PERSPECTIVE

Periostin in cerebrovascular disease

Cerebrovascular diseases, which include ischemic and hemorrhagic strokes, remain serious conditions with high mortality and disability worldwide (He et al., 2018). Ischemic stroke accounts for around 80% of all strokes (He et al., 2018). Hemorrhagic stroke consisting of intracerebral hemorrhage and subarachnoid hemorrhage (SAH) occurs less frequently but may cause poorer outcomes than ischemic stroke (Ji et al., 2017; Luo et al., 2018). It is also well known that aneurysmal SAH may have delayed cerebral ischemia (DCI): thus aneurysmal SAH has both characteristics of hemorrhagic and ischemic strokes (Kanamaru et al., 2019). In spite of enormous efforts to improve outcomes, no conclusive treatment exists thus far, once stroke is completed.

Matricellular proteins are special entities of extracellular matrix proteins to have unique property and multiple functions, and therefore they are recently attracting attention in various diseases (Nishikawa and Suzuki, 2017). Understanding the roles of a matricellular protein may have great potential in its use as a prognostic biomarker and a therapeutic molecular target (Kanamaru et al., 2019). In this paper, we address publications evaluating potential roles of periostin, which belongs to matricellular proteins, and discuss a future direction of periostin researches in cerebrovascular diseases.

Molecular features of periostin: Periostin is an around 90-kDa N-glycoprotein with a N-terminal cysteine-rich EMI domain, fourfold repeated fasciclin I domain in the middle, and a carboxyl-terminal alternative splicing domain (Nishikawa and Suzuki, 2017). Each domain directly binds to different proteins including extracellular matrix proteins and integrin receptors, modulating cellular functions (Kudo, 2017). The carboxyl-terminal domain contains exons 15 to 23 (Kudo, 2017), and the presence of at least 9 splicing variants of periostin lacking some of the exons are known (Nishikawa and Suzuki, 2017). Up to now, clinically important and well-known variants are a full-length form containing all the 9 exons, a variant lacking exon 17, one lacking exon 21, and one lacking exons 17 and 21 (Nishikawa and Suzuki, 2017).

Potential function of periostin: Periostin mediates interactions between cells and extracellular matrix as well as cellular functions including cell adhesion, migration, survival, proliferation or regeneration in various cell types, and has been involved in many pathological conditions such as airway inflammation, retinopathy, bone marrow fibrosis, and tumors (Ma et al., 2015; Kudo, 2017; Nishikawa and Suzuki, 2017). Generally, periostin is expressed at low levels in adult healthy tissues, but is rapidly upregulated by various cytokines, growth factors or mechanical stress in pathophysiological processes (Kudo, 2017; Nishikawa and Suzuki, 2017). For example, experimental studies have demonstrated that periostin is upregulated and essential for tissue remodeling processes in bone fracture healing, cutaneous wound repair, and acute myocardial infarction (He et al., 2018). In a rat model of traumatic spinal cord injury, astroglial-derived periostin was also protective: periostin deficiency inhibited axonal regeneration of neurons *in vivo* possibly by suppressing the signaling activation through focal adhesion kinase and protein kinase B (Akt) (Shih et al., 2014). In bronchial asthma, however, periostin has been reported to play nociceptive roles as an inflammatory effector by upregulating transforming growth factor-β and matrix metalloproteinase-2/9 through integrins (Nishikawa and Suzuki, 2017). As to splicing variants of periostin, full-length periostin induced the progression and metastasis of breast cancer in mice, while the variant lacking exon 17 prevented lung metastasis in human bladder cancer cells and inhibited the proliferation, migration and invasion of mouse breast cancer cells (Shimamura et al., 2012): periostin is also implicated in the migration and invasion of glioma, but effects of splicing variants of periostin on glioma cell biology are unknown (Kudo, 2017). In pre-retinal neovascularization, expression of variants lacking exon 17 or 21 was reported: exon 17 may promote both pathological and physiological revascularization, while exon 21 may facilitate only pathological neovascularization (Kudo, 2017). In a mouse model of myocardial infarction, variants lacking exons 17 and 21 were expressed in the early stage to induce cell migration and proliferation through integrin-focal adhesion kinase signaling, and full-length periostin is increased later toward scar formation (Kudo, 2017). Periostin variants may have different functions, but the function of alternative splicing variants has not been completely elucidated (Nishikawa and Suzuki, 2017).

