S100B Raises the Alert in Subarachnoid Hemorrhage

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Abstract

Subarachnoid hemorrhage (SAH) is a devastating disease with high mortality and mobility, the novel therapeutic strategies of which are essentially required. The calcium binding protein S100B has emerged as a brain injury biomarker that is implicated in pathogenic process of SAH. S100B is mainly expressed in astrocytes of the central nervous system and functions through initiating intracellular signaling or *via* interacting with cell surface receptor, such as the receptor of advanced glycation end products. The biological roles of S100B in neurons have been closely associated with its concentrations, resulting in either neuroprotection or neurotoxicity. The levels of S100B in the blood have been suggested as a biomarker to predict the progress or the prognosis of SAH. The role of S100B in the development of cerebral vasospasm and brain damage may result from the induction of oxidative stress and neuroinflammation after SAH. To get further insight into mechanisms underlying the role of S100B in SAH based on this review might help us to find novel therapeutic targets for SAH.

Keywords: Neuroinflammation; Nuclear factor-kappa B; Oxidative stress; Phosphoinositide 3 kinase; RAGE; Stroke

Introduction

Subarachnoid hemorrhage (SAH) is one type of hemorrhagic strokes and a devastating category with mortality as high as 50%, although it only represents about 5% of all stroke cases. However, the effective treatment for SAH is limited. To get further insight into the pathogenic mechanism for SAH induced brain injury might function formulate novel therapeutic strategies for SAH. The clinical observations have recognized S100 calcium-binding protein B (S100B) as a new biomarker for SAH. In this regard, S100B has become a new hot research target for SAH.

S100B is one of the members of the S100 family, which contains at least 25 proteins. S100B is the one that is closely associated with the central nervous system (CNS), in which other S100 family members, such as S100A1, also express (Donato 1999). S100B is a homodimer that constitutes of two β subunits and its gene locates at chromosome locus 21q22 (Heizmann 2002b). S100B can also form heterodimers with other members of the S100 family, such as S100A1 or S100A6 in melanoma cells (Yang et al. 1999). S100 proteins contain two calcium-binding domains (EF-hand) linked by a hinge region and 4 α-helix components (Donato 2001, Heizmann 2002a, Streicher, Lopez, and Makhatadze 2010). In addition to binding to calcium, S100B is also a zinc binding protein (Marshak, Watterson, and Van Eldik 1981, Baudier, Holtzscherer, and Gerard 1982); the binding site of zinc on S100B may regulate the interaction between S100B and p53 (Whitlow et al. 2009). The C-terminal EF-hand undergoes conformational changes upon calcium binding (Castagnola et al. 2013, Rustandi, Baldisseri, and Weber 2000). S100B can function both intracellularly and extracellularly.

Intracellular S100B plays significant roles in cell proliferation, survival, and differentiation through associating with intracellular membrane, cytoskeleton proteins, transcriptional factors, cell cycle proteins, and calcium homeostasis (Arcuri et al. 2005, Beccafico et al. 2011a, Lin et al.

2010, Reeves et al. 1994, Tubaro et al. 2011, Xiong et al. 2000, Tsoporis et al. 2009). S100B can also physically interact with the pro-apoptotic and tumor repressor, p53, and functionally regulate cAMP by the way of the 5-HT receptor (Baudier et al. 1992, Stroth and Svenningsson 2015, Rustandi et al. 1998). Further study indicates that S100B can interact with the third cytoplasmic loop of the dopamine D2 receptor to promote extracellular signal-regulated kinase (ERK)1/2-mediated inhibition of adenylyl cyclase activity in striatal neurons (Liu, Buck, and Neve 2008). Moreover, S100B has been recognized as a calcium-dependent activator of membrane-bound guanylate cyclase in retina (Pozdnyakov et al. 1997, Rambotti et al. 1999).

The cellular expression of S100B was primarily found in the cytoplasm of astrocytes and currently, its expression was found mainly in astrocytes, oligodendrocytes, neural progenitor cells, and Schwann cells of the nervous system (Hachem et al. 2005, Darlot et al. 2008, Perrone, Peluso, and Melone 2008, Steiner et al. 2007, Streitburger et al. 2012, Spreca et al. 1989) (Table 1). S100B expresses in both the cytoplasm and the nucleus of cells. Other cells that express S100B in the CNS include ependymal cells, the choroid plexus epithelium, microglia, and neurons (Steiner et al. 2007, Ellis et al. 2007a, Adami et al. 2001). However, S100B has also been found in non-nervous system cells, such as vascular endothelial cells, adipocytes (Michetti et al. 1983, Goncalves et al. 2010), chondrocytes, peripheral lymphocytes (Moutsatsou et al. 2014), bone marrow cells (Faye et al. 2008), skeletal myoblast cells (Beccafico et al. 2011b, Tubaro et al. 2010), and melanocytes (Cocchia, Michetti, and Donato 1981, Sviatoha et al. 2010). Although S100B does not express in cardiomyocytes under physiological conditions, its expression in cardiomyocytes can be induced by cardiac infarction (Tsoporis et al. 2005). The extensive expression of S100B suggests it may hold a variety of bioactivities.

Extracellular S100B can interact with several cell surface receptors to initiate its biological functions. In some scenarios, extracellular S100B exerts its biological activities through the receptor of advanced glycation end products (RAGE) (Huttunen et al. 2000). S100B has also been demonstrated to promote and/or stabilize the binding of basic fibroblast growth factor (bFGF) to its receptor 1 (FGFR1) in myoblast, increasing the proliferation and inhibiting differentiation of myoblast (Riuzzi, Sorci, and Donato 2011). In addition, extracellular S100B may be more associated with pathological conditions. Both S100B leakage from damaged cells and active secretion by astrocytes contribute to increased extracellular S100B (Gerlach et al. 2006). The increased levels of S100B in body fluid, including blood, urine, cerebrospinal fluid (CSF), and amniotic fluid, have been recognized as biomarker for diseases, especially for brain injury (Michetti et al. 2012, Chong et al. 2016).

S100B has been implicated in diseases of many systems, including neurodegenerative diseases, cancer, diabetes mellitus, and mood disorders (Chong et al. 2016). The review will mainly discuss S100B as a biomarker and its contribution to the development of brain injury following SAH. The pathogenic role of S100B in the development of cerebral vasospasm that is associated with neuroinflammation and oxidative stress will be reviewed.

