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Thematic Mini-Review Series Thrombospondins in physiology and disease: new tricks for old dogs

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Thrombospondins (TSPs) belong to a family of five, secreted, modular glycoproteins encoded by separate genes (Adams and Lawler, 2004, 2011). Group A TSPs (TSP1 and TSP2) are homotrimers, whereas group B TSPs (TSP3, -4, and -5/COMP) are homopentamers (Adams, 2001), and all are secreted as disulfide-bonded complexes. Although the five members of the TSP family differ with respect to structure, cell type, and temporal expression, all TSPs bind to components of the extracellular matrix as well as to a number of cell surface receptors, enabling TSPs to modulate cellular behaviors in a wide array of tissue contexts. TSPs are the prototype of the matricellular protein (Bornstein, 1995) and have been the subject of intense study for four decades.

First identified in 1971 as protein released from thrombin-stimulated platelets, TSP1 (thrombin sensitive protein) was initially studied for its role in platelet aggregation and related hemostatic functions (Baenziger et al., 1971; Gartner and Dockter, 1984; Lahav et al., 1982; Lawler et al., 1978; Phillips et al., 1980). The eponym thrombospondin was proposed by Lawler and co-workers (Lawler et al., 1978) who isolated intact thrombospondin complexes from thrombin-treated platelets in physiological saline. Thrombospondin is a filamentous glycoprotein ~70 nm long and binds to heparin-affinity columns, and thus, to heparan sulfate proteoglycans *in vivo* (Fig. 1). Over the next two decades, it was discovered that TSP1 is synthesized and secreted by endothelial cells as well as other cell types in culture (Asch et al., 1986; Jaffe et al., 1982; Jaffe et al., 1985; Jaffe et al., 1983; McPherson et al., 1981; Mosher et al., 1982; Raugi and Lovett, 1987). The expression of TSP1 by diverse cell types, identification of interacting proteins, and the subsequent recognition that TSP1 binds to specific cell surface molecules in a saturable manner (Asch et al., 1987; McKeown-Longo et al., 1984; Murphy-Ullrich and Mosher, 1987; Roberts et al., 1985; Silverstein et al., 1984) provided the first evidence that TSPs might regulate cell behavior through direct interactions with cell surface receptors to

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activate intracellular signaling pathways: these first known receptors turned out to be CD36 (GP88) and heparan sulfate proteolgycans (syndecans) and established precedents for identification of other TSP receptors (Asch et al., 1987; Asch et al., 1992; Chung et al., 1999; Godyna et al., 1995; Goicoechea et al., 2000; Lawler and Hynes, 1989; Lawler et al., 1988; Murphy-Ullrich et al., 1988; Sun et al., 1989; Tuszynski et al., 1993; Wang and Frazier, 1998). Subsequent work showed that TSP1 expression is regulated by growth factors (PDGF, TGF-β), that TSP1 can enhance cellular responses to growth factors such as EGF, antagonize VEGF signaling, or variably regulate FGF family signaling (Gupta et al., 1999; Iruela-Arispe et al., 1999; Majack et al., 1985, 1986; Orr et al., 2003; Penttinen et al., 1988; Taraboletti et al., 1992). Elegant biochemistry, protein structural studies, and cloning and sequencing of the TSP1 gene further elucidated relationships between discrete modular domains of TSPs and specific cellular functions as well as regulators of gene expression (Bornstein et al., 1990; Dixit et al., 1986; Frazier et al., 1987; Lawler, 1986; Slane et al., 1988; Sun and Mosher, 1991). Together these early findings stimulated many diverse and fruitful avenues of investigation which have yielded surprising insights into the diverse functions of this remarkable family of proteins.

This thematic series of interrelated mini-reviews will focus on recent additions to the armamentarium of TSP functions.

The review by Mosher and Adams (2012, this issue) employs both evolutionary and structural perspectives to discern the functions of thrombospondins as well as other matricellular proteins, especially in the context of the complex network of intermolecular interactions occurring in the extracellular matrix and at the cell surface.

