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Dendritic cells in host response to biologic scaffolds

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ABSTRACT

Tissue regeneration and repair require a highly complex and orchestrated series of events that require inflammation, but can be compromised when inflammation is excessive or becomes chronic. Macrophages are one of the first cells to contact and respond to implanted materials, and mediate the inflammatory response. The series of events following macrophage association with biomaterials has been well-studied. Dendritic cells (DCs) also directly interact with biomaterials, are critical for specific immune responses, and can be activated in response to interactions with biomaterials. Yet, much less is known about the responses by DCs. This review discusses what we know about DC response to biomaterials, the underlying mechanisms involved, and how DCs can be influenced by the macrophage response to biomaterials. Lastly, I will discuss how biomaterials can be manipulated to enhance or suppress DC function to promote a specific desirable immune response – a major goal for implantable biologically active therapeutics.

Contents

Abbreviations: AIM, absent in melanoma; ALR, AIM-like receptors; CD, cluster of differentiation; CLR, C-type lectin receptor; DC, dendritic cell; ECM, extracellular matrix; FBR, foreign body reaction; HMGB1, high mobility group box 1 protein; IL, interleukin; NLR, NOD-like receptors; NOD, nucleotide-binding oligomerization domain; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response 88; PLGA, poly(lactic-co-glycolic acid); PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene 1; RLR, RIG-I-like receptor; TIMP, tissue inhibitors of metalloproteinases; TIR, Toll-IL-1 resistance; TLR, Toll-like receptor; TRIF, TIR-domain-containing adapter-inducing interferon-β.

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1. Introduction

The goal of using therapeutic biologic scaffolds is to provide the structure and signals necessary to promote tissue repair and regeneration. Such scaffolds have been successfully used in both tissue engineering and regenerative medicine [1]. To promote repair and regeneration, scaffolds should be biocompatible with and have mechanical properties and structure similar to the tissue into which they are to be implanted. Scaffolds should also be biodegradable so that they are naturally replaced over time within the tissue [2]. Most scaffolds, such as tissue-derived extracellular matrix (ECM), are collected from natural host sources [3]. ECM scaffold composition differs by source tissue and thus can vary in the ratio of various components including collagen types I, III, IV, V, and VI; glycosaminoglycans; fibronectin; and growth factors [4]. The beneficial activity of scaffolds can be compromised when excessive inflammation, foreign body reactions, and generation of specific adaptive immune responses result in the production of antibodies and activated T cells [5].

The immune system is composed of innate and adaptive arms, which work together to elicit the inflammatory response. Initiation of the adaptive response requires dendritic cells (DCs) to integrate innate immune signals and process and present antigen to T cells. Innate immune signals are derived primarily from molecular structures associated with infectious agents, which alert the immune system to the infection. Without such signals, DCs can induce immune tolerance, or absence of response [6]. To fully activate DCs, and therefore adaptive immune response, vaccines include purified or synthetic versions of such structures (adjuvants) [7]. However, during regenerative medical applications, DC activation is an undesirable outcome. When DCs attach to scaffolds and become activated, they can impair the longevity and usefulness of scaffolds [8]. Understanding the response of DCs to scaffolds would be helpful in designing materials to drive DC responses toward tolerance and inhibit potent immune activation, which would improve the therapeutic activity of the scaffolds [9]. Yet, compared to the vast information we have about macrophage interactions with scaffolds, much less is known about DC interaction with therapeutic biologic scaffolds. Much of what we do know is based on DC interaction with synthetic biomaterials such as poly(lactic-co-glycolic acid) (PLGA), and extrapolated from response to biologic scaffolds by other cell types like macrophages.

2. Dendritic cells initiate immune responses

2.1. Types of dendritic cells

DCs are typically classified as classical dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs) [10]. Langerhans cells are an additional type of DC that resides in the epidermal layer of the skin. pDCs primarily circulate in the blood, express innate immune receptors such as nucleic acid-sensing Toll-like receptor 7 (TLR7) and TLR9, and are important for response to viral infections [11]. In contrast, cDCs reside in tissues and are the most potent antigen presenting cells in response to infectious agents [12].

