PERSPECTIVE

# Implications of periostin in the development of subarachnoid hemorrhage-induced brain injuries

**Target of research in subarachnoid hemorrhage (SAH):** The outcome of aneurysmal SAH remains poor despite advances in the diagnosis and treatment. Although many factors related to patients, aneurysms, and institutions, as well as physiological parameters and medical complications were reported as prognostic factors, the most important determinant of poor outcome is the devastating effect of acute SAH on the brain causing early brain injury (EBI) (Suzuki, 2015). In acute SAH, the brain faces numerous deleterious conditions, including transient global ischemia induced by elevated intracranial pressure, mechanical stress, intracerebral hemorrhage due to an aneurysmal rupture, acute hydrocephalus, early cerebral infarction, seizure, direct effects of subarachnoid blood, and iatrogenic causes. EBI is a concept to explain acute pathophysiological events that occur in brain before onset of cerebral vasospasm within the first 72 hours of SAH, and consists of the pathophysiological mechanisms responsible for any type of brain insults other than iatrogenic brain injury (Suzuki, 2015). Recent experimental studies emphasize that EBI may be more important than cerebral vasospasm, a classically important determinant of poor outcome, in post-SAH outcome.

**Mechanisms of EBI:** The molecular mechanisms of EBI are very complex, though EBI finally induces the major pathological conditions, blood-brain barrier (BBB) disruption and apoptotic neuronal death through inflammation and microcirculatory disturbance. Major trigger factors of EBI after SAH are as follows: elevated intracranial pressure and subsequent transient global ischemia, mechanical stress due to aneurysmal rupture, and subarachnoid blood degradation products including heme and fibrinogen. Although these factors can stimulate diverse cells and extracellular matrices (ECMs) with activating proinflammatory mediators and multiple signaling pathways, mitogen-activated protein kinase (MAPK) pathway was found to play a crucial role in EBI, and matrix metalloproteinase (MMP)-9 was identified as one of the important downstream candidates relating to BBB permeability and neuronal apoptosis (Suzuki and Kawakita, 2016; Liu et al., 2017). In addition, our recent studies manifested that tenascin-C (TNC), which is a representative of matricellular proteins, strongly mediates deleterious effects of SAH and is involved in post-SAH brain injury at several different levels (Suzuki and Kawakita, 2016). Meanwhile, BBB is mainly composed of microvascular endothelial cells with tight junctions, and astrocytes play a fundamental role in brain hemostasis regulating the entry of intravascular molecules into brain. Degradation of zonula occludens-1 (ZO-1) and occludin, which are members of tight junction proteins, was reported to cause tight junction opening and BBB permeability in the early stage of SAH (Suzuki and Kawakita, 2016; Liu et al., 2017). BBB disruption causes brain edema as well as greater influx of blood-borne cells and substances into brain parenchyma, thus exacerbating neuroinflammation and brain injuries.

