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Humanized mouse model for evaluating biocompatibility and human immune cell interactions to biomaterials

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Immune system humanized mice provide unique platforms for improving preclinical evaluation of the human immune response to novel biomaterial therapies. Wild-type animals and human immune cell *in vitro* cultures provide limited representation of the human immune response, leading to unexpected responses to therapies in human patients. Introducing human tissue, cells, and genes into immunodeficient mice have advanced these animal models to reconstitute multiple lineages of functional and maturely differentiated human immune cell populations. Safe implantation and remodeling responses promoting stable tissue resolutions are critical parameters coordinated by the immune response, which should be evaluated for new biomaterial therapeutics. This review discusses the development of immune system humanized mice, and highlights demonstrated use in biomaterial and related human immune response studies.

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Introduction

Tissue engineering advancements have created numerous biomaterial therapies with promising preclinical results in post-injury and tissue disease models. Several biomaterials have successfully been translated into standard therapies in human patients [1–3] with more currently undergoing clinical trial evaluations [4–6]. Despite this progress, there are currently no set standards for preclinical evaluations that would recapitulate the human immune response, often leading to poor or unexpected outcomes in human recipients [7,8]. One major challenge is that commonly utilized animal models in these preclinical studies such as wild-type or immunodeficient murine models provide limited representation of the human immune response. Human immune cells are known to have numerous unique characteristics and interactions not observed in murine cells [9–11]. Particularly for biomaterial based therapies, ensuring biocompatibility and stimulating particular immune responses involved in

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tissue remodeling are critical for safe uptake and stable tissue resolutions [12,13]. Although these can be partially addressed by studying human immune cells *in vitro*, the temporally dynamic cytokine signaling and cell–cell interactions between different immune cell populations *in vivo* cannot be properly represented.

One method to address this challenge is the use of immune system humanized mouse models. Humanized mouse models are created by implantation of human tissue, cells or genes into mice that allow these animals to produce functional human cells and gene products *in vivo*. These mice have been advantageous in studies of human diseases involving human immune cell interactions, such as oncology [14] or infectious diseases [15], along with testing for potential therapeutic toxicity [16] and graft rejection [17]. Currently underutilized in the biomaterial field, humanized mice provide a potential platform for improving our understanding and tailoring our biomaterials for safer and more effective interactions with the human immune response. In this review, we will focus our discussion on a humanized mice model generated by engraftment of human tissue and cells for studying the human immune response, discuss the demonstrated uses of this humanized mice for studying biomaterial relevant therapies, and address the current limitations and future developments that should be considered for its use in biomaterials studies.

Importance of the immune cell response for safety and efficacy of biomaterial therapies

The functionality of the immune system acting both as a protective barrier to foreign materials and a coordinator of tissue remodeling mechanisms makes it a critical response to evaluate for new biomaterial therapies. The immune response is a dynamic process involving recruitment, cytokine signaling, and phenotypic polarization of a plethora of cell populations. In particular, cell polarizations are considered indicators of the type of immune response elicited. For example, macrophages can polarize between type 1 pro-inflammatory (M1) and type 2 pro-remodeling (M2) phenotypes that correlate with the production of cytokines such as TNFα, IL-6, and IL-1β versus IL-12, IL-23, and IL-10, respectively [18]. Similarly, T-helper cells can differentiate towards type 1 (Th1) and type 2 (Th2) polarizations that release high levels of cytokines such as IL-2 and IFNγ versus IL-4, IL-5, IL-10, and IL-13, respectively [19]. Alternative categorizations of macrophage and T-helper cell polarization have also been designated based on their specific roles in the immune response [20,21]. However, these strict designations are a classic and oversimplified representation of the *in vivo* immune response. *In vivo* responses also involve multiple states of polarized cells simultaneously, mixed phenotypic characteristics, and shifts in polarization over time based on environmental cues [22–24]. Changes to polarized response have been further associated with downstream tissue repair such as a dynamic M1 to M2 macrophage shift observed in healing tissue and enhanced biomaterial vascularization [12,25]. Thus, proper controls and assessment of multiple markers at different timepoints during experimental evaluations are necessary to distinguish the overall response elicited.

Biomaterials modulate the immune response based on their biocompatibility and material characteristics. Immune cell populations respond to surface [26], physical [27], mechanical [28,29], degradative [30,31], and biochemical [32–34] material properties influencing the degree and timing of immune cell recruitment, subsequent polarization, and type of downstream tissue resolution. For non-biocompatible biomaterials, the immune response stimulates rapid recruitment and differentiation of immune cells leading to a high-density of pro-inflammatory polarized immune cells to breakdown and reject the transplanted material. These cells include pro-inflammatory M1 macrophage, Th1 cells, natural killer (NK) cells, cytotoxic T cells, and foreign-body giant cells [35]. In contrast, biocompatible materials elicit milder immune cell recruitment along with alternatively polarized immune cell populations such as M2 macrophages and Th2 cells [36]. In comparison to bioinert materials that commonly form a fibrous capsule that walls off the material [37], bioactive materials seek to promote tissue ingrowth and endogenous repair mechanisms through these immune cell populations. Response of immune cells to biomaterial properties promote secretion of cytokines that influence downstream endothelial cell and fibroblast populations for promoting vascular development and restoration of a physiological ECM microenvironment [34,38,39]. Thus, the assessment of the immune cell populations can be utilized to determine whether specific downstream tissue remodeling resolutions will be effectively elicited by a biomaterial therapy.

Background of humanized mouse models by cell and tissue engraftment

Humanized mice are classified as chimeric mice that have been surgically or transgenically modified by the incorporation of human cells, tissue, and/or genes to create models of human biological responses. The creation of humanized mice producing human immune cells stems from the discovery of genetic mutations creating immunodeficient mouse lines that allow for the engraftment of multiple human derived tissues and cells. Particular selections and practices have been noted to have greater reconstitution of the human immune response. This has led to several versions of humanized mice being developed and utilized for studying the human immune response based on their phenotypic characteristics, functionality of their immune response and parameters of the study [40].

Early humanized mice models involved human peripheral blood lymphocyte engrafted SCID mice (Hu-PBL-SCID),

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