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Macrophage phenotype as a predictor of constructive remodeling following the implantation of biologically derived surgical mesh materials

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ABSTRACT

Macrophages have been classified as having plastic phenotypes which exist along a spectrum between M1 (classically activated; pro-inflammatory) and M2 (alternatively activated; regulatory, homeostatic). To date, the effects of polarization towards an M1 or M2 phenotype have been studied largely in the context of response to pathogen or cancer. Recently, M1 and M2 macrophages have been shown to play distinct roles in tissue remodeling following injury. In the present study, the M1/M2 paradigm was utilized to examine the role of macrophages in the remodeling process following implantation of 14 biologically derived surgical mesh materials in the rat abdominal wall. In situ polarization of macrophages responding to the materials was examined and correlated to a quantitative measure of the observed tissue remodeling response to determine whether macrophage polarization is an accurate predictor of the ability of a biologic scaffold to promote constructive tissue remodeling. Additionally the ability of M1 and M2 macrophages to differentially recruit progenitor-like cells in vitro, which are commonly observed to participate in the remodeling of those ECM scaffolds which have a positive clinical outcome, was examined as a possible mechanism underlying the differences in the observed remodeling responses. The results of the present study show that there is a strong correlation between the early macrophage response to implanted materials and the outcome of tissue remodeling. Increased numbers of M2 macrophages and higher ratios of M2:M1 macrophages within the site of remodeling at 14 days were associated with more positive remodeling outcomes ($r^2 = 0.525–0.686$, $p < 0.05$). Further, the results of the present study suggest that the constructive remodeling outcome may be due to the recruitment and survival of different cell populations to the sites of remodeling associated with materials that elicit an M1 vs. M2 response. Both M2 and M0 macrophage conditioned media were shown to have higher chemotactic activities than media conditioned by M1 macrophages ($p < 0.05$). A more thorough understanding of these issues will logically influence the design of next generation biomaterials and the development of regenerative medicine strategies for the formation of functional host tissues.

1. Introduction

Biologic materials composed of extracellular matrix (ECM) have been harvested from a wide variety of tissues and organs and have been used in a similarly wide variety of preclinical and clinical applications [1,2]. It has been shown that ECM based materials, if prepared and utilized appropriately, are capable of acting as inductive templates for the formation of site-specific functional host tissues following implantation [3–5]. Alternatively, if processing methods do not effectively decellularize the source tissue, involve chemicals that create non-degradable molecular cross-links, or leave residual reagents in the ECM, then the in vivo remodeling response is less desirable and characterized by chronic inflammation, fibrotic encapsulation, and scar tissue formation [6–8]. The mechanisms by which biologic mesh materials elicit either "constructive remodeling" or chronic inflammation, however, are only partially understood.

The process of tissue remodeling following implantation has been shown to be invariably associated with a robust macrophage response beginning as early as two days post-implantation and continuing for several months depending on the mesh material and the clinical application in which it is used [8]. The prolonged presence of macrophages at a site in which the remodeling outcome can range from scarring to healthy functional tissue formation suggests a central, and perhaps determinant, role for macrophages in tissue remodeling following surgical mesh implantation.

Activated macrophages possess diverse, plastic phenotypes that play an important role in the host inflammatory response and the process of tissue repair and remodeling following injury [9–14].

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