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Mini review

Current understanding of the thrombospondin-1 interactome

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ABSTRACT

The multifaceted action of thrombospondin-1 (TSP-1) depends on its ability to physically interact with different ligands, including structural components of the extracellular matrix, other matricellular proteins, cell receptors, growth factors, cytokines and proteases. Through this network, TSP-1 regulates the ligand activity, availability and structure, ultimately tuning the cell response to environmental stimuli in a context-dependent manner, contributing to physiological and pathological processes. Complete mapping of the TSP-1 interactome is needed to understand its diverse functions and to lay the basis for the rational design of TSP-1-based therapeutic approaches. So far, large-scale approaches to identify TSP-1 ligands have been rarely used, but many interactions have been identified in small-scale studies in defined biological systems. This review, based on information from protein interaction databases and the literature, illustrates current knowledge of the TSP-1 interactome map.

Contents

1. Introduction

In his 1995 seminal paper, Paul Bornstein defined matricellular proteins as extracellular molecules which function by binding to multiple ligands (Bornstein, 1995). Although this definition has been updated and tuned in recent years (as discussed elsewhere in this issue), the establishment of multiple protein–ligand interactions is still considered a key trait of these molecules, explaining their typical range of functions. Thrombospondin-1 (TSP-1) is a prototype matricellular protein that can physically interact with a variety of ligands, including structural components of the extracellular matrix, other matricellular proteins, cell receptors, growth factors, cytokines and proteases. These interactions involve distinct binding sites and can occur simultaneously, leading to a variety of scenarios, spanning from the activation of receptors and downstream signaling pathways, to the formation of multimolecular complexes, sequestration and inactivation of growth factors and enzymes, alterations of protein localization, proteolytic processing and internalization, and effects on the receptor/ligand equilibrium and downstream signaling. Comprehensive mapping of the TSP-1 interactome is needed to clarify its context-dependent functional role. Furthermore, the identification of new ligands and protein–protein interaction (PPI) networks might indicate new roles for TSP-1 in physiological and pathological processes, providing tools for designing TSP-1-based therapeutic agents to perturb or mimic these interactions (Zhang and Lawler, 2007; Taraboletti and Bonezzi, 2009; Belotti et al., 2011).

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Table 1
TSP-1 ligands.

Name	Entry name UniProt	Gene name	Affinity (Kd)	Methodology	Binding site	Reference
Aggrecan	PGCA	ACAN		SP	N-term	Kuznetsova et al., 2006
Amyloid beta A4 protein	A4	APP		SPR		Faye et al., 2009
Angiocidin (26S proteasome non-ATPase regulatory subunit 4)	PSMD4	PSMD4	47 nM	SP, CoIP	Type I rep (CSVTCG)	Zhou et al., 2004
Apolipoprotein E receptor 2 (LDL receptor-related protein 8)	LRP8	LRP8 (APOER2)	32 nM	SP		Blake et al., 2008
ATF6α (cAMP-dependent transcription factor ATF-6α)	ATF6A	ATF6		PD	Type III rep	Lynch et al., 2012
Biglycan	PGS1	BGN		SPR		Faye et al., 2009
Calcium					Type III rep	Kvansakul et al., 2004; Lawler et al., 1982
Calreticulin	CALR	CALR		CoIP	N-term (ELTGAARKGSGRRLVKGPD)	Goicoechea et al., 2000; Yan et al., 2010
Calumenin	CALU	CALU	0.4 μM	AC, SPR		Hansen et al., 2009
Cathepsin G	CATG	CTSG	2 nM	SP	Type III rep (NCPFHYNP)	Hogg et al., 1993a
CD148 (R-PTP-eta)	PTPRJ	PTPRJ	13 nM	CoIP		Takahashi et al., 2012
CD36 (Platelet glycoprotein 4)	CD36	CD36	nM range	SP	Type I rep	Asch et al., 1992; Dawson et al., 1997; Klenotic et al., 2013
CD47 (Integrin associated protein, IAP)	CD47	CD47	pM range	CoIP, CBA	C-term G domain (RFYVVMWK)	Gao et al., 1996; Isenberg et al., 2009
Chondroitin sulfate PG	CSPG	CSPG	235–648 nM	ACE		Herndon et al., 1999
Chymotrypsin	CTR	CTR		SP		Lawler et al., 1986
Collagen I	CO1A1	COL1A1		SPR		Faye et al., 2009; Galvin et al., 1987
Collagen II	CO2A1	COL2A1		SP		Galvin et al., 1987
Collagen III	CO3A1	COL3A1		SP		Galvin et al., 1987
Collagen IV	CO4A1	COL4A1		SP		Galvin et al., 1987
Collagen V	CO5A1	COL5A1		SP	Type I rep	Galvin et al., 1987; Mumby et al., 1984
Collagen VI	CO6A1	COL6A1		SPR		Faye et al., 2009
Collagen VII	CO7A1	COL7A1		Y2H	Type I rep	Aho and Uitto., 1998
Collagen XI	COBA1	COL11A1		SPR		Faye et al., 2009
Collagen XVIII (endostatin)	COIA1	COL18A1		SPR		Faye et al., 2009
Complement factor H	CFAH	CFH	49 nM	SPR		Vaziri-Sani et al., 2005
Decorin	PGS2	DCN		SP	Main site: N-term (KKTR)	Merle et al., 1997
Elastase, neutrophil	ELNE	ELANE	17 nM	SP	Type III rep (NCQYVYNV)	Hogg et al., 1993b
ERK (Extracellular signal-regulated kinase)	MK	MAPK/ERK		CoIP		Baek et al., 2013
Extracellular matrix protein 1	ECM1	ECM1		Y2H		Sercu et al., 2009
Fibrillin-2	FBN2	FBN2		Y2H		Aho and Uitto., 1998
Fibrinogen/fibrin	FIBA	FGA	3–127 nM	SP	Type I rep and N-term	Lahav et al., 1984; Leung and Nachman, 1982; Bonnefoy et al., 2001
Fibroblast growth factor 2	FGF2	FGF2		SP, SPR, NMR	Type III rep (DDDDDNDKIPDDRDN)	Margosio et al., 2003, 2008; Taraboletti et al., 1997
Fibronectin	FINC	FN1	112 nM	SP	70 kDa stalk region	Dardik and Lahav, 1989
Galectin-1, Gal-1	LEG1	LGALS1		SP		Moiseeva et al., 2000
Glypican (cerebroglycan)	GPC	GPC	33 nM	ACE		Herndon et al., 1999
Heparan sulfate proteoglycans			180–260 nM	ACE	N-term (R42, R76 and R77)	Feitsma et al., 2000; Herndon et al.1999; Sun et al.1989
Heparin			41 nM	ACE	N-term	Dixit et al., 1984; Herndon et al., 1999
Hepatocyte growth factor	HGF	HGF		SP		Lamszus et al., 1996
Histidine-rich glycoprotein	HRG	HRG		SP	Type I rep (CSVTCG)	Silverstein et al., 1985; Simantov et al., 2001
Insulin-like growth factor binding protein 5	IBP5	IGFBP5	7 nM	CoIP		Nam et al., 2000