

S100 protein family and its application in clinical practice

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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 Zn²⁺ and Cu²⁺ 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

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S100 protein structure and functions

S100 protein family consists the largest subgroup of the Ca²⁺-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 1965¹. 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 secretion⁵. 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 biological processes.

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 binding⁶. Upon calcium binding, the helices of S100 proteins rearrange, revealing a cleft, which forms the target protein binding site⁷. In addition, some S100 members have been shown to bind Zn²⁺ and Cu²⁺, suggesting the possibility that their biological activity in some cases might be regulated by Zn²⁺ and/or Cu²⁺, rather than by Ca²⁺⁸⁻¹⁰. An example of a Ca²⁺-independent but Zn²⁺-dependent target protein recognition is the interaction of S100B with tau protein (inhibition of tau protein phosphorylation by protein kinase II). Also Cu²⁺ 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 granulocytes¹³.

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 inflammation¹⁴, S100B exhibits neurotrophic (at physiologic concentration: nanomolar levels) or neurotoxic (at higher concentration: micromolar levels) activity^{15,16} and S100A4 has angiogenic effects¹⁷.

Methods of measurement

Analytical methods such as immunoradiometric assay (IRMA)¹⁸, mass spectroscopy, western blot, ELISA (enzyme linked immunosorbent assay), electrochemiluminescence and quantitative PCR, can detect S100 changes in immunohistochemical expression or in serum concentration with high sensitivity, providing an important tool in clinical diagnosis¹⁹.

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 types²⁰. 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 dis-

ruption, ischemia) and serum levels of S100B seems to be glucocorticoid independent²³.

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 impairment²⁴. Furthermore, the serum levels of S100B and C-tau protein are not reliable predictors of the long outcome in such cases²⁵, particularly in children with TBI²⁶. However, with a cutoff limit of 0.1 μ g/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 scans²⁷. 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 injury²⁸. The separate analysis of the two dimers S100A1B and S100BB (which account for the total measured concentration of S100B) does not offer any essential advantage²⁹. 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 damage³⁰. 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 encephalopathy³³. Also, significantly higher S100B levels in cord artery have been noted in neonates with acidosis and pathological patterns (leading to appropriate interventions) in cardiocography and fetal electrocardiography during labour³⁴.

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-up³⁵ and are good predictors of the outcome³⁶. S100B serum levels above 0.3 μ g/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 disease³⁷⁻³⁹. 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 management⁴⁰.

Interestingly, in patients suffering from amyotrophic lateral sclerosis, the serum concentration of S100B is decreased⁴¹, whereas the expression of S100A6 is greatly increased⁴². No clinically meaningful fluctuations of S100B serum levels have been noted in multiple sclerosis (MS) patients⁴³. In MS patients, S100B cerebrospinal fluid (CSF) level is increased and correlates with CSF ferritin⁴⁴.

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 damage⁴⁵⁻⁴⁷. Also, the elevated and persistent expression of S100B induced by hyperammonemia may contribute to the brain impairment observed in hepatic encephalopathy⁴⁸. 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 disease⁴⁹.

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 inflammation⁵⁰.

2. Neoplastic disorders

Different forms of cancer exhibit dramatic changes in the expression of S100 proteins such as S100B, S100A2, S100A4, S100A6, and S100P⁵¹. The S100-RAGE signaling 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 metastasis⁵². Also, S100A4 at nanomolar levels stimulates ma-

trix metalloproteinase 13 release from chondrocytes in a RAGE-mediated manner⁵³.

There is a high (stage-dependent) secretion of S100B in malignant melanoma, reflecting tumour load, stage and prognosis⁵⁴. 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 patients⁵⁶. 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 processes⁵⁷.

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 tumours⁵⁸.

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 cancer⁶³
- 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 survival⁶⁶.

There is accumulating evidence that BRCA1 negative breast carcinomas exhibit increased expression of S100A7⁶⁷.

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.

and S100 ($> 1.5\mu\text{g/l}$) 48-72h after cardiopulmonary resuscitation for cardiac arrest, lead to prediction of a poor

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 phosphorylation⁶⁹, leading to p53 down-regulation in a calcium dependent manner⁷⁰. Efforts are made to restore functional wild-type p53 in neoplasms with elevated S100B through the inhibition of the S100B-p53 interaction⁷¹. 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 hypertrophy⁷² and down-regulated in end-stage heart failure⁷³, 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 ($> 65\text{ng/ml}$)

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- fold⁷⁸.

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 performed⁷⁹.

4. Inflammatory diseases

S100A8, S100A9, and S100A12, 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 disease⁷. Antiallergic drugs which bind to S100A12 might block the S100 protein-RAGE interaction⁸⁴, implying a promising approach to anti-inflammatory therapy⁸⁵. 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 production⁸⁶.

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 nerves⁸⁷ and on the reliable monitoring of alcohol detoxification treatment⁸⁸. 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 sequelae⁸⁹.

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 tumorigenesis 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 settings⁹⁰.

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