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Review

The fundamental role of subcellular topography in peripheral nerve repair therapies

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ABSTRACT

Clinical evidence suggests that nano- and microtopography incorporated into scaffolds does not merely improve peripheral nerve regeneration, but is in fact a prerequisite for meaningful restoration of nerve function. Although the biological mechanisms involved are not fully understood, grafts incorporating physical guides that mimic microscopic nerve tissue features (e.g., basal laminae) appear to provide a significant advantage over grafts that rely on purely chemical or macroscopic similarities to nerve tissue. Investigators consistently demonstrate the fundamental importance of nano- and micro-scale physical features for appropriate cell response in a wide range of biological scenarios. Additionally, recent *in vivo* research demonstrates that nerve regeneration scaffolds with cell-scale physical features are more effective than those that rely only on chemical or macro-scale features. Physical guidance at the cell-scale is especially important for long (>20 mm) nerve defects, for which the only reliable treatment is the autologous nerve graft. The lack of other available options exposes a clear need for the application of nano- and microfabrication techniques that will allow the next generation of engineered nerve guides to more closely mimic native tissue at those scales. This review examines current research to determine what elements of cell-scale topography in experimental scaffolds are most effective at stimulating functional recovery, and then presents an overview of fabrication techniques that could potentially improve future treatment paradigms. Relative advantages and disadvantages of these techniques are discussed, with respect to both clinical adaptation and likely effectiveness. Our intent is to more clearly delineate the remaining obstacles in the development of a next generation nerve guide, particularly for long defects, and offer new perspectives on steering current technologies towards clinically viable solutions.

1. Introduction

Although a clear and compelling need exists for strategies that can restore motor and sensory nerves following injury, clinical technologies for promoting nerve regeneration remain limited [1]. Despite an improved understanding of the natural process of peripheral nerve regeneration and the availability of sophisticated biomaterials and fabrication techniques, no artificial nerve guide has been developed that approaches the “gold standard” for peripheral nervous system (PNS) repair, the autologous nerve graft (“autograft”). The autograft has been successful at effecting regeneration, but leaves patients with functional deficits caused by removal of the graft nerve from the donor site, particularly in cases where defects extend over several centimeters or more [2].

In an effort to avoid the problems associated with the autograft, several artificial nerve guides have been developed and approved for clinical use. In a recent review of these clinically approved nerve guides [3], the authors summarize criteria for an idealized guide based on the results of current research. Among the stated criteria, the authors conclude that the guide should be biocompatibile and nonimmunogenic, selectively biodegradable over the time period required for regeneration, flexible and soft, and semi-permeable. The most commonly used artificial nerve guide in clinical use is NeuraGen® (a product of Integra Lifesciences), which is a hollow, resorbable collagen tube. Although NeuraGen® meets the above-mentioned criteria, and is quite successful for short defects (<20 mm) [4], it is limited in its utility for longer defects. As a result, artificial nerve guides like NeuraGen® could not be considered a viable alternative for the autograft, except for short nerve defects.

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