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Key players in the immune response to biomaterial scaffolds for regenerative medicine☆

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ABSTRACT

The compatibility of biomaterials is critical to their structural and biological function in medical applications. The immune system is the first responder to tissue trauma and to a biomaterial implant. The innate immune effector cells, most notably macrophages, play a significant role in the defense against foreign bodies and the formation of a fibrous capsule around synthetic implants. Alternatively, macrophages participate in the pro-regenerative capacity of tissue-derived biological scaffolds. Research is now elucidating the role of the adaptive immune system, and T cells in particular, in directing macrophage response to synthetic and biological materials. Here, we review basic immune cell types and discuss recent research on the role of the immune system in tissue repair and its potential relevance to scaffold design. We will also discuss new emerging immune cell types relevant to biomaterial responses and tissue repair. Finally, prospects for specifically targeting and modulating the immune response to biomaterial scaffolds for enhancing tissue repair and regeneration will be presented.

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1. Introduction

The goal of regenerative medicine is to provide a substitute for tissues lost due to trauma, disease, or congenital abnormalities [1–3]. Historically, the general approach for engineering tissues entailed the use of a biomaterial scaffold in combination with cells and biological signals [4,5]. More recently, individual components of the tissue engineering triad are employed to stimulate tissue repair and new tissue

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development [6]. In the case of scaffolds, the biomaterial component is broadly defined as a naturally or synthetically derived substance designed to interact with complex biological systems, aiming to support functional tissue outcomes. While biomaterials have been used clinically for many years, regenerative medicine inspired a shift towards increasing the biological activity and immunological interaction of these materials [2,7]. For example, biological signals in the form of adhesion peptides and growth factors can be incorporated into the biomaterial scaffolds through chemical or physical conjugation. These and other material modifications designed to enhance biological activity contribute to the extensive "toolbox" that is available today for tissue engineers. *In vitro* studies with somatic and stem cells have elucidated cell-material responses and effects on tissue development [8–10]. These studies provided a foundation for engineering tissue microenvironments to control cell function and ultimately new tissue development. Translating these findings and biomaterial scaffolds to an *in vivo* setting and ultimately clinical application provides new insights into mechanisms of action and therapeutic potential.

Preclinical and clinical translation introduces new variables and challenges in the scaffold design process. While the response of single cell types to biomaterials can be tested *in vitro*, *in vivo* the environment includes many cell types that interact and communicate together to orchestrate the immune response. Moreover, preclinical models may not always predict a biomaterial immunogenic or regenerative capacity in patients. The immune system is composed of an innate and adaptive arms that intimately crosstalk [11]. The innate immune system includes a vast variety of cells such as polymorphonuclear cells (granulocytes, eosinophils, basophils), mononuclear phagocyte cells (dendritic cells, monocytes and macrophage cells), and lymphocytes (natural killer cells, gamma delta T cells and innate lymphoid cells) whereas the adaptive immunity includes T and B lymphocytes. The reaction to implantation of a biomaterial is primarily immunological with both innate and adaptive components. The anatomical location of the implant will dictate the nature of the tissue-specific innate response. Different types of tissue are defined by their locally selective innate defenses, which further contribute to the induction of adaptive immune responses stemming from secondary lymphoid organs. For example, our work translating a soft tissue filler material found a tissue-specific immune reaction around implants in patients [12,13]. The crosstalk between the host immunity and the synthetic-biological composite hydrogel material depended on which tissue was adjacent, producing a tissue-specific reaction to the biomaterial. Thus, the translation process has highlighted the immune response as a potential key factor to be considered in regenerative medicine applications.

The immune system is an active component of tissue repair and regeneration. Following injury, a cascade of complex cellular responses is characterized by the recruitment, proliferation, and differentiation of both hematopoietic and non-hematopoietic cells. Several immune cells and their secreted cytokines have been implicated in promoting regeneration. For example, eosinophil secretion of interleukin (IL)-4 enhanced skeletal muscle repair in a cardiotoxin model, while different classes of macrophages are critical for cardiac regeneration *versus* destructive scar formation [14,15]. Recently, IL-4 has been shown to be an important factor for skin and liver regeneration [16,17]. These and other recent discoveries on the role of the immune system in tissue regeneration will help guide future scaffold development. This review will discuss the rapidly evolving view of the immune system in the biomaterial response and its potential implications in regeneration. We will also discuss nontraditional immune cell subsets with innate and adaptive properties and their relevance to biomaterials and regenerative medicine.

