REVIEW ARTICLE

S100 protein family and its application in clinical practice

Sedaghat F[1], Notopoulos A[2]

[1] 1st Neurology Department, Aristotelian University of Thessaloniki, AHEPA General Hospital, Greece
[2] 1st Laboratory of Nuclear Medicine, Aristotelian University of Thessaloniki, Hippokratio General Hospital, Greece

Abstract

The members of the S100 protein family are multifunctional proteins with a regulatory role in a variety of cellular processes. They exert their actions usually through calcium binding, although Zn^{2+} and Cu^{2+} have also been shown to regulate their biological activity.

The most studied member, protein S100B, exhibits neurotrophic (at physiologic concentration) or neurotoxic (at higher concentration) activity and its immunohistochemical expression or serum levels have been determined in various clinical disorders. S100B has been well documented as a marker of astrocytic activation mediating its effects via interaction with receptor for advanced glycation end products (RAGE).

We herein provide a wide range of information concerning their clinical application in traumatic brain injuries, Alzheimer disease, subarachnoid haemorrhage and other neurologic disorders, malignant melanoma and several other neoplasms (as S100B has been shown to down-regulate p53), as well as inflammatory diseases. Also its use on predicting neurologic outcome after resuscitation for cardiac arrest or in intrauterine growth retardation newborns is discussed. Hippokratia 2008; 12 (4): 198-204

Key words: S100 protein family, protein S100B, traumatic brain injury, neurodegenerative disorders, malignant melanoma

Corresponding author: Notopoulos A, 28, Kilkisiou Street, Thessaloniki 54638, Greece, tel: 2310892092, e-mail: notopoulkon@ath.forthnet.gr

S100 protein structure and functions

S100 protein family consists the largest subgroup of the Ca^{2+}-binding EF-hand (helix E-loop-helix F) protein group. These proteins are called S100 because of their solubility in a 100%-saturated solution with ammonium sulphate at neutral pH. They were first identified by B.W. Moore in 1965[1]. S100 proteins are small, acidic proteins of 10-12kDa 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. In contrast to the abundance of S100 genes in vertebrates, they are completely absent in invertebrates. At present, at least 25 proteins have been identified as belonging to the S100 protein family, 21 of them having genes clustered at chromosome locus 1q21, known as the epidermal differentiation complex (Table 1)[2-4].

The members of the S100 protein family are multifunctional proteins expressed in a diverse spectrum of tissues. Through their interaction with several effector proteins within cells they are involved in the regulation of a variety of cellular processes such as contraction, motility, cell growth and differentiation, cell cycle progression, transcription, structural organization of membranes, dynamics of cytoskeleton constituents, protection from oxidative cell damage, protein phosphorylation and secretion[5]. This variety of functions appears due to:

a. broad diversification of the different members (25 members in human)

b. different metal ion-binding properties of the individual S100 proteins

c. spatial distribution in specific intracellular compartments or extracellular space, and

d. their ability to form non-covalent homo- and hetero-dimers, allowing for dynamic exchange of the S100 subunits.

S100 proteins do not have intrinsic catalytic activity. They are generally thought to be calcium sensor proteins that – in a manner similar to calmodulin and troponin C – undergo conformational changes and modulate biologi-

Table 1: The members of S100 protein family and the location of their specific genes.

Members of S100 protein family	Chromosome loci
S100A1-S100A18 trichohylin fillagrin repetin	1q21
S100B	21q22
S100G	Xp22
S100P	4p16
S100Z	5q14

cal activity via calcium binding[6]. Upon calcium binding, the helices of S100 proteins rearrange, revealing a cleft, which forms the target protein binding site[7]. In addition, some S100 members have been shown to bind Zn^{2+} and Cu^{2+}, suggesting the possibility that their biological activity in some cases might be regulated by Zn^{2+} and/or Cu^{2+}, rather than by Ca^{2+} [8-10]. An example of a Ca^{2+}-independent but Zn^{2+}-dependent target protein recognition is the interaction of S100B with tau protein (inhibition of tau protein phosphorylation by protein kinase II). Also Cu^{2+} binding to S100B might have a neuroprotective function[11,12]. Calcium and zinc binding proteins S100A9 and S100A8, abundant in myeloid cells, are considered to play important roles in both calcium signaling and zinc homeostasis, but they do neither serve as calcium nor as zinc buffering proteins in granulocytes[13].

Several S100 proteins, such as S100B, SA4, S100A8, S100A9, S100A12, and S100A13, are secreted and act in a cytokine-like manner. For example, the S100A8/A9 heterodimer acts as a chemotactic molecule in inflammation[14], S100B exhibits neurotrophic (at physiologic concentration: nanomolar levels) or neurotoxic (at higher concentration: micromolar levels) activity[15,16] and S100A4 has angiogenic effects[17].

Methods of measurement

Analytical methods such as immunoradiometric assay (IRMA)[18], mass spectroscopy, western blot, ELISA (enzyme linked immunosorbent assay), electrochemiluminence and quantitative PCR, can detect S100 changes in immunohistochemical expression or in serum concentration with high sensitivity, providing an important tool in clinical diagnosis[19].

Protein S100B (homodimer of the β subunit) has a molecular weight of 21kD and is coded on the long arm of chromosome 21 (21q22.3). The biological half-life of S100B approximates 30 minutes. This implies that any persistent elevation of its serum levels reflects continuous release from affected tissues. S100B is mainly eliminated by the kidneys.

S100 expression in related diseases

Diseases associated with altered expression levels of S100 proteins can be classified into four categories:

1. Neurologic disorders

As protein S100B is primarily produced by astrocytes in CNS, its increased expression – as well as that of glial fibrillary acidic protein (GFAP) – represents a hallmark of astrocytic activation. It is less astrocyte-specific than GFAP, as it is localized in many neural cell types[20]. S100B protein's autocrine effects on astrocytes (upregulation of IL-6, TNF-alpha expression) are mediated through its interaction with RAGE (Receptor for Advanced Glycation End products)[5,21]. Secretion of S100B is an early process during the glial response to metabolic injury (oxygen, serum and glucose deprivation)[22]. The relationship between stress conditions (brain traumas, blood-brain barrier disruption, ischemia) and serum levels of S100B seems to be glucocorticoid independent[23].

Traumatic brain injuries (TBI) result in an increase in S100B levels in blood and CSF. After mild traumatic brain injuries, increased concentrations of S100B and S100A1B occur in 31% and 48% of the patients, without significant association with symptoms or signs of cognitive impairment[24]. Furthermore, the serum levels of S100B and C-tau protein are not reliable predictors of the long outcome in such cases[25], particularly in children with TBI[26]. However, with a cutoff limit of 0.1μg/l, the measurement of S100B has been shown to help to identify the subgroup of patients with trauma-relevant intracerebral lesions on CT scan with a sensitivity of 99% and a specificity of 30%. So, due to its excellent negative predictive value, the addition of S100B test to the clinical decision rules for the evaluation of patients with a mild head injury helps avoiding 30% of unnecessary CT scans[27]. Opposing results have also been presented, suggesting that S100B determinations can not replace the physical examination or CT scan (which has an indisputable role in assessing moderate or severe TBI) in the approach of patients with mild head injury[28]. The separate analysis of the two dimers S100A1B and S100BB (which account for the total measured concentration of S100B) does not offer any essential advantage[29]. As extracerebral sources of S100B, particularly adipocytes or chondrocytes, contribute to its serum levels, caution is needed when interpreting serum S100B increase as a clinical marker of brain damage[30]. It should also be noted that serum levels of S100B depend on the integrity of the blood-brain barrier. So, its early increase after TBI can be attributed either to mechanical discharge from a destroyed blood-brain barrier or to active expression by a brain involved in systemic inflammatory reaction. The role of S100 in TBI poses some challenging issues, as recent research provides growing evidence that S100B may decrease neuronal injury and/or contribute to repair following TBI, triggering wound repair events in the border of trauma and exerting paracrine trophic actions on the adjacent regions[31,32].

In newborns with birth asphyxia, serum S100B levels provide a biochemical indication for the presence of hypoxic-ischemic encephalopathy[33]. Also, significantly higher S100B levels in cord artery have been noted in neonates with acidosis and pathological patterns (leading to appropriate interventions) in cardiotocography and fetal electrocardiography during labour[34].

The increased levels of S100B and GFAP after spontaneous subarachnoid haemorrhage correlate well with the clinical and neuroimaging severity of the disease, contributing to the better initial assessment and follow-up[35] and are good predictors of the outcome[36]. S100B serum levels above 0.3μg/l on admission of such patients are associated with unfavourable outcome.

Such elevated levels are also observed in patients suffering from chronic neurodegenerative disorders such as Alzheimer's disease[37-39]. Elevated levels of S100B originating from necrotic tissues might enhance

or even amplify neurodegeneration by S100B-induced apoptosis.

S100B serum levels can also provide independent information about the individual risk of a patient with acute stroke experiencing intracerebral haemorrhagic complications under thrombolytic therapy (intravenous recombinant tissue plasminogen activator). But its low diagnostic accuracy (parallel to that of metalloproteinase-9 or fibronectin which have also been investigated in this context) is a limiting factor for it to function as a reliable biomarker in acute stroke management[40].

