Revisiting the matricellular concept

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Abstract

The concept of a matricellular protein was first proposed by Paul Bornstein in the mid-1990s to account for the non-lethal phenotypes of mice with inactivated genes encoding thrombospondin-1, tenascin-C, or SPARC. It was also recognized that these extracellular matrix proteins were primarily counter or de-adhesive. This review reappraises the matricellular concept after nearly two decades of continuous investigation. The expanded matricellular family as well as the diverse and often unexpected functions, cellular location, and interacting partners/receptors of matricellular proteins are considered. Development of therapeutic strategies that target matricellular proteins are discussed in the context of pathology and regenerative medicine.

Keywords
Matricellular; Thrombospondins; SPARC; Hevin; Tenascins; CCN; Osteopontin; Fibulin; Periostin; R-spondin; Extracellular matrix; Cell adhesion; Regenerative medicine

1. Introduction

The concept of a matricellular protein arose nearly twenty years ago from Paul Bornstein's group at the University of Washington with the advent of data from several laboratories showing that some secreted and/or extracellular matrix (ECM) proteins were “de-adhesive” (Murphy-Ullrich and Hook, 1989; Lane and Sage, 1990; Murphy-Ullrich et al., 1991; Sage and Bornstein, 1991; Murphy-Ullrich et al., 1995). Substrata composed of these proteins failed to support cell adhesion characterized by the formation of focal adhesions and stress fibers in contrast to adhesive extracellular matrix proteins such as fibronectin, vitronectin, and collagen. These matricellular proteins also antagonized cell adhesion when presented to cells as soluble molecules and induced reorganization of focal adhesions and actin stress fibers, a state termed intermediate adhesion (reviewed in (Sage and Bornstein, 1991; Lane and Sage, 1994; Sage, 1997b, 2001; Murphy-Ullrich, 2001)). It was also disturbing that mice with targeted inactivation of these genes were born alive and, on first glance, had no apparent or only subtle phenotypes (Erickson, 1993). There was even speculation that these extracellular proteins did not have any important role in cell biology. Fortunately, work over
the past twenty years has quelled this speculation. Indeed, the importance of matricellular proteins to development, health, and disease has never been more apparent. In July 2013, the 6th conference dedicated to matricellular proteins was held in Saxtons River, Vermont. The articles in this themed issue reflect the profound and broad importance of matricellular proteins in diverse cellular processes and diseases as well as the incredible complexity of their regulation and functions.

In this review, we will re-visit the initial matricellular concept as defined by Paul Bornstein in 1995 in the context of recent findings from the matricellular field, with an emphasis on data presented at the FASEB Scientific Research Conference on Matricellular Proteins in Development, Health, and Disease (Bornstein, 1995).

1.1. Early history of the matricellular idea

The concept of “matricellular” is credited to Paul Bornstein, M.D. (1934–2013) and members of his laboratory who worked on two prototypes that defined this novel family of proteins — SPARC and thrombospondin (TSP)-1. This idea, nearly 20 years in development, started in 1975 when Paul spent sabbatical time in Jon Singer's laboratory at Cal Tech, where immunofluorescence techniques revealing cell-surface and ECM components were being used for the first time in biochemistry and cell biology. Paul was fascinated by what he called “cell coats” and set several of his postdocs to defining the fibroblast and endothelial cell integuments. The work led to his concept of “dynamic reciprocity” to explain the apparent influence exerted by the ECM on the very cells that initially produced it (Bornstein et al., 1982). In a recent review on wound healing and tissue regeneration, dynamic reciprocity is defined as “an ongoing, bidirectional interaction among cells and their surrounding microenvironment. Such cell-extracellular matrix interactions not only guide and regulate cellular morphology, but also cellular differentiation, migration, proliferation, and survival during tissue development, including, e.g., embryogenesis, angiogenesis, as well as during pathologic processes including cancer, diabetes, hypertension, and chronic wound healing” (Schultz et al., 2011). It was initially envisioned that certain fibrillar ECM proteins (e.g., collagen types I and III and fibronectin) interact in some manner with the cytoskeleton (admittedly indirectly) to effect changes in cell shape, ion fluxes, secretory patterns, and mitosis (Bornstein et al., 1982). Subsequently, two important discoveries lent credence to this early model: integrin receptors spanning the plasma membrane provided a link between extracellular macromolecules and the cytoskeleton/signaling cascades, and matricellular proteins as extracellular but non-structural components provided specific functions and a vastly expanded dimension to what a somewhat inert ECM was formerly thought to comprise. In 1995, Bornstein published the seminal article defining matricellular proteins: “Matricellular is used in this analysis to refer to a group of modular, extracellular proteins whose functions are achieved by binding to matrix proteins as well as to cell surface receptors, or to other molecules such as cytokines and proteases that interact, in turn, with the cell surface”. Furthermore, although matricellular proteins “can be associated with structural elements such as collagen fibrils and basement membranes, it is assumed that they do not contribute to the structural integrity of these elements” (Bornstein, 1995). An in-depth review of this topic can be found in
Bornstein and Sage (2002). The dynamic nature of “established” ECM has also evolved accordingly (Hynes, 2009).

The original matricellular triumvirate consisted of SPARC (secreted protein, acidic and rich in cysteine, also known as osteonectin and BM-40), thrombospondin (now TSP-1), and tenascin (now tenascin-C) (TN-C) (Sage and Bornstein, 1991). Although unrelated in primary structure, their unifying characteristics were that they were 1) secreted by diverse types of cells, 2) associated with, but not necessarily a part of, the insoluble/fibrillar ECM, 3) counter-adhesive for cells under various conditions, 4) prevalent in areas of tissue remodeling associated with normal and pathologic processes, and 5) featured prominently in mammalian and avian embryogenesis. As the literature expanded with additions to the matricellular group as well as to its individual protein families (e.g., hevin/SC-1 of the SPARC family and TSP-2 of the thrombospondin family), screening became more difficult with the discovery of new functions appropriate for matricellular membership and classification. There could be no greater compliment to Paul Bornstein’s scientific career than the growth and success of this family, the FASEB Symposium in 2013 devoted to these interesting and important proteins, and their recognition in this themed issue of Matrix Biology.

