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Review

The Role of Periostin in Brain Injury Caused by Subarachnoid Hemorrhage

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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) causes serious brain injury, and its mechanisms have not been completely unraveled so far. The causative factors for the brain injury initiated by an aneurysm rupture, which is referred to as the early brain injury (EBI), include elevated intracranial pressure, cerebral hypoperfusion, and blood contents that are directly exposed to the brain surface. At Day 4–14 post aSAH, delayed cerebral ischemia (DCI) often develops, which may worsen the neurological outcomes critically. DCI may be a consequence of EBI. Understanding the complex mechanisms underlying the post-aSAH brain injury (EBI and DCI) is, therefore, important in order to improve the neurological outcomes. In addition, several biomarkers possibly associated with EBI, DCI, and neurological outcome have been investigated, although none of these has been conclusive. A matricellular protein periostin has emerged as an important potential contributor to EBI and DCI, and may serve as the biomarker and a therapeutic molecular target for EBI and DCI. In the present report, the possible role of periostin in aSAH has been reviewed.

Keywords
Periostin; subarachnoid hemorrhage; early brain injury; delayed cerebral ischemia; biomarker

1. Introduction

1.1 Epidemiology of Subarachnoid Hemorrhage (SAH)

Aneurysmal SAH (aSAH) is one among several hemorrhagic strokes, which often results in severe neurological disorder, and even death [1]. Aneurysm rupture causes the blood components to spread into the subarachnoid space and initiates various pathological conditions [2]. The incidence of aSAH, which varies with region, falls in the range of 2–16 cases per 100,000 people [3]. The risk factors for aSAH are older age, residing in particular regions (especially in Finland and Japan), female sex, family history, certain genetic syndromes, history of hypertension, use of tobacco, alcohol abuse, sympathomimetic drugs such as cocaine, and the association of unruptured intracranial aneurysms [1]. Larger size, a particular location (such as anterior and posterior communicating arteries), and irregular shape of the unruptured intracranial aneurysms constitute the positive factors for the risk of rupture [1, 4, 5]. The major predictors of poor outcome in aSAH are initial clinical severity—which is evaluated using a clinical scale such as Hunt and Hess scale or using the World Federation of Neurological Surgeons grades—and rebleeding or premature rupture prior to aneurysmal obliteration through clipping or endovascular coiling [1]. Other clinical factors associated with poor outcome in aSAH include older age, a previous medical history, cerebral vasospasm, delayed cerebral infarction, and systemic complications [1, 6]. Therefore, providing intensive care for managing these clinical factors is crucial in aSAH treatment.

1.2 Early Brain Injury (EBI) and Delayed Cerebral Ischemia (DCI) in aSAH

Aneurysm rupture causes multiple pathological changes in the brain environment [7, 8]. Elevation in the intracranial pressure, cerebral hypoperfusion, global cerebral ischemia, and spreading of the blood contents into the subarachnoid space occur after the aneurysm rupture, and these events, whether transient or persistent, induce EBI [7]. EBI further activates multiple cellular and molecular events, including the inflammatory, apoptotic, or necrotic cell death pathways, in the brain capillary endothelial, glial, and neuronal cells [9]. Apoptosis of the brain capillary endothelial cells, along with the other causes of neurovascular unit injury, leads to disruption of the blood-brain barrier, which exposes the brain tissues directly to harmful blood contents and immune cells, exacerbating the EBI further [5]. Since the aneurysmal rebleeding worsens the brain damage and neurological outcomes, early aneurysmal obliteration through clipping or endovascular coiling is the crucial first step in aSAH treatment. However, even if the aneurysmal obliteration is performed successfully and the patient is having good initial clinical conditions, delayed neurological disorder may occur. Delayed neurological disorder comprises DCI and other conditions such as hydrocephalus and systemic complications. The latter may be diagnosed using clinical assessments, including chest X-ray, brain computed tomography, magnetic resonance imaging, and laboratory examinations [10]. The already-known pathogeneses