Interestingly, in patients suffering from amyotrophic lateral sclerosis, the serum concentration of S100B is decreased[41], whereas the expression of S100A6 is greatly increased[42]. No clinically meaningful fluctuations of S100B serum levels have been noted in multiple sclerosis (MS) patients[43]. In MS patients, S100B cerebrospinal fluid (CSF) level is increased and correlates with CSF ferritin[44].

It has been reported that serum and CSF S100 level is raised in systemic lupus erythematosus with neuropsychiatric involvement (i.e. organic brain syndrome, seizures, cerebral vascular accident, psychosis) and in obstructive sleep apnea syndrome, reflecting the ongoing neurological damage[45-47]. Also, the elevated and persistent expression of S100B induced by hyperammonemia may contribute to the brain impairment observed in hepatic encephalopathy[48]. Finally, significant increase of serum S100B is observed during exacerbations of bipolar disorder (episodes of mania and depression), but not during the remission phases of the disease[49].

The above described wide range of applications has led to the consideration of S100B measurement in neurologic disorders as analogous to that of CRP in systemic inflammation[50].

2. Neoplastic disorders

Different forms of cancer exhibit dramatic changes in the expression of S100 proteins such as S100B, S100A2, S100A4, S100A6, and S100P[51]. The S100-RAGE signalling pathway plays an important role in linking inflammation and cancer and in tumour cell survival and malignant progression (RAGE-deficient tumours are characterized by accelerated apoptosis, reduced activation of NFκB and significantly impaired proliferation).

For example, elevated levels of S100A4 (metastasin) are associated with poor survival rates in breast cancer patients and have been found to induce metastasis in mouse models. Increased serum concentration of S100A4 is also found in esophageal squamous and colon carcinoma, invasive pancreatic carcinoma, non small cell lung cancer, bladder carcinoma and correlates with a worse outcome and more aggressive disease. S100A4 interacts with annexin II, an endothelial plasminogen co-receptor, and accelerates tPA-mediated plasminogen activation. The resulting local plasmin formation could contribute to tumor-induced angiogenesis and metastasis[52]. Also, S100A4 at nanomolar levels stimulates matrix metalloproteinase 13 release from chondrocytes in a RAGE-mediated manner[53].

There is a high (stage-dependent) secretion of S100B in malignant melanoma, reflecting tumour load, stage and prognosis[54]. S100B serum levels are widely used for the early detection of recurrence or metastases in combination with MIA (Melanoma-Inhibiting Activity) protein and TA90-IC (TA90-Immune Complex)[55]. A cutoff of 0.12μg/l has been suggested and is associated with a sensitivity and specificity of 0.29 and 0.93, respectively. Due to the possibility of false positive S-100B tumour marker determinations, repetition of its measurement is recommended if elevated S-100B levels occur during the follow up of high risk melanoma patients[56]. In such cases, FDG-PET/CT can be used for the accurate identification of lymph node or distant metastases and/or the reliable exclusion of metastases, reaching an accuracy of 98%. Also, S100B remains the most sensitive immunohistochemical marker of melanoma, despite the emergence of newer markers (HMB-45, MART-1/Melan-A, tyrosinase, MITF, etc) reflecting differentiation, proliferation, immunomodulation and other relevant processes[57].

Concerning the detection of brain metastases, serum concentration of S100B has a good negative predictive value comparable to radiologic investigations. As its levels may also reflect the existence of cerebrovascular ischemic changes without infiltrating tumour, it may be used in conjunction with proApolipoprotein A1 for a sufficiently specific serum-based diagnosis of the presence of metastatic brain tumours[58].

Recent studies have shown that S100A2 is highly expressed in tumours such as:

a. non-small lung cancer (in stage I NSCLC overexpression of S100A2 is associated with a significantly lower overall survival and disease-specific survival rate)[59-62]

b. gastric / oesophageal squamous cancer[63]

c. lymphoma

d. granular cell tumours of the gastrointestinal tract (in correlation with nestin, a cytoskeletal filament protein expressed in neuroectodermal stem cells and skeletal muscle progenitor cells)[64]

e. renal tumours (specially in papillary renal cell carcinomas and oncocytomas)[65]

f. papillary and anaplastic thyroid carcinomas (while it is not expressed in follicular carcinomas)

On the contrary, in early-stage oral squamous cell carcinoma patients at high risk of recurrence, down regulation of S100A2 is significantly associated with shorter disease free survival[66].

There is accumulating evidence that BRCA1 negative breast carcinomas exhibit increased expression of S100A7[67].

S100A8 and S100A9 form a heterodimer complex implicated in regulating cell proliferation and in the metastatic process (increasing the motility of cancer cells and facilitating the homing of migrating cells to pre-metastatic “niches” within the target tissues)[68].