**Periostin mediates various pathological conditions:** Periostin (originally named osteoblast-specific factor 2) is a 90-kDa N-glycoprotein that modulates cell matrix interactions and cell functions in the ECM (Dong et al., 2017), and belongs to matricellular proteins (Liu et al., 2017). Though periostin was originally found as a molecule differentially expressed in osteoblasts and fibroblasts, recent studies showed that periostin plays pivotal roles in cell survival under hypoxic conditions, migration of cancer cells, and proliferation of cardiomyocytes after acute myocardial infarction (Liu et al., 2014). In addition, expression levels of periostin are generally low in most adult tissues, however, at sites of injury and inflammation or in tumors within adult organisms, periostin is highly secreted by stromal cells, which are stimulated by transforming growth factor (TGF)-β and other local and systemic cytokines or growth factors that are produced by epithelial cells and other cells (Liu et al., 2014). Clinically, blood concentrations of periostin are markedly high in brachial asthma, chronic obstructive pulmonary disease, cancers, idiopathic pulmonary fibrosis, atopic dermatitis and acute myocardial infarction (Izuhara et al., 2016). As to the central nervous system, recently we found that periostin was upregulated in cerebral cortex after experimental SAH in mice and responsible for EBI through activating downstream signaling pathways and interacting with TNC (Liu et al., 2017). In patients with severe traumatic brain injury, increased serum periostin concentrations clearly reflected trauma severity and mortality following traumatic brain injury (Dong et al., 2017). However, there are contradictory findings about periostin's effects. In spinal cord injury in mice, periostin promoted scar formation and improved functional outcome through the interaction between pericytes and infiltrating monocytes/macrophages (Yokota et al. 2017), and astroglial-derived periostin played an essential role in axonal regeneration by signaling through focal adhesion kinase (FAK) and Akt (Shih et al., 2014). Periostin was also identified as a neurite outgrowth-promoting factor, which significantly enhances neural stem cell proliferation and differentiation after hypoxia-ischemia in neonate rodent models (Dong et al., 2017). In addition, periostin revealed neuroprotective effects and accelerated neurite outgrowth after transient middle cerebral artery occlusion in mice (Shimamura et al., 2014). The seemingly conflicting findings of periostin may be due to the presence of its splicing variants. Intracerebroventricular injections of periostin splicing variant, lacking exon 17, exhibited neuroprotective effects after transient middle cerebral artery occlusion in mice (Shimamura et al., 2014), while neutralizing full-length periostin prevented post-SAH EBI in mice (Liu et al., 2017).

**Molecular mechanisms of periostin:** Periostin contains an amino-terminal cysteine-rich EMI domain in its N-terminal portion, four tandemly lined fasciclin I domains in the middle, and an alternative splicing domain in its C-terminal portion (Dong et al., 2017). The *drosophilia* protein, fasciclin I, is known to be involved in neural cell-cell adhesion, and periostin seems to be expressed as multiple spliced isoforms with different C-terminal regions under circumstances related to pathological fibrogenesis (Shih et al., 2014; Shimamura et al., 2014). Though up to 9 splicing variants have been identified, the function of the different splicing variants is not fully understood (Izuhara et al., 2016). At present, clinically important or well-known variants are as follows: periostin-1, a full length form containing 23 exons; periostin-2, which lacks exon 17; periostin-3, which lacks exon 21; and periostin-4, which lacks exon 17 and 21 (Shimamura et al., 2014; Izuhara et al., 2016). In tumor microenvironment, secreted periostin can bind to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins to activate various downstream signaling pathways, including phosphatidylinositol 3-kinase/Akt and FAK signaling (Liu et al., 2014). Activation of these signaling cascades can promote