of DCI include cerebral vasospasm, inflammation, microthrombosis, and cortical spreading ischemia [11], and a measure of intracranial hematoma is one of the strong predictors of DCI [12]. Cerebral vasospasm has been considered as the main player in DCI for a long time, although the drugs targeting cerebral vasospasm have failed to cause any improvement in the neurological outcomes [13]. Therefore, nowadays, cerebral vasospasm is believed to be only a part of DCI, and EBI and the non-vasospastic causes of DCI are recognized as the more important determinants of neurological outcomes [5, 14]. In order to predict or understand DCI, several biomarkers, such as the inflammatory, metabolic, vascular, coagulation cascade-related, genetic, oxidative stress-related, ischemic, hemoglobin breakdown products, brain injury-related, and diverse pathways-related ones, have been investigated, although the evidence levels have been low [15]. Recently, machine learning analyses have demonstrated that the measurement of plasma periostin at an acute stage is the most important feature for the prediction of DCI among the various clinical factors including the established predictors according to the World Federation of Neurological Surgeons and Fisher grades [16].

2. Periostin

The extracellular matrix (ECM) proteins are part of a dynamic structural network, and modulate the tissue microenvironment and maintain homeostasis [17, 18]. Periostin is one of the several matricellular proteins, which are a group of secretory non-structural ECM proteins [17, 18]. Matricellular proteins including periostin are present in low levels in most of the adult tissues in normal conditions and are highly expressed in the injured or inflamed tissues [17, 18]. Periostin, a protein approximately 90 kDa in size, was originally reported in 1993 as an osteoblast-specific factor-2 in a mouse osteoblastic cell line [19]. Periostin has a typical sequence, consisting of an amino-terminal cysteine-rich EMI domain, a tandem repeat of four Fasciclin-1 domains, and a carboxyl-terminal hydrophilic domain (Figure 1) [20]. The EMI domain potentially binds to other ECM proteins such as collagen (types I and V), fibronectin, and a matricellular protein βig-h3 (also known as keratoepithelin, RGD-CAP, or transforming growth factor [TGF]-β-induced protein), and it is essential for the multimerization of periostin from a dimer to a hexamer [20-22]. The four Fasciclin-1 domains bind to a pro-collagen C-proteinase (i.e., bone morphogenetic protein (BMP)-1), matricellular proteins tenascin-C, cellular communication network factor 3 (also referred to nephroblastoma overexpressed), and integrins [21-25]. The carboxyl-terminal domain binds to heparin and proteoglycan [22]. The gene that codes for the carboxyl-terminal domain comprises 9 exons (exon 15 to exon 23) and the alternative splicing that deletes certain exons occurs between exons 17 and 21 [20]. The carboxyl-terminal domain inhibits the interaction of the Fasciclin-1 domains with tenascin-C [24]. This interaction requires the cleavage of the carboxyl-terminal domain by the matrix metalloproteases (MMPs) MMP-2 and MMP-9 [20]. The variations in the cleavage allow periostin to have different functional roles [26, 27].

Periostin is known to be induced by various stimuli, such as interleukin (IL)-4, IL-13, TGF-β1, TGF-β3, fibroblast growth factor 1, connective tissue growth factor 2, angiotensin II, BMP-2, platelet-derived growth factor, and mechanical stretch and cancer-derived factors. Periostin is also known to activate downstream signals, including focal adhesion kinase (FAK), phosphoinositide 3-kinase, protein kinase B (Akt), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38, nuclear factor (NF)-κB, signal transducers and activator of transcription (STAT) 3, and

mammalian target of rapamycin (mTOR), possibly via integrins (αvβ1, αvβ3, αvβ5, α6β4, and αMβ2) [18, 20, 22, 24, 28], resulting in the regulation of cell adhesion, migration, proliferation, signaling, and phenotype [25, 29]. Additionally, periostin is known to remodel the local tissue microenvironment through the recruitment of Wnt, Notch1, or other ligands, leading to the modulation of their signaling [18].