The associations between members of the S100 pro-

tein family and several types of cancer are summarised in Table 2.

Table 2: Summary of the links that have been noted between various types of cancer and members of the S100 protein family.

Cancer	Members of the S100 protein family
Melanoma	S100B (established use), S100A4, S100A2
Breast	S100A4, S100A7 (promising results) S100A8, S100A9, S100A2, S100A6, S100A11
Pancreatic	S100A4, S100A10, S100A11, S100P (8-fold increase)
Colorectal	S100A4, S100A6, S100A8, S100A9, S100A11
Castric	S100A2, S100A4, S100A8, S100A9, S100A11
Bladder	S100A4, S100A11 (down-regulation associated with decreased survival)
Ovarian	S100A1, S100A4
Prostate	S100A2, S100A4, S100A11 (up-regulation associated with advanced stage)
Lung (squamous cell)	S100A2, S100A4, S100P
Renal	S100A1, S100A11, S100A2 (3.8-fold decrease in 93% of patients)
Thyroid	S100A2, S100A4
Lymphoma	S100A2, S100P

Although in most cases the function of S100 proteins in cancer cells is still unknown, the specific expression patterns of these proteins can be used as a valuable prognostic tool. S100A4 and S100B proteins bind to p53 tumour suppressor gene and inhibit its phosphorylation[69], leading to p53 down-regulation in a calcium dependent manner[70]. Efforts are made to restore functional wild-type p53 in neoplasms with elevated S100B through the inhibition of the S100B-p53 interaction[71]. Other S100 proteins exert different effects on p53 activity (S100A2 promotes p53 transcriptional activity, etc).

3. Cardiac diseases

S100A1 is specifically and highly expressed in the mammalian myocardium, where it modulates contractile performance of the heart via interaction with contractile filaments and with proteins of the sarcoplasmic reticulum (SR). It also increases the release of calcium from the sarcoplasmic reticulum by interacting with the ryanodine receptor. S100A1 is up-regulated in right ventricular hypertrophy[72] and down-regulated in end-stage heart failure[73], indicating a correlation between S100A1 expression and contractile performance. In patients with acute myocardial ischemia, a rise in the plasma concentration of S100A1 was observed, which might be associated with a role of S100A1 as a cardioprotective factor with anti-apoptotic function[74,75].

The combination of Glasgow Coma Scale (< 6 points) with elevated serum concentrations of NSE (> 65ng/ml) and S100 (> 1.5μg/l) 48-72h after cardiopulmonary resuscitation for cardiac arrest, lead to prediction of a poor neurological outcome and cognitive impairment with a specificity of 100% (sensitivity around 42%)[76,77]. Elevation of S100 alone increases the risk of death and persistent vegetative state 12.6- fold[78].

It is known that processing of pericardial shed blood with a cell-saving device helps to prevent lipid microembolization and to protect from neurocognitive dysfunction after cardiopulmonary bypass and this may be associated with the reduction of S100B release observed when this method is performed[79].

4. Inflammatory diseases

S100A8, S100A9, and S100Al2, are predominantly expressed in phagocytes and are strongly associated with pro-inflammatory functions. They are secreted especially at sites of inflammation. The serum concentrations of these S100 proteins correlate with inflammatory disease activity; high levels were identified in several inflammatory disorders such as rheumatoid arthritis, chronic bronchitis, and cystic fibrosis[80,81]. S100A7, S100A8, S100A9, and S100A12 are up-regulated in active psoriatic lesions[82,83]. Overexpression of S100A7 (acting as a keratinocyte-derived chemotactic agent for immune cells) is also seen in many epidermal inflammatory diseases, like atopic dermatitis, mycosis fungoides and Darier's disease[7]. Antiallergic drugs which bind to S100A12 might b1ock the S100 protein-RAGE interaction[84], implying a promising approach to anti-inflammatory therapy[85]. Enteric glial-derived S100B (associated with the onset of

inflammation) is increased in the duodenum of patients with celiac disease and contributes to nitric oxide production[86].

Apart from the above mentioned clinical applications, S100B serum measurement may provide helpful information on the neuromuscular system activation induced by physical training, as S100B is released from the involved muscles and nerves[87] and on the reliable monitoring of alcohol detoxification treatment[88]. Finally, increased urine S100B protein levels are found in intrauterine growth retardation newborns in the first week after birth suggesting the presence of brain damage. S100B protein measurements soon after birth contribute to the stratification of these patients concerning the risk of possible neurologic sequelae[89].

Conclusion

The members of the S100 protein family through their interaction with several effector proteins are involved in the regulation of a diverse spectrum of cellular processes. Although their pathophysiologic implications still require further clarification, some of these proteins have already been successfully investigated in clinical context.

