and traumatic brain injuries alone affect 90,000 people every year; approximately 10,000 mostly young individuals are affected by acute spinal cord injury and 50,000 die from traumatic brain injury each year (Stabenfeldt et al., 2006). It is also important to note that neurodegenerative diseases, such as Alzheimer's or Parkinson's disease, are affecting a large portion of the aged population worldwide. As the average human lifespan is expected to increase over time, the number of people within the population affected by such diseases is projected to grow by mid-century (Alzheimer's Association, 2016). Thus, by recovering nerve functionality after injury, nerve regeneration techniques have great potential to conquer the problems that are projected to affect a significant amount of the general population. Therefore, techniques such as neural tissue engineering is a rapidly growing field of research that has the potential to achieve efficient nerve regeneration. Nevertheless, most clinical treatments are limited to symptomatic methods, as in vivo approaches in neural regeneration are yet to be utilized. In this article, current limitations and newly developed methods of neural regeneration are to be introduced, as well as suggestions on possible future improvements for clinical adaptations.

One of the greatest problems in neural injuries is that, in contrast to the peripheral nervous system, the central nervous system (CNS) is generally incapable of self-repair or regeneration. Spontaneous regeneration of the CNS is mainly due to functions of inhibitory factors, and little is uncovered about this mechanism of inhibition. Yet in the late twentieth century, an explanation for the functional recovery of the CNS was introduced based on the concept of neuroplasticity, the CNS's ability to anatomically and functionally adapt to changes. In addition, the concept of reactive synaptogenesis was also proposed in 1979. Reactive synaptogenesis is the process in which neighboring neurons form new synaptic contacts to replace those lost, contributing to a restoration of function following brain injury. As a result, several methods, including the use of stem cells, brain drug delivery, and implanting degradable biomaterial, have been actively researched to enhance regeneration in CNS. Studies have found that specific brain regions including the subventricular zone (SVZ), the adjacent rostral migratory stream (RMS), and the circumventricular organs (CVOs) might be responsible for modulating the regenerative ability of neural stem or progenitor cells. Neural stem cells that are possibly responsible for neurogenesis are expressed by filament proteins, nestin, vimentin, GFAP, and transcription factor Sox2 in the SVZ of the anterolateral ventricle and subgranular zone of the hippocampus. Similarly, studies using rat models identified Sox2 and the cell cycle-regulating protein Ki67 in CVOs, and therefore proposed that CVOs play important roles in stem-cell based neurogenesis as well as SVZ and RMS (Bennett et al., 2009).

SVZ, RMS, and CVOs share the common trait of lacking protection provided by the blood-brain barrier (BBB) compared to other parts of the brain. BBB is a unique form of cellular membrane that is relatively impermeable compared to the membranes of other body parts because its capillary walls have no pores and the capillaries are lined by astrocytes. Limited permeability of BBB has been one of the most limiting restrictions in brain drug delivery research. However, because SVZ, RMS, and CVOs have more "leaky" BBBs, they are more likely to perceive damage and engage in brain repair by producing new neurons which cross to other parts of the brain.

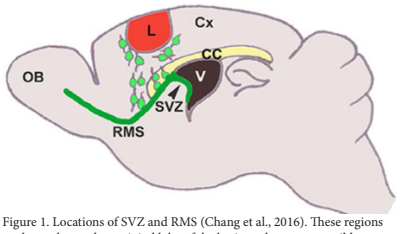

Figure 1. Locations of SVZ and RMS (Chang et al., 2016). These regions are located near the occipital lobe of the brain and serve as possible sources of stem cell regulation.

