

S100 β : A Predictive Biomarker for Neural Trauma with Therapeutic Potential

Introduction

In normal and trauma-inducing conditions, expression patterns of neuronal biomarkers of discrete neuronal groups can be utilized to map functional and phenotypic alterations. A key aspect in tissue remodeling resides in enhancing repair. One protein implicated in structural plasticity and repair in the nervous system is S100 β . S100 β is a calcium-binding protein that has been well documented to regulate axonal extension. In addition, studies have documented that S100 β protein levels are elevated after neural damage. Moreover, elevated sera levels of S100 β have been associated with poor patient outcomes after neural insult. These features make S100 β an excellent biomarker for making both diagnoses and prognoses of neurological injury. Of the more than 20 isoforms S100 protein family, S100 β displays unique biomarker and diagnostic properties in ectodermic derived normal neurons and certain malignancies. The purpose of this focused review is to highlight and discuss findings that support the notion that S100 β can be used as a biomarker to indicate the presence and extent of neural trauma.

S100 β is a member of the S100 protein family and has largely implicated in neuronal structural plasticity. Members of the S100 protein family contain two calcium-binding sites in a classic EF hand conformation. In particular, S100 β has been demonstrated to promote both neuronal viability as well as neurite extension in the cerebral cortex.¹ Moreover, S100 β over expression increases MAP2, a cytoskeletal protein enriched in dendrites, levels in adult mice.² One property of S100 β is that it oligomerizes upon neuronal activation. In fact, it is the oligomer state of S100 β that acts as a neurotrophic factor³ and promotes neurite extension.^{1,4,5} Upon activation, neurons demonstrate marked changes in structural plasticity. Such activity-regulated changes in neuronal morphology include dendritic spine and length alterations, axonal extensions, and changes in gap junction size. Given its activity-dependent oligomerization and involvement in structural modifications of neurons, S100 β has the unique potential to indicate changes in neural activity and neuronal morphology.

Peptide levels of S100 β are modulated by multiple factors involved in neural development and structural plasticity. Djalali and colleagues provided immunohistochemical evidence that transgenic mice lacking Brain-Derived Neurotrophic Factor (BDNF) have decreased levels of S100 β . Moreover, this group also showed that exogenous application of BDNF increased peptide levels of S100 β in cultured astrocytes (2005). Transcript and protein levels of S100 β are also increased by prolonged administration of fibroblast growth factor-2.⁶ This finding is particularly noteworthy given the role of fibroblast growth factor-2 in promoting adult neurogenesis.⁷ In all, these results point to S100 β as a key indicator of rising levels of neurotrophic factors.

Multiple groups have linked S100 β and its modulatory neurotrophins to neural insult.⁸⁻¹⁰ These studies range from *in vitro* work to clinical findings in human patients. Kacinski et al. noted that pediatric patients who suffered a seizure attack during polysomnographic recordings had augmented sera levels of S100 β compared to epileptic pediatric patients that did not have seizures

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during testing. This piece of data indicates that peripheral S100 β levels can rapidly increase after a neural insult (blood was taken 30 minutes after a seizure attack). This finding also presents a source of debate of the interpretation of S100 β levels in relation to neural injury: distinguishing rising levels of S100 β release from a decreasing integrity of the blood-brain barrier (BBB). Pinto et al.¹¹ utilized ELISA to show that S100 β can be released from primary astrocyte cultures. This finding alone would suggest that an increase in peripheral S100 β is reflective of enhanced central release. However, other groups have noted that S100 β levels are particularly increased in response to astrocytic damage and support an interpretation of augmented S100 β sera levels indicating a disturbed blood-brain barrier^{12,13}

While the specific explanation that accounts for rising S100 β peptide levels after neural damage requires further experimentation, it is clear that S100 β peripheral concentrations do reflect insults to the central nervous system.

