The S100 protein family and its application in cardiac diseases

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The S100 protein family is the largest group of EF-hand signaling proteins in humans. The members of the S100 protein family are expressed in many tissues and play different functions. Many diseases are related to S100 proteins, which function as new biochemical markers especially in cardiac diseases. The most studied members, protein S100B and protein S100A1, exhibit activities in cardiac diseases, and these immunohistochemical expressions or serum levels have been used in predicting neurologic outcome after resuscitation of cardiac arrest or recovery of cardioprotective function.

KEY WORDS: Cardiac function; S100 proteins; Markers

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S100 protein structure and functions

In 1965, Moore et al. isolated a subcellular fraction from bovine brain, which is an acidic cytoplasmic protein specific for the nervous system. The protein is called as S100 because of its solubility in a 100% saturated solution with ammonium sulphate at neutral pH. Later, the S100 fraction in the brain was found to be composed of two homologous proteins, namely S100B and S100A1. Since then, more than twenty S100 proteins have been discovered. The proteins are localized primarily to glial elements of the brain, Schwann cells in the peripheral nervous system, and satellite cells in sympathetic ganglia. They are small, acidic proteins with 10-12kDa molecular weight, 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. At least 25 proteins which have been identified in recent years, belong to the S100 protein family, and 21 of them are encoded in the epidermal differentiation complex (EDC) located on chromosome 1q21 (Table 1).

The exact functions of S100 proteins are not well known; and the proteins comprise a multigene family of low molecular weight proteins. It is generally agreed that S100 proteins are expressed in a cell-specific manner and serve as modulators and integrators of calcium signaling. Such functional specificity is realized by the interaction of one or more S100 proteins with

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

<table>
<thead>
<tr>
<th>Members of the S100 protein family</th>
<th>Chromosome loci</th>
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<tbody>
<tr>
<td>S100A1-S100A18 trichohylin fillagrin repeatin</td>
<td>1q21</td>
</tr>
<tr>
<td>S100B</td>
<td>21q22</td>
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<tr>
<td>S100G</td>
<td>Xp22</td>
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<td>S100P</td>
<td>4p16</td>
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<td>S100Z</td>
<td>5q14</td>
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other proteins termed “target proteins”, resulting in the modulation of highly specific cellular function(s). S100 proteins are a group of dimeric Ca\(^{2+}\) binding proteins (-10 kDa per subunit) with diverse yet highly specialized functions. Calcium-binding proteins in the EF-hand superfamily typically use calcium influx as a signal for regulating varied cellular processes including apoptosis, contraction, differentiation, gene expression, and many others.

S100 proteins do not have intrinsic catalytic activity. We consider that calcium sensor proteins in a manner similar to calmodulin and troponin C should undergo conformational changes and modulate biological activity via calcium binding.\[^{[9]}\] The proteins of the S100 family have two EF-hand calcium binding motifs per monomer, and generally exist as homodimers. Upon calcium binding, the S100 proteins undergo a conformational change which exposes a region on the surface of the protein that has been shown to be responsible for binding several target proteins or peptides. In addition, some of the 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\(^{2+}\).\[^{[7]}\]

### Methods of measurement

There are some methods for the S100 proteins to be described such as immunoradiometric assay (IRMA), mass spectroscopy, western blot, ELISA (enzyme linked immunosorbent assay), electrochemiluminescence and quantitative PCR with a high sensitivity. The S100 proteins can’t be detected in serum, but after appearance of stroke, CPB, cancer or cardiac diseases, etc. Thus the S100 proteins can be implicated in clinical diagnosis.\[^{[7,10,11]}\]

### S100 expression in related diseases

Many diseases are related to the S100 proteins, and are usually classified into neurologic, neoplastic, inflammatory and cardiac categories.\[^{[7]}\] In the cardiac category, sudden cardiac arrest (SCA) is the main cause of death in the world annually. The S100 proteins are more important as the biochemical markers.

