The effect of source animal age upon the in vivo remodeling characteristics of an extracellular matrix scaffold

Brian M. Sicaria, Scott A. Johnson, Bernard F. Siu, Peter M. Crapo, Kerry A. Daly, Hongbin Jiang, Christopher J. Medberry, Stephen Tottey, Neill J. Turner, Stephen F. Badyla

ABSTRACT

Biologic scaffolds composed of mammalian extracellular matrix (ECM) are routinely used for the repair and reconstruction of damaged or missing tissues in a variety of pre-clinical and clinical applications. However, the structural and functional outcomes have varied considerably. An important variable of xenogeneic biologic scaffolds is the age of the animal from which the ECM is derived. The present study compared the in vivo host response and remodeling outcomes of biologic scaffolds composed of small intestinal submucosa (SIS)-ECM harvested from pigs that differed only in age. Results showed that there are distinct differences in the remodeling characteristics as a consequence of source animal age. Scaffolds derived from younger animals were associated with a more constructive, site appropriate, tissue remodeling response than scaffolds derived from older animals. Furthermore, the constructive remodeling response was associated with a dominant M2 macrophage response.

1. Introduction

Biologic scaffolds composed of xenogeneic extracellular matrix (ECM) are derived by the decellularization of mammalian tissues and have been used in both pre-clinical and clinical settings for the reconstruction of damaged or missing tissues [1–3]. ECM scaffolds can alter the default wound healing response from the well described pro-inflammatory and scarring events toward a more constructive remodeling response, i.e., the site appropriate formation of functional tissue, in a variety of anatomic locations including dermis [4], esophagus [5,6], skeletal muscle [3,7,8], and heart [10–12], among others. Results of such clinical applications have varied considerably [13–18], and the variables, which affect outcome, are only partially understood. Two intuitively important determinants of the remodeling outcome are the physical and biologic properties of the ECM scaffold material itself, and the innate immune response of the recipient. Modulation of macrophage phenotype, a critical component of the innate immune response, has been shown to play a prominent role in the scaffold remodeling outcome [19,20], but the effect of the age of tissue from which the ECM scaffold is prepared has been largely ignored.

Mammalian fetal wound healing is characterized by site- and tissue-specific regeneration and minimal scar tissue formation; a distinct contrast to wound healing in adults [21]. This tissue regeneration response is associated with selected pro-inflammatory events [22,23], increased capacity for wound closure [24,25], and a distinct ECM composition [26–29]. The ECM present in fetal tissues is enriched in glycosaminoglycans, which facilitate the proliferation and migration of a number of cell types [26,30,31]. The collagen content of fetal ECM is less mature and contains fewer cross-links when compared to adult ECM [32]. Minimal collagen cross-linking facilitates rapid ECM turnover and remodeling. Because of these characteristics, it is plausible that biologic materials derived from neonatal or newborn tissues may be better suited as inductive scaffolds than biologic scaffold materials derived from older animals.

The diverse remodeling outcomes associated with ECM scaffold use can also be attributed to variables such as processing methods [8], source species and tissue origin of the ECM [33], post implantation mechanical load [34], and decellularization efficiency [35]. Because the response to tissue injury is known to be more favorable and robust in young vs. aged mammals, some biologic scaffolds use source materials that include ECM derived from fetal cells or...