The roles of S100B in neuronal survival

The bioactivities of S100B in neurons are dependent on its concentrations. S100B has either trophic or toxic effect with different levels of its local concentrations (Table 2). At a low nanomolar physiological concentrations, S100B stimulates the neurite growth, increases neuronal survival during both development and injury (Rothermundt et al. 2003, Nishiyama et al. 2002, Bluhm et al. 2015, Falcone et al. 2015), plays a role during the neuronal maturation and

glial cell proliferation *in vitro*, protects against glucose deprivation induced cell death and mitochondrial dysfunction (Ellis et al. 2007b, Ahlemeyer et al. 2000b, Alexanian and Bamburg 1999b, Kleindienst and Ross Bullock 2006a, Serbinek et al. 2010a). S100B, at nanomolar concentrations, can protect neuroblastoma cell line LAN5 against the toxicity of amyloid beta peptide (Aβ) in a RAGE dependent manner; in contrast, micromolar levels of S100B increase Aβ neurotoxicity (Businaro et al. 2006). S100B at 50 nM reduces glutamate induced neuronal death, while S100B at 1 μM increases glutamate induced cell death of primary cortical neurons (Villarreal et al. 2011). Similarly, S100B at 100 nM promotes, and at 5 μM decreases, cell survival in serum-starved N18 neuroblastoma cells (Huttunen et al. 2000). Low concentrations of S100B (0.02-2 ng/ml) can also significantly protect primary rat hippocampal neurons against N-methyl-D-aspartate (NMDA) toxicity (Kogel et al. 2004).

However, the activity of S100B associates with its concentrations that do not really have clear-cut point between nanomolar and micromolar levels. The final effects of S100B may also be dependent on the insults and the conditions of the experiments. For examples, S100B, at the doses of (1- 10 ng/ml, corresponds to about 476 nM- 476 μM), reduces staurosporine-induced damage in pure neuronal cultures from chick embryo telencephalon as well as in mixed neuronal/glial cultures from neonatal rat hippocampus (Ahlemeyer et al. 2000a). S100B (0.2-20 μg/ml) can increase the survival of embryonic chick forebrain neurons in a dose-dependent manner (Alexanian and Bamburg 1999a). Even at higher concentration, S100B can also demonstrate neuroprotection. At 30 ng/ml (1.4 mM), S100B can protect against ethanol-induced apoptosis in fetal rhombencephalic neurons (Druse et al. 2007). In brain slice, a higher concentration of S100B (50 μg/ml) can counteract neurodegeneration of cholinergic neurons

after oxygen-glucose deprivation (OGD), an *in vitro* model of cerebral ischemia, in organotypic brain slices of basal nucleus of Meynert (Serbinek et al. 2010b).

The underlying mechanism that S100B promotes neuronal survival may include multiple signaling pathways (Figure 1). The protective effects of S100B in fetal rhombencephalic neurons during ethanol treatment have been associated with the activation of phosphoinositide 3 kinase (PI3K), since inhibition of PI3K diminishes the efficacy of S100B (Druse et al. 2007). As one of the most important kinases in the body, PI3K, in response to survival factors, is recruited to the plasma membrane, where it preferentially phosphorylates membrane phosphoinositides, resulting in the recruitment and activation of protein kinase B, also named as Akt, an important cell growth and cell survival factor (Chong et al. 2012, Chong 2015). S100B activates Src kinase (Brozzi et al. 2009), resulting in the phosphorylation of the cannabinoid receptor Cbl and subsequent activation of PI3K and Akt (Koga et al. 2006, Arcuri et al. 2005). S100B increases the activation of Akt with increased expression of phosphorylated Akt followed by up-regulation of X-linked inhibitor of apoptosis protein (XIAP) and anti-apoptotic protein Bcl-2 (Druse et al. 2007). Nanomolar S100B up-regulates the expression of Bcl-2 in neurons during serum deprivation and improves cell survival (Huttunen et al. 2000). Nuclear factor-kappa B (NF-κB) is another target of S100B for neuroprotection. S100B can increase the activity of NF-κB and promote neuronal survival, while inhibition of NF-κB can not only reduce the expression of active NF-κB, but also decrease the survival of neurons (Alexanian and Bamburg 1999a).

The detrimental effects of S100B at high levels may be regulated through stimulating neuroinflammation and inducing apoptosis *in vitro* (Figure 1). S100B exerts its neurotoxic effects *in vitro* by inducing apoptosis in neurons, contributing to the progress of neurodegenerative and neuroinflammatory diseases (Huttunen et al. 2000). The detrimental

effects of S100B in neurons may also associate with oxidative stress, since increased expression of S100B in spinal cord with motor neuron degeneration is accompanied by increased product of lipid peroxidation (Corvino et al. 2003). However, the role of S100B in cell survival is variably associated with its concentrations, for examples, S100B induces apoptosis in myoblasts at nanomolar concentrations in the absence of serum, whereas it stimulates myoblast proliferation and reduces myoblast apoptosis at the nanomolar doses in the presence of serum (Sorci et al. 2004, Riuzzi, Sorci, and Donato 2006), and at micromolar levels, S100B increases cellular proliferation and promotes the recruitment of cell survival proteins in a neuronal cell line although it induces the formation of reactive oxygen species (ROS) (Leclerc et al. 2007). These results suggest that S100B might be a double-edged sword, the effects of which are dependent on multiple factors.

S100B functions as a biomarker for brain injury

The levels of S100B have been recognized as a marker to predict the progress of brain injury after traumatic brain injury (TBI). In patients with severe head traumas, the serum levels of S100B closely correlate with Glasgow Coma Scale (GCS) and CT scan findings 48 hrs after trauma (Shakeri, Mahdkhah, and Panahi 2013). The serum levels of S100B at the admission have been closely associated with the length of hospital stay and injury severity score after bicycle trauma (Thelin et al. 2015). In severe TBI, the serum levels of S100B combined with papillary responsiveness at admission can predict the risk of brain death (Egea-Guerrero et al. 2013). In addition, the levels of S100B may also function to predict the development of post-concussion syndrome (PCS) after TBI, the levels of S100B at 6 hrs after mild TBI is an independently significant predictor of PCS 1 month later (Heidari et al. 2015). In patients with

alcohol-intoxicated minor head injury, the serum level of 0.21 μg/ml has been suggested as a cut-off point to predict primary brain damage (Mussack et al. 2002).