The compelling feature of S100 β as a biomarker of neural trauma lies in its potential to be both diagnostic and prognostic. Much work revealing these values have come from oncological research findings. Among 670 high-risk melanoma patients, individuals with baseline “high” S100 β sera levels had worse prognosis than those with “low” S100 β levels. This finding was consistent in terms of five-year overall survival and three-year relapse-free survival probabilities.¹⁴ A more recent study focusing on melanoma metastasis demonstrated that patients with elevated (versus normal) baseline S100 β sera levels had decreased survival rates.¹⁵ Others have also noted the prognostic value of S100 β in melanoma patients.^{16,17} One caveat of the discussed work is that patients were placed into “high” versus “low” or “elevated” versus “normal” groups for statistical comparisons. The data might have been more convincing and telling if pure linear regressions were performed to note the correlational strength of S100 β levels and survival rates. Nonetheless, these data do provide strong support for the prognostic power of S100 β as a biomarker.

Sera levels of S100 β have also demonstrated promise for predicting patient outcomes after brain injury. Fink et al.¹⁸ showed that S100 β was the first biomarker to show elevation after cardiac arrest in pediatric patients.¹⁸ Similar to the cancer studies, patients with higher S100 β sera levels had poorer outcomes, including death. Moreover, this study indicated that a pronounced rise of S100 β levels was the strongest indicator (of three biomarkers tested) of patient death within six months (2014). A meta-analysis of 41 studies involving a total of 1,862 moderate and severe traumatic brain injury patients revealed

a statistically significant correlation between S100 β sera levels and poor patient outcome and mortality.¹⁹ In contrast, a focused study of patients with mild traumatic brain did not detect any significant correlations between S100 β sera levels and patient outcome.²⁰ These studies simultaneously highlight the potential to utilize S100 β as a biomarker after a neural insult and the need for future investigations for the peptide's proper use in predicting patient outcome.

Conclusion

In conclusion, multiple lines of evidence indicate that S100 β is an ideal biomarker not only for noting the presence of severe neural trauma but also predicting patient outcome after the neural insult. Future research that directly compares different types and levels of brain injury would lead to better use of S100 β sera levels in the clinic. Also, more work deciphering the mechanism(s) responsible for and meaning of the correlation between elevated sera levels of S100 β and poor patient outcome must be done. More specifically, it is critical to make the differentiation between

- I. S100 β leaking from the central nervous system after injury because of BBB disruption or
- II. S100 β rising in the periphery due to increased secretion from glial cells.

The authors do not rule out the possibility of both of these actions working in concert. Understanding the meaning of elevated S100 β has the potential to lead to better therapeutic interventions after brain injury. For instance, if S100 β is being secreted in higher amounts to enhance neurogenesis and structural plasticity to repair the brain after insult, perhaps more intensive measures to stabilize patients to allow for recovery could be performed. For example, neurosurgical procedures could infuse S100 β to facilitate neural recovery after injury. This may be highly likely given that increased central levels of S100 β have been associated with both enhanced neural plasticity and memory performance.^{21,22} Thus, S100 β , a clear biomarker of neural insult, could, in turn, be a remedy for the injury itself. Overall, the findings indicate S100 β as a distinctive biomarker with prognostic and theranostic properties.

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Conflict of interest

The author declares no conflict of interest.

