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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.

Keywords

Matricellular; extracellular matrix; biomaterials; foreign body response; biocompatible; decellularization

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 (Bryers et al., 2012; Cao and Hench, 1996; Hench, 1998; Shin et al., 2003). 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.

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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; Geetha et al., 2009; Heness and Ben-Nissan, 2004; Ratner, 2002).

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 (Figure 1) (Anderson et al., 2008; Ratner and Bryant, 2004; Ratner, 2002). Following protein adsorption, cells interact with the proteinaceous layer on the surface of the material leading to adhesion and activation (Anderson et al., 2008; Ratner and Bryant, 2004; Ratner, 2002). 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) (Anderson et al., 2008; Ratner and Bryant, 2004; Ratner, 2002; Xia and Triffitt, 2006). 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 (Anderson et al., 2008; Ratner and Bryant, 2004; Ratner, 2002). 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 (Bryers et al., 2012; Causa et al., 2007; Ratner, 2001; Roach et al., 2007; Shin et al., 2003). 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 (Brodbeck et al., 2002; Bryers et al., 2012; Healy et al., 1996; Lan et al., 2005; Puleo and Nanci, 1999; Ratner, 2002, 2001; Roach et al., 2007; Shin et al., 2003). Commonly, biomimetic materials modify functional groups on the surface of a material or coat the material with ECM molecules (Brodbeck et al., 2002; Chen et al., 2013; Esch et al., 2011; Healy et al., 1996; Lan et al., 2005; Puleo and Nanci, 1999; Roach et al., 2007; Shin et al., 2003). 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 (Boudriot et al., 2006; Esch et al., 2011; Roach et al., 2007; Stevens and George, 2005).

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, enzymatic, physical, and more recently-induction of apoptosis (Bourget et al., 2012; Bourgine et al., 2013; Crapo et al., 2011; Gilbert et al., 2006; Song and Ott, 2011). 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. (Bourget et al., 2012; Gilbert et al., 2006; Petersen et al., 2010; Reing et al., 2010; Song and Ott, 2011). 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 what ECM components remain after decellularization and found a variety of matricellular proteins including: periostin, tenascin-X, and tenascin-C (Booth et al., 2012). Therefore, it is important to consider the possibility that matricellular proteins that remain in the ECM could modulate cell functions and response to these materials (Figure 2). Consistent with this suggestion, we have shown that TSP2-null-derived decellularized ECM caused changes in cellular phenotype that were not rescued with administration of exogenous TSP-2, suggesting that changes in ECM architecture can influence cell function (Krady et al., 2008).

Clearly, there has been significant effort to modify materials such that they will elicit a minimal FBR; however, material based strategies must be developed independently for different materials and applications. Another method to limit the foreign body response, altering the biological response, could influence the FBR to most materials. Coating materials with matricellular proteins or specific DNA molecules that modulate the levels of matricellular proteins has shown promise as a method for biologically manipulating the host environment leading to reduced FBR (Bryers et al., 2012; Kyriakides et al., 2001; Ratner, 2002, 2001; Shin et al., 2003).

3. Matricellular Proteins

Matricellular proteins are a class of ECM proteins that primarily serve non-structural roles and regulate cell function by influencing cell adhesion, migration, proliferation, differentiation, and apoptosis (Bornstein and Sage, 2002; Bornstein, 2009; Bornstein et al., 2004; Murphy-Ullrich, 2001). Typically matricellular proteins are expressed at low levels in adult tissues, but are highly expressed in development and following injury or pathology

(Alford and Hankenson, 2006; Bornstein and Sage, 2002; Kyriakides and Bornstein, 2003; Kyriakides and Maclauchlan, 2009). These proteins have both soluble and insoluble states, which allow them to differentially influence cells (Murphy-Ullrich, 2001). Additionally, matricellular proteins can interact with growth factors, for example TSP-1 binds to and activates latent TGF-β1 (Murphy-Ullrich et al., 1992; Schultz-Cherry and Murphy-Ullrich, 1993; Schultz and Wysocki, 2009).

Matricellular proteins are grouped together because of similar functions such as: promoting an intermediate cell adhesive state (which may encourage cell migration), interactions with growth factors, facilitating matrix-cell interactions (including binding to both ECM and cells), and bridging inorganic matter and the ECM (Bornstein and Sage, 2002; Murphy-Ullrich, 2001). Interestingly, most mice with genetic deletion of one or more matricellular proteins display a mild phenotype. In addition, they are composed of several different structural domains. These common structural domains include: EGF-like repeats that are common in the TSPs, SPARC, and the tenascins; the calcium binding domains common to TSPs, SPARC, and osteopontin; and the TSP type 1 repeats and von willebrand factor type C repeats common to the TSPs and CCNs (Adams and Lawler, 2004; Brekken and Sage, 2001; Frangogiannis, 2012; Giachelli and Steitz, 2000; Hsia and Schwarzbauer, 2005). (Table 1) Despite these common motifs, the structure of matricellular proteins is generally quite varied and it is instead their similar functions that unify them as a group.