Accumulating findings for S100B in brain injury have pointed to that S100B plays a role in the development of neuronal dysfunction after brain trauma. In an experimental cortical impact TBI in mice, S100B knockout or application of neutralizing S100B antibody can significantly reduce TBI-induced lesion volume, improve retention memory, and attenuate microglial activation (Kabadi et al. 2015). S100B mediated oxidative stress and neuroinflammation may contribute to the development of TBI brain injury. Oxidative stress is well documented in the brain after TBI (Rodriguez-Rodriguez et al. 2014, Toklu and Tumer 2015, Wang et al. 2016). Anti-oxidants have been demonstrated to attenuate S100B induced neuronal injury, suggesting that S100B plays a role in oxidative stress. However, direct evidence that links S100B induced oxidative stress and TBI brain injury is absent and confirmation requires further investigation. S100B induced inflammation may also contribute to TBI. The CSF S100B was significantly increased for 6 hrs after injury in patients with severe TBI accompanied by significant increase of cytokines, such as IL-6 and IL-8. Interestingly, only the peak CSF IL-1β concentration correlated significantly and positively with the peak S100B concentrations within 24 h after severe TBI, suggesting that CSF S100B combined with IL-1β may be useful as outcome predictors of severe TBI (Hayakata et al. 2004) and also indicating that S100B induced inflammation may be involved in the pathogenesis of TBI.

The contribution of S100B to the development of brain damage in trauma might be associated with its effects on endothelial dysfunctions. The rationale is based on the fact that the increased levels of S100B in patients with multiple traumatic injuries were accompanied by increase in soluble E-selectin and Von willebrand factor (vWF), the two injury markers of

endothelial cells (Dang et al. 2014). Moreover, overexpression of S100B increases apoptotic cell death and elevated the levels of IL-6 and IL-8 in human umbilical vein endothelial cells, suggesting that S100B mediated endothelial cell dysfunction (Dang et al. 2014).

Increased serum levels of S100B may come from the brain through impaired the blood-brain barrier (BBB), the notion has been observed by Pazza et al. (Piazza et al. 2007), demonstrating that increased serum levels of S100B after brain injury reflect the mechanical discharge through a destroyed BBB. This was further supported by another study showing that serum levels of S100B are dependent primarily on the integrity of BBB and are independent of the brain level of S100B after TBI (Kleindienst and Ross Bullock 2006b). The phenomena that brain S100B is not elevated during TBI may be due to the release of increased production of S100B into the blood or to the extracellular space. The time point selection of the determination of brain S100B may also account for the observation. However, in patients with a variety of neurodegenerative diseases, the CSF and serum S100B did not correlate well with the impairment of blood-CSF barrier, although serum S100B level correlates well with the CSF level (Steinacker et al. 2013). As shown in Table 1, a variety of nervous system cells can produce S100B; the S100B may somehow actively get its path into the blood flow, since astrocyte-cerebrovascular coupling has been well documented. The peripheral cells may also contribute to serum S100B levels as discussed below.

For the source of serum S100B during TBI, someone may argue that S100B can also be released from the peripheral tissues, since non-nervous tissues can also express S100B (Kleine, Benes, and Zofel 2003, Geyer et al. 2009). In severe ill patients in the absence of an apparent brain damage, serum levels of S100B were increased, seeming to argue against S100B as a brain damage indicator. The important finding in this setting is that increased S100B values correlate

positively with lactate levels and negatively with blood pressure and pH accompanied by low hemoglobin suggesting that increased serum S100B concentration may be related to tissue hypoperfusion (Routsi et al. 2006). However, how does TBI stimulate the release of S100B from peripheral cells and how much can peripheral cells contribute to the increased level of serum S100B during TBI have not yet been addressed. Moreover, the increased S100B may not always be detrimental, as in some scenarios, S100B promotes delayed reparative processes and reduces neuronal injury (Sorci et al. 2010). What factors, such as concentration, determine the detrimental or reparative functions of S100B require further elucidation, which might help us to get best use of S100B as a therapeutic target practically for TBI.

S100B and subarachnoid hemorrhage

Recently, S100B has been recognized as a potential biomarker in the evaluation of the progress and prognosis of SAH and a possible therapeutic target against brain injury following SAH. The increased serum levels of S100B have been observed in both experimental and clinical SAH (Table 3). In rat SAH, the serum S100B was increased within 1 h after intraluminal perforation of the cerebral vessels (Tanaka et al. 2008a). The combined increase of serum S100B levels and decrease of the secreted isoform RAGE (sRAGE), which can act as decoy receptors to form heterocomplex with full-length RAGE to interfere with RAGE activation (Koch et al. 2010), within 6 hrs of stroke onset has been noted (Montaner et al. 2012). In post-surgical aneurysmal SAH patients, CSF levels of S100B on 3 and 14 days were significantly associated with poor outcomes (Kaneda et al. 2010). The levels of S100B in both the serum and CSF have also been found to be able to differentiate the severity of the outcomes in patients with spontaneous SAH (Moritz et al. 2010). In this study, neuron-specific enolase

(NSE) and S100B in both CSF and serum were determined within 8 d days following spontaneous SAH; the results indicate that mean and CSF NSE, CSF S100B, and serum S100B are valuable to predict cerebral infarction and intracranial hypertension. In addition, mean daily values of serum S100B have been proposed as a prognostic marker for patients with aneurysmal SAH; the elevated serum levels of S100B linked to poor neurological outcomes after SAH (Weiss et al. 2006, Sanchez-Pena et al. 2008, Wiesmann et al. 1997, Pereira et al. 2007). By systemic review of clinical trials, higher serum S100B level was associated with cerebral infarction and worse Glasgow Outcome Scale scores following aneurysm SAH (Lai and Du 2016). In this respect, serum S100B has been proposed as a potential prognostic biomarker for neurological outcomes of SAH.