S100B protein has gained a role as a complementary specific index of early diagnosis and prognosis judgement after TBI. Unraveling the mechanism of S100B neurotoxicity and assessment of the therapeutic effect of S100B protein are promising research directions for accomplishing the optimal clinical treatment of TBI.

S100B is already widely used in malignant melanoma patients with a particular help in staging, in assessing the therapeutic outcome and in the early detection of recurrence.

As S100A4 has molecular interactions involved in tumourigenesis and metastasis, it would seem feasible that it may be used as a complementary staging and prognostic tool in patients with breast, colorectal and gastric carcinomas.

Finally, other members of the S100 protein family may prove to be useful biomarkers in future applications and may S100 protein-targeted therapies emerge as useful opportunities in specific clinical settings[90].

References

1. Moore BW. A soluble protein characteristic of the nervous system. Biochem Biophys Res Commun 1965; 19: 739-744
2. Marenholz I, Heinzman CW, Fritz G. S100 protein in mouse and man: from evolution to function and pathology. Biochem Biophys Res Commun 2004; 322: 1111-1122
3. Michetti F, Gazzolo D. S100B protein in biological fluids: a tool for perinatal medicine. Clin Chem 2002; 48: 2097-2104
4. Donato R. Intracellular and extracellular roles of S100 proteins. Microsc Res Tech 2003; 60: 540-551
5. Santamaria-Kisiel L, Rintala-Dempsey AC, Shaw GS. Calcium –dependent and –independent interactions of the S100 protein family. Biochem J 2006; 396: 201-214
6. Ikura M. Calcium binding and conformational response in EF-hand proteins. Trends Biochem Sci 1996; 21: 14–17
7. Eckert RL, Broome A-M, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. J Invest Dermatol 2004; 123: 23-33
8. Nishikawa T, Lee ISM, Shiraishi T, Ishikawa T, Ohta Y, Nishikimi M. Identification of S100b protein as copper-binding protein and its suppression of copper-induced cell damage. J Biol Chem 1997; 272: 23037–23041
9. Schafer BW, Fritschy JM, Murmann P, et al. Brain S100A5 is a novel calcium-zinc-, and copper ion-binding protein of the EF-hand superfamily. J Biol Chem 2000; 275: 30623–30630
10. Heizmann CW, Cox JA. New perspectives on S100 proteins: a multifunctional $Ca(2+)^{-}$, $Zn(2+)^{-}$, and $Cu(2+)^{-}$ -binding protein family. Biometals 1998; 11: 383–397
11. Yu WH, Fraser PE. S100b interaction with tau is promoted by zinc and inhibited by hyperphosphorylation in Alzheimer's disease. J Neurosci 2001; 21: 2240–2246
12. Shiraishi N, Nishikimi M. Suppression of copper-induced cellular damage by copper sequestration with S100b protein. Arch Biochem Biophys 1998; 357: 225–230
13. Nacken W, Mooren FC, Manitz MP, Bond G, Sorg C, Kerkhoff C. S100A9 deficiency alters adenosine-5'-triphosphate induced calcium signalling but does not generally interfere with calcium and zinc homeostasis in murine neutrophils. Int J Biochem Cell Biol 2005; 37: 1241-1253
14. Newton RA, Hogg N. The human S100 protein MRP-14 is a novel activator of the b2 integrin Mac-1 on neutrophils. J Immunol 1998; 160: 1427–1435
15. Huttunen HJ, Kuja-Panula J, Sorci G, Agneletti AL, Donato R, Rauvala H. Coregulation of neurite outgrowth and cell survival by amphoterin and S100 proteins through receptor for advanced glycation end products (RAGE) activation. J Biol Chem 2000; 275: 40096–40105
16. Korfias S, Stranjalis G, Papadimitriou A, et al. Serum S-100B protein as a biochemical marker of brain injury: a review of current concepts. Curr Med Chem 2006; 13: 3719-3731
17. Ambartsumian N, Klingelhofer J, Grigorian M, et al. The metastasis associated Mts1 (S100A4) protein could act as an angiogenic factor. Oncogene 2001; 20: 4685–4695
18. AB Sangtec Medical, Sangtec 100 IRMA; Immunoradiometric assay for the quantification of protein S100B. Instruction for use 2000
19. Wild D. The immunoassay handbook. 2nd ed. London: Nature Publishing Group; 2001. p. 660
20. Steiner J, Bernstein HG, Bielau H, et al. Evidence for a wide extra-astrocytic distribution of S100B in human brain. BMC Neurosci 2007; 8: 2
21. Ponath G, Schettler C, Kaestner F, et al. Autocrine S100B effects on astrocytes are mediated via RAGE. J Neuroimmunol 2007; 184: 214-222
22. Gerlach R, Demel G, Konig HG, et al. Active secretion of S100B from astrocytes during metabolic stress. Neuroscience 2006; 141: 1697-1701
23. Scaccianoce S, Del Bianco P, Pannitteri G, Passarelli F. Relationship between stress and circulating levels of S100B protein. Brain Res 2004; 1004: 208-211
24. de Boussard CN, Lundin A, Karlstedt D, Edman G, Bartfai A, Borg J. S100 and cognitive impairment after mild traumatic brain injury. J Rehabil Med 2005; 37: 53-57
25. Bazarian JJ, Zemlan FP, Mookerjee S, Stigbrand T. Serum S-100B and cleaved-tau are poor predictors of long-term outcome after mild traumatic brain injury. Brain Inj 2006; 20: 759-765
26. Piazza O, Storti MP, Cotena S, et al. S100B is not a reliable prognostic index in paediatric TBI. Pediatr Neurosurg 2007; 43: 258-264
27. Biberthaler P, Linsenmeier U, Pfeifer KJ, et al. Serum S-100B concentration provides additional information for the indication of computed tomography in patients after minor head injury: a prospective multicenter study. Shock 2006; 25: 446-453
28. Muller K, Townend W, Biasca N, et al. S100B serum level predicts computed tomography findings after minor head injury. J Trauma 2007; 62: 1452-1456
29. Nylen K, Ost M, Csajbok LZ, et al. Serum levels of S100B,