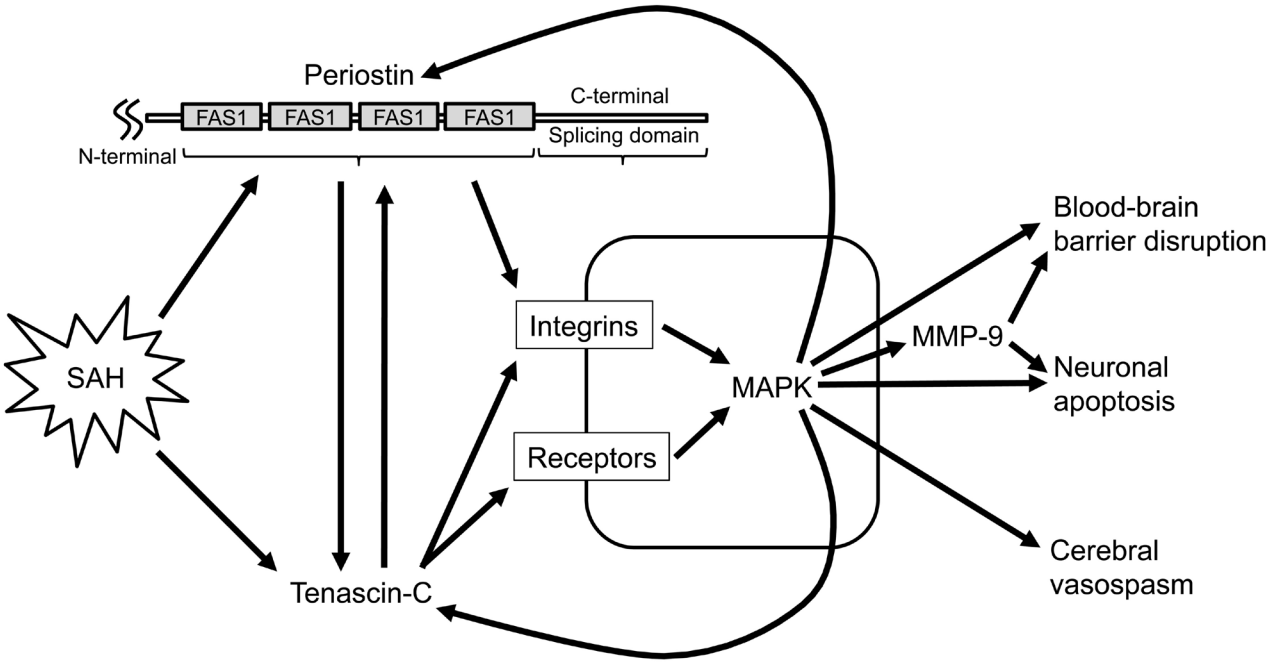


**Figure 1 Possible mechanisms of periostin-induced brain injuries after subarachnoid hemorrhage (SAH).**
After SAH, periostin and tenascin-C, both of which are matricellular proteins, are induced. Fascilin I (FAS1) domain of periostin binds to tenascin-C, regulating the expression each other. Periostin and tenascin-C activate mitogen-activated protein kinases (MAPKs) *via* integrins and other receptors, causing blood-brain barrier disruption, neuronal apoptosis and cerebral vasospasm. Activated MAPKs also induce periostin and tenascin-C, forming a positive feedback mechanism to aggravate post-SAH brain injuries *via* MAPK pathway. MMP-9: Matrix metalloproteinase-9.

tumor cell survival, migration, invasion and angiogenesis (Liu et al., 2014). Periostin-2 lacking exon 17, but not periostin-1, inhibited neuronal cell death, and stimulated neurite outgrowth with activating Akt in cerebral ischemia mice (Shimamura et al., 2014). Periostin continued to be expressed up to 28 days after cerebral ischemia in various cells, such as reactive astrocytes/microglia, fibroblasts and neuronal progenitor cells, and the expression pattern was dependent on the slicing variants, associated with pathophysiology in post-ischemic inflammation and neurogenesis (Shimamura et al., 2014). As to inflammation, periostin was recognized as an inflammatory effector in brachial asthma, and periostin which is secreted by brachial epithelium cells and inflammatory cells in response to interleukin (IL)-4 and IL-13 has autocrine effects to upregulate the expression of TGF-β and type 1 collagen through integrins and MMP-2/9 production (Izuhara et al., 2016). Periostin can also regulate inflammatory responses either by changing the biophysical and biochemical properties of the ECM or by binding to its integrin receptors to initiate intracellular signaling cascades: periostin directly interacts with type 1 collagen and fibronectin through its EMI domain, and with TNC and bone morphogenetic protein 1 through its fasciclin I domains (Liu et al., 2014). In addition, periostin is upregulated dramatically in the wall of abdominal aortic aneurysm, which is characterized by chronic inflammation, and periostin and FAK axis form a vicious cycle to sustain inflammatory responses by activating extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, monocyte chemoattractant protein-1 and MMPs secretion *in vitro* (Liu et al., 2014).

