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Mini review

Matricellular proteins and biomaterials

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ABSTRACT

Biomaterials are essential to modern medicine as components of reconstructive implants, implantable sensors, and vehicles for localized drug delivery. Advances in biomaterials have led to progression from simply making implants that are nontoxic to making implants that are specifically designed to elicit particular functions within the host. The interaction of implants and the extracellular matrix during the foreign body response is a growing area of concern for the field of biomaterials, because it can lead to implant failure. Expression of matricellular proteins is modulated during the foreign body response and these proteins interact with biomaterials. The design of biomaterials to specifically alter the levels of matricellular proteins surrounding implants provides a new avenue for the design and fabrication of biomimetic biomaterials.

Contents

1. Introduction

The study of biomaterials began in the early nineteenth century when H.S. Levert first implanted a variety of materials into dogs to analyze the in vivo reaction and found metals to cause the least irritation (Levert, 1829). Of course, the study of biomaterials has advanced significantly since then leading to the creation of three major classes of modern biomaterials: bioinerts, biodegradables, and bioactive or biomimetic materials (Cao and Hench, 1996; Hench, 1998; Shin et al., 2003;

Abbreviations: FBR, foreign body response; FBGCs, foreign body giant cells; TSP, thrombospondin; CD36, cluster of differentiation 36; LDL, low density lipoprotein; ECM, extracellular matrix; PEI, poly(ethylene imine); EC, endothelial cell; PEG, polyethylene glycol; GAM, gene-activated matrix; WT, wild type; SPARC, Secreted Protein, Acidic and Rich in Cysteine; MMP, matrix metalloproteinase; OPN, osteopontin; BSP, bone sialoprotein; RGD, Arginine–Glycine–Aspartic acid; HUVEC, human umbilical vein endothelial cells; TNC, tenascin-C.

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Bryers et al., 2012). This review will discuss the role of the matricellular proteins in tissue–biomaterial interactions with a focus on the design of a new generation of biomimetic materials from matricellular proteins and their functional domains.

2. Biomaterials

Implantable materials have been useful for years as a way to create devices, replace tissues, deliver drugs, etc. A major goal of the field of biomaterials is to create bioinert materials — materials that are nontoxic and remain functional after implantation (Cao and Hench, 1996; Hench, 1998; Heness and Ben-Nissan, 2004). For example, many metals (steel, titanium, and cobalt–chromium alloys), ceramics (zirconia and alumina), silicone, and polyester are often considered bioinert because they are nontoxic and exhibit little tissue integration with the material (Cao and Hench, 1996; Hench, 1998; Heness and Ben-Nissan, 2004). However, the term bioinert is a misnomer because even these materials elicit a foreign body response (FBR) (Cao and Hench, 1996; Ratner, 2002; Heness and Ben-Nissan, 2004; Geetha et al., 2009).

Nearly all materials regardless of composition elicit a FBR, which is a unique inflammatory response and initiates with the rapid adsorption of proteins in random orientations and configurations (Fig. 1) (Ratner, 2002; Ratner and Bryant, 2004; Anderson et al., 2008). Following protein adsorption, cells interact with the proteinaceous layer on the surface of the material leading to adhesion and activation (Ratner, 2002; Ratner and Bryant, 2004; Anderson et al., 2008). At the cellular level, the initial phase of the response is dominated by neutrophils and macrophages, similar to acute inflammation. After several days, macrophages undergo cell–cell fusion to form foreign body giant cells (FGBCs) (Ratner, 2002; Ratner and Bryant, 2004; Xia and Triffitt, 2006; Anderson et al., 2008). In addition to attacking the biomaterial surface, FBGCs and macrophages secrete factors that promote fibroblast migration and deposition of ECM, which leads to encapsulation of the implant by a largely avascular, fibrotic tissue. Consisting primarily of collagen, the collagenous capsule forms within 4 weeks and isolates the implant from the surrounding tissue (Ratner, 2002; Ratner and Bryant, 2004; Anderson et al., 2008). It is important to consider the unique alignment of collagen fibers in an orientation parallel to the implant surface and the striking paucity of blood vessels within the capsule. These differences distinguish the FBR from normal wound healing. In the latter, collagen organization is loose and there is an abundance of blood vessels. In some applications, such as implantable glucose sensors, the FBR often leads to device failure due to isolation of the sensing unit from the surrounding tissue and blood vessels. Therefore, tissue remodeling and blood vessel inhibition in the FBR has become a significant area of interest.