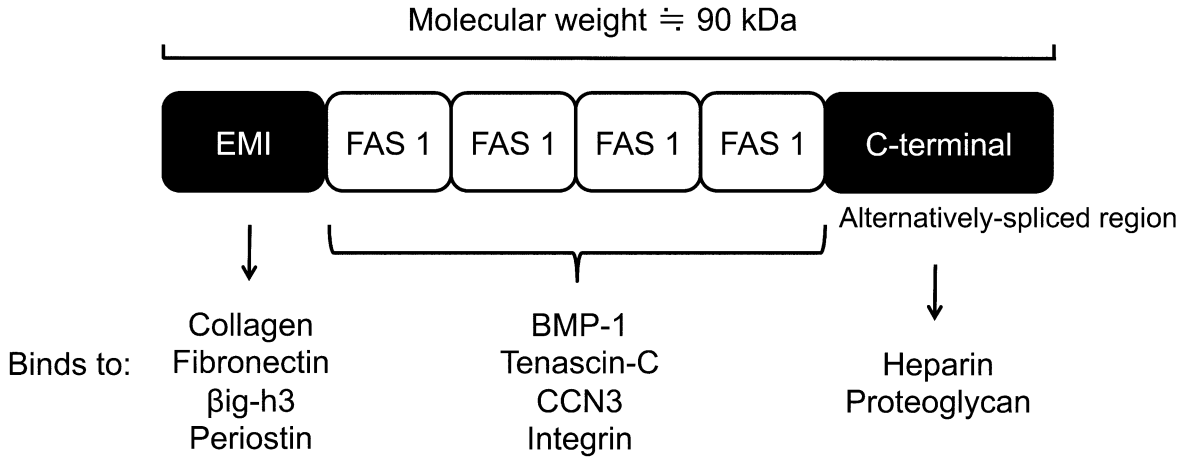

Figure 1 The structure and binding partners of periostin. BMP: bone morphogenetic protein; CCN: cellular communication network factor; FAS: fasciclin.

2.1 Periostin in Various Disorders

Recently, investigations regarding periostin have revealed that it plays important roles in a diverse set of diseases, by contributing to tissue injury, inflammation, fibrosis, and tumor progression (Figure 2) [18, 30]. The investigations regarding periostin may assist in understanding the functions and mechanisms of periostin, and therefore, in developing novel therapies for the associated pathologies. For instance, periostin has been implicated in the process of skin wound healing by serving as both an ECM and a matricellular protein [28, 29]. Periostin has also been reported to be upregulated and deposited in chronic inflammation sites associated with fibrosis, and to further augment the inflammatory reactions through the activation of both immune and non-immune cells by serving as a matricellular protein. Periostin is a critical player in the inflammatory microenvironment in various diseases such as asthma [31], atopic dermatitis [32], chronic rhinosinusitis with nasal polyp [33], allergic conjunctivitis [34], atherosclerosis [35], scleroderma [36], and pulmonary fibrosis [37]. Izuhara et al. reported that ILs-4 and ILs-13 were able to activate the NF-κB pathway in the fibroblasts and promote periostin expression [28]. As NF-κB is expressed extensively along with multiple inflammatory cytokines in aSAH [38], it is compatible that periostin is upregulated with the NF-κB activation in aSAH as in other pathologies [2, 39]. In order to conduct the mechanisms underlying the fibrotic diseases with inflammation, the cross-talk between periostin and TGF-β or the pro-inflammatory cytokines may be important [28]. In the process of development of atherosclerosis, periostin is mainly secreted by the infiltrating inflammatory cells and myofibroblasts. This, in turn, causes the advancement of the atherosclerotic degeneration and progression by promoting angiogenesis via Akt and FAK pathways, by upregulating MMP-2, MMP-9, and MMP-13, as well as by facilitating vascular

