Amino Acids (2011) 41:843–847
DOI 10.1007/s00726-010-0527-1

REVIEW ARTICLE

S100B: a multifunctional role in cardiovascular pathophysiology

James N. Tsoporis · Forough Mohammadzadeh · Thomas G. Parker

Received: 21 December 2009 / Accepted: 11 February 2010 / Published online: 4 March 2010

Abstract S100B, a calcium-binding protein of the EF-hand type exerts both intracellular and extracellular functions. S100B is induced in the myocardium of human subjects and an experimental rat model following myocardial infarction. Forced expression of S100B in neonatal rat myocyte cultures, and high level expression of S100B in transgenic mice hearts and aortic smooth muscle cells inhibit cardiac hypertrophy and the associated phenotype, arterial smooth muscle proliferation, respectively, but demonstrate increased apoptosis following α_1-adrenergic stimulation or myocardial infarction. Knocking out S100B, augmented hypertrophy, decreased apoptosis and preserved cardiac function following myocardial infarction. S100B induces apoptosis by an extracellular mechanism by interacting with the receptor for advanced glycation end products and activating ERK1/2 and p53 signaling. The intracellular, and extracellular, roles of S100B are attractive therapeutic targets for the treatment of both cardiac and vascular disease.

Keywords S100B · Myocyte hypertrophy · Apoptosis · Receptor for advanced glycation end products

The family of S100 proteins

S100 proteins entail a multigenic family of calcium binding proteins of the EF-hand type (helix E-loop-helix F). These proteins are called S100 because of their solubility in a 100%-saturated solution with ammonium sulphate at neutral pH. They are small acidic proteins, 10–12 KDa and contain two distinct EF-hands, 4 α-helical segments, a central hinge region of variable length and the N-and C-terminal variable domains. To date, 25 members of this family have been identified. Of these, 21 family members (S100A1-S100A18, trichohyalin, filaggrin and repetin) have genes clustered on a 1.6-Mbp segment of human chromosome 1 (1q21) while other members are found at chromosome loci 4q16 (S100P), 5q14 (S100Z), 21q22 (S100B), and Xp22 (S100G). S100 proteins widely express in a variety of cell types and tissues. For example, S100A1 and S100A2 are found in the cytoplasm and nucleus, respectively, of smooth-muscle cells of skeletal muscle (Donato 2001), S100P is located in the cytoplasm of placental tissue (Becker et al. 1992; Emoto et al. 1992) and S100B in cytoplasm of astrocytes of nervous system (Kligman and Marshak 1985). However, their expression might be repressed in other cell types by negative regulatory factors which are controlled by environmental condition. For instance induction of S100B in rat myocardium post-infarction (Tsoporis et al. 1997) implies that transcription regulation of these proteins is strongly controlled by negative and positive elements (Tsoporis et al. 2003a, b).

S100 proteins do not express intrinsic catalytic activity. However, they are calcium sensor proteins and through interaction with several intracellular effector proteins they contribute to the regulation of a broad range of functions such as contraction, motility, cell growth and differentiation, cell cycle transcription, organization of membrane-associated cytoskeleton elements, cell survival, apoptosis, protein phosphorylation and secretion (Donato 1999, 2001). In order to modulate these types of activities S100

J. N. Tsoporis · F. Mohammadzadeh · T. G. Parker (✉)
Division of Cardiology, Department of Medicine,
Keenan Research Centre, Li Ka Shing Knowledge Institute,
St. Michael's Hospital, University of Toronto, 30 Bond St.,
Queen Wing, Room 6-044, Toronto, ON M5B 1W8, Canada
e-mail: parkertg@smh.toronto.on.ca

