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Review

Expanded applications, shifting paradigms and an improved understanding of host–biomaterial interactions

Bryan N. Brown [a,b], Stephen F. Badylak [a,b,c,*]

[a] McGowan Institute for Regenerative Medicine, University of Pittsburgh, Suite 300, 450 Technology Drive, Pittsburgh, PA 15219, USA
[b] Department of Bioengineering, University of Pittsburgh, 360B CNBIO, 300 Technology Drive, Pittsburgh, PA 15219, USA
[c] Department of Surgery, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA

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ABSTRACT

The conventional approach to biomaterial design and development typically focuses upon the mechanical and material properties with long-term objectives that include an inert host immune response and long-lasting mechanical and structural support. The emergence of and interest in tissue engineering and regenerative medicine have driven the development of novel cell-friendly biomaterials, materials with tailored degradation rates, materials with highly specific architectures and surfaces, and vehicles for delivery of bioactive molecules, among numerous other advancements. Each of these biomaterial developments supports specific strategies for tissue repair and reconstruction. These advancements in biomaterial form and function, combined with new knowledge of innate and acquired immune system biology, provide an impetus for re-examination of host–biomaterial interactions, including host–biomaterial interface events, spatial and temporal patterns of in vivo biomaterial remodeling, and related downstream functional outcomes. An examination of such issues is provided herein with a particular focus on macrophage polarization and its implications in tissue engineering and regenerative medicine.

1. Introduction

The "Inflammatory response to implants" [1] is one of the most cited publications with respect to the mechanisms by which mammalian tissues respond to the implantation and presence of synthetic biomaterials. This landmark paper provides a surgical pathology-based perspective on the host response to commonly used biomaterials. As expected, with time and the inevitable advancements in understanding of the innate and acquired immune system, the development of new biomaterials and the emergence of new techniques to interrogate the host cellular response, some of the principles identified in that paper remain valid while others are worthy of modification. The present paper attempts to examine and discuss those principles which remain central components of the host–biomaterial response paradigm, and those principles which have since been re-defined or require modification, with particular emphasis placed upon the newly described phenomena of macrophage polarization and heterogeneity.

2. The classical perspective

It is well accepted that the host response to implantable biomaterials is an extension of the default mammalian response following tissue injury. That is, the host response to injury is inextricable from the host response to implantable materials. By their very nature (i.e. implantable), some degree of tissue injury will occur during in vivo placement. Therefore the host response to injury is an important part of the host response to biomaterials and is a component of both the classical and emerging perspective, as will be further described below. Briefly, the host response to injury is generally considered to occur in four overlapping phases including hemostasis, inflammation, proliferation and remodeling. The end result in adult mammals for most tissues is typically scar tissue formation. This type of response has evolved as a protective mechanism for the host, and although the resulting scar tissue will continue to remodel long after the inflammatory response has subsided, it for all practical reasons represents the end of the wound-healing process. However, it is important to note (and will be described in more detail below) that component events of this default injury response are also critical components of tissue and organ development, homeostasis with the implied turnover of structural and functional molecules and the process of constructive tissue remodeling or regeneration that results in a functional, non-scar-tissue outcome. The four phases of wound-healing have been

* Corresponding author at: McGowan Institute for Regenerative Medicine, University of Pittsburgh, Suite 300, 450 Technology Drive, Pittsburgh, PA 15219, USA. Tel.: +1 412 624 5253; fax: +1 412 624 5256.
E-mail address: badylaks@upmc.edu (S.F. Badylak).

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reviewed at length elsewhere [2–7], and therefore are not reviewed herein; however, a fundamental understanding of the default wound-healing response is essential for a rational approach to the host response to biomaterials.

A classical description of the host response to implanted biomaterials, as defined by Anderson in 1988 [1], includes a number of overlapping stages including injury, protein adsorption, acute inflammation, chronic inflammation, foreign body reaction (FBR), granulation tissue formation and encapsulation. The acute phase is dominated by neutrophils and this phase transitions within 24–48 h to a response dominated by macrophages showing "frustrated phagocytosis" as described by Henson [8], and eventually the formation of foreign body giant cells (FBGCs). The profile of proteins adsorbed onto the biomaterial surface, the surface chemistry of the material and the topographic features have been considered important and determinant factors in the degree and severity of the host response [9–28]. This description of the host response to biomaterials with minor variations can be found in numerous texts across surgical, pathological and medical disciplines.