1.1. The immune response and synthetic materials

Synthetic biomaterials have a long history in modern medicine with application ranging from artificial articulating joints to vascular grafts engineered from metals, plastics, and fabrics. Synthetic (nondegradable) materials also served as components of early commercial tissue engineering [18,19]. Synthetic degradable polymers, such as polyesters,

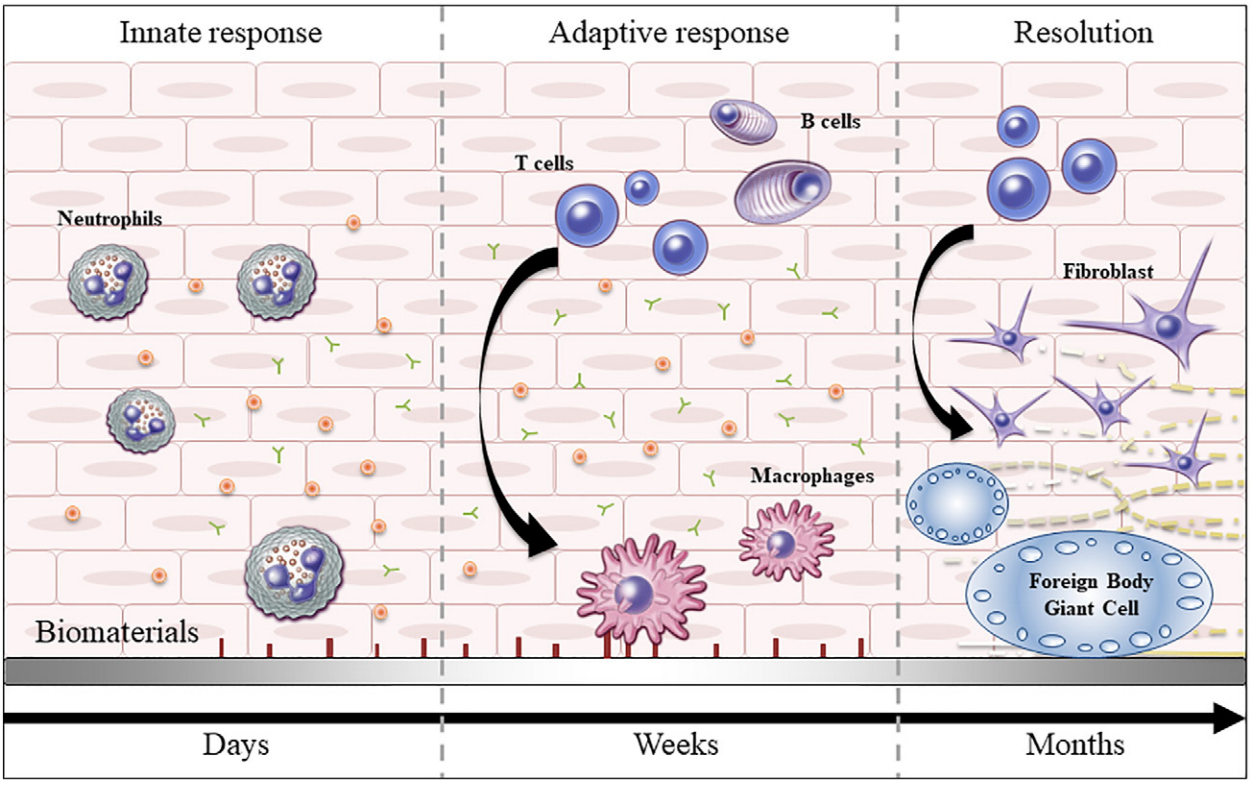

Fig. 1. Temporal sequence of events after biomaterial implantation. This figure highlights the main cellular players in the biomaterial-tissue microenvironment from the initial implantation to fibrous encapsulation. Therapeutic intervention through targeting of neutrophils, lymphocytes (T helper cells and B cells), and macrophages all stand as attractive options.