proteins undergo conformational changes (Ikura 1996). Upon calcium binding the helices of S100 proteins rearrange, revealing a cleft, which forms the target protein binding site (Rustandi et al. 2000). Although target binding of S100 proteins is calcium-dependent, calcium independent interactions have been reported (Santamaria-Kisiel et al. 2006). Enzymes are the most common calcium independent target binding for the S100 proteins. For instance, S100B and S100A1 bind with glycogen phosphorylase (Zimmer and Dubuisson 1993). The most significant calcium-independent interactions of S100 proteins are their ability to bind to each other. Typically, they are homodimers, but heterodimerization adds to the complexity of this multiprotein family. Each subunit consists of two helix-loop-helix motifs connected by a central linker or so-called hinge region. The C-terminal canonical EF-hand motif is composed of 12 amino acids, whereas the N-terminal S100-specific EF-hand comprises 14 residues (Donato 2001; Heizmann and Cox 1998).

Growing evidence indicates that in addition to intracellular activities, some S100 proteins (e.g. S100B, S100A1, S100A4, S100A8, S100A9) exhibit extracellular functions (Donato 2003). However, secretion has been shown only for S100B, S100A8, and S100A9 (Donato 2003). The S100A8/A9 heterodimer is secreted by a novel secretion pathway that depends on an intact MT network and acts as a chemotactic molecule in inflammation (Kerkhoff et al. 1998; Newton and Hogg 1998). The extracellular effects of some S100 proteins require binding to the receptor for advanced glycosylation end products (RAGE) (Schmidt et al. 2001; Bierhaus et al. 2005). RAGE belongs to the immunoglobulin superfamily of cell surface molecules and is composed of an extra-cellular region containing one "V"-type immunoglobulin domain and 2 "C"-type immunoglobulin domains. The extracellular portion of the receptor is followed by a hydrophobic transmembrane-spanning domain and then by a highly charged, short cytoplasmic domain that is essential for post-RAGE signaling. Binding studies show that S100B binds RAGE via the "V" domain (Leclerc et al. 2007).

Non-cardiovascular actions of S100B

S100B is predominantly expressed in astrocytes, oligodendrocytes, and Schwann cells. S100B has intracellular and extracellular affects (Donato et al. 2009). Intracellularly, S100B regulates the cytoskeletal dynamics through disassembly of tubulin filaments, type III intermediate filaments (Donato et al. 2009) and binding to fibrillary proteins such as CapZ (Kilby et al. 1997) or inhibiting GFAP phosphorylation when stimulated by cAMP or calcium/calmodulin (Frizzo et al. 2004). S100B interacts in a calcium-dependent manner with the cytoplasmic domain of myelin-associated glycoprotein and inhibits its phosphorylation by protein kinase (Kursula et al. 2000). It is implicated in the phosphorylation of tau protein (Baudier and Cole 1988) and the modulation of kinase activity by NDR kinase (nuclear Dbf2-related protein kinase) (Millward et al. 1998), GTPase Rac1 (Mbele et al. 2002), the Cdc effector, IQGAP (Mbele et al. 2002) and p53 (Markowitz et al. 2005). S100B can also be secreted by a number of cell types (e.g. astrocytes, glial cells) (Van Eldik and Zimmer 1987). Astrocytes and glial cells secrete S100B, by a complex system involving alterations in intracellular calcium concentration (Van Eldik and Zimmer 1987). S100B after secretion, or simply leakage from damaged cells, could accumulate in the extracellular space and/or enter the blood stream and cerebrospinal fluid (Peskind et al. 2001; Portela et al. 2002). The action of S100B is strongly dependent on its extracellular concentration. At nanomolar quantities it has trophic effects on neurite outgrowth, however, at micromolar concentrations it promotes apoptosis (Hu and Van Eldik 1996, 1999; Huttunen et al. 2000). Such high extracellular levels are detected after brain injury or in neurodegenerative disorders like Down's syndrome, Alzheimer disease or encephalitis (Van Eldik and Griffin 1994; Griffin et al. 1998). Both trophic and toxic effects of extracellular S100B are mediated in the brain by RAGE (Huttunen et al. 2000). In addition, to playing a major role in brain physiology (Donato et al. 2009), S100B is considered a biochemical marker for brain injuries after bypass graft surgery (Anderson et al. 1999) and dilated cardiomyopathy (Mazzini et al. 2007).