The functional diversity of DCs is due to differential expression of various lineage-defining transcription factors [13] and surface markers [14,15]. Master transcription factors are expressed by different DC subsets and dictate lineage commitment. For example, cDCs express the transcription factor zinc finger and BTB domain containing 46 (Zbtb46) [16,17]; whereas pDCs express basic helix-loop-helix transcription factor (E protein), E2-2 [18]. Depletion and reconstitution experiments in mouse have been used to tease out the functions of specific subsets of DCs expressing different surface markers such as CD8α, CD11b, and CD103 [14]. Some functions of DC subsets include 1) an enhanced ability to cross-present antigens, leading to potent activation of $CD8^+$ T cell responses [19]; 2) the ability to migrate to secondary lymphoid organs and activate naïve T cells; 3) the ability to migrate to the thymus and participate in development of central tolerance through elimination of certain T cell specificities [20]; and 4) maintenance of tolerance in the periphery [21]. However, some of these functions are based on expression of CD11b, which is shared with macrophages, making it challenging to assign specific functions to this class of DCs. Regardless, DCs are capable of inducing immune responses and mediating tolerance, both of which are critical to regulating host response to biologic scaffolds.

2.2. Dendritic cell activation

DCs are equipped with the ability to activate naïve T cells; however, this requires a multi-step maturation process. First, the DC must encounter specific antigens, process them and present them in the context of MHC molecules on the cell surface. When this occurs in the absence of innate immune receptor recognition of microbial structures, DCs induce anergy, or tolerance of T cells. However, when innate immune receptors are stimulated at the same time as antigen acquisition, DCs upregulate the costimulatory molecules necessary to fully activate naïve T cells. Innate immune receptor stimulation also mobilizes the DCs and upregulates chemokine receptors required for appropriate trafficking to the site of T cell activation in the secondary lymphoid organs. Innate immune receptor recognition of microbial structures initiates intracellular signaling cascades that mediate these outcomes. In pDCs, this results in high levels of type I interferon; while in cDCs, it results in production of specific cytokines that dictate the type of T cell response (e.g. T_H1, T_H2, T_H17).

Natural ECM-derived biomaterials most closely mimic endogenous ECM and thus should elicit no, or limited, immune responses. However, ECM is typically prepared for implantation by decellularization or chemical treatments and may contain residual cellular components capable of activating innate immune receptors. Additionally, they may adsorb immunoreactive proteins immediately following implantation. Babensee coined the term "biomaterial associated molecular patterns" to describe adsorbed structures capable of eliciting DC activation from biomaterials [22]. The magnitude and type of response of macrophages and DCs to different biomaterials is determined by the composition, form and surface area of the contact with the material [23–26]. For example, human DCs cultured on agarose films induced some T cell activation, but T cell activation was greater when the DCs were cultured with other biomaterials such as PLGA, chitosan and alginate [23]. Using 12 different polymethacrylates and principal component analysis, surface carbon was found to be associated with increased human DC activation [27]. Such systematic analysis of parameters affecting DC activation will provide necessary information to rationally synthesize or modify biomaterials to elicit desired DC phenotypes in vivo. When foreign or autoantigens are present during mouse DC activation, DCs can subsequently initiate specific adaptive immune responses through naïve T cells, resulting in activation of B cells to produce antibody [28]. These antibodies can then bind to the biomaterial to induce its degradation, as described below. Thus, DCs can elicit immune responses that directly target scaffolds. For these reasons, there is often an attempt during the manufacturing process to mask ligands from innate immune receptors [8].

2.3. Innate immune receptors for DC activation

Innate immune receptors that can activate and mature DCs can be divided into five families: TLRs, C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors