Matrix Biology 37 (2014) 1–14

Contents lists available at ScienceDirect

Matrix Biology

journal homepage: www.elsevier.com/locate/matbio

Revisiting the matricellular concept

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ARTICLE INFO

Available online 24 July 2014

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

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.

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

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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http://dx.doi.org/10.1016/j.matbio.2014.07.005

"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