S100A1B and S100BB are all related to outcome after severe traumatic brain injury. Acta Neurochir (Wien) 2008; 150: 221-227.
30. Netto CB, Conte S, Leite MC, et al. Serum S100B protein is increased in fasting rats. Arch Med Res 2006; 37: 683-686
31. Kleindienst A, Ross Bullock M. A critical analysis of the role of the neurotrophic protein S100B in acute brain injury. J Neurotrauma 2006; 23: 1185-1200
32. Ellis EF, Willoughby KA, Sparks SA, Chen T. S100B protein is released from rat neonatal neurons, astrocytes, and microglia by in vitro trauma and anti-S100 increases trauma-induced delayed neuronal injury and negates the protective effect of exogenous S100B on neurons. J Neurochem 2007; 101: 1463-1470
33. Murabayashi M, Minato M, Okuhata Y, et al. Kinetics of serum S100B in newborns with intracranial lesions. Pediatr Int 2008; 50: 17-22
34. Stuart A, Edvinsson L, Kallen K, Olofsson P, Hellsten C, Amer-Wahlin I. Fetal electrocardiographic monitoring during labor in relation to cord blood levels of the brain-injury marker protein S-100. J Perinat Med 2008; 36: 136-141
35. Vos PE, van Gils M, Beems T, Zimmerman C, Verbeek MM. Increased GFAP and S100beta but not NSE serum levels after subarachnoid haemorrhage are associated with clinical severity. Eur J Neurol 2006; 13: 632-638
36. Oertel M, Schumacher U, McArthur DL, Kastner S, Boker DK. S-100B and NSE: markers of initial impact of subarachnoid haemorrhage and their relation to vasospasm and outcome. J Clin Neurosci 2006; 13: 834-840
37. Li Y, Wang J, Sheng JG, et al. S100 b increases levels of b-amyloid precursor protein and its encoding mRNA in rat neuronal cultures. J Neurochem 1998; 71: 1421–1428
38. Sheng JG, Mrak RE, Griffin WS. S100 b protein expression in Alzheimer disease: potential role in the pathogenesis of neuritic plaques. J Neurosci Res 1994; 39: 398–404
39. Van Eldik LJ, Griffin WS. S100 b expression in Alzheimer's disease: relation to neuropathology in brain regions. Biochim Biophys Acta 1994; 1223: 398–403
40. Foerch C, Wunderlich MT, Dvorak F, et al. Elevated serum S100B levels indicate a higher risk of hemorrhagic transformation after thrombolytic therapy in acute stroke. Stroke 2007; 38: 2491-2495
41. Sussmuth SD, Tumani H, Ecker D, Ludolph AC. Amyotrophic lateral sclerosis: disease stage related changes of tau protein and S100 b in cerebrospinal fluid and creatine kinase in serum. Neurosci Lett 2003; 353: 57–60
42. Hoyaux D, Decaestecker C, Heizmann CW, et al. S100 proteins in corpora amylacea from normal human brain. Brain Res 2000; 867: 280–288
43. Koch M, Mostert J, Heersema D, Teelken A, De Keyser J. Plasma S100beta and NSE levels and progression in multiple sclerosis. J Neurol Sci 2007; 252: 154-158
44. Rejdak K, Petzold A, Stelmasiak Z, Giovannoni G. Cerebrospinal fluid brain specific proteins in relation to nitric oxide metabolites during relapse of multiple sclerosis. Mult Scler 2008; 14: 59-66
45. Schenatto CB, Xavier RM, Bredemeier M, et al. Raised serum S100B protein levels in neuropsychiatric lupus. Ann Rheum Dis 2006; 65: 829-831
46. Braga CW, Martinez D, Wofchuk S, Portela LV, Souza DO. S100B and NSE serum levels in obstructive sleep apnea syndrome. Sleep Med 2006; 7: 431-435
47. Yang XY, Lin J, Lu XY, Zhao XY. Expression of S100B protein levels in serum and cerebrospinal fluid with different forms of neuropsychiatric systemic lupus erythematosus. Clin Rheumatol 2008; 27: 353-357
48. Leite MC, Brolese G, de Almeida LM, Pinero CC, Gottfried C, Goncalves CA. Ammonia-induced alteration in S100B secretion in astrocytes is not reverted by creatine addition. Brain Res Bull 2006; 70: 179-185
