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Living scaffolds for neuroregeneration

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ABSTRACT

Neural tissue engineers are exploiting key mechanisms responsible for neural cell migration and axonal pathfinding during embryonic development to create living scaffolds for neuroregeneration following injury and disease. These mechanisms involve the combined use of haptotactic, chemotactic, and mechanical cues to direct cell movement and re-growth. Living scaffolds provide these cues through the use of cells engineered in a predefined architecture, generally in combination with biomaterial strategies. Although several hurdles exist in the implementation of living regenerative scaffolds, there are considerable therapeutic advantages to using living cells in conjunction with biomaterials. The leading contemporary living scaffolds for neurorepair are utilizing aligned glial cells and neuronal/axonal tracts to direct regenerating axons across damaged tissue to appropriate targets, and in some cases to directly replace the function of lost cells. Future advances in technology, including the use of exogenous stimulation and genetically engineered stem cells, will further the potential of living scaffolds and drive a new era of personalized medicine for neuroregeneration.

1. Overview

The brain, spinal cord, and peripheral nervous system have limited capacity for regeneration, making the effects of neurotrauma or neurodegenerative disease particularly devastating and often permanent. Successful regeneration would involve a precisely orchestrated reestablishment of neural connections and reformation of cellular structure, often requiring directed long-distance axonal pathfinding and neuronal/glial migration. The objective of the field of neural tissue engineering is to utilize biomaterial- and cell-based strategies to augment endogenous regeneration and/or to provide direct replacement of neural cells and circuitry. A particularly promising tissue engineering approach involves the development of "living scaffolds", which are regenerative scaffolds comprised of living neural cells in a preformed, often anisotropic, three-dimensional (3-D) architecture. Living scaffolds may facilitate targeted neural cell migration and axonal pathfinding by mimicking key developmental mechanisms. Indeed, directed axon growth and cell migration along pathways formed by other cells is a common tactic in nervous system development and is crucial to the proper formation of axonal connectivity and cellular localization. Growth and migration along living neural cells is driven by juxtacrine signaling involving the concurrent and often synergistic presentation of a panoply of cell-mediated haptotactic, chemotactic, and neurotrophic cues (Fig. 1). Living scaffolds exploiting these cues possess considerable advantages over more traditional acellular biomaterial approaches due to their capacity to *actively* drive and direct regeneration rather than simply being *permissive* substrates. Moreover, living scaffolds have the ability for constitutive and sustained interactions rather than transient, often short-lived influence on the host. Importantly, living scaffolds may act based on feedback and cross talk with regenerating cells/axons and thus are able to modulate their signaling based on the state and progression of the regenerative process. On this front, there are a number of promising emerging strategies for the development of living regenerative scaffolds consisting of aligned glial cells and/or longitudinal axonal tracts that have driven robust and targeted axonal re-growth and neural cell migration. However, there are several significant challenges to the development and translation of living scaffolds, including advancing tissue engineering techniques for the creation of living cellular constructs in a defined 3-D architecture, establishing transplantation strategies to ensure preservation of construct vitality and architecture, and devising strategies for immunological tolerance

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in both acute and chronic time frames. As these challenges are overcome, living scaffolds have the potential to transform the field of neuroregenerative medicine by driving the re-establishment of complex neural structures and axonal connections, ultimately facilitating functional recovery following a range of currently untreatable traumatic and neurodegenerative disorders.

2. Definition of living scaffolds

The field of regenerative medicine encompasses the use of biomaterials, cell replacement strategies, and tissue engineering to promote regeneration following injury or disease. Biomaterials can provide 3-D structure for host cell infiltration and organization, and may also serve as a means for drug administration (e.g., controlled release). Cell delivery strategies can replace lost cells in cases where endogenous cells are insufficient or unavailable (e.g., new neurons). Tissue engineering combines aspects of both biomaterial and cell replacement techniques to create 3-D constructs to facilitate regeneration of native tissue and/or to directly restore lost function based on permanent structural integration [1]. An emerging strategy in neural tissue engineering involves the development and application of "living scaffolds", which are defined as constructs with a controlled, often heterogeneous and anisotropic 3-D cellular architecture and biomaterial composition. The objective of these living cellular-biomaterial scaffolds is to serve as chaperones to support, guide, and aid regenerating cells and/or processes (e.g. axons) – mimicking crucial aspects of developmental pathfinding. The cells impart the "living" component of the scaffold, and incorporated cell types may include primary, stem, differentiated, genetically engineered, autologous, allogeneic, or heterologous cells [1,2]. Biomaterials utilized within the scaffold often provide structure and produce an environment in which cells can adhere, migrate, differentiate, and signal to each other and to the host [3]. The biomaterial composition often governs the mechanical properties of the construct and resulting tissue [3]. A crucial property of a living scaffold is that it must possess a defined architecture, encompassing both the structural composition as well as the organization of the cells/processes (Fig. 2). This architecture must be precisely engineered to match the structure and properties of the tissue it will integrate with, or to provide directionality for infiltration and targeted re-growth of host cells. Biomaterials may be synthesized to promote such a desired cellular organization or to give directional dependence to mechanical properties, such as rigidity and elasticity [3]. Likewise, gradients of co-delivered factors, such as growth factors and signaling molecules, may be used within living scaffolds to generate an anisotropic cytoarchitecture [4].