Cardiovascular actions of S100B

The adult cardiac myocyte is terminally differentiated and has lost the ability to proliferate. The myocardium therefore adapts to increasing workloads through hypertrophy of individual cells in response to hormonal, paracrine, and mechanical signals (Morgan and Baker 1991; Chien et al. 1993). This process is initially compensatory but it can progress to irreversible enlargement and dilatation of the ventricle resulting in heart failure (Katz 1990). Myocyte hypertrophy is accompanied by a program of fetal gene re-expression including the embryonic β-myosin heavy chain, the skeletal isoform of α actin, and atrial natriuretic factor (Parker and Schneider 1991; Parker 1993). This response can be reproduced in vitro in cultured neonatal cardiac myocytes by treatment with a number of trophic factors including peptide growth factors and α_1-adrenergic agonists (Tsoporis et al. 1997). Negative modulators of the hypertrophic response are essential to maintain a balance

between compensatory hypertrophy and unchecked progression. Experimental evidence suggests that S100B acts as an intrinsic negative regulator of the myocardial hypertrophic response (Tsoporis et al. 1998, 2005, 2009). S100B not normally expressed in the myocardium, is induced in the peri-infarct region of the human heart after myocardial infarction (Tsoporis et al. 1998) and in rat heart commencing at day 7 following myocardial infarction as a result of experimental coronary artery ligation (Tsoporis et al. 1997). In co-transfection experiments in vitro in cultured neonatal rat cardiac myocytes, S100B inhibits the α_1-adrenergic induction of the fetal genes β-myosin heavy chain and the skeletal isoform of α actin (Tsoporis et al. 1997). This inhibition involves the interruption by S100B of the protein kinase C (PKC)-signaling pathway in a calcium dependent manner. The transcriptional regulation of S100B is strongly controlled by negative and positive elements (Tsoporis et al. 2003a, b). S100B is specifically activated by α_1-adrenergic agonists through the α_{1A}-adrenergic receptor but not by any other trophic hormonal stimuli (Tsoporis et al. 2003a, b). The α_1-adrenergic induction of S100B is through the PKC-signaling pathway and involves the transcription factors transcription enhancer factor-1 (TEF-1) and related to TEF-1 (RTEF-1) (Tsoporis et al. 2003a, b) (Fig. 1). This suggests that the same α_1-adrenergic pathway that initiates and sustains the hypertrophic response in cardiac myocytes by activating PKC and is subject to negative modulation by S100B also induces the S100B gene.

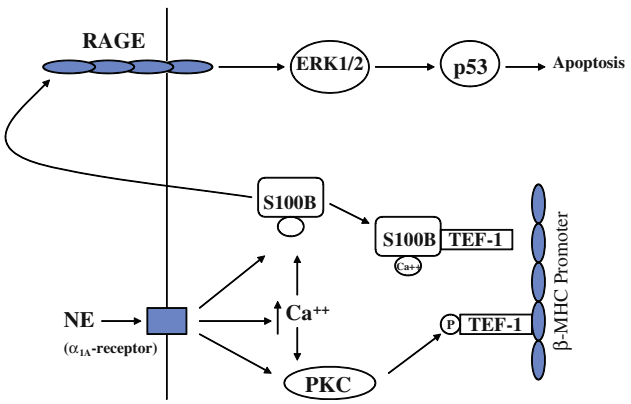

Fig. 1 Schematic representation of proposed intracellular and extracellular effects of S100B in cardiac myocytes. Norepinephrine (*NE*) activation of the calcium dependent protein kinase C (*PKC*), mediated by the α_1-adrenergic receptor, phosphorylates (*P*) transcriptional enhancer factor (1) TEF-1, resulting in DNA binding and transactivation of the β-myosin heavy chain promoter. By contrast, S100B induction by NE and other hypertrophic signals (not shown) results in calcium dependent block of PKC phosphorylation of TEF-1 and inhibition of β-MHC transcription. S100B is also secreted and via activation of the receptor for advanced glycation end products (*RAGE*), and ensuing stimulation of the MEK-ERK1/2 pathway leading to activation of p53 results in apoptosis