References

1. Winningham-Major F, Staecker JL, Barger SW, et al. Neurite extension and neuronal survival activities of recombinant S100 beta proteins that differ in the content and position of cysteine residues. *J Cell Biol.* 1989;109(6):3063–3071.
2. Shapiro LA, Whitaker-Azmitia PM. Expression levels of cytoskeletal proteins indicate pathological aging of S100B transgenic mice: an immunohistochemical study of MAP-2, drebrin and GAP-43. *Brain Res.* 2004;1019(2):39–46.
3. Djalali S, Höltje M, Grosse G, et al. Effects of brain-derived neurotrophic factor (BDNF) on glial cells and serotonergic neurones during development. *J Neurochem.* 2005;92(3):616–627.
4. Fermin CD, Martin DS. Expression of S100 beta in sensory and secretory cells of the vertebrate inner ear. *Cell Mol Biol (Noisy-le-grand).* 1995;41(2):213–225.
5. Marshak DR. S100 beta as a neurotrophic factor. *Prog Brain Res.* 1990;86:169–181.
6. Hinkle DA, Baldwin SA, Scheff SW, et al. GFAP and S100beta expression in the cortex and hippocampus in response to mild cortical contusion. *J Neurotrauma.* 1997;14(10):729–738.
7. Werner S, Unsicker K, von Bohlen und Halbach O. Fibroblast growth factor-2 deficiency causes defects in adult hippocampal neurogenesis, which are not rescued by exogenous fibroblast growth factor-2. *J Neurosci Res.* 2011;89(10):1605–1617.
8. Duobles T, Lima Tde S, Levy B, et al. S100beta and fibroblast growth factor-2 are present in cultured Schwann cells and may exert paracrine actions on the peripheral nerve injury. *Acta Cir Bras.* 2008;23(6):555–560.
9. Ganz J, Arie I, Ben-Zur T, et al. Astrocyte-like cells derived from human oral mucosa stem cells provide neuroprotection *in vitro* and *in vivo*. *Stem Cells Transl Med.* 2014;3(3):375–386.
10. Kaciński M, Budziszewska B, Lason W, et al. Level of S100B protein, neuron specific enolase, orexin A, adiponectin and insulin-like growth factor in serum of pediatric patients suffering from sleep disorders with or without epilepsy. *Pharmacol Rep.* 2012;64(6):1427–1433.
11. Pinto SS, Gottfried C, Mendez A, et al. Immunocontent and secretion of S100B in astrocyte cultures from different brain regions in relation to morphology. *FEBS Lett.* 2000;486(3):203–207.
12. Abdul-Khaliq H, Schubert S, Stoltenburg-Diding G, et al. Protein S-100beta in brain and serum after deep hypothermic circulatory arrest in rabbits: relationship to perivascular astrocytic swelling. *Clin Chem Lab Med.* 2000;38(11):1169–1172.
13. Schroeter ML, Mertsch K, Giese H, et al. Astrocytes enhance radical defence in capillary endothelial cells constituting the blood-brain barrier. *FEBS Lett.* 1999;449(2–3):241–244.
14. Tarhini AA, Stuckert J, Lee S, et al. Prognostic significance of serum S100B protein in high-risk surgically resected melanoma patients participating in Intergroup Trial ECOG 1694. *J Clin Oncol.* 2009;27(1):38–44.
15. Weide B1, Richter S, Büttner P, et al. Serum S100B, lactate dehydrogenase and brain metastasis are prognostic factors in patients with distant melanoma metastasis and systemic therapy. *PLoS One.* 2013;8(11):e81624.
16. Deichmann M, Benner A, Bock M, et al. S100-Beta, melanoma-inhibiting activity, and lactate dehydrogenase discriminate progressive from nonprogressive American Joint Committee on Cancer stage IV melanoma. *J Clin Oncol.* 1999;17(6):1891–1896.
17. Smit LH, Korse CM, Hart AA, et al. Normal values of serum S-100B predict prolonged survival for stage IV melanoma patients. *Eur J Cancer.* 2005;41(3):386–392.
18. Fink EL, Berger RP, Clark RS, et al. Serum biomarkers of brain injury to classify outcome after pediatric cardiac arrest. *Crit Care Med.* 2014;42(3):664–674.
19. Mercier E, Boutin A, Lauzier F, et al. Predictive value of S-100beta protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis. *BMJ.* 2013;346:f1757.
20. Ryb GE, Dischinger PC, Auman KM, et al. S-100 β does not predict outcome after mild traumatic brain injury. *Brain Inj.* 2014;28(11):1430–1435.
21. Nishiyama H, Knopfel T, Endo S, et al. Glial protein S100 β modulates long-term neuronal synaptic plasticity. *Proc Natl Acad Sci USA.* 2002;99(6):4037–4042.
22. Kleindienst A, McGinn MJ, Harvey HB, et al. Enhanced hippocampal neurogenesis by intraventricular S100B infusion is associated with improved cognitive recovery after traumatic brain injury. *J Neurotrauma.* 2005;22(6):645–655.