Possible roles of periostin in cerebrovascular disease

Cerebral ischemia: In neonatal hypoxic-ischemic encephalopathy, the proliferation and differentiation of neural stem cells are important to recover brain function. Ma et al. (2015) demonstrated that periostin was upregulated in differentiating neural stem cells, and that the proliferation and differentiation of neural stem cells into neurons and astrocytes were suppressed by periostin knockdown in mouse pups. In addition, recombinant periostin treatment induced the proliferation and differentiation of neural stem cells and improved functional recovery in a rat model of neonatal hypoxic-ischemic brain injury, suggesting periostin's pivotal roles in brain development and repair from neonatal brain injury possibly via phosphoinositide-3 kinase/Akt/survivin pathway or transforming growth factor-β signaling (Ma et al., 2015).

In normal brain of adult mice, periostin was mainly expressed in neurons (Shimamura et al., 2012). Transient middle cerebral artery occlusion caused a temporal decrease in expression levels of periostin variants lacking exon 17 in the ischemic core at 3 hours, followed by an increase in periostin variants lacking exon 17 in astrocytes and capillary endothelial cells in both the peri-ischemic and ischemic regions at 24 hours post-ischemia; in contrast, expression levels of full-length periostin were unchanged during 24 hours after the ischemia (Shimamura et al., 2012). An intracerebroventricular injection of recombinant periostin variant lacking exon 17, but not full-length periostin, significantly decreased cerebral infarct volume and ameliorated neurological deficits in association with Akt activation in a mouse model of transient middle cerebral artery occlusion (Shimamura et al., 2012). *In vitro* studies also showed that recombinant periostin variant lacking exon 17 prevented post-hypoxia neuronal cell death and promoted neurite outgrowth (Shimamura et al., 2012). During 3 to 28 days after transient middle cerebral artery occlusion in mice, periostin variants lacking exon 17 were upregulated more in reactive astrocytes, microglia, fibroblasts and neural stem cells, and peaked at 7 days; full-length periostin was also induced mainly in fibroblasts in a more modest and delayed fashion compared with the variant lacking exon 17 (Shimamura et al., 2014). These findings suggest the beneficial roles of periostin, especially of the variant lacking exon 17, in neuroprotection, inflammation and neurogenesis after transient cerebral ischemia possibly by controlling migration and proliferation of neural stem cells or neural progenitor cells as well as neurite outgrowth via integrin αv or through the phosphoinositide-3 kinase/Akt signaling pathway via integrin β1, modulating matrix metalloproteinases in microglia, and inducing T regulatory cell differ-

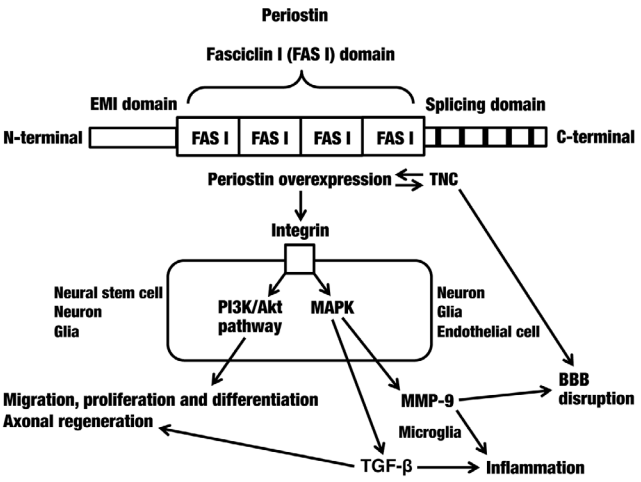

Figure 1 Possible mechanisms of periostin-induced brain development, repair and injury.

Fasciclin I domain of periostin binds to integrins and activates mitogen-activated protein kinases (MAPKs), which control neuroinflammation, blood-brain barrier (BBB) disruption, brain development and repair via upregulation of matrix metalloproteinase (MMP)-9 and transforming growth factor (TGF)-β. Binding of periostin to integrins also activates phosphoinositide-3 kinase (PI3K)/protein kinase B (Akt) pathways and induces brain development and repair. Fasciclin I domain of periostin binds to another matricellular protein tenascin-C (TNC), regulating the expression each other and causing BBB disruption.

entiation via transforming growth factor-β1 (Shimamura et al., 2012, 2014).