1.2. SPARC as a matricellular prototype

Although not the first of the matricellular group to be described, SPARC became known as its prototype due in part to the relative simplicity of its structure (a monomer of Mr ~32,000 excluding the signal peptide and carbohydrate) and the apparent myriad of functions that it displayed (reviewed in (Sage, 2009)). Dominant features included its counter-adhesive activity, later described as a condition of “intermediate adhesion” by Murphy-Ullrich and colleagues in 1995 and an impetus for Bornstein’s subsequent matricellular concept (reviewed in (Murphy-Ullrich, 2001)). Later studies identified the interaction of SPARC with integrin beta 1 and signaling through integrin-linked kinase and/or GSK-3 beta as effectors of cell shape, adhesion, and differentiation (Barker et al., 2005a; Weaver et al., 2008; Nie and Sage, 2009b).

Another compelling feature of SPARC was its abundant levels of secretion by cultured cells and, in vivo, at sites of tissue injury (e.g., wound healing), cancer, and remodeling (bone, gut epithelia, hair follicles, and steroid-producing organs). These data were suggestive of processes involving changes in cell shape, cell cycle, protein secretion, and motility, all of which were subsequently verified experimentally (Lane and Sage, 1994; Sage, 1997b; Bradshaw and Sage, 2001; Emerson et al., 2006). Related lines of evidence also pointed to the interactions of SPARC with ECM components such as collagens (principally types I and IV) and with growth factors (e.g., VEGF-A and platelet-derived growth factor) that inhibited their binding to cognate receptors. The consequences of these activities became apparent in later developmental studies with mice harboring an inactivated SPARC gene (Delany et al., 2000; Yan et al., 2002; Bradshaw et al., 2003a, 2003b; Gruber et al., 2005). Indeed, with their thin skins and brittle bones (impaired collagen I production and fibrillogenesis), progressive cataracts (poorly assembled collagen IV in the lens capsule), accumulation of excessive adipose tissue (compromised osteoblast formation and survival), and
intervertebral disc degeneration, the SPARC-null mice appeared to be aging well before their time. These characteristics reflecting alterations in tissues during development became more evident, or were exacerbated, in disease models. For example, Brekken et al., reported enhanced growth of pancreatic tumors in SPARC-null mice, due to a compromised ECM, poor encapsulation of the tumor, reduced infiltration of macrophages, and attenuated levels of tumor cell apoptosis (Brekken et al., 2003). The reduced foreign body response in mice lacking SPARC was similarly characterized by a reduction of ECM deposition (Puolakkainen et al., 2003).

As most (if not all) of the matricellular proteins have a modular primary structure, we had proposed that, if specific proteinases could be identified, cleavage of SPARC into bioactive peptides might not only reveal new functions for the protein but also could present potential therapeutic targets in the treatment of certain pathologies (Sage, 1997a). To this end, Lane et al., identified copper-binding peptides of SPARC that regulated angiogenesis, and subsequent studies showed that matrix metalloproteinase 3 (stromelysin) released polypeptides from SPARC with similar activity (Lane et al., 1994; Sage et al., 2003). Moreover, the copper-binding domain of SPARC was identified as a mediator of cell survival in vitro via its interaction with integrin beta 1 and signaling through integrin-linked kinase (Weaver et al., 2008); similar peptides have been implicated in the inhibition of angiogenesis in neuroblastoma (Chlenski et al., 2004). Clearly, there is a future for SPARC (and its homolog hevin, see below) in the diagnosis and treatment of cancers, as indicated by gene array analyses (Clark and Sage, 2008; Sage, 2009).

Since the first descriptions of SPARC/osteonectin/BM-40, several new family members, based on the signature ECM calcium-binding (EC) domain, have been added to the fold: hevin (also known as SPARC-like 1, SC-1, Mast 9, Ecm 1 SMOC 1 and 2, and several of the testicans. Hevin particularly has received attention as a potential tumor suppressor expressed abundantly in certain tumor cells, their stroma, and their neovasculature (reviewed in (Sullivan and Sage, 2004)). Both counter-adhesive and implicated in neuronal migration, it was surprising that hevin-null mice initially appeared “normal.” However, Sullivan et al. later found that mice lacking hevin had an unusually stiff dermis with a high tensile modulus and aberrant collagen fibrils, due to the impaired regulation of the collagen-binding accessory proteoglycan decorin (Sullivan et al., 2006). Other similarities between hevin-null and SPARC-null mice were the appearance of cataracts (albeit at different ages), enhanced growth of solid tumors, and alterations in dermal wound repair (Sullivan et al., 2008; Sage, 2009). Using hevin/SPARC single- and double-null mice in a model of the foreign body response, Barker et al. showed that hevin alone suppressed inflammation, whereas both proteins diminished angiogenesis (Barker et al., 2005b; Sullivan et al., 2008). Because the copper-binding and EC domains of SPARC and hevin are similar, one might predict that a synergy occurs, especially at the peptide level that would result in an enhanced angiogenic response.

From the description of a SPARC homolog in Caenorhabditis elegans that influenced the morphology and mobility of this invertebrate (Schwarzbauer and Spencer, 1993), hevin appeared to be an excellent candidate to test the hypothesis that hevin and SPARC might compensate for each other developmentally through the release of peptides or domains by

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endogenous proteolysis at evolutionarily conserved sites. Although more examples of this interesting phenomenon are required, Weaver et al. showed that a SPARC-like fragment of hevin (termed SLF) was indeed produced by matrix metalloproteinase 3 and was found in the neovasculature of murine glioma (Weaver et al., 2011).

This section is intended to provide an historical perspective for the continued study of the matricellular proteins, and has used one of them, SPARC, as an example of the varied functions attributed to this structurally diverse group of extracellular (and in some cases, intracellular) macro-molecules. Many of the functions (e.g., counter-/intermediate adhesion, regulation of ECM deposition, inhibition of growth factor activity, signaling via integrins) appear to be overlapping, yet it is clear that specific molecular targets and mechanisms exist for each matricellular entity. The articles presented in this themed issue of Matrix Biology attest to the broad spectrum of biological activities facilitated by the matricellular proteins. In retrospect, a need for this functional class was correctly perceived, as evidenced by the recent studies, discussed in succeeding sections that correlate the early and basic observations with the complex mechanisms that operate in health and disease.

2. Members of the matricellular family

The original members of the matricellular family included SPARC, TSP-1, and TN-C (Bornstein, 1995), previously grouped as secreted proteins that modulated cell-ECM interactions (Sage and Bornstein, 1991). It had become clear that there were additional molecules in the ECM that interacted with cells, but did not play a primarily physical role in the structure of the ECM. The family now includes additional members of the SPARC (hevin/SC-1), TSP (TSP1–4, TSP-5 or cartilage oligomeric protein) (COMP), and tenascin families (tenascins-C, R, W, X, and Y) (Sage and Bornstein, 1991; Brekken and Sage, 2001; Sullivan et al., 2008; Sage, 2009; Acharya et al., 2014-in this issue; Chiquet-Ehrismann et al., 2014-in this issue; Posey et al., 2014-in this issue; Resovi et al., 2014-in this issue).

Furthermore, many other components of the ECM microenvironment have been proposed to be matricellular: most are readily identified as components of the ECM, but some are not typically categorized as ECM components. The expanded matricellular family includes osteopontin, members of the CCN family (Cyr61, CCN2, CCN3), peristin, R-spondins, the short fibulins including hemicentin, galectins, small leucine rich proteoglycans (SLRPs), autotaxin, pigment epithelium derived factor (PEDF), and plasminogen activator inhibitor-1 (PAI-1) (Giachelli and Steitz, 2000; Moiseeva et al., 2000; Sodek et al., 2002; Czekay et al., 2003; Leask and Abraham, 2006; Yeger and Perbal, 2007; Hamilton, 2008; Perbal, 2008; Yuelling and Fuss, 2008; Merline et al., 2009; Yanagisawa et al., 2009; Hankenson et al., 2010; Kular et al., 2011; Fitchev et al., 2013; Bedore et al., 2014-in this issue; Knight and Hankenson, 2014-in this issue; Liu et al., 2014-in this issue; Papke and Yanagisawa, 2014-in this issue; Shevde and Samant, 2014-in this issue). The SLRPs are the subject of an extensive recent review and as the SLRPs are usually considered in the context of proteoglycans, they will not be addressed further in this review (Ioizzo et al., 2011). Although these proteins are structurally diverse, most, but not all, contain repeats of common ECM structural motifs such as thrombospondin type 1 repeats (TSRs), fibronectin type III repeats, EGF-like repeats, among others, and many are also calcium binding proteins (Adams and Engel, 2007; Mosher and Adams, 2012). As reviewed previously
Martinek et al., 2007; Mosher and Adams, 2012), matricellular proteins with thrombospondin and SPARC-like structures appeared in early metazoans. Despite their diversity, common to all matricellular proteins is the capacity to interact with cellular receptors, ECM macromolecules, growth factors, and proteases and thereby to directly or indirectly regulate cellular function, either at the plasma membrane, intracellularly, in body fluids, or from the ECM.

2.1. Matricellular proteins: functions within and without

Matricellular proteins were first identified as transient, rather than constitutive, components of the ECM. They are incorporated into the ECM of remodeling tissues during development, wound healing, and in response to injury and stress, especially in fibrotic ECM and tumor-associated stroma. In addition, many matricellular proteins are present in body fluids and can bind cells as soluble ligands. Matricellular proteins can also bind soluble growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and (latent) transforming growth factor-β (TGF-β) and can modulate the actions of these factors through presentation to their receptors, by blocking receptor binding, or by induction of conformational alterations to modulate activity. Interestingly, two different matricellular proteins, TSP1 and tenasin-X can convert latent TGF-β to its biologically active form, indirectly regulation ECM expression (Schultz-Cherry and Murphy-Ullrich, 1993; Alcaraz et al., 2014). Matricellular proteins can also directly or indirectly alter growth factor receptor signaling (Schultz-Cherry and Murphy-Ullrich, 1993; Brekken and Sage, 2001; Schiemann et al., 2003; Nozaki et al., 2006; Iyer et al., 2007; Liu et al., 2009; Garg et al., 2011; Kazerounian et al., 2011).

Recent evidence suggests that some matricellular proteins can regulate cell function from intracellular compartments. Intracellular SPARC co-localized with intracellular collagen IV in the endoplasmic reticulum (ER) of adipocytes from Drosophila larvae (Martinek et al., 2007, 2008): SPARC is thought to be important for basement membrane formation during development (Yan et al., 2002). OPN is also located intracellularly on the inner surface of the plasma membrane as part of the CD44-ezrin/radixin/moesin complex where it regulates cellular functions related to cytoskeletal organization (Zohar et al., 2000). Thrombospondins also play a role in the ER. TSP4 binds to ATF6α in the ER and regulates its ER-nuclear shuttling and ER adaptive responses in the myocardium (Lynch et al., 2012). TSP-1 also binds to STIM1 (stromal interaction molecule 1), an ER and plasma membrane protein that detects calcium depletion, at the platelet plasma membrane and potentially regulates STIM1 calcium sensing that is important for platelet aggregation (Ambily et al., 2014). Multiple TSPs (TSP-1, TSP-4, and COMP) were shown to bind to the N-terminal domain of STIM1, which is exposed to the ER lumen and on the external side of the plasma membrane. TSPs bind to STIM1 through the TSP C-terminal signature domains, independent of the presence of calcium (Duquette et al., 2014-in this issue). Overexpression of COMP promoted arachidonate-regulated calcium channel activity which is regulated by plasma membrane STIM1 (Duquette et al., 2014-in this issue). These provocative findings indicate that the capacity of TSPs to bind to multiple receptors and molecules affects the functions of macromolecular assemblies not only in the ECM, but also at the cell membrane and in intracellular compartments. Mutations in COMP associated with pseudoachondroplasia
result in accumulation of misfolded COMP in the ER which induces ER stress and chondrocyte apoptosis and also leads to abnormal intra-ER assembly of ECM proteins (Posey et al., 2009; Coustry et al., 2012). Given the capacity of matricellular proteins to bind other ECM components, their putative roles as chaperones for these molecules and perhaps growth factors are reasonable (Chlenski et al., 2004; Emerson et al., 2006). Some matricellular proteins have also been identified in nuclear compartments (SPARC, CCN5, amino-domain truncated CCN3) (Gooden et al., 1999; Planque et al., 2006; Wiesman et al., 2010), although the nuclear roles of matricellular proteins remain unclear. Nonetheless, the possibility that matricellular proteins act as intracellular targeting or transport molecules warrants further investigation.

2.2. Regulation of matricellular protein expression

Since the initial report that TSP-1 and SPARC secretion are inversely proportional to cell density (Mumby et al., 1984), the precise regulation of matricellular protein expression has been appreciated. Not unexpectedly, regulation of matricellular proteins is complex. Many labs have characterized the regulation of expression of specific matricellular proteins through characterization of promoter regions and their interactions with transcription factors: the regulation of TSPs and tenascins is discussed extensively in reviews in this issue (Chiquet-Ehrismann et al., 2014-in this issue; Stenina-Adognravi, 2014-in this issue). These proteins can also be regulated post-transcriptionally, at the level of translation, and via secretory pathways. These points are extensively discussed for the TSPs in a review in this issue by Stenina-Adognravi (2014-in this issue). Matricellular proteins are also regulated by microRNA and other epigenetic mechanisms (DNA methylation, histone acetylation/deacetylation) (Whitcomb et al., 2003; Suzuki et al., 2005; Rodriguez-Jimenez et al., 2007; Hanna et al., 2009; Dew et al., 2010; Greco et al., 2010; Galvez et al., 2011; Lindner et al., 2013; Qin et al., 2013; Dogar et al., 2014; Stein et al., 2014; Wang et al., 2014). Matricellular proteins can also be auto-regulated through their receptors: It has recently been shown that TSP-1 expression is attenuated by CD47, and that genetic disruption of CD47 results in increased TSP-1 expression and downstream increases in TGF-β activity (Soto-Pantoja et al., 2014-in this issue). One interesting area that has not been fully explored is the regulation of matricellular proteins by circadian clock genes. Clock genes have been implicated in many cellular processes including metabolic regulation, cancer, and immune responses, cellular events in which matricellular proteins play key roles (Li et al., 2012; P. Chen et al., 2013; Kelleher et al., 2014). The aryl hydrocarbon receptor, a member of the clock gene family, has been shown to regulate glucose dependent stimulation of TSP-1 (Dabir et al., 2008); otherwise, there is little information concerning the regulation of matricellular proteins by clock genes. In recent years, extracellular matrix stiffness and cellular contractility have been shown to regulate cellular differentiation and gene expression, especially of genes involved in fibrosis (Wells and Discher, 2008; Brown et al., 2013; Godbout et al., 2013; Karsdal et al., 2013). There is strong evidence that mechanical forces regulate TN-C expression (Fluck et al., 2008; Maier et al., 2008; Jiang et al., 2009; Asparuhova et al., 2011). There are reports of cell contractility, shear forces, or mechanical stretch increasing TSP-1 expression under fibrotic conditions (Warburton and Kaartinen, 2007; Chen et al., 2011; Holliday et al., 2011), suggesting possible amplification of TSP-1 in fibrotic tissues. Mechanical strain also enhanced SPARC expression by podocytes, with
implications for glomerulosclerosis (Durvasula and Shankland, 2005). In contrast to increased forces, osteopontin was decreased by microgravity (Kumei et al., 2006). Mechanical regulation of matricellular proteins is likely to regulate stem cell differentiation in tissue specific niches and also has implications for tissue engineering (Chiquet-Ehrismann et al., 2014-in this issue).

2.3. Alternate splicing and post-translational modifications of matricellular proteins

Further contextual specificity of matricellular protein interactions and functions can be derived from mRNA splicing or post-translational modifications such as specialized forms of glycosylation, gamma-carboxylation, and phosphorylation. It has long been known that the transcript for TN-C can undergo splicing to generate “large” and “small” forms with different tissue-specific associations for the TN-C isoforms containing or lacking the alternatively-spliced domain (Borsi et al., 1992; Ghert et al., 2002; Keller et al., 2007). A recent paper reports that overexpression in skin of a splicing factor SRSF6, which promotes exon inclusion, increases expression of “large” TN-C associated with a hyperplastic wound healing response, consistent with observations that the large form is a marker of tumor invasion (Jensen et al., 2014). Splice variants of osteopontin and its receptor CD44 are also associated with malignant tumor progression (Gimba and Tilli, 2013; Tang et al., 2013; Shevde and Samant, 2014-in this issue). Matricellular proteins are also subject to post-translational modifications. In addition to the more common O-glycosylation, the type I (TSR) repeats of TSP-1 are subject to C-mannosylation on tryptophan residues and O-fucosylation (Hofsteenge et al., 2001; Leonhard-Melief and Haltiwanger, 2010). The EGF-like module 1 of TSP-1 is also modified by O-linked N-acetylgalactosamine (Hoffmann et al., 2012). Although, the functional significance of TSP glycosylation is not clear, there is evidence that C-mannosylated peptides of the WSPW motif enhance lipopolysaccharide-induced signaling (Muroi et al., 2007) and that C-mannosylation is increased in diabetic tissues (Ihara et al., 2005). O-fucosylation of TSRs might regulate epithelial differentiation during gastrulation (Du et al., 2010). The role of glycosylation of the type 1 repeats in binding of ligands such as heparin and TGF-β to TSP-1 has not been addressed. Periostin is γ-carboxylated on glutamic acids, a post-translational modification common to vitamin K dependent clotting factors (Coutu et al., 2008). In addition, phosphorylation, glycosylation, tyrosine sulfation, and sialylation of osteopontin are known to regulate its interactions with cells (Kazanecki et al., 2007; Wang and Denhardt, 2008; Shevde and Samant, 2014-in this issue).

2.4. Receptors for matricellular proteins

Matricellular proteins bind to a diverse array of receptors (Table 1) (see reviews in this issue (Acharya et al., 2014-in this issue; Bedore et al., 2014-in this issue; Chiquet-Ehrismann et al., 2014-in this issue; Resovi et al., 2014-in this issue)). Most matricellular proteins bind to and activate signaling through multiple integrins. In at least one case, fibulin-5 binds to α5β1 and α6β1 integrins, but does not activate signaling via these receptors that mediate focal adhesion formation or stress fiber formation (Lomas et al., 2007; Papke and Yanagisawa, 2014-in this issue). In addition to integrins, multiple matricellular proteins bind to cell membrane heparan sulfate proteoglycans, particularly syndecan-4: these include TSP-1, TSP-2, TN-C, CCN1, CCN2, and R-spondins. Matricellular proteins also bind to scavenger
receptors such as LDL-receptor related protein 1 (LRP-1) and CD36. Matricellular protein binding to scavenger receptors is consistent with a mechanism to spatially and temporally limit the action of matricellular proteins and/or their binding partners, such as matrix metalloproteinases. TSPs-1 and 2 and CCN2 bind to LRP-1, which mediates endocytosis of TSPs and CCN2 (Godyna et al., 1995; Segarini et al., 2001; Mason, 2013). Alternately, LRP-1 can also act as a co-receptor for a cell surface form of the TSP binding protein calreticulin to mediate activation of G-protein-dependent ERK and PI3K signaling (Orr et al., 2003). CCN2 binding to LRP-1 can also stimulate phosphorylation of the cytoplasmic tail of LRP-1 (Yang et al., 2004). Stabilin-1, a scavenger receptor expressed on alternatively-activated macrophages and on endothelial cells during inflammation, mediates the endocytic clearance of SPARC (Kzhyshkowska et al., 2006; Workman and Sage, 2011). R-spondins bind to Wnt-receptors LRP6, LGR4 and LGR 5 (leucine rich repeat G protein coupled receptors) and through membrane E3 ubiquitin ligases ZNRF3 (Jin and Yoon, 2012; Xie et al., 2013; Knight and Hankenson, 2014-in this issue). PEDF binds to ECM components and to a cell membrane protein with phospholipase activity, a laminin receptor, F1 ATP synthase, and LRP6 (Becerra and Notario, 2013). Autotaxin, a matricellular protein with phosphodiesterase activity binds to P2Y12 on oligodendrocytes (Dennis et al., 2012). Matricellular proteins can bind multiple receptors on a cell and there is evidence that binding of one domain of a matricellular protein to a particular receptor and its net downstream signaling can be regulated through binding to receptors or binding ligands in other domains of the matricellular protein. For example, fibronectin binding to the stalk region of TSP-1 affects the ability of the TSP-1 N-terminus to bind integrin α3β1 (Rodrigues et al., 2001). The complement of receptors on a particular cell type can also govern cellular responses to a matricellular ligand. Furthermore, the availability of a particular matricellular receptor binding domain can be modulated by the binding of soluble matricellular ligands which sterically block matricellular protein–receptor interactions, such as the ability of heparin to prevent binding of the N-terminus of TSP-1 to calreticulin (Goicoechea et al., 2000). More recently described functions of matricellular proteins have been reported to occur through signaling from receptors not typically associated with ECM proteins. These include the calcium channel gabapentin receptor (α2δ-1) for TSP-1 and TSP-4 and toll-like receptor 4 (TLR4) for TN-C (Eroglu et al., 2009; Midwood et al., 2009; Risher and Eroglu, 2012; Chiquet-Ehrismann et al., 2014-in this issue). Like TLR4, CD36, a receptor for TSPs, can also act as a pattern recognition receptor, suggesting a broader role for matricellular proteins in innate immunity (Areschoug and Gordon, 2009; Sheedy et al., 2013). The role of osteopontin in inflammation and autoimmune diseases has long been appreciated (Uede, 2011). The binding of many of the matricellular proteins to these diverse receptors has been shown to regulate most known signaling pathways, including those activated by VEGF receptors and nitric oxide (Nozaki et al., 2006; Lawler and Lawler, 2012; Roberts et al., 2012; Rogers et al., 2014-in this issue). Matricellular proteins can either directly (TN-C) or indirectly (TSP-1) stimulate signaling through the epidermal growth factor receptor (Swindle et al., 2001; Liu et al., 2009; Garg et al., 2011).
3. Roles in diseases

It is not surprising that matricellular proteins have been shown to play important roles in disease. Because the early studies established that the original matricellular proteins (TSP-1, TN-C, and SPARC) are primarily de-adhesive and pro-migratory, their roles in wound healing and cancer were initial targets for investigation. From a myriad of studies, it became apparent that gene inactivation, overexpression, or antagonism of a matricellular protein receptor changed the course of wound healing, tumor growth and/or metastasis, and the production of connective tissue proteins such as collagen. Because results of these studies were highly contextual, it has been difficult to draw broad conclusions regarding the role of a specific matricellular protein in a given pathology. Instead, as additional functions of matricellular proteins in biological processes were elucidated, such as the regulation of growth factor and soluble mediator activity, cell death, cell senescence, cell–cell adhesion and vascular permeability, inflammation, innate and acquired immune function, fibrosis, modulation of ECM assembly, and angiogenesis, the context-specific roles of a given matricellular protein in a certain disease environment on a specific cell or tumor type have become better appreciated and more clearly defined. It is now well established that various matricellular proteins play critical roles in disease processes of all organ systems, including the stem cell niche and in stem cell fate (Gattu et al., 2013; Qin et al., 2013; Chiquet-Ehrismann et al., 2014; Lee et al., 2014b); many of the reviews and articles in this issue will deal with particular roles of specific matricellular proteins in development and disease in detail. Typically matricellular proteins are involved in disease because of abnormal regulation leading to either over or underexpression of the protein, but there are examples of disease due to inherited mutations or gene deficiency. Mutations leading to protein misfolding and ER retention of mutant COMP result in skeletal defects such as pseudoachondroplasia and multiple epiphyseal dysplasia (Posey et al., 2009, 2014-in this issue). Tenascin-X deficiency is associated with the Ehlers-Danlos syndrome (Burch et al., 1997; Schalkwijk et al., 2001). Single nucleotide polymorphisms of TSP-4 are associated with increased cardiovascular risk (Pluskota et al., 2005; Corsetti et al., 2011), a decrease in TSP-2 polymorphisms in plaque erosion (Burke et al., 2010), and a polymorphism of TSP-1 with increased corneal allograft rejection (Winton et al., 2014). Mutations in the THBS1 type 1 repeats are associated with familial pulmonary arterial hypertension (Maloney et al., 2012). Because some matricellular proteins are components of the ECM, we have traditionally thought of them in the context of solid tissues, particularly in connective tissue compartments. However, matricellular proteins are also secreted proteins that can influence cell behavior or disease progression as soluble moieties interacting with cell surface receptors or ECM components implicating matricellular proteins in both paracrine and autocrine cellular regulation. Recent findings that matricellular proteins, particularly TN-C, function as damage-associated molecular pattern (DAMP) molecules in tissue damage-induced inflammation expand our concept of the matricellular protein in tissue remodeling (Udalova et al., 2011; Ruhmann et al., 2012; Chiquet-Ehrismann et al., 2014). Matricellular proteins can also regulate multiple components of the immune system as seen for TSP-1 in Sj gren's syndrome in the eye and in multiple myeloma (Kukreja et al., 2009; Turpie et al., 2009). Matricellular proteins also are involved in metabolic diseases such as diabetes and obesity. The roles of matricellular proteins, such as CCN2, osteopontin, TSP-1, and SPARC,
in fibrotic diabetic complications is well-established (Taneda et al., 2003; Belmadani et al., 2007; Daniel et al., 2007; Mason, 2009; Lu et al., 2011; Yoshida et al., 2011; Sorenson et al., 2013). Moreover, the involvement of matricellular proteins such as TSP-1 in insulin sensitivity and obesity-induced inflammation and fibrosis and of SPARC in insulin resistance and adipose tissue accumulation is emerging (Nie and Sage, 2009a; Kos and Wilding, 2010; Li et al., 2011; Olerud et al., 2011; Drott et al., 2012; Finlin et al., 2013; M. Inoue et al., 2013; Kong et al., 2013; Gattu et al., 2014). Over the last several years, unexpected roles of thrombospondins, tenasin-R, and SPARC family members in synapse formation and maturation and of NOV/CCN3, TSP-4, and SPARC in chronic and neuropathic pain have emerged (Kucukdereli et al., 2011; Kim et al., 2012; Kular et al., 2012; Millecamps et al., 2012; Risher and Eroglu, 2012; Li et al., 2014; Xu et al., 2014).

