Mechanical Loading / Rehabilitation as a Determinant Factor in Constructive Remodeling of Biologic Scaffolds

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Introduction

A need exists for regenerative medicine strategies that can enhance the innate regenerative ability of skeletal muscle and/or induce de novo formation of functional muscle tissue following volumetric muscle loss (VML). Biologic scaffolds composed of extracellular matrix (ECM) have been successfully used in numerous preclinical and clinical studies to promote constructive remodeling of a variety of damaged tissues, including skeletal muscle (1-6). The ECM scaffold provides an instructive and inductive microenvironment that modulates the default scar tissue response following injury toward a constructive remodeling response. While the exact mechanisms responsible for this ECM-mediated constructive remodeling response are only partially understood; several preclinical in vitro and in vivo studies as well as an ongoing clinical trial have suggested that tissue-specific mechanical loading is essential for a functional outcome (7,8). The objective of the present study was to define the mechanisms by which mechanical loading facilitates the constructive remodeling response of biologic scaffolds.

Materials and Methods

The effect of mechanical loading on the constructive remodeling response of biologic scaffolds was examined using in vitro and in vivo test systems. In the in vitro experiments, uniaxial or equibiaxial mechanical loading for 24 or 72 hours was used to evaluate the effect of biologic scaffolds on the proliferation, differentiation, and polarization of multipotent perivascular stem cells (PVSC) and naïve macrophages, respectively. In the in vivo experiments, a rodent VML model (9) with and without administration of site appropriate mechanical loading was used to examine the host response to a biologic scaffold following 3, 7, 14, or 90 days (n=4 / group / time point). The host response to each experimental group was determined by quantitative evaluation of histology, stem cell accumulation, and macrophage polarization (M1/M2) immunolabeling of explants.

Results

In the in vitro model, mechanical loading in conjunction with biologic scaffold materials increased the rate of proliferation and myogenic differentiation of PVSC. In the rodent model, application of mechanical loading to a biologic scaffold in a site of VML augmented the macrophage polarization response and facilitated a constructive remodeling response following 14 days.

Discussion and Conclusions

The present study shows that the combination of a biologic scaffold with an immediate and robust site appropriate mechanical loading / physical rehabilitation regimen is essential for the generation of de novo formation of functional skeletal muscle tissue in a site of VML, likely through the recruitment and differentiation of multipotent stem cells and augmented macrophage polarization. Such a regimen differs markedly from the current standard of care and would represent a significant advancement in the clinical treatment of traumatic soft tissue injury.

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References