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Review

Dendritic cells in the host response to implanted materials

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ABSTRACT

The role of dendritic cells (DCs) and their targeted manipulation in the body's response to implanted materials is an important and developing area of investigation, and a large component of the emerging field of biomaterials-based immune engineering. The key position of DCs in the immune system, serving to bridge innate and adaptive immunity, is facilitated by rich diversity in type and function and places DCs as a critical mediator to biomaterials of both synthetic and natural origins. This review presents current views regarding DC biology and summarizes recent findings in DC responses to implanted biomaterials. Based on these findings, there is promise that the directed programming of application-specific DC responses to biomaterials can become a reality, enabling and enhancing applications almost as diverse as the larger field of biomaterials itself.

1. Introduction

Biomaterials are used as tools for regenerative therapies aimed at replacing lost or dysfunctional tissues [1]. Emerging tissue engineering approaches typically employ some combination of materials, cells and biomolecules (e.g., proteins). It has long been recognized that the cellular component of these combination products, depending on the source, could trigger severe immunological reactions similar to that seen in transplantation of allogeneic or xenogeneic tissue [2]. More recently, researchers have reported that the biomaterial component may also evoke significant immunological barriers to integration and tissue regeneration [3]. This inflammatory response against the biomaterial component of tissue-engineered constructs has been very well characterized and is collectively known as the foreign body response (FBR). The known primary cellular mediators of this inflammatory response are macrophages, along with neutrophils. Briefly, following implantation, protein adsorption on the surface of the biomaterial results in initiation of the coagulation cascade, complement system (which can polarize immune cells towards an inflammatory response) and the formation of a provisional matrix. These phenomena have been extensively investigated on different biomaterial surfaces and it is thought that they are correlated to the physico-chemical surface properties of the biomaterial, thereby linking biomaterial properties with host immune cell responses [4]. Following matrix formation, antigen presenting cells, including macrophages and dendritic cells (DCs), can be recruited to the implant site by chemokines released by the matrix as well as surrounding cells. Macrophages, in particular, persist at the implantation site, adhering to the implant surface and coalescing with neighboring macrophages to form a giant cell body, which attempts to engulf the material. Within this encapsulation, macrophages secrete a number of inflammatory mediators, including reactive oxygen species and degradative enzymes that can be detrimental to the structure and functionality of the implanted biomaterial [4]. The presence of exogenous biologics only exacerbates this immune response, with foreign cell-associated antigen release prompting chronic inflammation, typically mediated by T-cells. Dendritic cells play a critical role as enablers of this chronic adaptive response against tissue engineered constructs which typically deliver immunogenic cells, proteins and other biologics [3]. Interestingly, they may also contribute to immune response against the material component of these combination constructs. Herein, we discuss the current knowledge on DC responses to implanted biomaterials, with particular relevance to tissue engineering scaffolds (Table 1).

1.1. Dendritic cells in the immune response

The mammalian immune system is composed of two sets of mechanisms that collude to shield the host from would-be invaders, the innate and the adaptive immune systems. The innate immune system has evolved to recognize certain non-self-entities to which we, as a species are continually exposed (e.g., pathogen-associated molecular patterns; PAMPs), whereas adaptive immunity educates the body to never-before seen invaders. Notably, one cell type is distinctly efficient at bridging the innate immune system to adaptive immunity—the dendritic cell (DC) [5].

Dendritic cells are the 'sentinel' of the immune system for their role

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Table 1
Impact of material properties on dendritic cell phenotype.

Biomaterial Property	Resulting DC Phenotype	DC Responses from published studies	Reference
Presence of Antigen	Variable; dependent on local immunomodulatory microenvironment at the time of antigen interception	(1) A novel PLGA-based, microparticle system providing concurrent delivery of multiple encapsulated immuno-suppressive factors and antigen drove tolerance-promoting DCs to protect from the onset of insulitis in NOD mice.	[70]
		(2) Model antigen (OVA) delivered in either polymeric scaffolds or microparticles resulted in time-dependent generation of OVA-specific IgG, suggesting activation of DCs and downstream T_{H2} engagement.	[56]
Surface Chemistry	Variable/Inconclusive	(1) Murine BMDCs cultured with OVA antigen coated multi-walled carbon nanotubes of varying surface charges (zeta potentials ranging from −39 mV to +5. 8 mV) and length showed an activation state similar to that of iDCs. However, DCs incubated with more negatively charged MWNTs stimulated greater proliferation of OVA-specific T cells	[71]
		(2) Human monocyte-derived DCs were cultured on self-assembled monolayers (SAM) surfaces of alkanethiols terminated with defined chemical groups, of either −CH3, −OH, −COOH, and −NH2. By measure of expression of stimulatory markers, treatment with −OH, −COOH, or −NH2 terminated SAMs showed moderate maturation, while DCs treated with −CH3 SAMs were least activated.	[55]
Hydrophobicity	Dendritic Cell Maturation	In vitro studies using murine bone marrow-derived DCs showed that increased surface hydrophobicity supports microparticle engulfment and antigen internalization, and boosts expression of stimulatory molecules (CD86, MHC-II)	[68]
Topography/ Surface Roughness	Dendritic Cell Maturation	(1) Human peripheral blood-derived DCs cultured on relatively high roughness resemble LPS-activated DCs in morphology, and high expression of CD86;	[72]
		(2) Mature murine BMDCs resulted following culture on 3-D micropatterns with widths of 2, 5, 10 and 20 μm on well-studied, biomaterials. Surface expression of MHC-II molecules in DCs on 3-D micropatterns were significantly higher compared to flat substrates.	[73]
Protein Adsorption	Variable − dependent on type and configuration of protein deposited	(1) This study demonstrated that murine BMDC DC maturation status (based on morphology and differential production of pro- and anti-inflammatory cytokines [IL-12p40 and IL-10, respectively]) is adhesive substrate-dependent. For instance, DCs grown on collagen and vitronectin substrates generate higher levels of IL-12p40. Conversely, DCs cultured on albumin surfaces produce the higher levels of IL-10 indicating a tolerogenic phenotype.	[36]
		(2) This study revealed the role of integrins in the recognition and response of DCs to biomaterials. Succinctly, antibody-blocking techniques were used to demonstrate that β2 integrin signaling mediated increased expression of CD86 on human peripheral blood-derived DCs, when cultured on PLGA films.	[74]