With the recent findings for intracellular roles of matricellular proteins (Martinek et al., 2007; Chlenski et al., 2011; Lynch et al., 2012; Millecamps et al., 2012; Risher and Eroglu, 2012; Li et al., 2014; Xu et al., 2014), there is the distinct possibility that matricellular proteins regulate additional cellular functions relevant to disease.

4. Matricellular proteins as biomarkers

Matricellular proteins play key roles in tissue remodeling, inflammation, and in immune responses and therefore, it is not surprising that their levels will be altered in various disease states. Many matricellular proteins are present in body fluids as soluble proteins and are used clinically and experimentally to monitor disease progression. Tenascins, particularly TN-C, have been shown to be markers of tumor progression, cardiovascular disease, tumor angiogenesis, inflammation in arthritis, and in infection in the oral cavity (Orend and Chiquet-Ehrismann, 2006; Midwood et al., 2009; Ozacakir-Tomruk et al., 2012; K. Inoue et al., 2013; Karatas et al., 2013; Sakamoto et al., 2014; Chiquet-Ehrismann et al., 2014). Serum periostin is an indicator of eosinophilic airway inflammation and response to certain therapeutics (Jia et al., 2012; Parulekar et al., 2014). Periostin has also been described as a biomarker of systemic sclerosis and of cancer progression (Lv et al., 2013; Yamaguchi et al., 2013). Levels of SPARC were increased in the sera of patients after bariatric surgery and were also associated with hemoglobin A1c levels, suggesting a possible role for SPARC as an indicator of metabolic state (Kotani et al., 2011; Lee et al., 2014a). Osteopontin levels are measured as indicators of bone density, cardiovascular disease, and tumor progression (Cho et al., 2013; Kadoglou et al., 2013; Mardani et al., 2013). Fibulin-3 peptides are markers of osteoarthritis (Henrotin et al., 2012). Serum COMP levels correlate with early joint damage in both osteoarthritis and rheumatoid arthritis (Andersson et al., 2013; Verma and Dalal, 2013). As many matricellular proteins regulate different aspects of angiogenesis, they have been deemed biomarkers of pre-eclampsia (TSP-1, TSP-2, CCN1, CCN3) (Gellhaus et al., 2007; Stenczer et al., 2011; Stenczer et al., 2012). Nearly all of the matricellular proteins have been identified as tissue markers of specific tumors, grades of tumor, or prognosis and there is an abundant of literature on this topic. Exciting are the studies showing that expression of a particular matricellular protein is predictive of response to therapy. For example, Farina et al. showed that RNA levels of COMP and TSP-1 were part of a four gene biomarker panel that correlates with the modified Rodnan Skin Score, which is used as a clinical indicator of skin disease severity in systemic sclerosis (Farina et al., 2010),
suggesting that this four gene panel might have predictive value as a surrogate marker in clinical trials.

5. Translational potential and challenges

Matricellular proteins represent an underappreciated target for therapeutic interventions in a wide spectrum of diseases. The importance of matricellular proteins in disease is strongly supported by a wealth of literature from animal models and data from patients. It is less clear, however, how to target a specific function of a particular matricellular protein in a disease setting. As multifunctional proteins with multiple receptors, genetic ablation or the use of a blocking antibody to a particular matricellular protein raises the potential for adverse effects due to concomitant attenuation of beneficial functions in addition to ablation of the disease-inducing function. However, the use of antibody-based therapeutics directed against a matricellular protein has achieved some clinical success. For example, a monoclonal antibody against CCN2, also known as connective tissue growth factor (CTGF) (FG-3019) has been successful in phase I clinical trials in patients with diabetes/albuminuria and in pancreatic cancer and is entering phase 2 trials for idiopathic pulmonary fibrosis and liver fibrosis (www.ClinicalTrials.gov). Preclinical studies with FG-309 have shown utility in models of glaucoma and acute lymphoblastic leukemia (Lu et al., 2013; Wallace et al., 2013, 2014 -in this issue). A number of pharmaceutical firms are testing anti-sense approaches to reduce CCN2 expression for treatment of skin fibrosis. The use of synthetic microRNAs has been proposed to regulate TSP1 expression (Dogar et al., 2014). In some cases, there is functional antagonism between members of a matricellular protein family. For example, TSP-2 overexpression has been attempted as a means to block TSP-1-dependent TGF-β activation, because TSP-2 lacks the TGF-β activating sequence (Schultz-Cherry et al., 1995). Whereas TSP-2 overexpression does attenuate TGF-β activity in a model of diabetic nephropathy and in acute glomerulosclerosis, long-term overexpression of TSP-2 resulted in vascular rarefaction due to the potent anti-angiogenic effect of TSP-2 (Daniel et al., 2009, 2013). A more successful application of this idea is the overexpression of CCN3 to counteract the profibrotic effects of CCN2 in diabetic nephropathy (Riser et al., 2010). That many receptors for matricellular proteins, such as integrins, are promiscuous and bind multiple ligands, also raise the possibility of non-specific and unwanted side effects. More specific approaches, such as delivery of agonists and antagonists of a functional sequence of a matricellular protein, represent a more specific therapeutic approach. Second-generation octapeptides based on ABT-510 (peptide mimetics of the TSP-1 binding site for CD36) have been used in human and canine clinical trials to block angiogenesis for treatment of soft tissue sarcomas (Sahora et al., 2012). A synthetic fragment of the follistatin domain of SPARC has been used to inhibit tumor angiogenesis and another SPARC peptide enhances chemo sensitivity of tumors (Chlenski et al., 2004; Rahman et al., 2011). Another approach is the inhibition of matricellular protein interactions with receptors for pathways implicated in disease. For example, humanized anti-CD47 antibodies are in development for vascular and ischemic diseases (Rogers et al., 2014 -in this issue). PEDF peptidomimetics are being tested for oncologic applications (Becerra and Notario, 2013; Crawford et al., 2013). Disease-specific expression of matricellular protein splice variants, in particular osteopontin and TN-C, also presents new targets for antibody-based therapies (Weidle et al., 2011).
Finally, one could potentially modify post-translational modifications through the blocking of key processing enzymes, for example blocking periostin γ-carboxylation through use of Coumadin, although this type of approach would affect multiple targets.