S100B and cerebrovascular vasospasm

S100B has already been associated with delayed cerebral vasospasm, a major complication following SAH that contributes to high morbidity and mortality. Cerebral vasospasm that results from the constriction of smooth muscle in blood vessels to the brain causes reductions in cerebral blood flow and subsequent cerebral ischemia, leading to neurological deficit and long-term morbidity. Targeting cerebral vasospasm has become one of the major therapeutic strategies for SAH. Although serum or CSF S100B, in some scenarios, failed to predict cerebral vasospasm in patients suffering from SAH, the contributing role of S100B to vasospasm can't be excluded after SAH (Lai and Du 2016, Amiri, Astrand, and Romner 2013). The supporting data indicates that serum S100B levels significantly correlate with delayed ischemic lesions after SAH (Jung et al. 2013, Sanchez-Pena et al. 2012). Our recent experimental study found that CSF S100B was significantly increased 48 hrs following experimental SAH in rats (Changyaleket et al. 2016). Moreover, application of S100B by

intracerebroventricular infusion for 48 hrs results in the impairment of pial arteriole dilating reactivity. In this experiment, S100B attenuates the pial vasodilating responses to sciatic nerve stimulation and topical suffusion of acetylcholine, which is abrogated by the concomitant application of sRAGE, a decoy inhibitor of RAGE, suggesting that S100B is detrimental to the cerebrovascular dilating function following SAH in a RAGE-dependent pathway (Changyaleket et al. 2016). Further studies are undergoing to complement the results and explore the underlying mechanisms.

Neuroinflammation and subarachnoid hemorrhage

Inflammation has been closely associated with the progress of brain injury following SAH (Miller et al. 2014). First line of evidence is the activation of inflammatory microglia after SAH. Increasing the release of inflammatory cytokines, such as IL-1β, TNF-α, IL-6, IL-8, intercellular adhesion molecule (ICAM)-1, and monocyte chemoattractant protein-1 (MCP-1) has been observed after SAH (Prunell et al. 2005, Aihara et al. 2001, Gaetani, Tartara, et al. 1998). More interesting finding is that neuronal cell death and microglia accumulation follow a similar time course after experimental SAH and depletion of microglia significantly reduces neuronal cell death, suggesting that microglia accumulation contributes to secondary brain injury after SAH. More importantly, blockade of inflammatory cytokines reduces neuronal apoptosis after experimental SAH (Jiang et al. 2012). The underlying mechanisms that inflammation promotes neuronal injury during SAH needs to be further clarified.

One of possible results from neuroinflammation is its contribution to delayed brain injury after SAH through inducing delayed vasospasm following SAH (Vecchione et al. 2009). This was further confirmed by application of cytokine inhibitors that attenuate the vasospasm

following SAH (Jiang et al. 2012, Lin et al. 2005, Clatterbuck et al. 2003, Bowman et al. 2006, Nishino et al. 2010). Moreover, accumulation of neutrophils in cerebral vessels and in brain parenchyma in early phase of SAH has been identified (Friedrich et al. 2011) and higher percentage of neutrophils in CSF following SAH has been suggested as an independent predictor for cerebral vasospasm (Provencio et al. 2010). While depletion of neutrophils 3 days after SAH in mice abrogates tissue inflammation and reverses cerebral vasoconstriction in the middle cerebral artery territory with improved cognitive function (Provencio et al. 2016). In addition, general anti-inflammatory treatment by using corticosteroids also reduces cerebral vasospasm, attenuates the delayed cerebral ischemia, and improves the outcomes in both experimental and clinical SAH (Chyatte and Sundt 1984, Yoneko et al. 2010, Katayama et al. 2007).

S100B and neuroinflammation

S100B has been shown to modulate the activation of microglia. As monocyte derived cells that reside within the CNS, microglia is responsible for the inflammatory response in the CNS and in addition to its functions to clarify the cell debris and tissue reparative processes (Chong, Li, and Maiese 2005, 2007). Activated microglia acquires the capability to produce pro-inflammatory cytokines. S100B alone seems not to induce the activation of microglia, but potentiate the effects of other microglia activating agents, such as lipid A and interferon-gamma (IFN-γ), in this process (Petrova, Hu, and Van Eldik 2000, Adami et al. 2001).

S100B promote inflammation through inducing cytokine release. S100B can up-regulate macrophage production of IL-1β and C-C motif chemokine 22 (CCL22) to enhance the retinal inflammation, since S100B knockout in mice results in a reduced cytokine release and a reduced

degree of experimental autoimmune uveoretinitis (Niven et al. 2015). S100B can upregulate the expression of pro-inflammatory cytokines IL-1β and TNF-α in microglia with RAGE engagement (Bianchi, Giambanco, and Donato 2010a). S100B protein also stimulates microglia migration through RAGE-dependent recruitment of the adaptor protein, diaphanous-1, and activation of diaphanous-1/Rac1/JNK/AP-1, Ras/Rac1/NF-kB, and Src/Ras/PI3K/RhoA pathways to upregulate the expression of the chemokines, CCL3, CCL5, and CXCL12, and to increase the expression of chemokine receptors CCR1 and CCR5, which are required for microglia migration (Bianchi et al. 2011). Astrocytes with S100B exposure exhibit a pro-inflammatory phenotype with expression of IL-1β. S100B can stimulate the secretion of IL-6 and TNF-α in cultured astrocytes in a concentration- and time-dependent manner (Villarreal et al. 2014, Ponath et al. 2007).

As one of the mechanisms of neuroinflammatory induction, S100B can enhance the expression of pro-inflammatory cyclooxygenase 2 (COX-2) (Bianchi et al. 2007). COX-2 is an inducible COX and plays an important role in the conversion of arachidonic acid to pro-inflammatory prostaglandins (Hoozemans et al. 2005, Minghetti 2004). S100B up-regulates COX-2 in microglia in a RAGE-dependent manner through activating a Cdc42/Rac1/JNK (Jun amino-terminal kinase) pathway and Ras/Rac1/NF-κB pathway (Bianchi, Giambanco, and Donato 2010a). Cell division control protein 42 (Cdc42) and Ras-related C3 botulinum toxin substrate 1 (Rac1) are small GTPase of the Rho family members and function to regulate signaling pathways that are involved in cell cycle progression, cell growth, cytoskeletal reorganization, and the activation of protein kinases (Shinjo et al. 1990, Ridley 2006). Transfection with inactive Cdc42, inactive Rac1, or inactive Ras abrogates S100B-induced JNK phosphorylation and COX-2 expression (Bianchi, Giambanco, and Donato 2010b). Moreover,

S100B in microglia with inactive Cdc42, Rac1, or Ras, S100B failed to stimulate NF-κB transcriptional activity and the S100B/RAGE interaction was unable to up-regulate COX-2 (Bianchi, Giambanco, and Donato 2010b). In addition, S100B promotes the expression of COX-2 in microglia also through the activation of NF-κB and subsequent activation of the activator protein 1 (AP-1) in a RAGE dependent manner (Bianchi, Giambanco, and Donato 2010a) (Figure 2).