49. Andreazza AC, Cassini C, Rosa AR, et al. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res 2007; 41: 523-529
50. Sen J, Belli A. S100B in neuropathologic states: the CRP of the brain? J Neurosci Res 2007; 85: 1373-1380
51. Hsieh HL, Schafer BW, Sasaki N, Heizmann CW. Expression analysis of S100 proteins and RAGE in human tumors using tissue microarrays. Biochem Biophys Res Commun 2003; 307: 375–381
52. Semov A, Moreno MJ, Onichtchenko A, et al. Metastasis-associated protein S100A4 induces angiogenesis through interaction with Annexin II and accelerated plasmin formation. J Biol Chem 2005; 280: 20833-20841
53. Donato R. RAGE: a single receptor for several ligands and different cellular responses: the case of certain S100 proteins. Current Mol Med 2007; 7: 711-724
54. Von Schoultz E, Hansson LO, Djureen E, et al. Prognostic value of serum analyses of S100B protein in malignant melanoma. Melanoma Res 1996; 6: 133-137
55. Faries MB, Gupta RK, Ye X, et al. A Comparison of 3 tumor markers (MIA, TA90IC, S100B) in stage III melanoma patients. Cancer Invest 2007; 25: 285-293
56. Strobel K, Skalsky J, Kalff V, et al. Tumour assessment in advanced melanoma: value of FDG-PET/CT in patients with elevated serum S-100B. Eur J Nucl Med Mol Imaging 2007; 34: 1366-1375
57. Ohsie SJ, Sarantopoulos GP, Cochran AJ, Binder SW. Immunohistochemical characteristics of melanoma. J Cutan Pathol 2008; 35: 433-444.
58. Marchi N, Mazzone P, Fazio V, Mekhail T, Masaryk T, Janigro D. ProApolipoprotein A1: a serum marker of brain metastases in lung cancer patients. Cancer 2008; 112: 1313-1324
59. Nagy N, Hoyaux D, Gielen I, et al. The Ca2+-binding S100A2 protein is differentially expressed in epithelial tissue of glandular or squamous origin. Histol Histopathol 2002; 17: 123–130
60. Heighway J, Knapp T, Boyce L, et al. Expression profiling of primary non-small cell lung cancer for target identification. Oncogene 2002; 21: 7749–7763
61. Wang H, Zhang Z, Li R, et al. Overexpression of S100A2 protein as a prognostic marker for patients with stage I non small cell lung cancer. Int J Cancer 2005; 116: 285-290
62. Jassem E, Serkies K, Dziadziuszko R, et al. Prognostic value of S-100 immunostaining in tumour cells of non-small cell lung cancer. Biomarkers 2006; 11: 262-269
63. El-Rifai W, Moskaluk CA, Abdrabbo MK, et al. Gastric cancers overexpress S100A calcium-binding proteins. Cancer Res 2002; 62: 6823–6826
64. Parfitt JR, McLean CA, Joseph MG, Streutker CJ, Al-Haddad S, Driman DK. Granular cell tumours of the gastrointestinal tract: expression of nestin and clinicopathological evaluation of 11 patients. Histopathology 2006; 48: 424-430
65. Li G, Gentil-Perret A, Lambert C, Genin C, Tostain J. S100A1 and KIT gene expressions in common subtypes of renal tumours. Eur J Surg Oncol 2005; 31: 299-303
66. Tsai ST, Jin YT, Tsai WC, et al. S100A2, a potential marker for early recurrence in early-stage oral cancer. Oral Oncol 2005; 41: 349-357
67. Kennedy RD, Gorski JJ, Quinn JE, et al. BRCA1 and c-Myc associate to transcriptionally repress psoriasin, a DNA damage-inducible gene. Cancer Res 2005; 65: 10265-10272
68. Rafii S, Lyden D. S100 chemokines mediate bookmarking of premetastatic niches. Nat Cell Biol 2006; 8: 1321-1323
69. Fernandez-Fernandez MR, Veprintsev DB, Fersht AR. Proteins of the S100 family regulate the oligomerization of p53 tumor suppressor. Proc Natl Acad Sci USA 2005; 102: 4735-4740
70. Markowitz J, Mackerell AD Jr, Carrier F, Charpentier TH, Weber DJ. Design of Inhibitors for S100B. Curr Top Med Chem 2005; 5: 1093-1108