6. Matricellular proteins in tissue engineering and responses to biomaterials

Adhesive and structural extracellular matrix proteins such as collagens and fibronectin have been used to develop biomimetic scaffolds for tissue engineering. The incorporation of matricellular proteins into biomaterials has received less attention, however, possibly because of the relative unfamiliarity of these specialized ECM components to the tissue engineering community. Given their role in the regulation of processes important for development, stem cell differentiation, and tissue repair, matricellular proteins represent a promising resource for engineered “smart” biomaterials. The ability to incorporate specific functional domains of matricellular macromolecules into scaffolds provides another level of control over cellular responses to selected biomaterials. Matricellular-based engineered biomaterials could conceivably regulate angiogenesis, growth factor and protease activity, cell survival, migration, and differentiation. In addition, matricellular proteins such as TSPs-1 and 2, fibulins, OPN, and SPARC can regulate assembly and organization of other extracellular matrix components and thus modify cellular responses to biomaterials (Bale and Mosher, 1986; Giachelli et al., 1995; Kyriakides et al., 1999; Bradshaw et al., 2003b; Papke and Yanagisawa, 2014-in this issue). As matricellular proteins can regulate stem cell differentiation in different niches, these proteins or fragments thereof are candidates for biomaterial applications (Bailey Dubose et al., 2012; Kaur et al., 2013; Liu and Leask, 2013; Wang et al., 2013; Chiquet-Ehrismann et al., 2014; Jose et al., 2014; Lee et al., 2014b). Decellularized tissue-specific extracellular matrices have been widely used in regenerative medicine (Faulk et al., 2014). Artificial matrices derived from tissues with cells either lacking or overexpressing a particular matricellular molecule could direct host cellular responses via alteration of tissue repair processes such as angiogenesis, matrix assembly, and myofibroblast induction (Barker et al., 2005b; Elliott et al., 2012; Calabro et al., 2014; Morris and Kyriakides, 2014-in this issue). For example, coating either smooth or etched titanium implants with periostin increased cell adhesion as compared to metal surfaces without periostin, although periostin only improved osteoblastic differentiation of cells adherent to smooth titanium surface, suggesting that perhaps the surface bound conformation of periostin can differentially regulate cell behavior (Galli et al., 2013). One can also take advantage of sequence-specific matricellular interactions with growth factors or receptors to target molecules to biologic scaffolds: one of the TGF-β binding motifs of TSP-1 (GGWSHW) was coupled to a scaffold to localize TGF-β to hydrogels for local growth factor delivery (McCall et al., 2011).

Matricellular proteins also play important roles in tissue responses to biomaterials, for example TSP-2 and SPARC in host responses to foreign bodies (Kyriakides and Bornstein, 2003; Puolakkainen et al., 2003; Barker et al., 2005a; Kyriakides and Maclauchlan, 2009; Tian and Kyriakides, 2009; Morris and Kyriakides, 2014-in this issue). Pallero et al. showed that metal ions such as those released from metal-based implants stimulate increased TSP-1
expression and TGF-β activation, suggestive of a potential role in implant failure and encapsulation (Pallero et al., 2010). Because these matricellular proteins generally promote collagen deposition and fibrotic responses to foreign materials, attenuation of these activities could enhance successful tissue integration. This idea contrasts with the potentially beneficial roles of matricellular-based biomaterials in the promotion of “wound healing” and cellular differentiation, and highlights the complexity of matricellular function and especially, the mode of matricellular presentation to cells.

7. Being matricellular in 2014 and questions for the future

Matricellular proteins are important to more cellular functions and disease processes than we could have proposed in 1995. The original definition of matricellular still largely holds; today we have a greater appreciation of the significance of these modular proteins in the regulation of cell functions through an array of complex interactions with cellular receptors, soluble molecules, and ECM components. The context-dependent nature and the complexity of their roles and interactions are indeed greater than we initially thought (Fig. 1). If any part of Bornstein's original definition can be challenged, it is the finding that matricellular proteins can also have intracellular roles. However, with the exception of intracellular OPN which binds to the cytoplasmic domain of CD44, these roles to date have been primarily limited to locations in the nucleus and in the lumens or at the membranes of intracellular vesicular structures such as the endoplasmic reticulum. In this context, such vesicular lumens can be thought of as “inland lakes” mimicking the larger extracellular ocean where the matricellular protein can function as a soluble molecule or “at the shore” in the context of receptor binding at the plasma membrane. The chaperone function of matricellular proteins in the endoplasmic reticulum can similarly be considered as “intracellular matrix assembly;” e.g., *Drosophila* SPARC has been shown to be a chaperone facilitating the assembly of basement membrane (type IV) collagen (Martinek et al., 2008). The function(s) of nuclear SPARC remain elusive, despite reports of its cell-cycle dependent association with the nuclear matrix and of its uptake and translocation to the nuclei of lens epithelial cells (Gooden et al., 1999; Yan et al., 2005).

However, the translational potential of matricellular proteins has not been fully realized, partly due to their complexity and multifunctionality. What new knowledge do we need and how can we better frame our questions to utilize the potential therapeutic power of matricellular proteins? Is our current working definition of “matricellular” accurate, especially considering the intracellular roles of some of these proteins? Are there additional proteins or fragments of structural ECM proteins that could be considered “matricellular?” What can we learn from the study of one matricellular protein that applies or is relevant to other matricellular proteins? Clearly it is important to appreciate that the actions of one matricellular protein might oppose that of another. These questions and others are necessary to guide our thinking over the second twenty years of matricellular protein research and to advance knowledge and human health through matricellular-targeted therapeutics.