The role of S100B induced neuroinflammation in SAH

S100B induced neuroinflammation has been associated with cerebral vasospasm after SAH. We have investigated the role of S100B in experimental SAH and our primary results demonstrated that inhibition of S100B attenuate the pial venular leukocyte adhesion and improves pial vascular dilating reactivity (unpublished data). Inhibition of vascular adhesion protein-1 has been demonstrated to prevent leukocyte infiltration in SAH (Xu et al. 2014, Xu et al. 2015) and also attenuate S100B induced impairment of pial arteriole reactivity, indicating that S100B might promote inflammatory response to aggravate cerebral vasospasm following SAH (Figure 3).

Oxidative stress and subarachnoid hemorrhage

Oxidative stress through the generation of reactive oxygen species (ROS) has been closely linked to the pathogenesis of the diseases in the nervous system (Chong, Li, and Maiese 2005, Maiese et al. 2012). Overproduction of ROS that includes superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite impairs the balance between the oxidant and anti-oxidant systems in the body, leading to oxidative stress and cell damage (Chong and Maiese 2008).

The induction of rupture of aneurysm has been linked to oxidative stress. Increased expression of hemeoxygenase-1, a marker for oxidative stress, was detected in ruptured aneurysm wall accompanied by increased apoptosis (Laaksamo et al. 2013), the elevated level of which has been observed in ruptured aneurysm (Laaksamo et al. 2013, Pentimalli et al. 2004), suggesting that oxidative stress is possibly associated with increased risk of aneurysm rupture. The imbalance of the antioxidant enzymatic activities with increased superoxide dismutase (SOD) and glutathione peroxidase (GSHP) in the human brain after SAH has been illustrated. The SOD/GSHP ratio that represents the balance between the production of hydrogen peroxides by dismutation of superoxide radicals and the scavenging potential was increased in patients with the development of cerebral vasospasm (Gaetani, Pasqualin, et al. 1998). Increased production of ROS in CSF in experimental SAH (Mori et al. 2001) and elevated activity of myeloperoxidase and NADPH oxidase in CSF of patients (Provencio et al. 2010) with aneurysmal SAH have been illustrated. Hydrogen gas, which has been demonstrated to neutralize free radicals and reduce oxidative stress, significantly reduces brain edema and improves neurologic function at 24 h after SAH (Zhan et al. 2012). Increased oxidative stress markers have been observed in CSF of SAH patients with cerebral vasospasm (Pyne-Geithman et al. 2009). Inhibition of oxidative stress reduces cerebral vasospasm and brain injury after SAH (Echigo et al. 2012, Zhang et al. 2014, Gaetani and Lombardi 1992, Kim et al. 2002).

S100, oxidative stress, and subarachnoid hemorrhage

S100B induced oxidative stress may also contribute to the development of brain injury and delayed cerebral vasospasm after SAH. The toxicity of S100B has been linked to the induction of oxidative stress (Figure 2). The association of S100B with oxidative stress has been demonstrated when the neuronal cultures were pretreated with a hydrophilic antioxidant ascorbic

acid or a lipophilic antioxidant α-tocopherol prior to application of 5 μM S100B, in which the toxicity of S100B was significantly attenuated, suggesting that oxidative stress, at least in part, contributes to the toxicity of high concentrations of S100B in neurons (Huttunen et al. 2000).

S100B can stimulate ROS production in both microglia and astrocytes. In rat astrocyte cultures, S100B (1-40 μg/ml) dose dependently increases NO production, which results from the induction of inducible NO synthase (iNOS) (Hu et al. 1996). Although S100B itself failed to induce NO in microglia, it, at the concentration of 0.1~5 μM, significantly potentiates the effect of IFN-γ on NO production in a RAGE signaling independent manner (Adami et al. 2004). The C-terminal region of S100B may be necessary for iNOS induction, since truncation mutant S100B that lacks the C-terminal nine residues attenuates its effects on iNOS (Koppal et al. 2001). S100B increases NO release from microglia *in vitro* by activating the mitogen-activated protein kinases p38 and JNK (Adami et al. 2004).

In addition, the oxidized states of the S100B can affect its biological functions. The oxidization of S100B induces a conformational change in its structure (Zhukova et al. 2004) and has been associated with the mitogenic activity of S100B. Oxidative stress can promote the formation of intra-subunit disulfide-bridged S100B and the reduced form of S100B loses its activity towards neurite extension (Scotto et al. 1998).

S100B and cerebral ischemia

The pathogenic effects of S100B in ischemic stroke may also contribute to its effects in SAH, since delayed cerebral ischemia is a major complication of SAH as described above and S100B has been suggested to play a potential role in ischemic stroke. Here a brief description of the role of S100B in ischemic stroke was illustrated here.

A significant increase of S100B levels has been observed in both serum and CSF of patients with acute ischemic stroke. The serum levels of S100B was significantly increased over a 7 day period following infarction and the peak plasma levels of S100B correlated well with infarct volume and with the neurological score (Glasgow Outcome Scores) (Missler et al. 1997). Even transient ischemia caused by carotid endarterectomy (CEA) can induce an increase of serum S100B. S100B in ipsilateral internal jugular vein was increased during clamping and reperfusion, suggesting that transient ischemia during CEA induces brain injury (Arfvidsson, Nilsson, and Norgren 2015). The cerebral injury after CEA is exhibited by significant declines in neuropsychometric test performance with high S100B levels (Di Legge et al. 2003). Serum S100B concentrations in patients with severe infarction after proximal middle cerebral artery occlusion could be progressively increased to 2.41±1.59 μg/L at 24 hrs after hospital admission (Foerch et al. 2004). Moreover, the elevated serum S100B levels not only associate with enhanced infarction, but also have a strong correlation with depression symptoms at 60 days following acute ischemic stroke (Gonzalez-Garcia et al. 2012). These studies suggest that serum S100B levels may help to predict infarct volume and the long-term neurological outcome following acute ischemic stroke. Serum S100B also can function to evaluate the efficacy of treatment after ischemic stroke. In an embolic stroke model of rats, a combined therapy with t-PA (tissue plasminogen activator) and MK-801 (a potent N-methyl-D-aspartate antagonist) significantly attenuated brain edema accompanied by decreased serum S100B level 24 hrs following stroke (Tanaka et al. 2007).

Similarly, the CSF S100B was also significantly increased after ischemic stroke; however, the levels of S100B in CSF are higher and declined more quickly than that in serum (Tanaka et al.