To provide a physiologic model of S100B overexpression effects, transgenic mice were created that contained multiple copies of the human gene under the control of its own promoter. These animals demonstrate normal cardiac structure, and neuronal, but no basal cardiac, expression of the transgene. In S100B transgenic mice, after chronic α_1-adrenergic agonist infusion, S100B is detected in the heart and increased in the vasculature and the myocyte hypertrophy and arterial smooth muscle cell proliferation normally evoked in the heart and vasculature, respectively, in response to α_1-adrenergic stimulation in wild-type mice were abrogated (Tsoporis et al. 1998). In knockout mice devoid of S100B both the acute and chronic increase in blood pressure in response to α_1-adrenergic agonist infusion was attenuated compared with wild-type mice (Tsoporis et al. 2009). Furthermore, α_1-adrenergic agonist infusion provoked a potentiated myocyte hypertrophic response and augmented arterial smooth muscle cell proliferation in knockout mice. Similarly, 35 days after experimental myocardial infarction, the S100B knockout mice mounted an augmented hypertrophic response compared to wild-type mice (Tsoporis et al. 2005). Fetal gene expression was induced to a greater magnitude in knockout mice compared to wild-type mice. The S100B transgenic mice did not develop the hypertrophic phenotype but demonstrated increased apoptosis in the peri-infarct region compared to wild-type and knockout mice. These studies in S100B transgenic and knockout mice complement the culture data and support the hypothesis that S100B acts both as an intrinsic negative regulator of hypertrophy and an apoptotic agent. Intracellular S100B may modulate the apoptotic responses of post-infarct myocytes.

Increasing evidence suggests that S100B plays a role in the regulation of apoptosis in post-MI myocardium by an extracellular mechanism after cellular release from damaged myocytes and interaction with RAGE (Tsoporis et al. 2009). Exogenously administered S100B to neonatal rat cultures induced apoptosis in a dose-dependent manner beginning at 0.05 μmol/L, a local or regional concentration that may be achieved in the peri-infarct myocardium (Tsoporis et al. 2005, 2009). Myocyte apoptosis is accompanied by cytochrome C release from mitochondria to cytoplasm, increased expression and activity of pro-apoptotic caspase-3, decreased expression of anti-apoptotic Bcl-2 and phosphorylation of ERK1/2 and p53 (Delphin et al. 1999; Goncalves et al. 2000; Tsoporis et al. 2010). Transfection of a full-length cDNA of RAGE or a dominant-negative mutant of RAGE resulted in increased or attenuated S100B-induced myocyte apoptosis, respectively, implicating RAGE dependence. Inhibition of MEK signaling or overexpression of a dominant negative p53 inhibit S100B-induced myocyte apoptosis. This implies that RAGE activation by S100B increases MEK MAPK

kinase signaling, p53 phosphorylation at serine 15 and p53-dependent myocyte apoptosis (Fig. 1).

The effects of S100B on myocyte apoptosis stand in contrast to S100A1, the most abundant S100 protein expressed in cardiac muscle under basal conditions (Zimmer et al. 1995). S100A1 exhibits increased expression in compensated hypertrophy, decreased expression in human cardiomyopathy, and downregulation following experimental myocardial infarction (Rempiss et al. 1996; Tsoporis et al. 2003a, b). Like our proposed mechanism for S100B release, S100A1 is released into the extracellular space in the setting of myocardial injury, and can bind RAGE (Tsoporis et al. 2009). Unlike S100B, extracellular S100A1 inhibits apoptosis independent of RAGE (Most et al. 2003) or by RAGE signaling by interacting with a different extracellular domain of RAGE as has been shown with other RAGE ligands (Leclerc et al. 2007). Thus, S100 proteins may differentially regulate myocardial structure and function. Given the capacity of S100A1 and S100B to heterodimerize, phenotypic consequences may depend on the availability and stoichiometry of S100A1 and S100B homodimers and heterodimers.