in patrolling, scavenging and recognizing non-self-components throughout the host [5]. These cells are phagocytic, and the most efficient antigen presenting cells (APCs) with the capacity to instigate either inflammatory or anti-inflammatory adaptive immunity. Following tissue damage, *in situ* immature DCs capture released antigen and subsequently migrate back to lymphoid organs via chemokine gradients, where they initiate clonal selection and expansion of specific, rare T cells. These expanded T cell clones have receptors specific for antigens that are processed and present on the surfaces of DCs during the migration process. Moreover, antigen-specific T cells and subsequently mobilized B cells, macrophages, natural killer (NK) cells and eosinophils home to the site of insult where a combination of broad and specific assault is unleashed to abolish an invading threat. Critically, DCs also activate suppressive immune networks for induction of tolerance towards self-antigens. The direction and magnitude of immune responses are influenced by DC activation level and phenotype— either an activated phenotype providing an inflammatory reaction, or conversely, a tolerogenic phenotype for regulatory measures [6]. The versatility of DC responses is in part owing to the diversity of receptors on the surfaces of DCs, as well as, the heterogeneity of DC subsets.

1.2. Heterogeneity of dendritic cells

Dendritic cells were first discovered in the laboratory of Ralph Steinman in 1973. While controversial at the time, Steinman later shared the 2011 Nobel Prize in Physiology or Medicine for his discovery of the DC and its role in adaptive immunity. Steinman et al. described these cells as being large (~10 μm) mononuclear cells with elongated, stellate processes (or dendrites) extending in multiple directions from the cell body [7]. The subsets of this cell type varies between different mammals, so for the sake of brevity, here we only discuss DC heterogeneity in humans. Currently, cells are designated as DCs based on specific cell surface markers or clusters of differentiation (CD) and high expression levels of MHC class I and class II. Moreover, DCs are leukocytes distinguished based on their lack of markers found on other cells: CD3 (T cells), CD19 (B cells), CD56 (NK cells), CD14 (monocytes), CD15 (granulocytes), and CD34 (stem cells). Accordingly, DCs have been classically termed lineage-negative (lin-) DR+ cells [8].

Dendritic cells can be grouped on four different levels: i) precursor population (i.e. lineage), ii) function, iii) final polarity of immune response and, iv) anatomical localization. According to current understanding, DCs are identified as either 'myeloid' or 'plasmacytoid'. Myeloid DCs (mDCs) are characterized by the expression of CD11c, CD13, CD33 and CD11b, and its lack of expression of CD14 and CD16. Myeloid CD11c+ DCs can be further split into CD1c+, CD14+ and CD141+ fractions. On the other hand, plasmacytoid DCs (pDCs) typically do not express myeloid markers and are recognized via the surface markers CD123, CD303 and CD304 [6].

These two major subsets of DCs differentiate in an array of cells with differential functional capabilities and primary loci in mammalian hosts. In humans, there are 5 major classes that have been characterized, namely: (1) Peripheral Blood DC (PBDC), (2) Epithelial and Interstitial DC, (3) Thymic DC (TDC), (4) Lymphoid DC (LDC) and (5) Bone marrow DC (BM-DC) [9].

Peripheral blood DCs represents about 0.5–1.5% of the total peripheral blood mononuclear cells (PBMCs), and consists of both myeloid and plasmacytoid DCs. The mDCs in this compartment express CD13, CD33, CD45RO, and have impressive antigen uptake and T-cell stimulatory capacities. Exposure of this DC subtype to bacterial