In addition, several neuroprotective and neuroregenerative drugs have been developed to treat neurodegenerative diseases. Nevertheless, most of them are not utilized because they are generally incapable of crossing the BBB, followed by rapid clearance from the blood circulation by the reticuloendothelial system (RES). For example, molecules like Z-DEVD-FMK and basic fibroblast growth factor (bFGF) were found to significantly induce neuroregeneration in in vitro studies. However, neither can pass the BBB in their free form or do so in very low amounts, displaying limited efficacy in potential clinical uses (Yemisci et al, 2015). Thus, to stimulate these brain regions and to utilize the drug molecules that have been found to contribute to neurogenesis, intravenous injection of nanoparticles (NP)

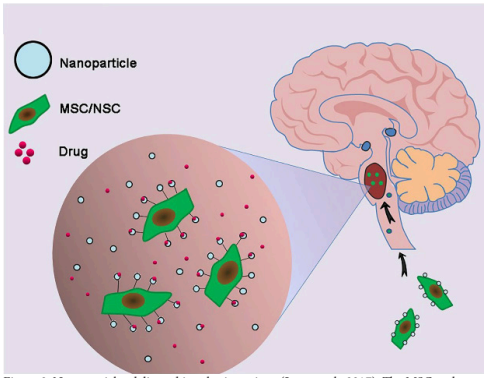

Figure 2. Nanoparticles delivered into brain regions (Long et al., 2017). The MSC and NSCs are types of stem cells that can carry nanoparticles into the brain and allow for transfusion and delivery of the desired drug, which has been experimented with for in vivo studies.

through.

NPs are well-defined particles ranging in sizes of approximately 10 to 1000 nm (1 μm) with a core-shell structure (nanocapsules) or a continuous matrix structure (nanospheres) (Kreuter, 2014). Researchers have uncovered that specific forms of NP (angiopep-conjugated poly(ethylene glycol)-copoly(ε-caprolactone) nanoparticles or ANG-PEG-NPs) pass through the BBB and accumulate in certain brain areas such as the ventricles, hippocampus, and cortical layer. Also, chitosan NPs and cationic bovine serum albumin-conjugated tanshinone IIA PEGylated NPs showed promising results in crossing the BBB and therefore increase drug efficacy. Moreover, these NPs have the inherent ability to elicit neuroprotective effects by themselves. For example, by down-regulating pro-inflammatory cytokines, up-regulating anti-inflammatory cytokines and transforming growth factor-β1 (TGF-β1) these NPs modulate inflammatory processes and neuronal signaling pathways (Saraiva et al., 2016).

More specifically, among other NP formulations, solid lipid nanoparticles (SLNs) are expected to enhance efficiency in brain-targeted drug delivery system. In the late 1900s, researchers found that surfactant coating on NPs increases blood NP level along with the total NP brain amount in in vivo studies. Several mechanisms were proposed to explain this increase, one being that increased NP retention in the brain blood capillaries, and their absorption into the capillary walls may create a higher concentration gradient, which enhances transportation across the BBB, leading to brain drug accumulation. Another explanation may be that NP endocytosis by endothelial cells can permit the drug release within these cells and the following drug diffusion in the brain parenchyma, or the transcytosis of NPs with the bound drug can release directly into the brain parenchyma, along with multiple other possible explanations. Although these mechanisms are still being studied, previous experimental results have shown that the use of surfactant-coated SLNs plays a role in brain-targeting drug delivery that induces neural regeneration as a possible treatment to neurodegenerative diseases (Blasi et al., 2007).

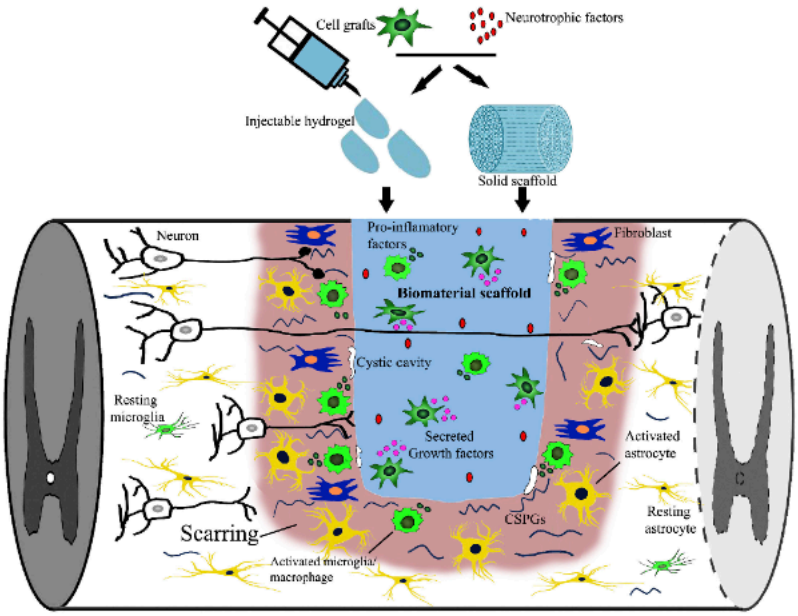

Figure 3. Mechanism of hydrogel-induced neural regeneration (Liu et al., 2018). The cell grafts and neurotrophic factors are injected via a hydrogel into the muscle scaffolding. The integration of the cells + neurotrophic factors lead to activation of astrocytes, microglia, and a variety of other neurons that are involved with the repair mechanism within the tissue.

Another way to induce enhance neuroregeneration is to directly implant active biomaterials such as hydrogels. Hydrogels are used in the same drug delivery system as NPs but act differently through inducing neurogenesis by mimicking neural growth conditions. Biomaterials can be useful because the systemic delivery of pharmaceuticals usually results in reduced efficacy over time. This is predominantly due to failure to meet the needs for continuous drug delivery, along with possible side effects followed by repeated drug administration (Gerndt et al., 1997). In treatments of spinal cord injury (SCI), the drug-releasing biomaterial has been proposed as a new solution to overcome these obstacles. Polymer-based materials, including hydrogels, particles, and fibers/conduits, are implantable or sometimes injectable; they can prevent detrimental side effects of drugs delivered systemically, such as a compromised immune system.

Such biomaterials are targeted to provide structural support to regenerating axons and glia migrating into the injury site. They also aim to provide a similar mechanical and biological environment as those of the nerve tissue matrix and degrade over time to be replaced by regenerating tissue. For instance, hydrogels are injected into the intrathecal space of the spinal cord, most commonly in treatments of contusive SCI. For an acute injury, hydrogels are injected onto the contusion injury site, and solidified gels onto the hemisection injury site. For secondary injury, hydrogels incorporating particles are injected onto the contusion injury site, and solidified gels with particles onto the hemisection injury site. A small cavity grows within the contusion injury during the proliferation and chronic injury phases. Fibers are positioned below the dura within the contusion injury space, while the conduit scaffolds within the hemisection injury connect to the healthy tissue. In a study conducted in 1995, Arg-Gly-Asp peptide-functionalized PHPMA hydrogels promoted angiogenesis and extension of axons and glial cells (Woerly et al., 1995). In addition, agarose is another injectable biodegradable material as it solidifies following injection according to changes in the environment such as temperature and pH. Brain-derived neurotrophic factors (BDNF)-formulated agarose can solidify when cooled post-injection; nevertheless, the appropriate mechanism to cool the material in situ should still be concerned (Nguyen & Lee, 2010).

Regenerative capability of biomaterials is based on

its ability to deliver appropriate growth factors or critical components of the extracellular matrix (ECM), bind the same receptor as their natural counterpart to promote cell attachment, spreading, and proliferation. These peptides, such as the most common examples, tripeptide RGD and multidomain peptide (MDP), are attached to syringe-deliverable hydrogels and are subcutaneously implanted into the injury site to provoke neurogenesis and angiogenesis resulting in the dense vascular network. As discussed above, these biomaterials predictably degrade over time and replaced with the regenerating cellular matrix.

One of the greatest concerns in this approach is the immune response to the implanted biomaterials. Injections generally lead to an acute inflammatory response as hydrogels are frequently recognized as foreign material (Moore et al., 2018). Several aspects such as the local context of biomaterials influence the innate properties of the implanted biomaterials that form the extent of the immune response (Sadtler et al., 2016). Thus, multiple approaches are being discovered to minimize the potentially harmful immune response in treatments involving biomaterial injection.

As both approaches, drug delivery via nanoparticles and direct injection of biomaterials, have distinct compatibility in treating different neuroregeneration-related diseases or injuries, combining these techniques can be a possible solution to overcome inherent problems in these methods (Schmidt & Leach, 2003). Followed by more extensive research in individual techniques, an appropriate combination of these could result in significant improvements of multiple neurological illnesses by inducing neural regeneration in different situations as needed.

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