Matricellular proteins have been shown to play significant roles in the FBR and genetically modified mice have been particularly useful in elucidating their roles in this process. (Table 2) (Barker et al., 2005; Bornstein et al., 2004; Kyriakides and Bornstein, 2003; Kyriakides and Maclauchlan, 2009; Kyriakides et al., 1999; Puolakkainen et al., 2003, 2005). Specifically, mice that lack matricellular proteins display decreased capsule thickness or increased vascularity, both interesting phenotypes from the perspective of designing materials to minimize the FBR (Barker et al., 2005; Bornstein et al., 2004; Kyriakides and Bornstein, 2003; Kyriakides and Maclauchlan, 2009; Kyriakides et al., 1999; Puolakkainen et al., 2003, 2005). Moreover, reduction of TSP-1 or TSP-2 led to altered structural properties of the collagenous capsule as well as increased vascularity within the capsule (Kyriakides and Bornstein, 2003; Kyriakides and Maclauchlan, 2009; Kyriakides et al., 2001; Kyriakides et al., 1999; Reinecke et al., 2013). Interestingly, mice that lack SPARC display a decrease in capsule thickness with decreased vascularity (Barker et al., 2005; Kyriakides and Bornstein, 2003; Puolakkainen et al., 2003). Finally, osteopontin KO mice display an exaggerated FBR associated with increased numbers of FBGCs surrounding implants (Tsai et al., 2005).

Because of the importance of matricellular proteins in the biological response to implanted materials, a review of the major matricellular proteins follows. Each section will introduce some of the major functions of the protein and discuss its use in bioinspired materials design/synthesis.

3.1 Thrombospondins

The TSPs are a family of ECM glycoproteins consisting of five members, TSP 1-5. Only TSP-1 and -2 are considered for this review because of their interactions with biomaterials

and their use in the design of biomimetic materials. For a comprehensive review of the entire thrombospondin family see Adams and Lawler (Adams and Lawler, 2004).

3.1.1 Thrombospondin-1—TSP-1 is a trimeric 420 kDa protein that consists of seven functional domains: N and C terminus globular domains, a coiled coil domain, a von Willebrand factor type c domain, type 1 repeats, type 2 repeats (EGF-like), and type 3 repeats (calcium binding) (Adams and Lawler, 2004; Lawler and Hynes, 1986). TSP-1 is a major component of platelets and can be readily isolated from human blood (Lawler, 2000). TSP-1 binds a variety of cell receptors including CD36, various integrins, CD47 (integrin associated protein), and LDL receptor related proteins as well as proteoglycans, and calcium (Adams and Lawler, 2004; Bornstein, 2009; Chen et al., 2000; Lawler, 2000). With its wide array of binding partners it is no surprise that TSP-1 is implicated in a variety of physiological functions including wound healing, angiogenesis, platelet aggregation, cell proliferation and migration, and influencing cellular interactions with growth factors (Adams and Lawler, 2004; Bornstein et al., 2004; Chen et al., 2000; Kyriakides and Maclauchlan, 2009; Lawler, 2000). TSP-1 null mice have been instrumental in assessing the functions of TSP-1 *in vivo*. For example, it was confirmed that TSP-1 activates latent TGF-β1 *in vivo* by combining studies of TSP-1 null mice and TGF- β1 null mice and that TSP-1 inhibits angiogenesis by studying cancer neovascularization (Chen et al., 2000; Crawford et al., 1998). TSP-1 null mice show slowed wound healing associated with reduced inflammation in the wounded area (Agah et al., 2002; Bornstein and Sage, 2002; Kyriakides and Bornstein, 2003).

Modulation of thrombospondin-1 expression and/or function by implanted biomaterials is an area of growing interest. To aid understanding of regions of the TSP-1, implants were coated with a gene activated matrix (GAM), which consisted of collagen gel laden with plasmid DNA expressing a GFP tagged N-terminal domain (NTD) of TSP-1. It was shown that this domain, which binds calreticulin and triggers focal adhesion disassembly, causes increased capsular density and promotes collagen deposition *in vitro* (Sweetwyne et al., 2010). It has been shown that upon degradation, implanted decellularized matrix can release peptides that contain the type-1 repeats of TSP-1, known to inhibit angiogenesis (Armstrong and Bornstein, 2003; Badylak, 2007). It is possible that this property could be useful in limiting undesired angiogenesis, however, it is likely that this consequence of ECM implantation is frequently overlooked. A similar discovery was that Choukroun's platelet-rich fibrin (PRF), a biomaterial that is isolated from blood and composed of leukocytes, platelets, and fibrin releases growth factors as well as large quantities of TSP-1 over a week-long period (even more TSP-1 than is initially in the material because the platelets continue to produce it) (Dohan Ehrenfest et al., 2009). While the growth factors from this material likely promote healing, the massive release of TSP-1 could inhibit angiogenesis and may confound results. Alginate nanoparticles have been created for sustained delivery of TSP-1 and TSP-1 peptides to inhibit tumor angiogenesis (Hartig et al., 2007). Saka and Bozkir created chitosan and Poly(ethylene imine) (PEI) hybrid polymeric nanoparticles coated in polyethylene glycol (PEG) as a gene delivery system to upregulate TSP-1 (Saka and Bozkir, 2012). The goal of the study was to use develop a method of using gene delivery to inhibit angiogenesis. The interactions of TSP-1 with TGF-β have been exploited by incubating the

type 1 repeats of TSP-1 with TGF-β to protect the growth factor during encapsulation into a PEG hydrogel (McCall et al., 2011). Additionally, TSP-1 expression in vascular smooth muscle cells leading to fibroproliferative activation is stimulated by stainless steel ions *in vitro* (Pallero et al., 2010). Expression of TSP-1 in histology from resected stainless steel stents identifies the ions as a possible contributor to in-stent restenosis.

3.1.2 Thrombospondin-2—TSP-2 is similar to TSP-1 in that it is an extracellular trimeric glycoprotein with an analogous structure, but has unique functional characteristics (Adams and Lawler, 2004). TSP-2 has been shown to be important in collagen fibrillogenesis and matrix assembly, as TSP-2 null mice exhibit altered fibril size and morphology (Bornstein, 2009; Bornstein et al., 2000; Calabro et al., 2014; Kyriakides and Maclauchlan, 2009; Kyriakides et al., 1998). Abnormalities in collagen fibrils are due, in part, to increased MMP-2 and MMP-9 levels (Krady et al., 2008; Yang et al., 2001). TSP-2 null mice also show increased rates of wound healing and angiogenesis (Bornstein et al., 2000; Kyriakides and Bornstein, 2003; Kyriakides et al., 1999). Consistent with these findings, TSP-2 has been shown to decrease endothelial cell (EC) migration by limiting MMP activity and is known to be an inhibitor of angiogenesis (Armstrong and Bornstein, 2003; Bornstein and Sage, 2002; Bornstein et al., 2000; Streit et al., 1999). Another interesting phenotype of TSP-2 null mice, particularly for the subject of this review, is that they display a decreased foreign body response with altered encapsulation and increased vascularization in response to the implantation of biomaterials as well as cell grafts (Bornstein et al., 2004; Bryers et al., 2012; Kyriakides and Bornstein, 2003; Kyriakides and Maclauchlan, 2009; Kyriakides et al., 1999; Reinecke et al., 2013).

In an early study to modulate TSP-2 in the context of the FBR, implants were coated with a gene activated matrix (GAM) consisting of a collagen gel laden with plasmid DNA expressing antisense TSP-2 (Kyriakides et al., 2001). When these GAM-coated materials were implanted in mice, TSP-2 expression (near the implant) was inhibited for 4 weeks and there was a decrease in capsule thickness and increase in vascularity of surrounding tissue. Additionally, when TSP-2 sense DNA coated materials were implanted in TSP-2 null animals, the FBR phenotype was reversed (Kyriakides et al., 2001). A similar approach was used in a wound model to inject TSP-2 sense and antisense DNA in a pH sensitive polymer (Kyriakides et al., 2002). This study found efficient transfection of the cells in the wound bed and significant changes in neovascularization and altered matrix deposition in WT mice that received antisense TSP-2 (Kyriakides et al., 2002). Gene delivery to modulate TSP-2 expression *in vivo* holds promise for limiting the foreign body response to improve the lifetime of implants and altering wound healing to encourage desirable phenotypes.

Increasing TSP-2 expression has also been considered as a potential therapeutic approach. For example, a method of sustained delivery of TSP-2 *in vivo* is the implantation of cells that overexpress TSP-2. A study in which fibroblasts were made to overexpress the protein were seeded on biodegradable scaffolds and implanted in the peritoneal cavity of nude mice showed that the cells maintained high levels of expression and increased circulating levels of TSP-2 (Streit et al., 2002). These implants inhibited tumor growth and angiogenesis of several model tumors and showed twice the rate of apoptotic tumor cells as controls. TSP-2 overexpressing cell grafts hold promise as a cancer treatment because anti-angiogenic

molecules are more effective when continuously perfused, but can be prohibitively expensive (Streit et al., 2002). Other groups are considering similar cellular generated TSP-2 therapies for endometriosis (Shubina et al., 2013).

3.2 Secreted Protein, Acidic and Rich in Cysteine

Secreted Protein, Acidic and Rich in Cysteine (SPARC), also known as osteonectin, is a 32 kDa glycoprotein consisting of an acidic domain, follistatin-like domain, and calcium binding domain (Brekken and Sage, 2001). SPARC has been shown to contribute to a state of intermediate cell adhesion, induce osteoblast differentiation and survival, and influence the assembly of collagen I (Alford and Hankenson, 2006; Bornstein and Sage, 2002; Bradshaw, 2009; Murphy-Ullrich, 2001; Puolakkainen et al., 2003). SPARC interacts with and regulates the activity of several growth factors including PGDF, VEGF, and FGF-2 making SPARC an important factor in wound healing, angiogenesis, and fibrotic diseases (Brekken and Sage, 2001). Additionally, SPARC may influence the activity of TGF-β (Bradshaw, 2009). SPARC plays a role in intracellular signaling by binding integrin-linked kinase and promoting the formation of actin stress fibers as well as cell mediated assembly of fibronectin in the ECM (Barker et al., 2005a). SPARC is expressed during development and response to injury in a variety of tissues as well as in the pericellular matrix in adult bone tissue (Alford and Hankenson, 2006; Puolakkainen et al., 2003). SPARC null mice display smaller uniform collagen fibrils as well as less overall collagen content in the skin, heart , and adipose tissue (approximately half) (Bradshaw, 2009; Bradshaw et al., 2003). SPARC null mice display accelerated wound healing (for small wounds), early formation of cataracts, and increased heart failure after myocardial infarction (Bornstein and Sage, 2002; Kyriakides and Bornstein, 2003; Okamoto and Imanaka-Yoshida, 2012). Another important phenotype of SPARC null mice is that they show a decreased foreign body response with a thin capsule, but interestingly also a decrease in functional vessels (Puolakkainen et al., 2003). The decreased FBR is consistent with the decreased overall collagen content in these mice. SPARC is clearly important during wound healing and the FBR and studies have shown that the extracellular levels of SPARC may be regulated by its binding to the receptor, stabilin-1 on macrophages and being targeted for degradation (Kzhyshkowska et al., 2006). This pathway suggests a possible mechanism for which macrophages can control tissue remodeling and angiogenesis by manipulating matricellular proteins in the extracellular matrix.

Another matricellular protein, hevin, is homologous to SPARC with a longer acidic region at the amino terminus and may compensate for some of the functions of SPARC in SPARC null animals (Alford and Hankenson, 2006; Brekken and Sage, 2001). Hevin likely induces a state of intermediate cell adhesion, similarly to many matricellular proteins, and plays a role in cancer metastasis (Sullivan and Sage, 2004). In the FBR it was found that hevin tends to regulate inflammatory processes, playing an anti-inflammatory role, whereas SPARC regulates capsule formation. Additionally SPARC-hevin double null animals displayed capsules with dramatically increased vascularity, suggesting that the proteins are likely both involved in inhibiting angiogenesis and implicating both as possible therapeutic targets (Barker et al., 2005b).

Peptide sequences from SPARC have led to bioinspired material designs mainly for orthopedic implant purposes. When the glutamic acid peptide sequence from the C terminus of SPARC was functionalized with an acrylate group, it bound a hydrogel and the peptide sequence bound hydroxyapatite. This led to ionic bonds between nanoscale hydroxyapatite crystals and the hydrogel (instead of the typical dipole interactions) and significantly increased the shear modulus of the gel, creating a “bone-mimetic nanocomposite” (Sarvestani et al., 2008). Another group took a similar approach, using collagen-SPARC composites to cause nanocrystalline hydroxyapatite to bind collagen fibrils and orient along the axis of the fibril, mimicking *in vivo* structure (Liao et al., 2009). *In vivo* SPARC is cleaved by a variety of proteases leading to the inspiration for incorporating SPARC peptides into PEG hydrogels as sites for proteolysis by plasmin, MMP-1, and MMP-2 (Patterson and Hubbell, 2011). In this study, the investigators showed that incorporation of cleavable linkers allowed for faster degradation and cell proliferation as well as increased cell spreading. Even though these effects were not due to released SPARC peptides, the approach highlights the utility of incorporating features of proteins like SPARC to tune the degradability of engineered scaffolds. An additional consideration for future investigation is that SPARC-TSP-2-double-null mice exhibit reduced FBR and improved wound healing (when compared to either single KO or WT mice) (Puolakkainen et al., 2005). Therefore, it could be beneficial to manipulate the levels of both proteins in wound healing and the FBR.

3.3 Osteopontin

Osteopontin (OPN), also called bone sialoprotein 1 (BSP-1), is an acidic ECM protein that has been shown to have a role in bone mineralization, wound healing, angiogenesis, cell adhesion, differentiation, tumor metastasis, and the foreign body response (Giachelli and Steitz, 2000; Wai and Kuo, 2008). Osteopontin has a variety of binding sites including: heparin, collagen, fibronectin, various integrins, hydroxyapatite crystals, and calcium ions (Giachelli and Steitz, 2000). Osteopontin expression is increased in several pathologies including fibrosis, atherosclerosis, tumor metastasis, etc. (Frangogiannis, 2012; Giachelli and Steitz, 2000; Wai and Kuo, 2008). In healthy human tissue, osteopontin is expressed in the kidney, epithelial tissues, and is highly expressed in bone (Giachelli and Steitz, 2000). In fact, osteopontin is one of the main proteins in decellularized/demineralized bone matrix and is one of the reasons the matrix retains an osteoinductive capacity (Decup et al., 2000). Interestingly, the presence of OPN leads to decreased FBGC formation and therefore a diminished FBR (Tsai et al., 2005). OPN's role in wound healing/fibrosis, osteoblast adhesion, and bone mineralization has led to an increased interest in using it in combination with biomaterials to limit the FBR and/or promote bone regeneration.

Dental implants have provided an avenue for exploration of matricellular molecules incorporated into biomaterials since 2000 (Decup et al., 2000; Ratner, 2001). Decup et al combined OPN with gelatin and implanted the mixture into the exposed pulp in cavities that they had drilled into the teeth (Decup et al., 2000). Subsequently, they filled the remainder of the cavity with liquid cement. The results of this study showed that repair was first slower with the OPN – gelatin material, but healing was improved at later stages. Later, the same group replicated these results and also found that the osteopontin-gelatin mixture outperformed other osseoinductive proteins and that there was little inflammatory reaction to

the OPN-gelatin (Goldberg et al., 2001). Overall OPN laden gelatin (under a protective layer of cement) has proven to induce more complete and ideal healing of cavities than standard dental treatments (Decup et al., 2000; Goldberg et al., 2009, 2008, 2001; Ratner, 2001). Wang et al showed OPN-gelatin caused increased regeneration when implanted in defects of the skull, but demonstrated that OPN in a collagen carrier performed much better (Xu et al., 2007).They showed that gelatin allowed for much faster release of the OPN, but that collagen-OPN blends healed significantly faster than gelatin-OPN or collagen or gelatin alone.

Another combination of OPN and biomaterials of interest is coating titanium femoral implants with osteopontin. Orthopedic implants wear and corrode over time, which can cause the implant to loosen and even fail. Coatings such as hydroxyapatite and RGD peptides cause the bone to integrate better with surrounding tissue. Because OPN is osteoinductive and contains RGD sequences, it was hypothesized that it could outperform other coatings (O'Toole et al., 2004). Titanium wires coated with an osteopontin-gelatin solution implanted into rat femurs did lead to increased osteoinduction, but this was not associated with stronger bonds to the bone (O'Toole et al., 2004).

Non-specific protein adsorption to the surface of the implant is one of the first events in the FBR and the randomness of this adsorption may be the cause of subsequent events (Ratner, 2002, 2001). In an attempt to present a surface that would minimize the FBR, Liu et al functionalized a polymer to have a charge over its entire surface and then placed the polymer into osteopontin solutions to allow OPN to adsorb in a more controlled fashion (the charge will control the orientation of the OPN molecule) (Pan et al., 2008). When implanted *in vivo* the positively charged polymer coated with OPN showed increased cell spreading after 7 days and a foreign body capsule that was significantly thinner after 4 weeks, suggesting that controlling OPN adsorption and orientation can be a successful strategy for minimizing the FBR (Pan et al., 2008). Additionally, OPN antisense oligodeoxynucleotides loaded into Pluronic gel promote wound closure at early time points and reduce wound fibrosis and scarring at later time points (Mori et al., 2008). Wounds that had antisense OPN delivered to them showed decreased leukocyte recruitment and more angiogenesis (Mori et al., 2008).

Osteopontin in combination with biomaterials has also proved to be useful for studies *in vitro*. In 1997 it was discovered that a 15 amino acid sequence from osteopontin (containing the RGD domain) increased cell adhesion, focal adhesion formation, and cell adhesion strength to quartz as compared to control surfaces (a peptide containing RGE sequence and a clean quartz surface) (Rezania et al., 1997). Recently it was found that coating surfaces with osteopontin promoted endothelial cell progenitor adhesion and spreading with dose dependency *in vitro* and may prove to be a useful system for the functionalization of vascular grafts to be endothelialized *in situ* (Yuan et al., 2013). Another group sought to make a protein that would both strongly bind collagen and hydroxyapatite to treat bone defects by making a chimeric protein containing a glutamic acid rich sequence from OPN (that nucleates hydroxyapatite crystals) and a segment from decorin known to have a high affinity for collagen (Hunter et al., 2001). This chimeric protein successfully bound collagen and served as a nucleation site for hydroxyapatite crystals and is potentially useful because

in collagen gels, it encouraged mineralization along the length of the collagen fibrils (instead of random crystal formation as seen in poly-L-glutamic acid controls) (Hunter et al., 2001).

OPN segments have also been immobilized onto gold in various patterns to influence cell adhesion and shape as well as response to growth factors (Mieszawska and Kaplan, 2010; Mitchell et al., 2010). Functionalizing biomaterials with osteopontin has proven to be a useful technique for influencing cell behavior, limiting the FBR to implants, and encouraging tissue regeneration, particularly for orthopedic implants.

3.4 Periostin

Periostin is a 90 kDa protein that can be divided into seven domains: a secretory peptide, one EMI domain, four FAS1 domains, and a hydrophobic C-terminus (Kudo et al., 2007). Periostin is expressed in connective tissues, cardiac tissues during development and after damage, and the wound bed (Hamilton, 2008; Norris et al., 2009, 2012). Periostin belongs to the fasciclin gene family and shares many residues with FAS1 in Drosophila (Hamilton, 2008; Norris et al., 2009, 2012). Periostin is involved in cell adhesion, MSC differentiation, cardiac development, wound healing, collagen fibrillogenesis, atherosclerosis, cancer metastasis, and possibly hypertrophic cardiomyopathy (Hamilton, 2008; Hixson et al., 2011; Kudo et al., 2007; Norris et al., 2009, 2012; Seidman and Seidman, 2011). Although periostin null mouse pups are phenotypically normal, these mice grow more slowly and exhibit higher mortality than WT (Frangogiannis, 2012). Periostin is implicated heavily in cancer metastasis and embryogenesis because it stimulates cell migration and differentiation after the epithelial-mesenchymal transition (EMT) (Lindsley et al., 2007; Ruan et al., 2009). Periostin has received significant attention recently because of the possible influence it may have on the cardiomyocyte cell cycle (Kühn et al., 2007; Lorts et al., 2009; Matsui et al., 2010; Polizzotti et al., 2012). The effects of periostin on cardiac cell cycle remain controversial because although several groups report that it causes cardiomyocytes to proliferate after injury, one report shows that periostin overexpressing and periostin null mice show no changes in cardiac cell proliferation or cardiac regeneration after injury, when compared to wild type (Lorts et al., 2009).

Because of the effects that periostin may have on stimulating cardiomyocytes to reenter the cell cycle, combinations of periostin and biomaterials are of interest in treating injured heart tissue, particular after myocardial infarction. Specifically, a group showed that periostin can cause differentiated adult cardiomyocytes to enter the cell cycle and begin replication, and demonstrated that periostin loaded gelfoam delivered after myocardial infarction reduced scar formation and improved cardiac function in rats (Kühn et al., 2007). A follow up paper demonstrated that when periostin loaded gelfoam was injected into the pericardial cavity of pigs, a fibrin rich hydrogel spontaneously encapsulated the material, creating a drug-eluting hydrogel that prolongs periostin release and forms *in situ* (Polizzotti et al., 2012). The use of periostin loaded biomaterials for cardiac regeneration is still a controversial topic and in need of further research.