71. Gieldon A, Mori M, Del Conte R. Theoretical study on binding of S100B protein. J Mol Model 2007; 13: 1123-1131
72. Ehlermann P, Remppis A, Guddat O, et al. Right ventricular upregulation of the Ca(2+) binding protein S100A1 in chronic pulmonary hypertension. Biochim Biophys Acta 2000; 1500: 249–255
73. Remppis A, Greten T, Schafer BW, et al. Altered expression of the Ca2+-binding protein S100A1 in human cardiomyopathy. Biochim Biophys Acta 1996; 1313: 253–257
74. Kiewitz R, Acklin C, Minder E, Huber PR, Schafer BW, Heizmann CW. S100A1, a new marker for acute myocardial ischemia. Biochem Biophys Res Commun 2000; 274: 865–871
75. Most P, Boerries M, Eicher C, et al. Extracellular S100A1 protein inhibits apoptosis in ventricular cardiomyocytes via activation of the extracellular signal-regulated protein kinase 1/2 (ERK1/2). J Biol Chem 2003; 278: 48404–48412
76. Grubb NR, Simpson C, Sherwood RA, et al. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. Heart 2007; 93: 1268-1273
77. Ekmektzoglou KA, Xanthos T, Papadimitriou L. Biochemical markers (NSE, S-100, IL-8) as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation. Resuscitation 2007; 75: 219-228
78. Pfeifer R, Borner A, Krack A, Sigusch HH, Surber R, Figulla HR. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 2005; 65: 49-55
79. Carrier M, Denault A, Lavoie J, Perrault LP. Randomized controlled trial of pericardial blood processing with a cell-saving device on neurologic markers in elderly patients undergoing coronary artery bypass graft surgery. Ann Thorac Surg 2006; 82: 51-55
80. Frosch M, Strey A, Vogl T, et al. Myeloid-related proteins 8 and 14 are specifically secreted during interaction of phagocytes and activated endothelium and are useful markers for monitoring disease activity in pauciarticular-onset juvenile rheumatoid arthritis. Arthritis Rheum 2000; 43: 628–637
81. Foell D, Wittkowski H, Hammerschmidt I, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum 2004; 50: 1286–1295
82. Broome AM, Ryan D, Eckert RL. S100 protein subcellular localization during epidermal differentiation and psoriasis. J Histochem Cytochem 2003; 51: 675–685
83. Semprini S, Capon F, Tacconelli A, et al. Evidence for differential S100 gene over-expression in psoriatic patients from genetically heterogeneous pedigrees. Hum Genet 2002; 111: 310–313
84. Shishibori T, Oyama Y, Matsushita O, et al. Three distinct anti-allergic drugs, amlexanox, cromolyn and tranilast, bind to S100A12 and S100A13 of the S100 protein family. Biochem J 1999; 338: 583–589
85. Morbini P, Villa C, Campo I, Zorzetto M, Inghilleri S, Luisetti M. The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease? Mod Pathol 2006; 19: 1437-1445
86. Esposito G, Cirillo C, Sarnelli G, et al. Enteric glial-derived S100B protein stimulates nitric oxide production in celiac disease. Gastroenterology 2007; 133: 918-925
87. Schulpis KH, Moukas M, Parthimos T, Tsakiris T, Parthimos N, Tsakiris S. The effect of alpha-Tocopherol supplementation on training-induced elevation of S100B protein in sera of basketball players. Clin Biochem 2007; 40: 900-906
88. Liappas I, Tzavellas EO, Kariyannis C, et al. Effect of alcohol detoxification on serum S-100B levels of alcohol-dependent individuals. In Vivo 2006; 20: 675-680
89. Florio P, Marinoni E, Di Iorio R, et al. Urinary S100B protein concentrations are increased in intrauterine growth-retarded newborns. Pediatrics 2006; 118: e747-e754
90. Salama I, Malone PS, Mihaimeed F, Jones JL. A review of the S100 proteins in cancer. Eur J Surg Oncol 2008; 34 : 357-364