The upregulation of periostin was also reported in a clinical setting. Serum periostin levels (detecting the above all 4 important variants together) were increased at 6 days and more at 4 weeks post-ischemia, and were positively correlated with the severity in terms of infarct volume and neurological deficits in patients with large-artery atherosclerotic stroke (He et al., 2018) (**Figure 1**).

Hemorrhagic stroke: As to intracerebral hemorrhage, there are no experimental studies as far as we know, and only one clinical paper is published (Ji et al., 2017). The prospective study reported that higher concentrations of serum periostin (no data as to the variants) at admission within 24 hours post-onset were correlated with increasing severity in terms of hematoma volume and neurological deficits, and poorer functional outcomes in patients with acute spontaneous basal ganglia hemorrhage, suggesting that serum periostin may be a prognostic biomarker in intracerebral hemorrhage (Ji et al., 2017).

In aneurysmal SAH, a clinical literature revealed that patients with more frequent development of DCI and poorer outcomes had higher serum periostin levels (no data as to the variants) at admission, which were also associated with worse admission neurological status and larger SAH volume (Luo et al., 2018). We for the first time reported that cerebrospinal fluid drainage decreased plasma periostin levels (detecting the above all 4 important variants together) from post-operative or post-interventional day 1 to post-SAH day 12, and that plasma periostin levels may increase preceding the development of DCI irrespective of the association of cerebral vasospasm (Kanamaru et al., 2019). Although periostin can be an inflammatory marker, the study revealed that there was no correlation between plasma periostin levels and serum levels of a systemic inflammatory marker C-reactive protein (Kanamaru et al., 2019). The findings that plasma periostin levels were influenced by cerebrospinal fluid drainage and unrelated with serum C-reactive protein levels strongly suggest that periostin in the peripheral blood comes from the central nervous system and is not produced in the systemic circulation or organs. Multivariate analyses demonstrated that plasma periostin levels on days 1–3 post-SAH (post-operative or post-interventional day 1) was an independent predictor of DCI irrespective of the subsequent development of cerebral vasospasm (Kanamaru et al., 2019).

In a mouse model of experimental SAH by endovascular perforation, full-length periostin was demonstrated to be upregulated in neurons and capillary endothelial cells in cerebral cortex after SAH and was responsible for early brain injury in terms of blood-brain barrier disruption, which was possibly mediated by p38/extracellular signal-related kinase 1/2-matrix metalloproteinase-9 signaling pathways (Liu et al., 2017). Accumulating evidences have demonstrated that early brain injury, an acute pathological process caused by aneurysmal rupture and the subsequent cascades, is the primary factor of poor outcome after SAH. Neutralization of full-length periostin prevented blood-brain barrier disruption constituting a core element of early brain injury, while the administration of recombinant full-length periostin re-exacerbated blood-brain barrier disruption (Liu et al., 2017). In addition, the study revealed the positive interaction of periostin with tenascin-C, another important mediator of early brain injury after SAH (Liu et al., 2017). The findings suggest that periostin and tenascin-C cause post-SAH early brain injury and DCI either separately or combinedly (**Figure 1**).

Future direction of periostin research in cerebrovascular diseases: As described above, the function of periostin is interesting, and literatures suggest that periostin may be involved in both ischemic and hemorrhagic cerebrovascular diseases. However, the information is still considerably limited. At present, available data suggest that 1) periostin variant lacking exon 17 exerts neuroprotective effects in an acute stage of ischemic stroke; 2) both full-length periostin and the variant lacking exon 17 may be involved in controlling inflammation and promoting neurogenesis in subacute and chronic stages of ischemic stroke; and 3) full-length periostin causes brain injury in an acute stage of at least one of hemorrhagic stroke, SAH. The reasons of these conflicting findings should be revealed in future studies. In addition, more experimental and clinical studies are needed to clarify the relationships of periostin induction with each type of diseases, the clinical manifestation and the time course as well as the underlying mechanisms including signaling pathways and interactions with other molecules and enzymes. Especially, the expression and functional roles of each periostin variant should be investigated in each disease and pathophysiology, because different periostin variants may have opposite functions. Further studies may prove that periostin is a critical regulator of cerebrovascular diseases, and that periostin is useful as a biomarker to predict, diagnose and monitor the disease progression and treatment effects as well as a therapeutic molecular target to improve outcomes of cerebrovascular diseases.

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