3.5 CCNs

The CCN family of proteins is involved in a variety of processes from development to inflammation, wound healing, and cancer (Chen and Lau, 2009). There are 6 members of the CCN family, but only CCN1 and CCN2 have been considered in the context of biomaterials. CCN2 (also called connective tissue growth factor) is thought to increase ECM production and is both a downstream target of and co-factor for TGF-β (Grotendorst, 1997; Perbal, 2004; Liu, Thompson, & Leask, 2014). Both CCN1 and 2 promote angiogenesis and endothelial cell survival (Perbal, 2004). Both CCN1 and CCN2 are known to interact with a variety of integrins and have been shown to regulate cell adhesion and migration (Chen and Lau, 2009). CCN1 also regulates proliferation, apoptosis, and the effects of TNFα. The CCNs have very similar structures and contain domains similar to those of many other matricellular proteins: a secretory peptide, four insulin-like growth factor binding domains, a von willebrand factor type C repeat, a TSP type 1 repeat, and a C-terminal domain (Frangogiannis, 2012).

3.5.1 CCN1—CCN1 has potent pro-angiogenic effects and has been shown to promote endothelial cell survival (Chen and Lau, 2009; Perbal, 2004). In an attempt to encourage the formation of a continuous endothelial cell coating on the lumen of decellularized vascular matrices, Bär et al coated their decellularized vessels with CCN1 (Bär et al., 2010). Twice as many endothelial cells adhered to vessels coated with CCN1 and showed increased metabolic activity in these cells (possibly due to increased cell viability) (Bär et al., 2010). Ravi et al created an elastin-like protein polymer that contained a sequence from CCN1 that is known to interact with the $\alpha_v\beta_3$ integrin of endothelial cells, in an attempt to promote endothelialization of the polymer (Ravi et al., 2012). They found increased HUVEC adhesion to this polymer (when compared to untreated plates), increased cell migration, and low levels of ICAM-1 and E-selectin expression, demonstrating a quiescent endothelium (Ravi et al., 2012). A more recent paper examined the effects of CCN1 coated decellularized carotid arteries when implanted *in vivo* in sheep and showed that CCN1 promoted the formation of a continuous endothelial layer and increased SMC invasion into the decellularized matrix when compared to uncoated decellularized arteries (Spengler et al., 2013). CCN1 coatings are a promising method for promoting endothelialization and maintaining vascular graft patency.

3.5.2 CCN2—Percutaneous implants require adequate wound healing in the area surrounding the implant to maximize success. To increase the healing surrounding titanium implants, Wei et al functionalized an implant surface with CCN2-loaded titania nanotubes to promote fibroblast activity and dermal healing surrounding the implant (Wei et al., 2012). *In vitro* these implants released most of their CCN2 within 2 hours but promoted fibroblast adhesion and rapid formation of actin stress fibers that became denser over time, suggesting increased fibroblast activity (Wei et al., 2012). It is unclear whether these benefits would remain if the devices were implanted *in vivo*, but the idea of drug loading the nanotopography of a metallic implant with matricellular proteins holds promise.

3.6 Tenascin-C

Tenascin-C (TNC) is a hexameric protein with each subunit approximately 200 kDa. It modulates cell adhesion, particularly by regulating cell-fibronectin interactions (Bornstein and Sage, 2002; Hsia and Schwarzbauer, 2005). TNC has multiple domains including: its N terminal domains, a fibrinogen-like C terminus, epidermal growth factor repeats, and fibronectin type III repeats which bind to integrins (Chiquet-Ehrismann, 2004; Erickson, 1993; Hsia and Schwarzbauer, 2005; Leahy et al., 1992). Tenascin-C is highly expressed during development and in areas of tissue formation (after injury, during angiogenesis, or tissue remodeling), and at low levels in adult tendons (Alford and Hankenson, 2006; Bornstein and Sage, 2002; Hsia and Schwarzbauer, 2005). Tenascin-C null mice have neurological changes resulting in altered behavior, as well as altered healing in models of skin and bone injuries (Alford and Hankenson, 2006; Bornstein and Sage, 2002; Kyriakides and Bornstein, 2003).

Fibronectin type III domains of TNC have been incorporated into elastic hydrogels as binding sites for cells to mimic the *in vivo* architecture (Lv et al., 2013). The domains from TNC promoted cell adhesion and spreading in these hydrogels, which could be tuned to have varying mechanical properties (Lv et al., 2013). Another group modified polyamide electrospun nanofibers to display tenascin-C peptides for neuronal cell culture (Ahmed et al., 2005). This unique approach combined a biomimetic ECM architecture with peptides that promoted cell attachment, neurite generation, and neurite extension, ultimately leading to neurons that had longer and more branched neurites than control materials (Ahmed et al., 2005). In addition, it was discovered that TNC-coated tissue culture treated plates promoted MSC survival in the presence of death signals (Rodrigues et al., 2013).

4. Conclusions and Future Directions

Matricellular proteins are an important class of ECM proteins that influence a variety of cell processes. Their diverse functions make them an important consideration when using materials such as decellularized ECM derived from tissues or cells *in vitro*. Moreover, matricellular proteins have functions that range from influencing ECM production to inhibiting angiogenesis and promoting adhesion. Therefore, biomaterials that contain matricellular proteins or their domains or DNA to influence their expression are emerging as a new generation of biomimetic materials. These materials may be key to promoting tissue regeneration and reducing the foreign body response to biomaterials (Bryers et al., 2012).