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Abbreviations

CCN
cyr61-CTGF-NOV

COMP
cartilage oligomeric protein

CTGF
connective tissue growth factor

DAMP
damage-associated molecular pattern

ECM
extracellular matrix

ER
endoplasmic reticulum

LRP
Low density lipoprotein receptor related protein

PAI-1
plasminogen activator inhibitor 1

PEDF
pigment epithelium derived factor

SLRPs
small leucine rich proteoglycans

SPARC
secreted protein acid and rich in cysteine

STIM1
stromal interaction molecule 1

TGF-β
transforming growth factor-β

TN
tenascin

TSP
thrombospondin

TLR4
toll-like receptor 4

VEGF
vascular endothelial growth factor

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Matricellular Proteins regulate cell function through interactions with diverse receptors and macromolecules in multiple cellular compartments

**Receptor Interactions**
- Cytoskeletal organization
- Activate signaling
- Inhibit nitric oxide signaling
- Growth factor receptor agonist and antagonist
- Cell-cell and cell-ECM de-adhesion (intermediate adhesion)
- Cell motility
- Cell cycle regulation
- Anoikis resistance; senescence
- Synapse formation and pain perception
- Cell fate determination

**Body fluids: TSPs, TNs, SPARC, OPN, CCNs, COMP, periostin, fibulins**
- Growth factor interactions
- Hemostasis
- Binding to immune cells (innate and adaptive)
- Innate immune functions

**Inner plasma membrane: OPN**
- Adhesion; migration

**Nucleus: SPARC**
- ECM chaperone
- ECM pre-assembly
- Calcium regulation
- ER function

**Extracellular matrix: TSPs, COMP, fibulins, TNs, OPN, SPARC, hevin, PEDF**
- Collagen fibril organization
- Elastin organization
- Fibronectin organization
- ECM calcification
- Proteoglycan interactions

**ER, TSP1, 4, COMP, SPARC**
- Integrins
- Proteoglycan
- CD47

**Fig. 1.**
Matricellular proteins in multiple extracellular, cell membrane, and intracellular locations regulate cell function and ECM organization. This cartoon depicts the complexity of matricellular protein interactions with cell receptors and other interacting macromolecules in multiple extracellular and intracellular compartments and the resulting cellular functions regulated by these interactions. This diagram is not meant to be comprehensive, but it is intended to highlight examples of actions of matricellular proteins.
Receptors for matricellular proteins.

| Matricellular protein       | Receptors                                                                                      |
|----------------------------|-------------------------------------------------------------------------------------------------|
| Thrombospondin-1,          | Integrins (αβ3, αβ1, αβ1, αβ1, αβ1) (Calzada et al., 2004; Calzada et al., 2003; Krutzsch et al., 1999; Lawler and Hynes, 1989; Lawler et al., 1988; Staniszewski et al., 2007) |
| Thrombospondin-2           | syndecans (Adams et al., 2001; Chen et al., 1996; Ferrara de Osteo-Dereins et al., 2002; Noron et al., 2008; Sun et al., 1999) |
|                            | sulfatides (Roberts et al., 1989; LRP-1 (Goday et al., 1995; Mikhailenko et al., 1993); calreticulin (Genoccio et al., 2000) |
|                            | Thrombospondin-4                                                                               |
|                            | Integrins (αβ3, αβ3, αβ3, αβ3) (Barnea et al., 1994)                                          |
|                            | COMP (TSP-5)                                                                                    |
|                            | Integrins (αβ3, αβ1, αβ1, αβ1) (Barry et al., 2000; Boyles et al., 1998; Denda et al., 1998; Green et al., 2001; Lin et al., 1995; Lin et al., 1995b; Yokosaki et al., 2005) |
|                            | Tenascin-C                                                                                      |
|                            | Integrins (αβ1, αβ1, αβ1, αβ1, αβ1, αβ1) (Bourdon and Ravussin, 1989; Jones et al., 1997; Katoh et al., 2013; Proto et al., 1993; Stimmann et al., 1993; Tanaka et al., 2014; Yokojukka et al., 2000; Schnupp et al., 1995; Yumura-Fukuyama et al., 1995; Yokosaki et al., 1994) |
|                            | CD44 (Kato et al., 1999; Weber et al., 1996)                                                   |
|                            | annexin II (Chung and Ericson, 1994; Chung et al., 1996)                                        |
|                            | phosphacan chondroitin sulfate proteoglycan (Bekers et al., 1994)                               |
|                            | Tenascin-X                                                                                      |
|                            | Integrins (αβ1, αβ1, αβ1, αβ1, αβ1, αβ1)                                                       |
|                            | Tenascin-R                                                                                      |
|                            | Myelin associated glycoprotein (Yang et al., 1999)                                              |
|                            | Tenascin-W                                                                                      |
|                            | Integrin αβ3 (Schneider et al., 2005)                                                           |
|                            | CCN2/CTGF                                                                                      |
|                            | Integrins (αβ1, αβ1, αβ1, αβ1, αβ1, αβ1)                                                       |
|                            | CCN1                                                                                           |
|                            | αβ1αβ1, αβ1αβ1, αβ1αβ1 (Lau, 2001); syndecan 4 (Todorovic et al., 2005)                          |
|                            | CCN3                                                                                           |
|                            | integrins (αβ1, αβ1, αβ1, αβ1) (in mice)                                                        |
|                            | SPARC                                                                                          |
|                            | αβ1                                         |
|                            | Periostin                                                                                       |
|                            | αβ1αβ1, αβ1αβ1, αβ1αβ1 (Gillan et al., 2002; Johansson et al., 2013; Lomas et al., 2007)          |
|                            | Fibulin-5                                                                                      |
|                            | αβ1, αβ1 (binds, but does not activate)                                                         |
|                            | R-spondin                                                                                      |
|                            | Leucine-rich repeat-containing G-protein coupled receptor 4–6 (P. Chen et al., 2013; ZNRF3/RNF43 (Jin and Yoon, 2012) |
| Matricellular protein       | Receptors                                                                 |
|----------------------------|---------------------------------------------------------------------------|
| Pigment epithelium derived factor | heparan sulfate proteoglycan (Nam et al., 2006; Ohkawara et al., 2011)    |
| Pigment epithelium derived factor receptor | (Alberdi et al., 1999), laminin receptor (Bernard et al., 2009), LRP6 (Park et al., 2011), F<sub>1</sub> ATP synthase (Deshpande et al., 2012), nutrin/phospholipaseA<sub>2</sub> (Notari et al., 2006) |
| Autotaxin | P2Y<sub>12</sub> (Dennis et al., 2012) |