3. The challenges to nervous system repair and regeneration

The nervous system, encompassing both the central nervous system (CNS) and peripheral nervous system (PNS), is comprised of two major cell types: neurons and glia. Neurons typically receive electrical signals via branched projections called "dendrites" and transmit these signals along fibers called "axons". Glia (CNS: astrocytes, oligodendrocytes, microglia; PNS: Schwann cells) generally act as support cells to provide structure, protection, and nutrients to neurons and insulation to axonal projections. A variety of insults can lead to neuronal and glial cell loss, including traumatic injury, stroke, and neurodegenerative diseases. In addition, disconnection of axonal pathways is a common feature across multiple types of neurotrauma and neurodegenerative disorders. Unfortunately, functional regeneration of these connections rarely occurs due to long distances to appropriate targets and a lack of directed guidance. Injury to the CNS often initiates a robust inflammatory response, leading to a non-permissive environment for regeneration. Astrocytes convert to a "reactive" state and may form a dense barrier of hypertrophic processes and inhibitory molecules in order to protect the nervous system from further damage. This barrier, termed the "glial scar", is long lasting and obstructs the growth

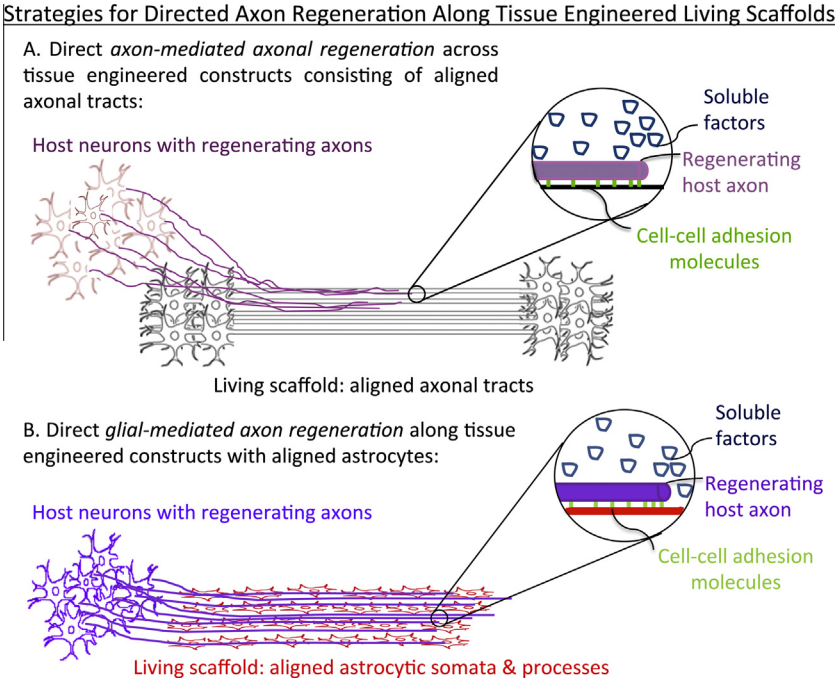

Fig. 1. Structural and soluble cues directing axonal outgrowth along "living scaffolds". (A) Axon growth is directed along existing axonal tracts ("pioneer" axons in development or tissue engineered axonal tracts in regeneration) due to a combination of a precise spatial presentation of cell-adhesion molecules (CAMs) and the intimate presentation of secreted chemotactic and neurotrophic factors. (B) Axon guidance may also progress along aligned astrocytic somata and processes, where the presentation and/or gradients of CAMs, extracellular matrix constituents, and secreted neurotrophic factors promote axon guidance. Similarly, "living scaffolds" may also be applied to facilitate and direct cell migration to reconstruct complex neural tissue structure (not shown).