smooth muscle cell migration through the activation of FAK by binding to the αvβ3 and αvβ5 integrins [18]. Periostin may serve as a marker of tumor progression, metastasis, angiogenesis, and poor prognosis in several types of human cancers or malignancies, including carcinomas of liver [40], head/neck [41], pancreas [42], breast [43], colon [44], esophagus [45], and ovary [46], and is believed to promote a tumor-supportive microenvironment [18, 25, 47]. For instance, periostin may cooperate with mutant p53 in case of tumor invasion through the STAT1 pathway in esophageal tumor [45], and binds to integrins α5 and β1 in order to activate the phosphoinositide 3-kinase/Akt pathway to promote tumor cell survival, migration, invasion, and angiogenesis in case of invasion by cholangiocarcinoma [48]. Periostin also plays an important role in diseases associated with the cardiovascular and central nervous systems. In cardiac diseases, periostin has been demonstrated to activate the integrin-associated p38, FAK, and phosphoinositide 3-kinase/Akt and Wnt/β-catenin signaling cascades in fibroblasts and vascular smooth muscle cells [49]. In addition, TGF-β in association with the subunits of the αv integrin is released as a result of mechanical stress, rendering the integrins available for interaction with periostin, which in turn may initiate a feed-forward loop of periostin signaling [49]. In a rat model of acute myocardial infarction, overexpression of full-length periostin was reported to be associated with ventricular dilatation along with collagen deposition, while the splicing variants of periostin (a variant of periostin lacking exon 17 and another one lacking exons 17 and 21) were reported to be associated with myocardial repair [50]. In a mouse model of cerebral ischemia, the administration of exogenous periostin lacking exon 2 was demonstrated to provide neuroprotection [51]. Owing to the findings stated above, periostin has received great attention as a biomarker for the prediction or monitoring of disease progression and treatment effects, and as a therapeutic target against several diseases [28]. The matricellular protein periostin may serve as an ideal biomarker because of its involvement in the pathogenesis of a disease, and the ability to conveniently measure its levels in the peripheral blood similar to other matricellular proteins [52-54]. In patients with severe traumatic brain injury, detection of higher levels of serum periostin at admission predicted 30-day mortality with high sensitivity and high specificity [55]. Serum periostin levels were also measured in acute spontaneous intracerebral hemorrhage patients, in which increased periostin levels correlated well with the hematoma volume and neurological severity [56].

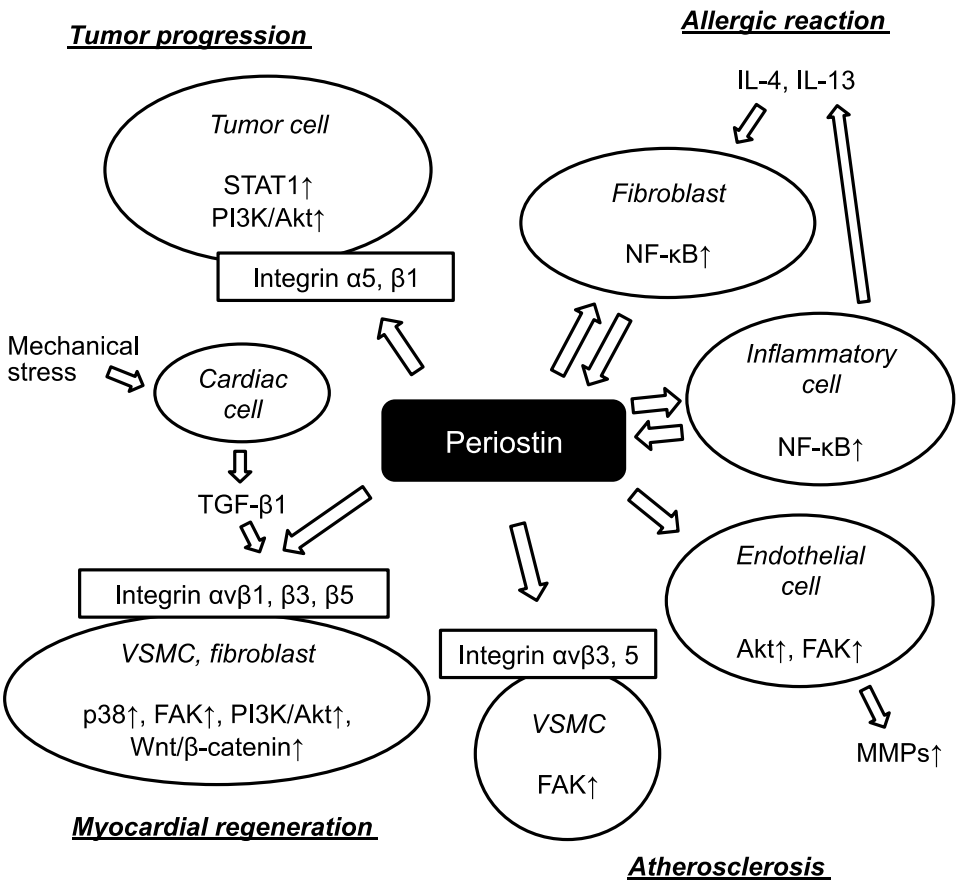

Figure 2 Potential roles of periostin in various diseases. FAK: focal adhesion kinase; IL: interleukin; MMP: matrix metalloprotease; NF: nuclear factor; PI3K: phosphoinositide 3-kinase; STAT: signal transducers and activator of transcription; TGF: transforming growth factor; VSMC: vascular smooth muscle cell.