The review by Roberts and co-workers (2012, this issue) highlights the role of TSP1 as a regulator of local and systemic physiology through its ability to attenuate nitric oxide signaling. The identification of TSP1 as a regulator of nitric oxide signaling has significantly broadened our understanding of the role of TSP1, especially in vascular physiology and pathology.

The review by Risher and Eroglu (2012, this issue) discusses exciting, novel findings documenting a role for TSP in synaptogenesis through interactions between astrocyte-secreted TSPs and their neuronal receptor, calcium channel subunit α2δ-1, also a receptor for gabapentin. Collectively, these new findings have implications for neuronal development and responses to CNS injury.

Finally, Sweetwyne and Murphy-Ullrich (2012, this issue) focus on distinct roles for TSP1 mediated by different domains which impact basic cellular processes key for wound healing, tissue repair, and fibrosis. These entail stimulation of collagen expression through the N-terminal domain calreticulin-binding sequence, transactivation of EGF receptor by the EGF-like domains, and regulation of latent TGF-β activation by the TSR type 1 repeats.

Many of these findings were initially presented at the 2010 FASEB Summer Research Conference on Thrombospondins and Other Matricellular Proteins in Tissue Organization and Homeostasis. Clearly, despite several decades of research, the thrombospondins continue to surprise us with their broad and clinically-significant roles in physiology and disease. The field of matrix biology has been enriched by the often unexpected roles of thrombospondins in normal development and physiology and in the pathophysiology of diverse disease processes.

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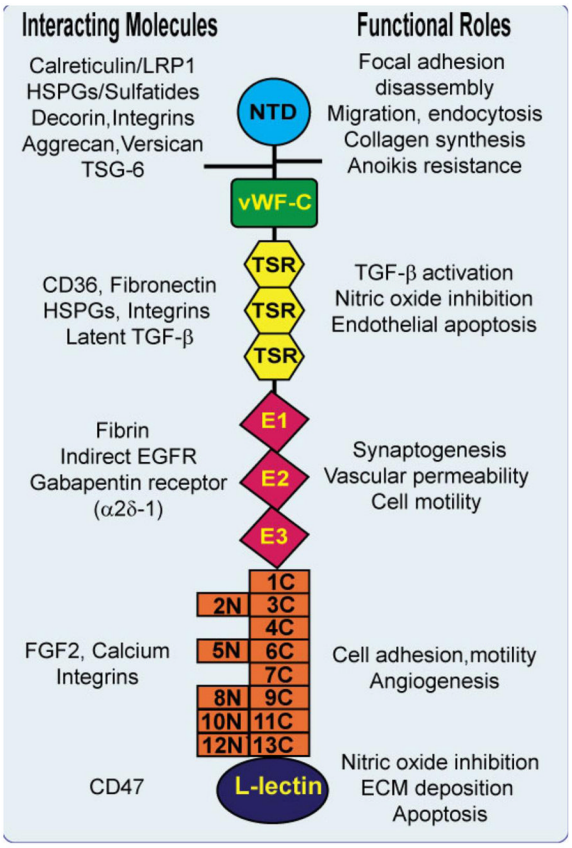

Fig. 1.

Model of TSP1 monomer showing the N-terminal laminin G-like domain, the oligomerization region of interchain disulfide bonding, the procolllagen-like, von Willebrand factor_C module, the properdin-like type 1 (TSR) repeats, the EGF-like repeats, and the TSP type 3 repeats which form the calcium-sensitive wire structure around the C-terminal L lectin type globular domain. The TSP receptors and interacting molecules discussed in this review series are shown to the left of the monomer and the functions induced by TSP interactions with these molecules are shown to the right of the monomer. For the sake of simplicity, only TSP1 is shown, although many of these interactions occur in other TSP family members. Some of the interacting molecules, such as integrins, heparan sulfate proteoglycans (HSPGs) and CD36 that will not be specifically discussed at length in this thematic minireview series, are also depicted. In addition, TSPs interact with other molecules (PDGF, cathepsin G and neutrophil elastase) whose binding site(s) on TSP have not been clearly elucidated and thus are not depicted. It is likely that future studies will identify additional binding molecules.