Biomimetic materials, or materials that seek to mimic the biology of the ECM to promote healing and integration into host tissues have garnered tremendous attention in recent years (Ratner, 2001; Shin et al., 2003; Causa et al., 2007; Roach et al., 2007; Bryers et al., 2012). Specifically, they are designed to actively influence protein adsorption (the first step of the FBR) and tissue interactions by controlling parameters such as material structure (on a micro/nano level), porosity, drug loading, and surface chemistry (Healy et al., 1996; Puleo and Nanci, 1999; Ratner, 2001; Brodbeck et al., 2002; Ratner, 2002; Shin et al., 2003; Lan et al., 2005; Roach et al., 2007; Bryers et al., 2012). Commonly, biomimetic materials modify functional groups on the surface of a material or coat the material with ECM molecules (Healy et al., 1996; Puleo and Nanci, 1999; Brodbeck et al., 2002; Shin et al., 2003; Lan et al., 2005; Roach et al., 2007; Esch et al., 2011; Chen et al., 2013). Another thrust of engineering biomimetic materials is to create topographies that either elicit specific biological responses (such as microchannels) or mimic the structure of the ECM (Stevens and George, 2005; Boudriot et al., 2006; Roach et al., 2007; Esch et al., 2011).

Decellularized ECM represents a new class of biomimetic materials that has garnered significant attention in recent years. Tissues have been decellularized in a variety of ways including: chemical methods,

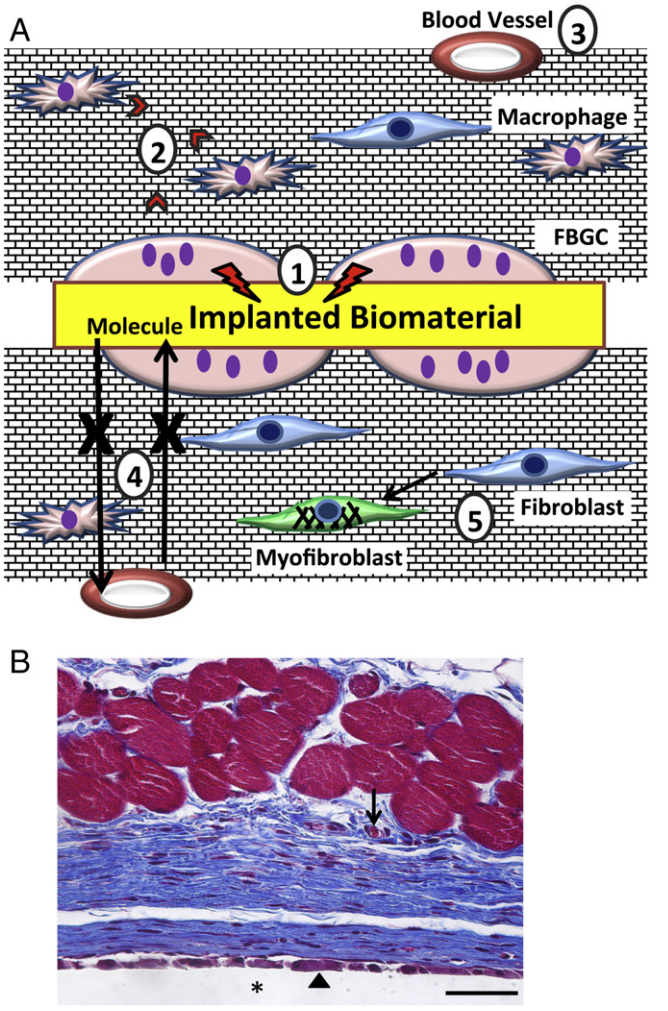

Fig. 1. Overview of the foreign body response. A. Implantation of biomaterial into soft tissues elicits a unique inflammatory response leading to encapsulation by a largely avascular capsule consisting of dense collagenous matrix. A number of complications are encountered including: 1) FBGCs form on the implant surface and can damage the implant; 2) FBGC and macrophages secrete pro-fibrotic factors; 3) blood vessels are generally excluded from the capsule; 4) the lack of vessels and the dense collagen arrangement limit diffusion of small molecules; and 5) fibroblasts can differentiate into myofibroblasts and contract the capsule. B. Representative image of the foreign body response to a PDMS disk implanted subcutaneously (SC) in a mouse for 4 wk. Sections were stained with Masson's trichrome to visualize collagen deposition (blue color) in between the implant (*) and muscle fibers (red). Arrowhead and arrow indicate FBGC and blood vessel, respectively. Scale bar = 50 μm.

enzymatic, physical, and more recently — induction of apoptosis (Gilbert et al., 2006; Crapo et al., 2011; Song and Ott, 2011; Bourget et al., 2012; Bourgine et al., 2013). The idea of creating decellularized ECM is to take tissue and remove all of its cellular and immunogenic components while retaining tissue architecture as well as (potentially) growth factors and cytokines that may be incorporated into the matrix. Many tissues throughout the body have been decellularized including blood vessels, lungs, liver, heart, skin, etc. (Gilbert et al., 2006; Petersen et al., 2010; Reing et al., 2010; Song and Ott, 2011; Bourget et al., 2012). These scaffolds are very attractive to the field of tissue engineering because they allow the retention of tissue architecture while eliminating immunogenic components and possibly minimizing the FBR.

Recently, the Badylak group has drawn attention to the bioinductive qualities of decellularized matrices and demonstrated that as they degrade, they release peptides from matricellular proteins (for example, peptides from thrombospondin (TSP) -1) that have a range of effects on the host tissue (Badylak, 2007). Additionally, recent work by the White group on decellularized human lung has probed the question of