S100A1 is specifically and highly expressed in the mammalian myocardium. S100A1 is up-regulated in patients with right ventricular hypertrophy\[^{[12]}\] and down-regulated in patients with end-stage heart failure\[^{[11]}\] this finding indicates a correlation between S100A1 expression and contractile performance. In patients with acute myocardial ischemia, a rise in the plasma concentration of S100A1 may be associated with the role of S100A1 as a cardioprotective factor with anti-apoptotic function.\[^{[14,15]}\] Cardiac S100A1 levels decrease in patients with heart failure,\[^{[10]}\] and multiple studies have demonstrated that removing S100A1 decreases the fractional cell shortening of myocytes as a result of functionally impaired ryanodine receptor (RyR).\[^{[17,18–20]}\] But S100A1 regulates myocyte calcium cycling not only by modulating the activity of RyR, but also by influencing SERCA/PLB and protein kinase A (PKA) activity. The molecular mechanism underlying this phenomenon is still unknown. Therefore, additional work needs to be done to clarify the role of S100A1 with regard to SERCA and PKA activation.\[^{[21–25]}\]

Evidences show that S100A1 can affect not only systolic (contracting) cytoplasmic calcium levels, but also diastolic (resting) calcium regulation.\[^{[25]}\] Thus overexpressing S100A1 in cells can decrease calcium leaks in cardiomyocytes by decreasing calcium spark activity. S100A1 may have other effects on the heart. If electrocardiography can be done on S100A1-deficient mice, it will display long intervals of QT, QTc, and ST, indicating a prolonged period of cardiac repolarization.\[^{[26]}\] And lack of S100A1 also leads to defects of ventricular conduction. But molecular basis for most of these cardiac phenotypes is still less understood.

**Because of improved public training of cardiopulmonary resuscitation (CPR) and advances in professional emergency medical response, the rate of return of spontaneous circulation (ROSC) has risen in the past decades. Hence biochemical markers in blood samples can be expected to serve as prognostic predictors of CA patient outcome after CPR and be more easily applicable to clinical practice.**\[^{[27]}\] S-100B is a kind of specific proteins of the central nervous system and potential biochemical markers of brain damage, thus it can serve as post-resuscitative predictors of neurological prognosis.

The S-100 proteins exist in various forms depending on alpha or beta unit configuration. S100B, a homodimer composed of two β subunits (ββ form), is present in glial cells and Schwann cells. And the S100 proteins are metabolized in the kidney and excreted in urine with a biological half-life of two hours.\[^{[28]}\] As the protein S100B is primarily produced by glial cells and Schwann cells, its increased expression represents a hallmark of the activation, with less specificity. Recent studies have suggested that S100B may play a role as a cytokine in brain inflammatory responses. Hence we
can make S100B measurement in neurologic disorders as analogous to that of CRP in systemic inflammation. Accordingly, in patients with high serum levels of S100B after CPR, if S100B presents at high levels in the brain, it is suspected to induce brain cell apoptosis, leading to the aggravation of post-CA brain injury.

Rosen and colleagues [29] studied 41 patients after CA in 1998, and they found that the levels of S100 proteins were the highest on the first day after arrest. Moreover, the levels of S100 proteins on day 2 were correlated with the degree of coma (r=0.49, P<0.01). Interestingly, all patients with a S100 protein level ≥0.2 μg/L on day 2 after cardiac arrest died within 14 days, and 89% of the patients with levels below this level survived. In 2001 [29], they collected blood samples in 66 patients at 10.5 ± 0.9 hours after CA. In consideration of these results, they thought that blood sampling at least once between 4 and 12 hours after resuscitation would be practicable and adoptable. Therefore, it is clear that the increased level of S100 protein after cardiac arrest is of clinical usefulness and reflects the degree of hypoxic brain damage and can become a kind of early predictors of neurological outcome of CA patients after CPR.

A systematic review in 2009 about S-100B and neuron-specific enolase (NSE) concluded that serum levels of protein neuron-specific enolase (NSE) and S-100B are considered neurological prognostic predictors in patients after CPR, and the measurements of serum levels of S100B within 24 hours after CA might be clinically more relevant than those of NSE in predicting neurological outcomes. [31]

CONCLUSION

The S100 protein family comprises at least 25 members of low molecular weight proteins with multiple functions in a wide variety of cell types and tissues. Furthermore S100A1 and S100B play an important role in predicting cardiac and neurological outcomes. But there are some limits. First, the detailed time-course of these biomarkers can’t be described now; second, there is not a specified time point for blood sample to be analysed. Finally, there are still some influencing factors worthying study. [32]

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REFERENCES


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