2.2 Periostin in SAH in Experimental and Clinical Settings

Inflammatory reactions have been implicated in both EBI and DCI in consequence to aSAH [2, 7]. After the rupture of a cerebral aneurysm, transient global cerebral ischemia and extravasation of blood components occur, inducing several inflammatory cascades, which may cause and aggravate EBI, and possibly lead to the development of DCI [2, 7]. It is believed that the endogenous ligands having damage-associated molecular patterns, such as heme, fibrinogen, and intracellular components released at the site of tissue injuries, activate a pattern recognition receptor named Toll-like receptor (TLR)-4, as an initial step of the inflammatory cascades induced in response to brain injuries (EBI and subsequently DCI) after SAH. TLR-4 is expressed in most of the cells in the brain and the cerebral arterial wall, as well as in the inflammatory cells and platelets, and has been reported to induce maximal inflammatory response among all the TLR family members (Figure 3) [2, 7, 57]. TLR-4 activates both NF-κB and mitogen-activated protein kinase (p38, ERK, and JNK) pathways, and induces various pro-inflammatory factors such as ILs, MMP-9, reactive oxygen species, and matricellular proteins including tenascin-C and periostin [2, 7, 58]. Among the matricellular proteins, periostin and tenascin-C positively affect each other's function and expression levels [59], and tenascin-C and galectin-3 are known to be the ligands of TLR-4 [7, 60]. Therefore, the matricellular proteins including periostin may be playing at least partial roles, if not

complete roles, in forming positive feedback loops for further activation of TLR-4 signaling. Certain experimental studies have demonstrated that TLR-4 is involved in neuroinflammation, blood-brain barrier disruption, neuronal apoptosis, and cerebral vasospasm, all of which are potential pathologies underlying EBI and/or DCI after SAH [2, 58, 60, 61].

In a previous study conducted by our research group on mice, it was demonstrated that the periostin expression was remarkably increased in the neurons and brain capillary endothelial cells post-SAH through the endovascular perforation, which is believed to simulate clinical SAH [59]. In that study, immunohistochemical analyses were not performed, and therefore, periostin expression in the other cells was not examined, although several other cells including microglia, astrocytes, endothelial and smooth muscle cells of cerebral arteries, and the peripheral blood cells such as leukocytes, macrophages, and platelets were observed to be potentially involved in the pathophysiology of post-SAH EBI and DCI, reflecting the complex mechanisms underlying these conditions [2, 7, 8]. In regard to the potential involvement of other cells in relation to periostin expression, further studies are required. Neutralization of full-length periostin was reported to inhibit the post-SAH activation of p38 and ERK1/2, as well as the post-SAH upregulation of MMP-9 and tenascin-C, resulting in a less severe form of EBI in terms of neuroscore, brain edema, and blood-brain barrier permeability [59]. In the same study, JNK activation was not observed [59], while the other studies conducted using the same model reported the involvement of JNK in blood-brain barrier disruption [62]. Since the administration of recombinant full-length periostin was reported to reaggravate EBI [59], it was believed that periostin at least caused blood-brain barrier disruption through MMP-9 activation, and also the resultant degradation of the ECM proteins, which comprised the components of blood-brain barrier, through the activation of p38 and ERK1/2 [59, 62]. In addition, periostin and tenascin-C were observed to regulate the expression levels of each other, in correlation with the severity of the post-SAH blood-brain barrier disruption [59]. Tenascin-C has been repeatedly reported to contribute to the development of neuroinflammation, blood-brain barrier disruption, neuronal apoptosis, and cerebral vasospasm after experimental SAH [62-65]. The aforementioned findings suggest that either periostin causes EBI and DCI through the regulation of tenascin-C expression, and the converse is also true, or that both periostin and tenascin-C separately cause these conditions.