The heretofore-described characteristics of an ideal implantable biomaterial have invariably included the concept of "inertness", with the expected host response being one of fibrous connective tissue encapsulation. A material that caused no harm to the recipient was considered to be acceptable and in fact desirable. That is, materials shown to be non-toxic, non-immunogenic, non-thrombogenic, non-carcinogenic and non-irritant were preferred. There exists today a battery of assays and protocols validated by organizations such as the International Organization for Standardization (ISO) for testing such aspects of biomaterials. Together, these characteristics have formed the basis for "biocompatibility", a difficult-to-define term which could, at the time, be equated with biological safety.

However, in addition to concerns of safety (i.e. the "non" approach), the concept of biocompatibility is inextricably linked to functionality and the elicited host innate and acquired immune response. A definition for the term biocompatibility which includes these concepts has been proposed by Williams [29]: "Biocompatibility refers to the ability of material to perform with an appropriate host response in a specific situation".

This generic and comprehensive definition acknowledges that a biomaterial is not simply an "inert" mechanical support, but also should serve a specific function, and that the type of response and function may vary depending upon its intended use and anatomic site of implantation. Many of these views remain the present-day basis for the design of medical devices and the biomaterials of which they are composed.

3. Current perspectives

With time and the inevitable advancements in understanding of the pathophysiology of the innate and acquired immune system, the development of new biomaterials and the emergence of new techniques to interrogate genomic and molecular aspects of the host cellular response, some previously accepted principles of the host response to biomaterials remain valid while others are worthy of reconsideration and modification. In concert, the advent of tissue engineering and regenerative medicine has created a demand for biomaterials with additional and specific functions such as the ability to support the attachment, viability, growth and even differentiation of a variety of cell types, the ability to modulate the release of bioactive molecules and various drugs and the ability to modify the host innate immune response. These demands have been met through the development of techniques for materials synthesis and modification as well as novel chemistry for the derivation of highly tunable synthetic materials. A description and discussion of scope and specific implications of each of these advancements in the context of tissue engineering and regenerative medicine, however, are too numerous and too broad to be reviewed herein. Consequently, the criteria of an ideal biomaterial have evolved and are viewed somewhat differently than in the past. Specifically, ideal materials for tissue engineering and regenerative medicine applications are evaluated for their ability to support the functional replacement of tissue rather than as a material simply to provide structural and mechanical support or replacement for a missing body part. Although biological safety and material properties such as ultimate tensile strength, suture retention strength and stress–strain characteristics remain important, the ultimate determinant of success or failure in tissue engineering and regenerative medicine applications is the elicited host response and associated effects upon biomaterial form and function. Regardless of the strength of the material or the degree to which the morphology and physical characteristics are matched to the anatomic site at the time of surgical implantation, the subsequent tissue response and remodeling events will determine the functional outcome. Stated differently, the similarity of the material to the recipient tissue at the time and anatomic site of implantation is less important that than the structural and functional similarity at 6 months, 1 year and beyond.

With new clinical applications of biomaterials, the concurrent development of new materials with varied and tunable physical properties, and an ever-increasing understanding of the pathophysiology of the mammalian immune system, a number of updated perspectives on the host response following in vivo implantation have emerged. A review by Anderson et al. in 2008 [9] maintained a focus upon synthetic materials and a macrophage/FBGC centric view of the host response but added significantly more depth on cell signaling events that may contribute to the phenomenon. This work incorporated new concepts of the underlying physiological mechanisms driving the host response to synthetic biomaterials, noting the effects of surface characteristics, degradation products and macrophage/FBGC–lymphocyte interactions in these processes while maintaining that "once a biomaterial is introduced into the body, a sequence of events occurs in the surrounding tissue and ultimately ends in the formation of FBGC at the tissue/material interface".

Obviously, this statement is incongruous with the goals of tissue engineering and regenerative medicine approaches to tissue reconstruction, many of which have been shown to induce the formation of site-appropriate functional host tissues without inducing encapsulation, scar tissue formation or an FBGC response. The above-mentioned review briefly describes devices for tissue engineering and regenerative medicine applications, and the fact that many of these materials are derived from allogeneic or xenogeneic sources that may include cells of allogeneic or xenogeneic origin. The review also comments that the addition of biologic materials introduces a myriad of additional challenges to the assessment of the host response to biomaterials but largely continues to equate biocompatibility with biological safety more than efficacy.

In light of the inconsistency of definitions of biocompatibility and shifting paradigms in tissue engineering and regenerative medicine from permanent "inert" biomaterials toward functional, degradable materials serving as delivery vehicles or scaffolding for cells, new definitions have been suggested. Williams [30] has suggested a unified definition of the term biocompatibility which encompasses both long term medical devices and those intended for use in tissue engineering and regenerative medicine applications: "Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific