Experimental Neurology 322 (2019) 113057

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review Article

Potential roles of matricellular proteins in stroke

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ARTICLE INFO

Keywords:
Cerebral infarction
Galectin
Inflammation
Intracerebral hemorrhage
Osteopontin
Periostin
Subarachnoid hemorrhage
Tenascin
Thrombospondin

ABSTRACT

Both ischemic and hemorrhagic strokes are still serious diseases with high mortalities and morbidities. To improve outcomes of strokes, new therapeutic approaches need to be developed. Matricellular proteins are inducible, multifunctional and non-structural extracellular matrix proteins, which are definitely differentiated from classical ones due to the unusual diversity of functions. There are many matricellular proteins known, most of which may be involved in the pathophysiology and the protective or repairing mechanisms of strokes. This article reviews the available information regarding potential roles of matricellular proteins in stroke, and discusses the potential therapeutic approaches against stroke using matricellular proteins.

1. Introduction

Irrespective of recent advances in stroke treatment, stroke remains a leading cause of long-term disabilities with different risk factors depending on stroke subtypes (O'Donnell et al., 2016). To improve outcomes of both ischemic and hemorrhagic strokes, further basic researches are needed to clarify the mechanisms of progression or regression of brain injury in each stroke subtype, which would lead to future development of new brain protection therapies.

Matricellular proteins are inducible and secretory non-structural proteins belonging to the extracellular matrix proteins (Suzuki et al., 2018a). Due to the unusual diversity of functions, the term "matricellular protein" was introduced in 1995, and the number of matricellular proteins is still increasing (Suzuki et al., 2018a). It is the common features of matricellular proteins that they are readily upregulated in almost any tissue and cell type under pathological conditions, bind to many cell surface receptors, other matrix proteins, growth factors, cytokines, chemokines and proteases, and modulate cell–cell or cell–matrix interactions to control cellular morphology and behavior (differentiation, adhesion, migration, and survival or apoptosis) (Suzuki et al., 2018a). Although matricellular protein-deficient mice undergo normal development, matricellular proteins serve as key mediators of various physiological reactions during developmental stages as well as diverse pathological processes depending on the biological scenario surrounding its induction (Suzuki et al., 2018a). This review summarizes the available information of potential roles of matricellular proteins in stroke (Table 1), and discusses the possibility to target a matricellular protein and to develop new therapies against stroke.

2. Matricellular proteins in Stroke

2.1. Tenascin

Tenascins have 4 members (tenascin-C, -R, -W and -X) in vertebrates (Roll and Faissner, 2019), among which only tenascin-C has been implicated in stroke. Tenascin-C typically forms a hexamer, but alternative splicing of the fibronectin type III repeats, post-translational modifications and proteolytic processing produce lots of tenascin-C isoforms with various functions and sizes, which can be present simultaneously in the specific tissues (Suzuki et al., 2018a). In a developing stage, radial glial progenitor cells and then primarily astrocytes express tenascin-C, which contributes to the proliferation of astrocyte progenitor cells, the maturation of neural progenitor cells and the proliferation and maintenance of oligodendrocyte precursors (Jayakumar et al., 2017).

In ischemic stroke, a neurotrophic factor L-serine treatment further upregulated tenascin-C at 5 days post-ischemia and exerted neuroprotective effects by proliferation of neural stem cells and microvessels, reconstruction of neurovascular units and the resultant neurorepair in

Abbreviations: BBB, blood-brain barrier; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MCA, middle cerebral artery; MMP, matrix metalloproteinase; NF, nuclear factor; PAI, plasminogen activator inhibitor; PEDF, pigment epithelium-derived factor; SC1, synaptic cleft-1; SPARC, secreted protein acidic and rich in cysteine; TGF, transforming growth factor; TLR, Toll-like receptor

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https://doi.org/10.1016/j.expneurol.2019.113057
Received 30 June 2019; Received in revised form 26 August 2019; Accepted 5 September 2019
Available online 06 September 2019
0014-4886/

Table 1

Potential roles of matricellular protein in stroke.

Matricellular protein	Cerebral infarction	Intracerebral hemorrhage	Subarachnoid hemorrhage
Tenascin-C	Protective: - Proliferation of NSCs and microvessels (rat)	ND	Harmful: - Tenascin-C knockout → Prevention of BBB disruption, inflammation, neuronal apoptosis, and cerebral VSP (mouse) - Blockage by cilostazol → Decrease in delayed cerebral infarct, chronic HCP, and poor outcome (human)
Periostin	Protective: - Recombinant periostin variant lacking exon 17 → Reduced cerebral infarct volume (mouse)	ND	Harmful: - Neutralization of full-length periostin → Prevention of BBB disruption (mouse)
Osteopontin	Protective: - Induction in a subacute stage → Anti-apoptotic and anti-inflammatory effects, BBB protection, neurogenesis, and remodeling (mouse/rat)	Protective: - Delayed induction → Migration of NSCs (mouse); anti-apoptotic and anti-inflammatory effects (rat)	Protective: - Peak induction at day 3 → Prevention of microcirculatory dysfunction, BBB disruption, neuronal apoptosis, and cerebral VSP (rat)
Galectin	Galectin-1 → Protective: anti-inflammation, neurogenesis and axonal regeneration (mouse/rat) Galectin-3 → Controversial: maybe toxic within 24 h, but protective thereafter (mouse/rat) Galectin-9 → Harmful: proinflammatory effects (rat)	Galectins-1 and 3 → Protective: anti-inflammatory effects (mouse) Galectin-9 → Harmful: proinflammatory effects to induce secondary brain injury (rat)	Galectin-3 → Harmful: BBB disruption (mouse)
Thrombospondin	Thrombospondins-1, 2 and 4 → Protective: control of angiogenesis, synapse formation and axonal outgrowth (mouse/rat)	Thrombospondins-1, and 2 → Protective: promotion of angiogenesis (rat)	Thrombospondin-1 → Harmful: subarachnoid fibrosis, chronic HCP, and neurocognitive disturbance (rat)
Secreted protein acidic and rich in cysteine (SPARC)	Harmful: - SPARC knockout → Increased microgliosis and enhanced functional recovery (mouse)	SC1 (ortholog of SPARC) induction at days 1 and 3 (rat) → Unknown significance	ND
Plasminogen activator inhibitor (PAI)-1	Harmful: - PAI-1suppression → Increased collateral perfusion and reduced cerebral infarct size (mouse/rat)	Protective: - Maybe suppression of thrombin-induced toxicity surrounding hematoma (rat)	ND
Glypican	Protective: - Direct infusion of glypican → Increased neurogenesis (rat)	ND	ND
Fibulin	Protective: - Overexpression of fibulin-5 → Anti-apoptotic and anti-oxidant effects, and reduced BBB disruption (rat)	ND	ND
Small leucine-rich proteoglycan (decorin and biglycan)	ND	ND	Protective - Recombinant decorin → Inhibition of subarachnoid fibrosis, chronic HCP, and neurocognitive disturbance (rat)
Pigment epithelium-derived factor	Protective - Overexpression of pigment epithelium-derived factor → Anti-oxidant, anti-inflammatory and anti-apoptotic effects, autophagy activation, increased glutamate clearance, downregulation of water channel aquaporin 4, and inhibited glial cell degeneration (rat)	ND	ND

BBB, blood-brain barrier; HCP, hydrocephalus; ND, no data; NSC, neural stem cell; SC1, synaptic cleft-1; VSP, vasospasm.

the ischemic boundary zone after permanent cerebral ischemia in rats (Sun et al., 2014). However, the mechanisms were not investigated.

In intracerebral hemorrhage, higher serum levels of large–splice variants of tenascin-C containing C domain in the fibronectin type III repeats at admission were correlated with larger hematoma volume, worse admission neurological status, early neurological deterioration and hematoma growth, and poorer 90-day functional outcomes in a clinical setting (Wang et al., 2018). No experimental studies have been conducted in intracerebral hemorrhage thus far.

In aneurysmal subarachnoid hemorrhage, cerebrospinal fluid levels of large–splice variants of tenascin-C containing C domain in the fibronectin type III repeats were the highest in the first 3 days of onset and decreased over time: the higher levels were related with worse admission neurological status and more massive hematoma volume, and predicted the development of angiographic vasospasm, delayed cerebral ischemia and chronic shunt-dependent hydrocephalus, as well as worse outcomes (Suzuki et al., 2008, 2011, 2015). In contrast, plasma levels of C domain-containing tenascin-C variants peaked at days 4–6 post-onset and were greater in patients with subsequent development of angiographic vasospasm and delayed cerebral ischemia (Suzuki et al., 2010b). A selective inhibitor of phosphodiesterase type III cilostazol suppressed plasma levels of tenascin-C (both B and C domains-containing variants), and prevented delayed cerebral infarction and chronic shunt-dependent hydrocephalus, resulting in better outcomes of patients with aneurysmal subarachnoid hemorrhage (Nakatsuka et al., 2017; Suzuki et al., 2019). In experimental studies, tenascin-C was induced in the spastic cerebral arteries (endothelial, smooth muscle, adventitial, and periarterial inflammatory cells) and brains (possibly astrocytes, neurons and brain capillary endothelial cells) after subarachnoid hemorrhage by endovascular perforation in rats and mice (Shiba and Suzuki, 2019). In experimental studies using tenascin-C-knockout mice with subarachnoid hemorrhage by endovascular perforation, tenascin-C deficiency prevented early brain injury in terms of 1) blood-brain barrier (BBB) disruption and brain edema formation by inhibiting 3 major mitogen-activated protein kinases (MAPKs: extracellular signal-regulated kinase [ERK] 1/2, c-Jun N-terminal kinase, and p38)-mediated matrix metalloproteinase (MMP)-9 activation and the resultant degradation of inter-endothelial tight junction proteins (Fujimoto et al., 2016) associated with downregulation of another matricellular protein periostin (Liu et al., 2017); and 2) neuroinflammation and caspase-dependent neuronal apoptosis by suppressing the upregulation and activation of Toll-like receptor (TLR) 4, phosphorylation of nuclear factor (NF)-κB, and induction of interleukins-1β and -6 (Liu et al., 2018a). Tenascin-C knockout also exerted preventive effects against cerebral vasospasm associated with the reduction of periarterial inflammatory cell infiltration and the inactivation of MAPKs in the arterial smooth muscle cells after subarachnoid hemorrhage in mice (Fujimoto et al., 2018). Although the mechanisms of how tenascin-C induces deleterious effects after subarachnoid hemorrhage are not completely revealed, TLR4-mediated MAPK and NF-κB signaling may be important (Okada and Suzuki, 2017) (Fig. 1).

2.2. Periostin

Periostin is a N-glycoprotein with a carboxyl-terminal alternative splicing domain containing exons 15–23, and there are at least 9 splicing variants lacking some of the exons (Kudo, 2017; Nishikawa and Suzuki, 2017). Periostin variants may exert different functions by directly binding to various extracellular matrix proteins and integrin receptors (Kudo, 2017).

In patients with large-artery atherosclerotic ischemic stroke, higher serum levels of periostin (unknown variants) were associated with larger cerebral infarction volume and more severe neurological deficits at 6–28 days post-ischemia (He et al., 2018). In adult mouse's brain, periostin was mainly expressed in neurons, but transient middle cerebral artery (MCA) occlusion downregulated periostin variants lacking exon 17 in the ischemic core at 3 h, followed by upregulation of periostin variants lacking exon 17 in reactive astrocytes, microglia, fibroblasts, capillary endothelial cells and neural stem cells in both peri-ischemic and ischemic regions at 1–28 days (peak, 7 days) post-ischemia; and full-length periostin was also induced mainly in fibroblasts in a more modest and delayed fashion (Shimamura et al., 2012, 2014). An intracerebroventricular injection of recombinant periostin variant lacking exon 17, but not full-length periostin, reduced the volume of cerebral infarction associated with Akt activation in a transient MCA occlusion model in mice, suggesting neuroprotective, anti-inflammatory and neurogenetic effects of the variant lacking exon 17 after transient cerebral ischemia (Shimamura et al., 2012).

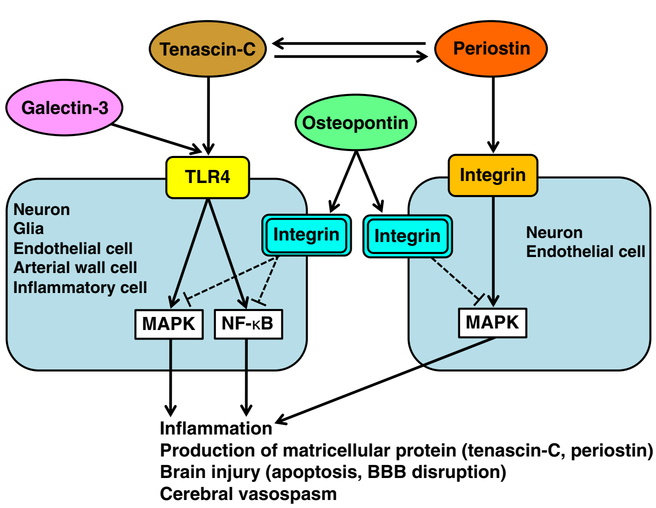

Fig. 1. Possible relationships among matricellular proteins in subarachnoid hemorrhage. Tenascin-C, periostin and galectin-3 may be neurotoxic, whereas osteopontin may be neuroprotective. BBB, blood-brain barrier; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR4, Toll-like receptor 4.

In acute spontaneous basal ganglia hemorrhage, higher serum levels of periostin (unknown variants) at admission were correlated with larger hematoma volume and poorer outcomes in a clinical setting (Ji et al., 2017). There are no experimental studies published as to intracerebral hemorrhage.

In patients with aneurysmal subarachnoid hemorrhage, higher serum levels of periostin (unknown variants) at admission were related to worse admission neurological status, larger hemorrhage volume, more frequent development of delayed cerebral ischemia and poorer outcomes (Luo et al., 2018). Plasma levels of periostin (unknown variants) were decreased by cerebrospinal fluid drainage and unrelated with serum levels of a systemic inflammatory marker C-reactive protein; however, periostin levels increased preceding the development of delayed cerebral ischemia irrespective of the presence or absence of cerebral vasospasm (Kanamaru et al., 2019b). After subarachnoid hemorrhage by endovascular perforation in mice, full-length periostin was upregulated in neurons and capillary endothelial cells in cerebral cortex and caused early brain injury in terms of BBB disruption possibly via p38/ERK1/2–MMP-9 signaling pathways and/or induction of tenascin-C (Liu et al., 2017). Neutralization of full-length periostin prevented BBB disruption, which was aggravated by administration of recombinant full-length periostin (Liu et al., 2017) (Fig. 1). The role of periostin isoforms resulting from alternative splicing has not been examined thus far in subarachnoid hemorrhage (Kanamaru et al., 2019a; Kawakita and Suzuki, 2020).

2.3. Osteopontin

Osteopontin is an acidic phosphoglycoprotein containing several functional domains, which allow for receptor bindings such as integrins and CD44, and is subjected to numerous posttranslational modifications including serine/threonine phosphorylation, glycosylation, tyrosine sulfation, and transglutamination generating a polymer, all of which regulate osteopontin's functions (Lok and Lyle, 2019). Alternative splicing generates 5 isoforms, and osteopontin can also undergo proteolytic cleavage by thrombin and MMPs-2, -3, -7, -9, and -12 (Lok and Lyle, 2019). Osteopontin is upregulated in response to injury, stress and inflammation in diverse cells, and is involved in homeostasis, angiogenesis, and immune responses (Rogall et al., 2018). Distinct from the above secreted osteopontin, less well-known intracellular osteopontin, which lacks the signal sequence that targets the protein to secretory vesicles possibly due to a down-stream alternative translational initiation signal, is expressed in dendritic cells and macrophages of the immune system (Baliga et al., 2011).

In acute ischemic stroke, plasma levels of thrombin-cleaved osteopontin N-terminal at admission, which might originate from vulnerable plaques, were significantly higher in patients with atherothrombotic stroke compared with those with non-atherothrombotic stroke (Ozaki et al., 2017). Serum osteopontin levels increased and peaked at day 7, being correlated with cerebral infarction volume, neurological status at an acute phase and 3-month functional outcomes (Carbone et al., 2015). In a subacute stage of experimental cerebral ischemia, osteopontin is induced in microglia and macrophages within the infarct core and in peri-infarct regions, and exerts direct neuroprotective effects on neurons by cell survival or anti-apoptotic effects via ERK1/2 activation and phosphoinositide 3-kinase/Akt signaling pathways, neurogenesis via Akt activation, anti-inflammatory effects via NF-κB inactivation, and BBB protection via inactivation of MAPK and MMP-9, as well as indirect neuroprotective effects via the blockade of inducible nitric oxide synthase and shifting microglia polarization towards more protective M2 phenotypes that modulate beneficially inflammatory responses post-ischemia, thus resulting in the reduction of secondary tissue damages (Doyle et al., 2008; Ladwig et al., 2017; Rogall et al., 2018; Zhu et al., 2017). Thrombin-cleaved osteopontin is a more effective neuroprotectant than intact osteopontin (Doyle et al., 2008). Osteopontin also promotes survival, proliferation, migration and neuronal differentiation of neural stem cells through the CXC chemokine receptor type 4 after focal cerebral ischemia, although endogenous neural stem cells residing in the subventricular zone and in the hippocampal dentate gyrus of the adult mammalian brain are mobilized to an injury site after cerebral ischemia and mediate pleiotropic functions such as neuroprotection, reduction of neuroinflammation, revascularization, induction of plasticity, neurogenesis and replacement of lost neurons, leading to functional recovery (Rabenstein et al., 2015). The induction of osteopontin may play a role in remodeling processes after focal cerebral ischemia including macrophage recruitment, matrix repair, astroglial cell migration, and gliosis (Wang et al., 1998). Intracellular osteopontin was upregulated in the right cerebral cortex at 45 min after transient global cerebral ischemia/reperfusion in rats, suggesting a role of the protein as a responder to stroke-induced cell damage and an adaptor (or scaffold) function facilitating signal transduction pathways, but nothing is known about how its expression is controlled (Baliga et al., 2011).

In patients with intracerebral hemorrhage, serum levels of osteopontin were increased within the first 24 h post-onset (Acar et al., 2012). In a mouse model of intracerebral hemorrhage, osteopontin was increased in the ipsilateral injured striatum from day 1 to day 28, and played roles in the lateral migration of neuroblasts from the ipsilateral subventricular zone towards the hematoma as well as the ipsilateral striatum remote to the hematoma at day 3 to day 28 possibly by integrin β1 receptor-mediated phosphorylation of focal adhesion kinase, associated with activated astrocytes and blood vessels in the injured striatum; however, osteopontin deficiency did not affect the proliferation of neural progenitors (Yan et al., 2009). Recombinant osteopontin treatment may provide a wide range of neuroprotection by suppressing apoptosis through the phosphoinositide 3-kinase/Akt/glycogen synthase kinase 3β signaling pathway (Zhang et al., 2018), and preventing neuroinflammation at least partly by integrin β1-induced inhibition of Janus kinase 2/signal transducer and activator of transcription-1 pathway after intracerebral hemorrhage in rats (Gong et al., 2018).