2008b). In addition, a strong correlation of S100B levels between CSF and serum 48 hrs after the onset of stroke was observed in a rat model of thromboembolic stroke (Tanaka et al. 2008b).

The pathogenic role of S100B in cerebral ischemia has also been observed in experimental stroke. Cerebral ischemia can increase the brain expression of S100B and inhibition of astrocytic S100B synthesis by arundic acid attenuates delayed infarct expansion and improves neurological behavior following permanent focal cerebral ischemia in mice (Asano et al. 2005, Mori et al. 2006). In contrast, overexpression of S100B increases the infarct volumes and neurological deficits. S100B also increases the expression of astrocyte marker glial fibrillary acidic protein (GAFP) and microglial marker ionized calcium-binding adapter molecule 1 (IBA1) in the peri-infarct area, suggesting of increased gliosis (Mori et al. 2008). The animal results combined with the clinical observation indicate that S100B might be one of the pathophysiological contributors to the ischemic neuronal injury.

Conclusive remarks

S100B, as a calcium binding protein, functions in cell proliferation, differentiation, inflammatory response, oxidative stress, cell survival, plays a role in the pathogenesis of SAH. S100B can either protect or promote neuronal damage, which is associated with its concentrations and physiological states. As a brain damage biomarker, S100B level is elevated in response to SAH and correlates well with severity of brain injury and the outcomes of neurological deficit following SAH. In this regard, monitoring the levels of S100B can assist to evaluate the progress and the efficacy of treatment of SAH. However, more data is required to get reference values of S100B for monitoring purpose in patients. Due to the variety of causes and different severity of SAH, it is difficult to give a cutoff point value of S100B at this time.

The grading levels of S100B might be needed with disease progression and severity. Nevertheless, as the research progresses, we hope to find proper times of sampling and cutoff point of S100B levels for evaluating the disease progression and treatment.

In addition, increased S100B levels contribute to impaired cerebral vascular reactivity, cerebral vasospasm and brain injury during SAH through inducing neuroinflammation and oxidative stress (Figure 3). The implication of S100B in development of brain injury during SAH suggests that S100B might be regarded as a potential therapeutic target for SAH.

Conflict of interest

There is no conflict of interest.

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Table 1. Cellular Expression of S100B

Cells of Nervous System	Cells of Non-Nervous System
Astrocytes	Endothelial cells
Oligodendrocytes	Adipocytes
Microglia	Chondrocytes
Neural progenitors	Lymphocytes
Neurons	
Schwann cells	Bone marrow cells
Ependymal cells	Melanocytes
Choroid plexus epithelium	Myoblast cells

Table 2. In vitro Effects of S100B in Neurons

S100B	Effects	Reference
0.2-20 ng/ml	Enhances the activity of NF-κB and increases the survival of embryonic chick forebrain neurons	Alexanian et al, 1999
100 nM-5 μM	Promotes (100 nM) or decreases (5 μM) cell survival in serum-starved N18 neuroblastoma cells	Huttunen et al, 2000
1-10 ng/ml	Reduces staurosporine-induced damage in pure neuronal cultures from chick embryo telencephalon as well as in mixed neuronal/glial cultures from neonatal rat hippocampus	Ahlemeyer et al, 2000
1 ng/ml	Reduces neuronal death induced by exposure to glutamate (0.25 mM, 30 min) in mixed neuronal/glial cultures from neonatal rat hippocampus	Ahlemeyer et al, 2000
0.02-2 ng/ml	Protect primary rat hippocampal neurons against NMDA toxicity by activation NF-κB	Kogel et al, 2004
30 ng/ml	Protects against ethanol (50 mM) induced apoptosis in fetal rhombencephalic neurons	Druse et al, 2007
50 μg/ml	Reduces OGD induced cell death in cholinergic neurons	Serbinek et al, 2010
50 nM-1 μM	S100B at 50 nM reduces and at 1 μM increases glutamate induced cell death in primary cortical neurons	Villarreal et al, 2011

Abbreviation: NF-κB: nuclear factor-kappa B; NMDA: N-methyl-D-aspartate; OGD: oxygen glucose deprivation.

Table 3. The Values of Serum or CSF S100B Levels in SAH

S100B Changing Pattern	Suggestions	Reference
Experimental SAH		
Significant increases of serum S100B levels at 1 h after cerebral hemorrhage in rats.	The higher level of S100B indicates cerebral hemorrhage rather than ischemia	Tanaka et al, 2008
CSF S100B was significantly increased after SAH in rats	S100B impairs the pial arteriole dilating response	Changyaleket et al, 2016
Clinical SAH		
CSF levels of S100B were significantly increased at 3 and 14 days after aneurysm SAH	Combined with increased CSF levels of MDA predict poor neurological outcomes at 6 months	Kaneda et al, 2010
Both serum and CSF levels were increased over 8-15 days after spontaneous SAH	Provide prognostic value for the poor outcomes of SAH	Moritz et al, 2010;Weiss et al, 2006;Sanchez-Pena et al, 2008
Serum S100B level was increased with decrease of RAGE at 24 h after cerebral hemorrhage	Help to identify hemorrhage from ischemia by a higher level of S100B and lower level of RAGE exist	Montaner et al, 2012
Serum S100B at 1, 3, and 7 days after SAH was increased	The levels correlate with neurological deficit 6 months later	Wiesmann et al, 1997
Serum S100B was increased	Only small portion (2/5) with increased S100B develop vasospasm	Amiri et al, 2013
Serum S100B was significantly increased	Serum S100B significantly correlates with delayed ischemia after SAH	Jung et al, 2013
Serum S100B was significantly increased within 15 days after SAH	Statins reduce infarct volume in patients with vasospasm accompanied by decreased S100B levels	Sanchez-Pena et al, 2012
Serum S100B was increased within 8 days after treated with endovascular coiling	Higher mean 8-day S100B correlates with 1-year neurological deficit	Pereira et al, 2007

Abbreviations: CSF, cerebrospinal fluid; SAH, subarachnoid hemorrhage

Figure legends

Figure 1. S100B induced cellular pathways that affect neuronal survival. The effects of S100B on neurons are dependent on its concentrations. S100B has either a trophic or toxic effects with different local concentrations. At low nanomolar (nM) physiological concentrations, S100B promote cell survival through activating phosphoinositide 3 kinase (PI3K) and subsequent activation of Akt followed by up-regulation of X-linked inhibitor of apoptosis protein (XIAP) and anti-apoptotic protein Bcl-2. S100B also increases the activation of nuclear factor-kappa B (NF-κB) to enhance neuronal survival. At high micromolar (μM), neurotoxicity of S100B is dependent on the induction of neuroinflammation and oxidative stress through generation of reactive oxygen species (ROS).

