Drug Discovery Today: Disease Models
Vol. xxx, No. xx 2018

Models for evaluating the immune response to naturally derived biomaterials

Jenna L. Dziki[1,2], Stephen F. Badylak[1,3,*]

[1]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, United States
[2]Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States
[3]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, United States

The immune response to biomaterials has emerged as a critical determinant of tissue repair outcomes and is complex, involving multiple cell types, distinct spatiotemporal phenotypes, and is influenced by variables including processing of the material and host-related factors. This interaction between implanted material and the host immune cells has stimulated interest in analytical methods to characterize the immune response. The present review discusses these methods including *in vitro*, *in vivo*, *ex vivo*, *in silico*, and combination models utilized to evaluate the immune response to biomaterials and their applicability to clinical scenarios. Recent developments in modeling the immune response to emerging technologies that may provide better predictors of the immune response to implanted materials and ultimately lead to improved clinical outcomes are reviewed.

Section editors:
Karen L. Christman – Department of Bioengineering, Sanford Consortium for Regenerative Medicine, University of California, San Diego. Roberto Gaetani – Department of Bioengineering, Sanford Consortium for Regenerative Medicine, University of California, San Diego.

Introduction

All implanted biomaterials prompt an immune response by the recipient. As our depth and breadth of understanding the adaptability, plasticity, paracrine capabilities, and molecular mechanisms of the various cell types that comprise the immune system continues to expand, it has become obvious that clinical outcomes that involve the use of biomaterials are largely dictated by the acute and chronic local immune response. If *in vitro* models could faithfully predict a patients' response to a particular biomaterial, it is certain that complications and failures associated with biomaterial implantation would be markedly reduced and successful outcomes could be enhanced.

Historically, the immune system has been believed to exist for the purpose of protecting the host from pathogens and assisting in tissue repair following injury. It is now recognized however, that the immune system plays essential roles in development [1], tissue and organ homeostasis [2–4], response to injury [3], response to pathogens [5], and in response to implanted biomaterials [6]. Therefore, attempts to regulate the local tissue immune response to biomaterials has become an important design consideration.

*Corresponding author.: S.F. Badylak (badylaks@upmc.edu)

 https://doi.org/10.1016/j.ddmod.2018.07.001

Please cite this article in press as: Dziki JL, Badylak SF. Models for evaluating the immune response to naturally derived biomaterials, Drug Discov Today: Dis Model (2018), https://doi.org/10.1016/j.ddmod.2018.07.001

Biomaterials can be categorized broadly as synthetic or biologic, (*i.e.* materials composed of naturally occurring components), or as hybrids of synthetic and biologic materials. Each of these categories can be further divided into degradable, non-degradable, or partially-degradable materials, properties which markedly affect the host response [7]. Biomaterials composed of naturally occurring components such as the extracellular matrix (ECM) typically elicit a different immune response than their synthetic counterparts [7]. The immune response to ECM biomaterials is complex, involving multiple cell types, a unique spatiotemporal component, and is modulated by many host-related variables including age, weight, co-morbidities, and environmental factors such as mechanical loading. The complexity of the immune response in normal physiology combined with the number of variables that can affect the response to an implanted biomaterial emphasizes the need for, and value of, *in-vitro* and *in-vivo* models that can predict such a response. The present review focuses upon one class of biomaterials, specifically biomaterials composed of ECM and the host immune response to ECM biomaterials following implantation. Both *in vitro* and *in vivo* models are discussed with reference to their ability to ability to direct biomaterial design and predict downstream outcomes.

What is the immune response to naturally derived biomaterials?

Any model of the immune response to naturally derived biomaterials must be based upon prerequisite facts. A significant amount of work has been conducted to characterize the immune response to ECM-based biomaterials and therefore at least some of these known facts are available for consideration when developing *in-vitro* models. It is worth noting that the host response to the ECM-based materials is dependent upon several biomaterial processing variables, one of which includes the efficacy of the decellularization process. The ultimate objective of the decellularization process is to remove antigenic epitopes which may prompt an adverse immune response (similar to xenogeneic transplant rejection) while simultaneously preserving the beneficial biomolecular composition and ultrastructure of the native matrix. Development of decellularization protocols and numerous preclinical and clinical studies have shown that fears of immune-mediated rejection of xenogeneic ECM-based biomaterials due to the presence of alpha galactosyl-3-galactose (alpha-Gal) epitope are unfounded [8]. The amount of the gal-epitope in these bioscaffolds is exceedingly small, and although *in-vivo* exposure to these materials elicits an IgG response, this response fails to cause complement activation and the amount of epitope present fails to cause measurable IgM binding [8–10]. Notably, repeated implantation of ECM bioscaffolds has not been associated with an adverse sensitization response [11].

When adequately decellularized, ECM-based materials elicit a robust localized cell response that transitions from a mixture of neutrophils and mononuclear cells to entirely mononuclear cells within 48–72 h [12]. These mononuclear cells are almost all macrophages which represent a major component of the innate immune response to any implanted biomaterial [13,14]. The downstream remodeling response after ECM bioscaffold implantation is different than the default response to either tissue injury or implantation of synthetic biomaterials, both of which eventually lead to fibrosis and scar tissue formation. A distinguishing factor between ECM-based materials and their synthetic counterparts is the responding phenotype (*i.e.* activation state) of macrophages (and other immune cells) and the spatiotemporal macrophage activation response. Specifically, ECM bioscaffolds promote an early transition of macrophages from an M1-like pro-inflammatory phenotype towards an M2-like pro-remodeling phenotype, and an adaptive immune response that is characterized by a predominantly Th2 phenotype [15–17]. In contrast, synthetic materials have been largely associated with a persistent M1-like or Th1 response following implantation [18]. While the signaling molecules that mediate the immunomodulatory effects of ECM bioscaffolds are not entirely understood, a growing body of evidence suggests that matrix components including matrix-bound nanovesicles (MBV) and their bioactive cargo play an important role [19]. These facts and variables can and should be considered during the development of models of the immune response to naturally derived biomaterials.

Factors which affect the immune response to ECM bioscaffolds

Processing factors among other controllable components of ECM bioscaffold production can have a profound impact upon the host response. Some of the more recognized processing variables include remnant cell surface epitopes and residual cytoplasmic and nuclear material including DNA [20] and mitochondria [21], the source tissue from which the ECM material is derived [22], the age of the animal from which the source tissue is harvested [23], residual detergents after decellularization [24], the form in which ECM is utilized (*i.e.* sheet, powder, hydrogel, single component, *etc.*) [25], the method of terminal sterilization utilized [26], and the use of chemical crosslinking agents [15]. Post-implantation variables also can affect the immune response including the provision of targeted mechanical loading *via* physical therapy and/or weight bearing [27]. Not only do processing and other external factors affect the host response to ECM biomaterials, but host-related factors including comorbidities like obesity, age, anatomic factors, chemotherapeutic and radiation ther-

Please cite this article in press as: Dziki JL, Badylak SF. Models for evaluating the immune response to naturally derived biomaterials, Drug Discov Today: Dis Model (2018), https://doi.org/10.1016/j.ddmod.2018.07.001