Biologic Scaffolds Composed of Extracellular Matrix Promote a Constructive Macrophage Phenotype

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Introduction

Macrophages are a heterogeneous cell population capable of obtaining distinct phenotypes with diverse functions [1]. Classically activated pro-inflammatory (M1) macrophages propagate a pro-inflammatory immune response while alternatively activated constructive (M2) macrophages are immunomodulatory and promote tissue repair. A heterogeneous macrophage cell population is an essential, required component for a regenerative response in adult mammals following skeletal muscle injury [2]. Moreover, specific depletion of M2 macrophages results in impaired inherent regeneration and the formation of scar tissue [3].

Biologic scaffolds composed of mammalian extracellular matrix (ECM) have been used to promote constructive and functional remodeling in a variety of tissues including skeletal muscle [4, 5]. The mechanisms behind this constructive response include local modulation of the host innate immune system, among others. Specifically, ECM implantation sites have been shown to be associated with a predominant M2 macrophage phenotype [6].

Materials and Methods

Bone marrow was harvested from C57BL6/J mouse long bones and treated with MCSF over 7 days for derivation of naïve (M0) macrophages. M0 macrophages were treated with: 20 ng/ml IFN-γ and 100 ng/ml LPS to derive M1 macrophages, 20 ng/ml IL-4 to derive M2 macrophages, or with 200 µg/ml ECM degradation products. Following 18 hrs of treatment the cells were fixed and immunolabeled for indicators of M1 (iNos) vs. M2 (Fizz1) macrophages.

ECM scaffolds were surgically placed within sites of skeletal muscle injury in a mouse model of volumetric muscle loss (VML) [5]. Scaffold implantation sites were examined for the presence of M1 vs. M2 macrophages in terms of their iNos and Fizz1 expression.

Results

Results show that degradation products of ECM directly promote the constructive M2 macrophage phenotype in vitro.

Discussion and Conclusions

The use of ECM bioscaffolds has resulted in favorable remodeling outcomes that are associated with a predominant M2/Th2 initial immune response. The present study suggests that degradation products of ECM directly promote M2 macrophage polarization.

References