Figure 2. Signaling pathways through which S100B induces neuroinflammation and oxidative stress. S100B protein can recruit the adaptor protein, diaphanous-1 and activate diaphanous-1/Rac1/JNK (Jun amino-terminal kinase) /AP-1 (activator protein 1), Ras/Rac1 (Ras-related C3 botulinum toxin substrate 1) /nuclear factor-kappa B (NF-κB), and Src/Ras/PI3K (phosphoinositide 3 kinase) /RhoA pathways, upregulating the expression of the chemokines to promote microglia migration. S100B can increase the release of inflammatory cytokines and also enhance the expression of pro-inflammatory cyclooxygenase 2 (COX-2), which functions to increase the production of pro-inflammatory prostaglandins (PGs). S100B increases COX-2 expression in microglia through activating a Cdc42 (cell division control protein 42)/ Rac1 /JNK

and Ras/Rac1/NF-κB pathways. S100B also promotes the expression of COX-2 in microglia through the activation of NF-κB and subsequent activation of the (AP-1). S100B promotes oxidative stress through increasing the production of reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and nitric oxide NO to promote cell apoptosis.

Figure 3. The diagram illustrates the possible roles of S100B in subarachnoid hemorrhage **(SAH).** S100B induced oxidative stress and neuroinflammation, which can promote neuronal death and impair the cerebral artery dilating reactivity, contributing to the development of cerebral vasospasm and brain injury after SAH. ROS: reactive oxygen species.

Figure 1

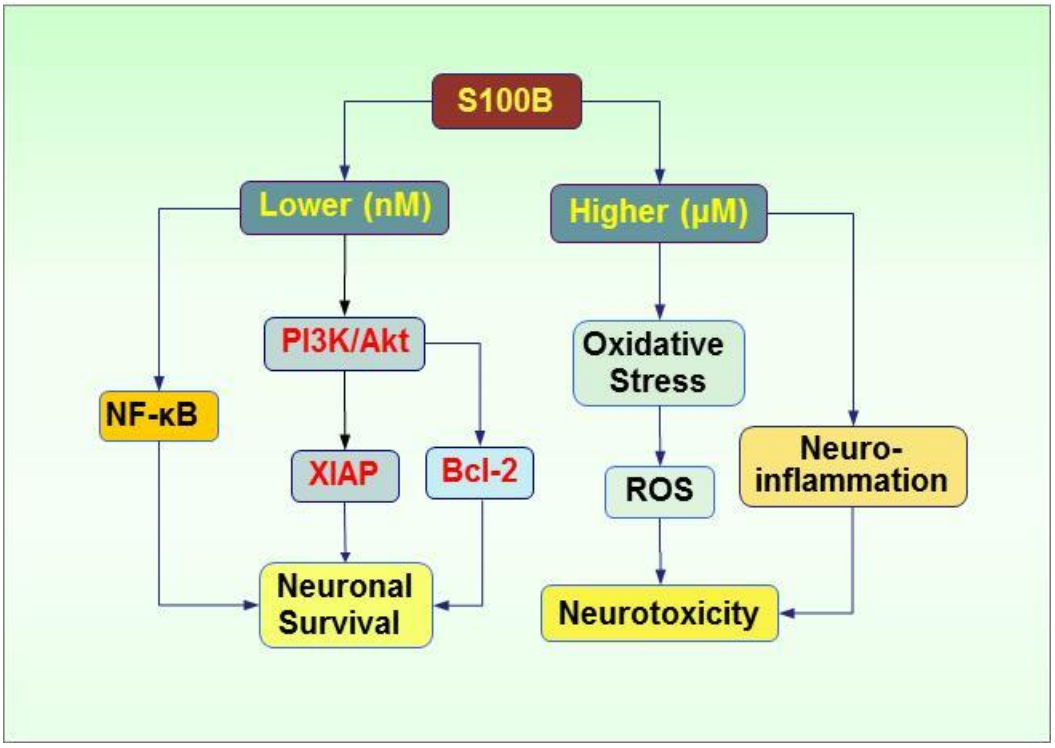

S100B
Lower (nM)
Higher (μM)
PI3K/Akt
Oxidative Stress
NF-κB
XIAP
Bcl-2
ROS
Neuro-inflammation
Neuronal Survival
Neurotoxicity