In conclusion, the S100 family constitutes the largest subgroup of the EF-hand family of calcium-binding proteins with 25 members. S100 proteins have been implicated in pleiotropic calcium-dependent cellular events, with specific functions for each of the family members. S100B is induced in peri-infarct myocytes post-myocardial infarction in human subjects and experimental rodent models of myocardial infarction and in response to α_1-adrenergic stimulation. S100B plays an important role in negative intrinsic regulation of aortic smooth muscle cell proliferation, cardiac myocyte hypertrophy and, via RAGE ligation, apoptosis. The intracellular, and extracellular, roles of S100B are attractive therapeutic targets for the treatment of both cardiac and vascular disease.

References

Anderson RE, Hansson LO, Vaage J (1999) Release of S100B during coronary artery bypass grafting is reduced by off-pump surgery. Ann Thorac Surg 67:1721–1725

Baudier J, Cole RD (1988) Interactions between the microtubule-associated tau proteins and S100b regulate tau phosphorylation by the Ca2+/calmodulin-dependent protein kinase II. J Biol Chem 263:5876–5883

Becker T, Gerke V, Kube E, Weber K (1992) S100P, a novel Ca(2+)-binding protein from human placenta. cDNA cloning, recombinant protein expression and Ca2+ binding properties. Eur J Biochem 207:541–547

Bierhaus A, Humpert PM, Morcos T, Wendt T, Chavakis T, Arnold B, Stern DM, Nawroth PP (2005) Understanding RAGE, the receptor for advanced glycation end products. J Mol Med 83:876–886

Chien KR, Zhiu H, Knowlton KU, Miller-Hence W, van Bilsen M, O'Brien TX, Evans S (1993) Transcriptional regulation during cardiac growth and development. Annu Rev Physiol 55:77–95

Delphin C, Ronjat M, Deloulme JC, Garin G, Debussche L, Higashimoto Y, Sakaguchi K, Baudier J (1999) Calcium-dependent interaction of S100B with the C-terminal domain of the tumor suppressor p53. J Biol Chem 274:10539–10544

Donato R (1999) Functional roles of S100 proteins, calcium-binding proteins of the EF-hand type. Biochim Biophys Acta 1450:191–231

Donato R (2001) S100: a multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. Int J Biochem Cell Biol 33:637–668

Donato R (2003) Intracellular and extracellular roles of S100 proteins. Microsc Res Tech 60:540–551

Donato R, Sorci G, Riuzzi F, Arcuri C, Bianchi R, Brozzi F, Tubaro C, Giambanco I (2009) S100B's double life: intracellular regulator and extracellular signal. Intracellular and extracellular roles of S100 proteins. Biochim Biophys Acta 1793:1008–1022

Emoto Y, Kobayashi R, Akatsuka H, Hidaka H (1992) Purification and characterization of a new member of the S-100 protein family from human placenta. Biochem Biophys Res Commun 182:1246–1253

Frizzo JK, Tramontina F, Bortoli E, Gottfried C, Leal RB, Lengyel I, Donato R, Dunkley PR, Goncalves CA (2004) S100B-mediated inhibition of the phosphorylation of GFAP is prevented by TRTK-12. Neurochem Res 29:735–740

Goncalves DS, Lenz G, Karl J, Goncalves CA, Rodnight R (2000) Extracellular S100B protein modulates ERK in astrocyte cultures. Neuroreport 11:807–809