As the number of materials that incorporate ECM components increases, it will be important to consider manipulation of the micro- and nano-architecture as well as matricellular protein content to achieve the desired effect. Additionally, double-null mice have shown that matricellular proteins can have synergestic effects (Agah et al., 2002; Barker et al., 2005b; Puolakkainen et al., 2005). Investigating combinations of multiple matricellular proteins or domains from these proteins will be an important area for further research. Ultimately, as knowledge of the mechanisms of action of matricellular proteins is elucidated, it will lead to improved design of materials to promote healing, reduce the FBR, and achieve greater successes in tissue engineering.

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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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Highlights

- Matricellular proteins participate in the foreign body response to biomaterials.
- Modulation of matricellular proteins or their components can alter the FBR.
- Biomimetic materials can incorporate matricellular proteins or their components.
- Matricellular proteins retained in decellularized ECM influence cell function.

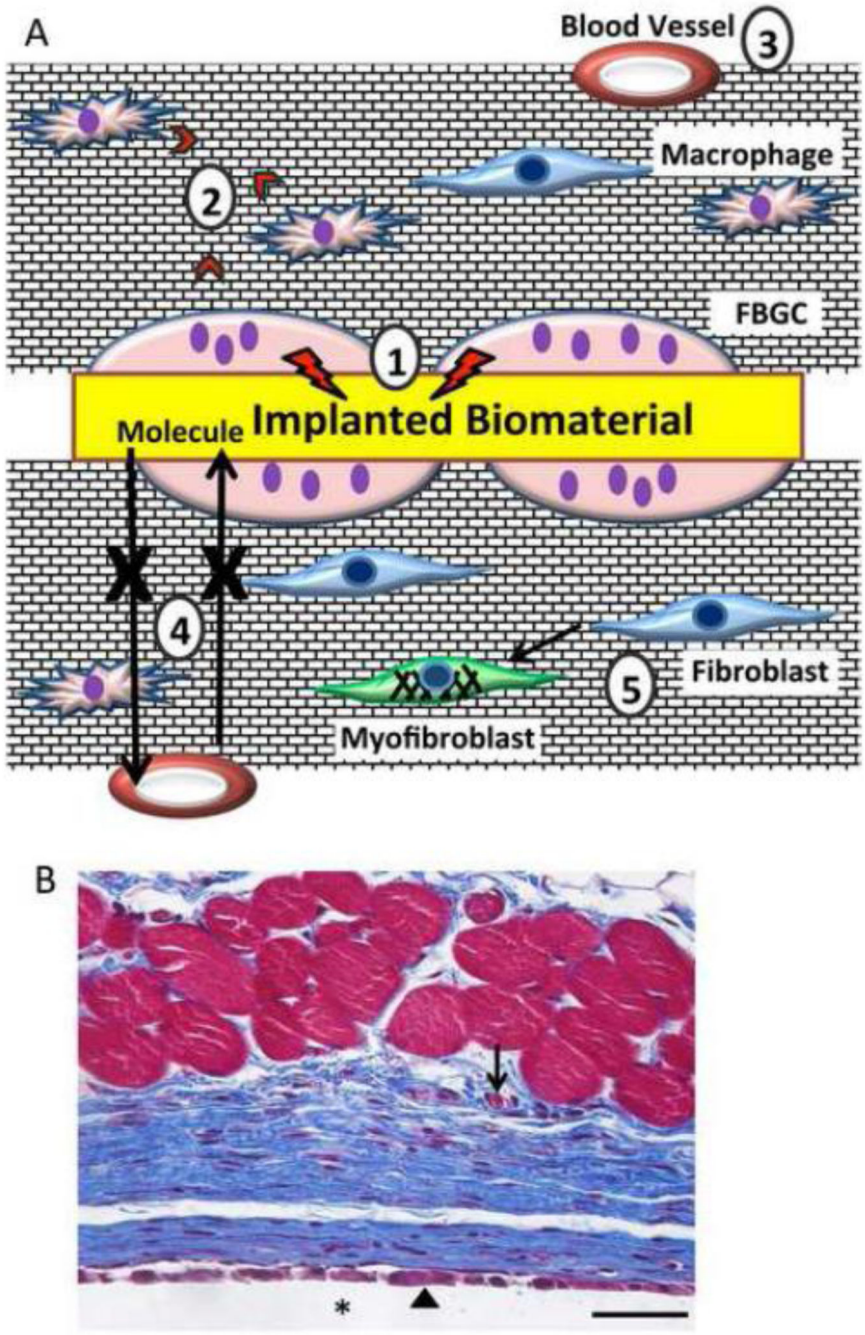

Figure 1.

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) FBGC 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 PDMS disk implanted subcutaneous (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.

