S100β: A Predictive Biomarker for Neural Trauma with Therapeutic Potential

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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 S100ß. S100ß is a calcium-binding protein that has been well documented to regulate axonal extension. In addition, studies have documented that S100ß protein levels are elevated after neural damage. Moreover, elevated sera levels of S100ß have been associated with poor patient outcomes after neural insult. These features make S100ß an excellent biomarker for making both diagnoses and prognoses of neurological injury. Of the more than 20 isoforms in the S100 protein family, S100ß 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 S100ß can be used as a biomarker to indicate the presence and extent of neural trauma.

S100ß is a member of the S100 protein family and has largely been implicated in neuronal structural plasticity. Members of the S100 protein family contain two calcium-binding sites in a classic EF hand conformation. In particular, S100ß has been demonstrated to promote both neuronal viability as well as neurite extension in the cerebral cortex [1]. Moreover, S100ß overexpression increases MAP2, a cytoskeletal protein enriched in dendrites, levels in adult mice [2]. One property of S100ß is that it oligomerizes upon neuronal activation. In fact, it is the oligomer state of S100ß that acts as a neurotrophic factor [3] 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, S100ß has the unique potential to indicate changes in neural activity and neuronal morphology.

Peptide levels of S100ß are modulated by multiple factors involved in neural development and structural plasticity. Djalali and colleagues provided immunohistochemical evidence that transgenic mice lacking Brain-Derived Neurotropic Factor (BDNF) have decreased levels of S100ß. Moreover, this group also showed that exogenous application of BDNF increased peptide levels of S100ß in cultured astrocytes [3]. Transcript and protein levels of S100ß 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 S100ß as a key indicator of rising levels of neurotrophic factors.

Multiple groups have linked S100ß 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 S100ß compared to epileptic pediatric patients that did not have seizures during testing. This piece of data indicates that peripheral S100ß 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 S100ß levels in relation to neural injury: distinguishing rising levels of S100ß release from a decreasing integrity of the blood-brain barrier (BBB). Pinto et al. [11] utilized ELISA to show that S100ß can be released from primary astrocyte cultures. This finding alone would suggest that an increase in peripheral S100ß is reflective of enhanced central release. However, other groups have noted that S100ß levels are particularly increased in response to astrocytic damage and support an interpretation of augmented S100ß sera levels indicating a disturbed blood-brain barrier [12,13].

While the specific explanation that accounts for rising S100ß peptide levels after neural damage requires further experimentation, it is clear that S100ß peripheral concentrations do reflect insults to the central nervous system.

The compelling feature of S100ß 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" S100ß sera levels had worse prognosis than those with "low" S100ß levels. This finding was consistent in terms for 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 S100ß sera levels had decreased survival rates [15]. Others have also noted the prognostic value of S100ß 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 S100ß levels and survival rates. Nonetheless, these data do provide strong support for the prognostic power of S100ß as a biomarker.

Sera levels of S100ß have also demonstrated promise for predicting patient outcomes after brain injury. Fink et al. [18] showed that S100ß was the first biomarker to show elevation after cardiac arrest in pediatric patients [18]. Similar to the cancer studies, patients with higher S100ß sera levels had poorer outcomes, including death. Moreover, this study indicated that a pronounced rise of S100ß 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 S100ß 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 S100ß sera levels and patient outcome [20]. These studies simultaneously highlight the potential to utilize S100ß 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 S100ß 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 S100ß sera levels in the clinic. Also, more work deciphering the mechanism(s) responsible for and meaning of the correlation between elevated sera levels of S100ß and poor patient outcome must be done. More specifically, it is critical to make the differentiation between:

I. S100ß leaking from the central nervous system after injury because of BBB disruption or,

II. S100ß 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 S100ß has the potential to lead to better therapeutic interventions after brain injury. For instance, if S100ß 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 S100ß to facilitate neural recovery after injury. This may be highly likely given that increased central levels of S100ß have been associated with both enhanced neural plasticity and memory performance [21,22]. Thus, S100ß, a clear biomarker of neural insult, could in turn be a remedy for the injury itself. Overall, the findings indicate S100ß as a distinctive biomarker with prognostic and theranostic properties.

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