Griffin WS, Sheng JG, McKenzie JE, Royston MC, Gentleman SM, Brumback RA, Cork LC, Del Bigio MR, Roberts GW, Mrak RE (1998) Life-long overexpression of S100beta in Down's syndrome: implications for Alzheimer pathogenesis. Neurobiol Aging 19:401–405

Heizmann CW, Cox JA (1998) New perspectives on S100 proteins: a multi-functional Ca(2+)-, Zn(2+)- and Cu(2+)-binding protein family. Biometals 11:383–397

Hu J, Van Eldik LJ (1996) S100 beta induces apoptotic cell death in cultured astrocytes via a nitric oxide-dependent pathway. Biochim Biophys Acta 1313:239–245

Hu J, Van Eldik LJ (1999) Glial-derived proteins activate cultured astrocytes and enhance beta amyloid-induced glial activation. Brain Res 842:46–54

Huttunen HJ, Kuja-Panula J, Sorci G, Agneletti AL, Donato R, Rauvala H (2000) Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through receptor for advanced glycation end products (RAGE) activation. J Biol Chem 275:40096–40105

Ikura M (1996) Calcium binding and conformational response in EF-hand proteins. Trends Biochem Sci 21:14–17

Katz AM (1990) Is heart failure an abnormality of myocardial cell growth? Cardiology 77:346–356

Kerkhoff C, Klempt M, Sorg C (1998) Novel insights into structure and function of MRP8 (S100A8) and MRP14 (S100A9). Biochim Biophys Acta 1448:200–211

Kilby PM, Van Eldik LJ, Roberts GC (1997) Identification of the binding site on S100B protein for the actin capping protein CapZ. Protein Sci 6:2494–2503

Kligman D, Marshak DR (1985) Purification and characterization of a neurite extension factor from bovine brain. Proc Natl Acad Sci USA 82:7136–7139

Kursula P, Lehto VP, Heape AM (2000) S100beta inhibits the phosphorylation of the L-MAG cytoplasmic domain by PKA. Brain Res Mol Brain Res 76:407–410

Leclerc E, Fritz G, Weibel M, Heizmann CW, Galichet A (2007) S100B and S100A6 differentially modulate cell survival by

interacting with distinct RAGE immunoglobulin domains. J Biol Chem 282:31317–31331

Markowitz J, Rustandi RR, Varney KM, Wilder PT, Udan R, Wu SL, Horrocks WD, Weber DJ (2005) Calcium-binding properties of wild-type and EF-hand mutants of S100B in the presence and absence of a peptide derived from the C-terminal negative regulatory domain of p53. Biochemistry 44:7305–7314

Mazzini GS, Schaf DV, Vinade ER, Horowitz E, Bruch RS, Brunm LM, Goncalves CA, Bacal F, Souza DO, Portela LV, Bordignon S (2007) Increased S100B serum levels in dilated cardiomyopathy patients. J Card Fail 13:850–854

Mbele GO, Deloulme JC, Gentil BJ, Delphin C, Ferro M, Garin J, Takahashi M, Baudier J (2002) The zinc- and calcium-binding S100B interacts and co-localizes with IQGAP1 during dynamic rearrangement of cell membranes. J Biol Chem 277:49998–50007

Millward TA, Heizmann CW, Schafer BW, Hemmings BA (1998) Calcium regulation of Ndr protein kinase mediated by S100 calcium-binding proteins. EMBO J 17:5913–5922

Morgan HE, Baker KM (1991) Cardiac hypertrophy: mechanical, neural and endocrine dependence. Circulation 83:13–25

Most P, Boerries M, Eicher C, Schweda C, Ehlermann P, Pleger ST, Loeffler E, Koch WJ, Katus HA, Schoenenberger CA, Remppis A (2003) Extracellular S100A1 protein inhibits apoptosis in ventricular cardiomyocytes via activation of the extracellular signal-regulated protein kinase ½ (ERK1/2). J Biol Chem 278:48404–48412

Newton RA, Hogg N (1998) The human S100 protein MRP-14 is a novel activator of the beta 2 integrin Mac-1 on neutrophils. J Immunol 160:1427–1435