**Possible role of periostin in post-SAH brain injury:** Liu et al. (2017) elucidated that anti-full-length periostin antibody, which was administrated intracerebroventricularly 30 minutes after experimental SAH, showed neuroprotective effects with improving neurological scores and brain edema in mice endovascular perforation model of SAH. Anti-full-length periostin antibody suppressed post-SAH periostin induction in brain capillary endothelial cells and neurons, as well as immunoglobulin G extravasation, associated with the inhibition of post-SAH induction of TNC, activation of p38, ERK1/2, and MMP-9 and the resultant ZO-1 degradation in the cerebral cortex, while recombinant full-length periostin administration exacerbated brain edema and TNC induction in SAH brain (Liu et al., 2017). In addition, TNC knockout mice significantly suppressed post-SAH neurobehavioral impairments and periostin induction (Liu et al., 2017). These results suggested that full-length periostin, strongly interacting with TNC, may contribute to post-SAH BBB disruption and neurobehavioral impairments *via* MAPK pathway (**Figure 1**), and that neutralizing full-length periostin may become a novel therapeutic target for EBI.

**Established deleterious effects of TNC on brain after SAH:** TNC belongs to the ECM proteins as with periostin, is composed of 14 epidermal growth factor-like repeats and a series of fibronectin type III repeats, and forms a typical disulfide-linked hexamer, in which six flexible arms emanate from a central globular particle (Suzuki and Kawakita, 2016). Experimental studies revealed that TNC was upregulated in both cerebral artery and brain parenchyma after experimental SAH in rats (Suzuki and Kawakita, 2016). Platelet-derived growth factor (PDGF) is a well-known potent inducer of TNC, and imatinib mesylate, which is a selective inhibitor of the tyrosine kinases of PDGF receptors, prevented post-SAH upregulation of TNC, cerebral vasospasm, neuronal apoptosis and neurological impairments associated with inactivation of MAPK (Suzuki and Kawakita, 2016). In contrast, a cisternal injection of recombi-

nant TNC aggravated cerebral vasospasm, neuronal apoptosis and neurological impairments in imatinib mesylate-treated experimental SAH rats (Suzuki and Kawakita, 2016). PDGF-induced TNC may have positive feedback mechanisms on TNC upregulation by TNC receptor-mediated MAPK activation, PDGF receptor upregulation *via* MAPK activation, and PDGF receptor activation *via* crosstalk signaling between TNC receptors and PDGF receptors, leading to more MAPK activation and therefore internally augmenting cerebral vasospasm, neuronal apoptosis and neurological impairments in SAH rats (Suzuki and Kawakita, 2016). Recent studies also demonstrated that TNC knockout mice attenuated both neurological impairments and BBB disruption associated with an inhibition of MMP-9 induction and the consequent preservation of the tight junction protein ZO-1 (Suzuki and Kawakita, 2016), and prevented cerebral vasospasm development *via* suppressing inflammation and inactivating MAPK pathway after experimental SAH (Fujimoto et al., 2017).

**Foresight into the future of periostin and other matricellular proteins:** Our recent study demonstrated that full length of periostin is induced in SAH brain, and that neutralization of full-length periostin attenuates the induction of TNC, and prevents the development of BBB disruption and neurobehavioral impairments after SAH (Liu et al., 2017). However, it remains undetermined whether some splicing variants of periostin are developed after SAH, and how splicing variants of periostin function if they are induced post-SAH. As splicing variants of periostin may have opposite functions, the time course of each variant of periostin induction and the relationships among splicing variants of periostin are also interesting. In addition, the role of periostin in cerebral vasospasm and neural apoptosis remains unclear.

As to strong interaction between periostin and TNC, the four tandem repeats of fascilin I domain of periostin is identified as the direct binding region for TNC, correlating with the C-terminal region cleavage of periostin (Liu et al., 2014, 2017). In addition, periostin and TNC may form a positive feedback mechanism to aggravate post-SAH EBI *via* MAPK pathway (Liu et al., 2017). On the other hand, osteopontin (OPN), another matricellular protein, shows the conflicting effects against TNC in the setting of SAH: that is, OPN induced the protective pathways including MAPK phosphatase-1, an endogenous MAPK inhibitor, *via* binding to L-arginyl-glycyl-L-asparate-dependent integrins in both cerebral vasospasm and BBB disruption after SAH (Suzuki and Kawakita, 2016). Thus, further studies focusing on not only the role of periostin in cerebral vasospasm and neuronal apoptosis but also the interactions between periostin and other matricellular proteins are needed in the future.