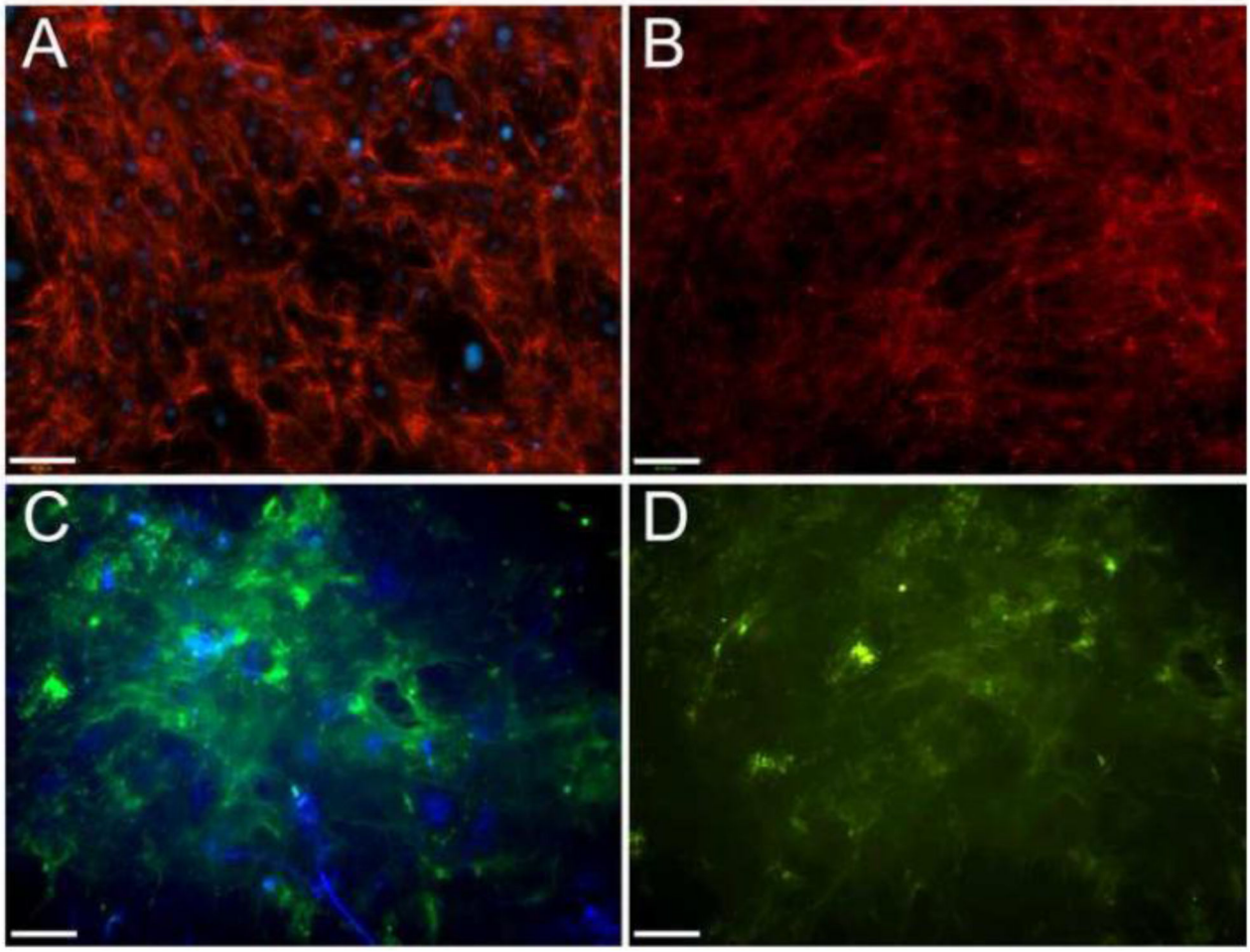

Figure 2.

ECM retention following decellularization. Dermal fibroblasts were cultured for 10 d in the presence of ascorbic acid to induce ECM production. Cultures were analyzed by immunohistochemistry for the deposition of fibronectin (red color in A, B) and TSP2 (green color in C, D) prior (A, C) or following decellularization (B, D). Nuclei were counterstained with DAPI (blue). Retention of both proteins was observed following decellularization. Scale bar = 100 μm.

Table 1

Structural motifs in matricellular proteins.

Matricellular Proteins	Common Protein Domains				
	Ca^{2+} binding	EGF-like	RGD/Integrin Binding Domains	TSP type I repeats	VWF type C
Thrombospondin-1/2	✓	✓	✓	✓	✓
Osteopontin	✓		✓		
Tenascin-C		✓	✓		
SPARC	✓	✓	✓		
CCNs			✓	✓	✓
Periostin			✓		

Table 2

Matricellular Proteins and the Foreign Body Response.

Protein	Knockout Mouse FBR Phenotype	*In Vivo* Molecular Strategies	References
TSP-1	Increased capsule vascularity. Irregular collagen fibrils.	Coated implants gene activated matrix expressing the N-terminal domain of TSP-1 resulted in increased capsular density	(Kyriakides and Bornstein, 2003; Sweetwyne et al., 2010)
TSP-2	Greatly increased capsule vascularity Irregular collagen fibrils	Coated implants in antisense gene-activated matrix to increase capsule vascularity	(Kyriakides et al., 2001; Kyriakides et al., 1999)
SPARC	Decreased capsule thickness and vascularity Small collagen fibrils		(Puolakkainen et al., 2003)
OPN	Increased FBGC formation	Coating implants in oriented OPN led to reduced capsule thickness OPN-gelatin mixtures promote repair of cavities and skull defects Coating titanium implants in OPN to increase osseointegration	(Liu et al., 2008; Tsai et al., 2005; Xu et al., 2007; Goldberg et al., 2001; O'Toole et al., 2004)
Periostin		Periostin loaded gelfoam delivered after myocardial infarction reduced scar formation and improved cardiac function in rats	(Kühn et al., 2007)
CCN1		Coating decellularized vascular grafts in CCN1 promotes endothelialization and graft patency	(Bär et al., 2010; Spengler et al., 2013)