Parker TG (1993) Molecular biology of cardiac growth and hypertrophy. Herz 18:245–255

Parker TG, Schneider MD (1991) Growth factors, proto-oncogenes and plasticity of the cardiac phenotype. Annu Rev Physiol 53:179–200

Peskind ER, Griffin WS, Akama KT, Raskind MA, Van Eldik LJ (2001) Cerebrospinal fluid S100B is elevated in the earlier stages of Alzheimer's disease. Neurochem Int 39:409–413

Portela LV, Brenol JC, Walz R, Bianchin M, Tort AB, Canabarro UP, Beheregaray S, Marasca JA, Xavier RM, Neto EC, Goncalves CA, Souza DO (2002) Serum S100B levels in patients with lupus erythematosus: preliminary observation. Clin Diagn Lab Immunol 9:164–166

Rempiss A, Greten T, Schafer BW, Hunziker P, Erne P, Katus HA, Heizmann CW (1996) Altered expression of the Ca(2+)-binding protein S100A1 in human cardiomyopathy. Biochim Biophys Acta 1313:253–257

Rustandi RR, Baldisseri DM, Weber DJ (2000) Structure of the negative regulatory domain of p53 bound to S100Bb. Nat Struct Biol 7:570–574

Santamaria-Kisiel L, Rintala-Dempsey AC, Shaw GS (2006) Calcium-dependent and -independent interactions of the S100 protein family. Biochem J 396:201–214

Schmidt AM, Yan SD, Yan SF, Stern DM (2001) The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J Clin Invest 108:949–955

Tsoporis JN, Marks A, Kahn HJ, Butany JW, Liu PP, O'Hanlon D, Parker TG (1997) S100B inhibits α_1-adrenergic induction of the hypertrophic phenotype in cardiac myocytes. J Biol Chem 272:31915–31921

Tsoporis JN, Marks A, Kahn HJ, Butany JW, Liu PP, O'Hanlon D, Parker TG (1998) Inhibition of norepinephrine-induced cardiac hypertrophy in S100beta transgenic mice. J Clin Invest 102:1609–1616

Tsoporis JN, Marks A, Van Eldik LJ, O'Hanlon D, Parker TG (2003a) Regulation of the S100B gene by α_1-adrenergic stimulation in cardiac myocytes. Am J Physiol 284:H193–H203

Tsoporis JN, Marks A, Zimmer DB, McMahon C, Parker TG (2003b) The myocardial protein S100A1, plays a role in the maintenance of normal gene expression in the adult heart. Mol Cell Biochem 242:27–33

Tsoporis JN, Marks A, Haddad A, Dawood F, Liu PP, Parker TG (2005) S100B expression modulates left ventricular remodeling after myocardial infarction in mice. Circulation 111:598–606

Tsoporis JN, Overgaard CB, Izhar S, Parker TG (2009) S100B modulates the hemodynamic response to norepinephrine stimulation. Am J Hypertens 22:1048–1053

Tsoporis JN, Izhar S, Leong-Poi H, Desjardins J-F, Huttunen HJ, Parker TG (2010) S100B interaction with the receptor for advanced glycation end products (RAGE). A novel receptor-mediated mechanism for myocyte apoptosis postinfarction. Circ Res 106 (in press)

Van Eldik LJ, Griffin WS (1994) S100 beta expression in Alzheimer's disease: relation to neuropathology in brain regions. Biochim Biophys Acta 1223:398–403

Van Eldik LJ, Zimmer DB (1987) Secretion of S-100 from rat C6 glioma cells. Brain Res 436:367–370

Zimmer DB, Dubuisson JG (1993) Identification of an S100 target protein: glycogen phosphorylase. Cell Calcium 14:323–332

Zimmer DB, Cornwall EH, Landar A, Song W (1995) The S100 protein family: history, function and expression. Brain Res Bull 37:417–429