*This work was supported by a Grant-in-Aid for Scientific Research from Mie Medical Research Foundation to HS.*

**Hirofumi Nishikawa, Hidenori Suzuki***
Department of Neurosurgery, Mie University Graduate School of Medicine, Tsu, Japan
***Correspondence to:** *Hidenori Suzuki, M.D., Ph.D., suzuki02@clin.medic.mie-u.ac.jp.*
***orcid:** 0000-0002-8555-5448 (Hidenori Suzuki)*

***Accepted:** 2017-10-12*

***doi:** 10.4103/1673-5374.221150*
***How to cite this article:** Nishikawa H, Suzuki H (2017) Implications of periostin in the development of subarachnoid hemorrhage-induced brain injuries. Neural Regen Res 12(12):1982-1984.*
***Plagiarism check:** Checked twice by iThenticate.*
***Peer review:** Externally peer reviewed.*

***Open peer review reports:***
*Reviewer 1: Shan Ping Yu, Emory University, USA.*
*Comments to authors: This is a perspective article summarizes the role of an extracellular matrix glycoprotein, periostin in pathophysiology of subarachnoid hemorrhage-induced brain injuries. Although periostin has been extensively investigated in a variety of diseases of peripheral organs and central nervous system, its potential role in stroke and brain hemorrhage has only been reported recently. This perspective provides some timely needed information in this area including the authors' own research.*
*Reviewer 2: Giovanni Casini, Emory University, USA.*
*Comments to authors: This is a very well-focused short review covering a relatively novel research area related to the multifaceted roles of ECM molecules in EBI, and in particular to the involvement of periostin.*

## References

Dong XQ, Yu WH, Du Q, Wang H, Zhu Q, Yang DB, Che ZH, Shen YF, Jiang L (2017) Serum periostin concentrations and outcomes after severe traumatic brain injury. Clin Chim Acta 471:298-303.

Fujimoto M, Shiba M, Kawakita F, Liu L, Shimojo N, Imanaka-Yoshida K, Yoshida T, Suzuki H (2017) Effects of tenascin-C knockout on cerebral vasospasm after experimental subarachnoid hemorrhage in mice. Mol Neurobiol doi: 10.1007/s12035-017-0466-x.

Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CT, Matthews JG, Arron JR (2016) Roles of periostin in respiratory disorders. Am J Respir Crit Care Med 193:949-956.

Liu AY, Zheng H, Ouyang G (2014) Periostin, a multifunctional matricellular protein in inflammatory and tumor microenvironments. Matrix Biol 37:150-156.

Liu L, Kawakita F, Fujimoto M, Nakano F, Imanaka-Yoshida K, Yoshida T, Suzuki H (2017) Role of periostin in early brain injury after subarachnoid hemorrhage in mice. Stroke 48:1108-1111.

Shih CH, Lacagnina M, Leuer-Bisciotti K, Pröschel C (2014) Astroglial-derived periostin promotes axonal regeneration after spinal cord injury. J Neurosci 34:2438-2443.

Shimamura M, Taniyama Y, Nakagami H, Katsuragi N, Wakayama K, Koriyama H, Kurinami H, Tenma A, Tomioka H, Morishita R (2014) Long-term expression of periostin during the chronic stage of ischemic stroke in mice. Hypertens Res 37:494-499.

Suzuki H (2015) What is early brain injury? Transl Stroke Res 6:1-3.

Suzuki H, Kawakita F (2016) Tenascin-C in aneurysmal subarachnoid hemorrhage: deleterious or protective? Neural Regen Res 11:230-231.

Yokota K, Kobayakawa K, Saito T, Hara M, Kijima K, Ohkawa Y, Harada A, Okazaki K, Ishihara K, Yoshida S, Kudo A, Iwamoto Y, Okada S (2017) Periostin promotes scar formation through the interaction between pericytes and infiltrating monocytes/macrophages after spinal cord injury. Am J Pathol 187:639-653.