In clinical settings, Luo et al. measured the serum periostin levels at admission and reported that higher levels of serum periostin were associated with a poorer clinical grade at admission, higher frequency of development of DCI, and worse neurological outcomes in the aSAH patients [66]. In a recent study conducted by our research group, plasma periostin levels were chronologically measured 4 times during the period between the post-operative or post-interventional Day 1 and post-aSAH Day 12; the plasma periostin levels were observed to peak at Day 4–6 after onset, and later, development of DCI was observed [39]. Although periostin is a kind of inflammatory marker [28], the study revealed that the plasma periostin levels exhibited no correlation with the serum levels of a systemic inflammatory marker named C-reactive protein [39]. However, cerebrospinal fluid drainage was observed to significantly lower the plasma periostin levels at all time points of measurement, possibly because the drainage of cerebrospinal fluid removed periostin before the latter moved from the brain extracellular fluid or the cerebrospinal fluid to peripheral blood [39]. Multivariate logistic regression analyses conducted using all the clinical variables by Day 3 post-aSAH demonstrated that the plasma periostin levels at Days 1-3 post-aSAH (post-operative or post-interventional Day 1) served as an independent

predictor of DCI, irrespective of the subsequent development of cerebral vasospasm [39]. At present, the commercially available enzyme-linked immunosorbent assay kits are able to measure the concentration of four well-known splicing variants of periostin (a full-length variant containing all 9 exons; a variant lacking exon 17; a variant lacking exon 21; and a variant lacking exons 17 and 21) together, although a separate measurement is not possible with these kits yet [27].

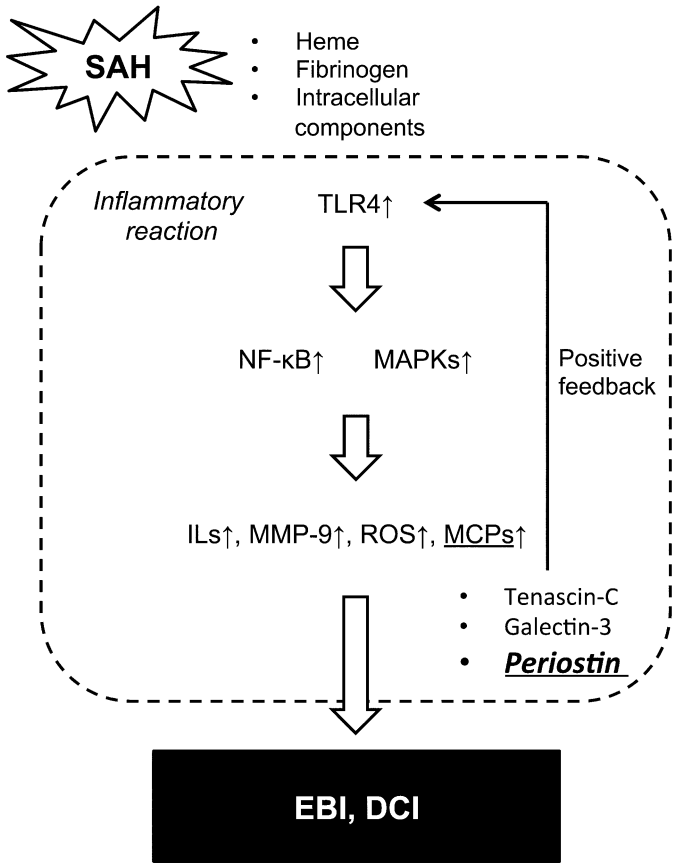

Figure 3 Toll-like receptor (TLR) 4-mediated inflammatory reactions in early brain injury (EBI) and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH). IL: interleukin; MCP: matricellular protein; MAPK: mitogen-activated protein kinase; MMP: matrix metalloprotease; NF: nuclear factor; ROS: reactive oxygen species.

