Genetic Approaches to Tissue Repair

DAVID V. SCHAFFER

University of California, Berkeley, Berkeley, California 94720-1462, USA

KEYWORDS: gene therapy; tissue engineering; stem cell replacement

Genetic approaches for tissue repair and regeneration lie at the interface of two exciting fields—gene therapy and tissue engineering. As these two fields advance towards maturity, combining their successes may yield new and powerful therapeutic avenues. However, a number of challenges must still be overcome before this promise can translate into a therapeutic reality.

Gene therapy for tissue regeneration is currently faced with a number of questions, and further research is required to elucidate the correct solutions for specific therapeutic applications. First, when tissue undergoes injury due to either disease or trauma, a choice must be made between rescuing the damaged cells or replacing them, and each path offers particular challenges. For cell rescue, the choices of the therapeutic gene and the mode of delivery will determine the outcome. For cell replacement, a new supply of cells, such as stem cells, must be identified, and the basic biology of their function and behavior must be sufficiently understood before we can most effectively coax them into integrating with and regenerating damaged tissue.

The first major challenge is then the development of improved gene delivery vehicles. Earlier in the development of this field, gene delivery was most often conducted *ex vivo*. For example, delivery to the nervous system, our laboratory's target tissue, often involved retroviral gene delivery of growth or neurotrophic factors to autologous fibroblasts or myoblasts, followed by grafting to the site of injury. Although this approach has recently entered clinical trials for Alzheimer's disease, the development of efficient direct gene delivery vehicles is generally more attractive than the *ex vivo* use of these cell types due to reduced complexity and potentially equal chances for success. A number of vehicles, both viral and synthetic, are under development for direct gene transfer, although they vary widely in a number of properties including efficiency, immunogenicity, and sustained and regulatable expression of the transgene cargo. Even with the more successful adeno-associated and lentiviral vehicles, improvements in efficiency are still required, and careful quanti-

Address for correspondence: David V. Schaffer, University of California, Berkeley, 201 Gilman Hall, Mail Stop 1462, Berkeley, CA 94720-1462.

Ann. N.Y. Acad. Sci. 961: 68–70 (2002).

tative analysis of the gene delivery pathway can provide the information needed for further vector engineering. Furthermore, the directed evolution of vectors is a promising, emerging approach that may lead to enhanced performance and mechanistic understanding of vehicles.

In addition to enhancing the capabilities of the vehicle, we must improve our understanding of the cargo. Specifically, gaining a deeper grasp of the molecular mechanisms of cell injury and death will provide us with data to guide our choice of a therapeutic gene. Apoptosis has emerged as a ubiquitous mode for cell death in many types of tissue injury, and the elucidation of signaling pathways involved in this process has led to identification of molecular targets for its inhibition. For example, the use of growth factors and antiapoptotic genes in models of CNS injury has led to cell rescue in animal models. However, further careful analysis of the branching of the apoptotic signaling cascade may lead to the identification of optimal targets for intervention since inhibiting or halting the process at different stages of its progress could make the difference between cell death, nonfunctional cell survival, or fully functional recovery.

Finally, we must deepen our understanding of the most attractive cellular targets for gene delivery. Stem cells have recently emerged as exciting targets for tissue regeneration, and it is particularly in this exciting area that the advances of gene therapy can combine with those of the field of tissue engineering. The gene therapy field recognizes that, in contrast to many differentiated cell phenotypes, stem cells are potentially permanent residents of the body, and transducing them will therefore potentially have the most lasting therapeutic effects. Tissue engineers view stem cells as promising renewable cell sources for the development of artificial tissues and organs. However, genetic modification of these cells may aid in their ability to differentiate and integrate into functional tissue, and this approach represents a combination of the most powerful aspects of both fields. However, we must understand stem cell biology at a more basic level before such efforts can be generally successful. In particular, the factors and signaling pathways that control stem cell survival, proliferation, and differentiation must be elucidated. As development has taught us, the quantitative nature of these instructive signals may be a key determinant of the resulting cell responses.

Progress has been made in utilizing principles from engineering product design to enhance the properties of vectors for *in vivo* gene delivery to the nervous system. In addition, signal transduction in adult neural stem cells has been analyzed, at a quantitative and mechanistic level, to gain a better understanding of how to control and harness these cells for neural regeneration.

Genetic enhancement of stem cells for tissue engineering and regeneration can potentially combine many of the advantages of the approaches described above. If stem cells can be instructed to differentiate towards a particular lineage and functionally integrate into a tissue, they can replace cells that have been lost in a patient. In addition, genetic modification not only may assist in controlling their behavior, but may also revive *ex vivo* gene delivery of growth or other therapeutic factors to regenerate the surrounding tissue. Quantitative and mechanistic analysis of gene delivery, stem cell biology, and the molecular pathology of disease will provide valuable data to enable such efforts and advances in the converging fields of gene therapy and tissue engineering.[1,2]

REFERENCES

1. SCHAFFER, D.V. & D.A. LAUFFENBURGER. 2000. Targeted synthetic gene delivery vectors. Curr. Opin. Mol. Ther. **2:** 155–161.
2. LAUFFENBURGER, D.A. & D.V. SCHAFFER. 1999. The matrix delivers. Nat. Med. **5:** 733–734.