Figure 2

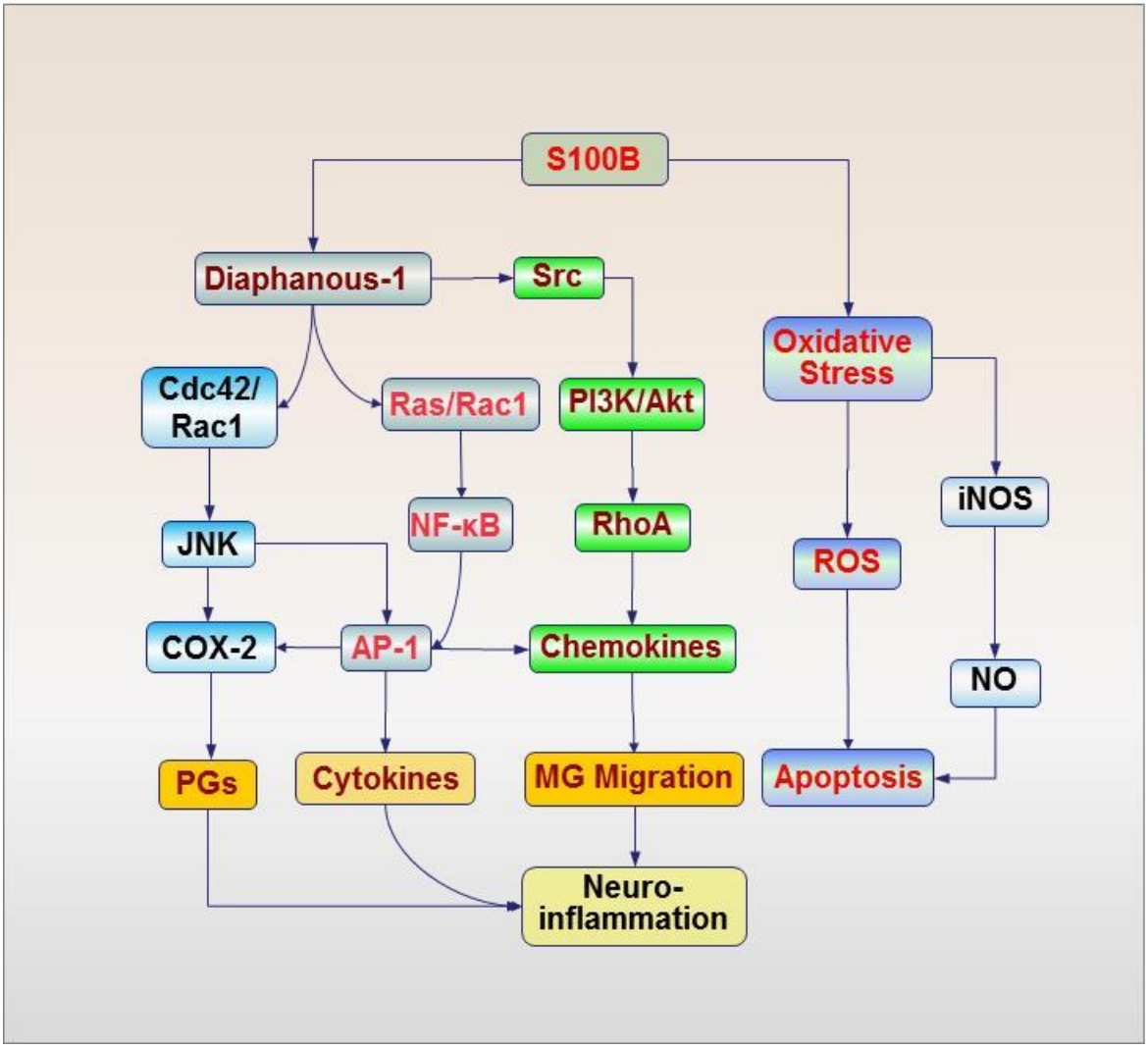
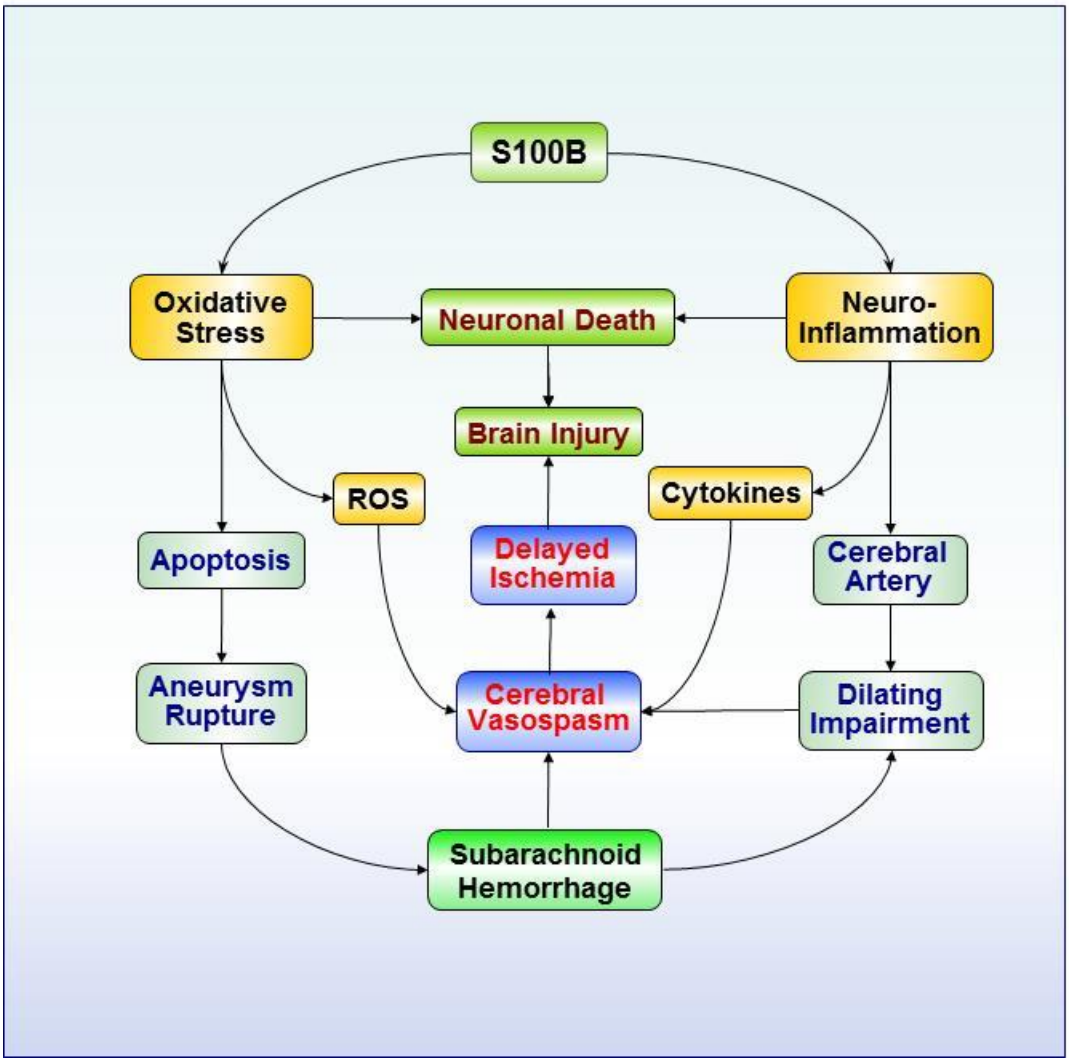

S100B
Diaphanous-1
Src
Oxidative Stress
Cdc42/ Rac1
Ras/Rac1
PI3K/Akt
iNOS
JNK
NF-κB
RhoA
ROS
COX-2
AP-1
Chemokines
NO
PGs
Cytokines
MG Migration
Apoptosis
Neuro-inflammation

Figure 3


S100B
Oxidative Stress
Neuronal Death
Neuro-Inflammation
Brain Injury
ROS
Cytokines
Apoptosis
Delayed Ischemia
Cerebral Artery
Aneurysm Rupture
Cerebral Vasospasm
Dilating Impairment
Subarachnoid Hemorrhage