3. Potential Limitations

Severe aSAH is well-known for causing systemic inflammatory response syndrome and extracerebral multiple organ dysfunction including respiratory, renal, hepatic, cardiovascular, and hematologic organ dysfunctions occurring due to sympathetic storm and catecholamine surge [67-69]. aSAH has also been reported to be probably associated with intracranial as well as systemic infections [69]. The severity of complications, such as extracerebral organ system dysfunctions and inflammation, has been reported to be correlated with the degree of neurological impairments in a graded fashion [68]. The extracranial complications not only exert direct effects on the clinical outcomes, but they may also exacerbate the intracranial complications including brain injuries [69]. Therefore, it is important to monitor, recognize, and manage these complications in parallel with the intracranial complications, thereby allowing the optimization of the management of aSAH

patients, leading to improvement in the overall outcomes. However, as described earlier in the present report, since periostin may be upregulated by a number of stimuli and interacts with several molecules [20-25], it may be difficult to identify the tissues or pathologies from which the observed increases in the plasma periostin levels might be originating. This implies potential limitations such as determining the specificity when applying periostin as a biomarker for predicting or monitoring the clinical events in the aSAH patients. In order to overcome these issues, it may become necessary to clarify the different roles of each isoform of periostin along with its distribution in tissues after aSAH, and to develop the methods that can detect the different isoforms of periostin in the peripheral blood. Using combinations of periostin isoforms and the other biomarkers reflecting different pathologies might prove to be reliable biomarkers for the diagnosis of complex intracranial and extracranial complications associated with aSAH in the near future.

4. Perspective

The role of periostin in aSAH is not well understood so far. Nonetheless, the information available in the literature suggests important roles of periostin in aSAH. Recently, it has become apparent that the pathogenesis underlying EBI and DCI is complex, and includes multiple pathophysiologies. However, in aSAH patients, no established methods, other than angiographic vasospasm and cortical spreading depolarization, are available for the diagnosis or prediction of individual pathophysiology in a clinical setting [7]. Recently, in preclinical studies, positron emission tomography (PET) was used to detect the relationships between the brain metabolisms and EBI after SAH or ischemic brain injury [70, 71]. In addition, a PET tracer specifically targeting periostin was developed, which allowed the specific imaging of periostin in the mouse models of esophageal squamous cell carcinoma [30, 72]. In the near future, detection of periostin in the post-SAH brain using PET could assist in the early detection, follow-up, and *in-situ* characterization of EBI and DCI.

Although further investigations are required, it would be useful if the plasma periostin levels could be utilized to predict the individual etiology of EBI and DCI, to diagnose the ongoing ones, and to monitor the effects of the treatments applied for them. In particular, the post-aSAH roles of periostin isoforms resulting from alternative splicing or cleavage by a protease have never been examined. Since the different isoforms may be having opposite functions, further studies including the time course of induction of each isoform and the relationships of these isoforms with the underlying mechanisms of EBI and DCI are required to provide novel insights into the matter [27]. Periostin is also interesting as a therapeutic target. The treatment target could be periostin itself, or the receptor integrins and the related molecules. In order to inhibit the post-aSAH induction of a representative of the periostin-related protein tenascin-C, cilostazol was used in a clinical setting of aSAH and promising efficacy was found [73, 74]. In consideration of the diverse signal transduction associated with periostin, it is believed that periostin may be involved in multiple pathophysiologies other than the blood-brain barrier disruption in aSAH. Since there is no doubt that periostin is one of the critical regulators of the mechanisms underlying EBI and DCI, further experimental and clinical studies would lead to the development of novel therapies that would improve the neurological outcomes after aSAH.

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Author Contributions

HK, FK, RA and HS wrote, reviewed and approved the final version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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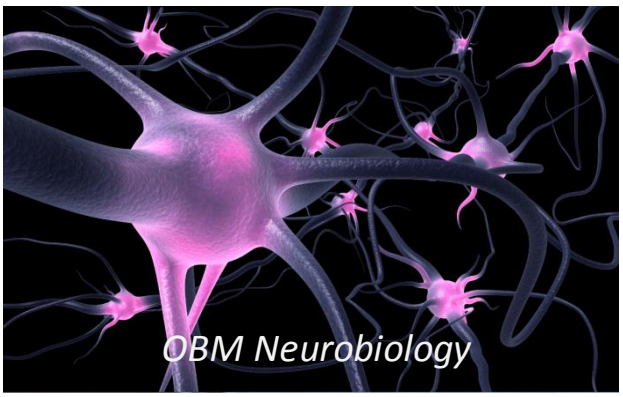

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