In patients with aneurysmal subarachnoid hemorrhage, plasma osteopontin levels were increased and peaked at days 4–6, and higher levels were an independent predictor of 3-month poor outcomes (Nakatsuka et al., 2018). In a rat model of subarachnoid hemorrhage by endovascular perforation, osteopontin is induced in reactive astrocytes and capillary endothelial cells and peaks at 72 h post-hemorrhage, when rat's neurological status recovers (Liu and Suzuki, 2018). Osteopontin is protective against early brain injury by suppressing microcirculatory dysfunctions via stabilizing vascular smooth muscle cell phenotype through the activation of integrin-linked kinase/Rac-1 signaling pathways; inhibiting neuronal apoptosis through integrin-mediated activation of focal adhesion kinase/phosphatidylinositol 3-kinase/Akt signaling pathway; and preventing BBB disruption through integrin-mediated inactivation of NF-κB/MMP-9 signaling pathway, integrin-mediated activation of MAPK phosphatase-1 that inhibits MAPKs/MMP-9 and/or vascular endothelial growth factor-A signaling pathways, or CD44-mediated increases in mature/full-length glycosylated P-glycoprotein in brain capillary endothelial cells (Liu and Suzuki, 2018). Recombinant osteopontin treatment increased an endogenous MAPK inhibitor, MAPK phophatase-1, in cerebral artery smooth muscle cells via binding to L-arginyl-glycyl-L-aspartate-dependent integrins, and inhibited the phosphorylation of MAPKs, then that of caldesmon and heat shock protein 27 in cerebral arteries, preventing cerebral vasospasm (Suzuki et al., 2010a) (Fig. 1).

2.4. Galectin

Galectins are a family of β-galactoside-binding lectins that consist of at least 20 members, which have a conserved carbohydrate-recognition domain sequence (Nishikawa and Suzuki, 2018). Galectins are classified as proto-type (galectins-1, 2, 5, 7, 10, 11, 13–20) including monomers or homodimers with one carbohydrate-recognition domain; chimera type (galectin-3) containing a non-lectin part made of proline- and glycine-rich short tandem repeats connected to a carbohydrate-recognition domain; and tandem-repeat type (galectins-4, 6, 8, 9, 12) containing two carbohydrate-recognition domains with different binding partners connected by a single polypeptide chain (Nishikawa and Suzuki, 2018). Galectins exist intracellularly and extracellularly: extracellular galectin exerts bivalent or multivalent interactions with glycans on cell surfaces to induce various cellular responses, while intracellular galectin functions in signaling pathways (Nishikawa and Suzuki, 2018).

In patients with large artery atherosclerotic stroke, only higher serum galectin-3 level was independently associated with poor outcomes both on days 1 and 6, and serum levels of galectins-9 and -1 were upregulated on day 6 and in the 4th week after ischemic stroke, respectively, with no relation to outcomes: galectin-1 may be protective, galectin-3 may be harmful by amplifying and prolonging inflammatory responses, and galectin-9 may be involved in inflammatory responses and neuronal injury (He et al., 2017). In experimental studies, galectin-1 has been consistently implicated in protection against ischemic brain injury by modulating the cytokine profile of microglia/macrophage towards an anti-inflammatory state, and stimulating neurogenesis and axonal regeneration (Ishibashi et al., 2007; Wang et al., 2015a). However, roles of galectin-3 remain controversial in cerebral ischemia: galectin-3 upregulation may be neurotoxic within 24 h post-ischemia, but neuroprotective thereafter (Rahimian et al., 2019). For example, in a mouse model of transient global ischemia, galectin-3-dependent TLR4 activation caused neuronal damage in the hippocampus at 24 h post-ischemia (Burguillos et al., 2015), whereas galectin-3 was expressed in insulin-like growth factor 1-labeled proliferating microglia as early as 48 h post-ischemia and sustained galectin-3 deficiency exacerbated ischemic injury in a rat transient MCA occlusion model (Lalancette-Hebert et al., 2007). Galectin-9/T cell immunoglobulin and mucin domain-3 signaling pathways are reported to be involved in post-ischemic inflammation and the development of cerebral infarction in a rat model of permanent MCA occlusion (Wei et al., 2015).

Plasma galectin-3 levels in patients with intracerebral hemorrhage were increased at admission, and correlated with serum C-reactive protein levels, hematoma volumes, admission neurological status, and 6-month outcomes (Yan et al., 2016b). In experimental intracerebral hemorrhage in mice, galectins-1 and -3 were increased in the perihematomal brain region from days 3 to 7 and peaked at day 5 post-hemorrhage: galectin-1 was mostly expressed in astrocytes, whereas galectin-3 was expressed mostly in microglia/macrophages (Bonsack and Sukumari-Ramesh, 2019). Both galectins-1 and -3 might act anti-inflammatorily (Bonsack and Sukumari-Ramesh, 2019). T cell immunoglobulin and mucin domain-3 was increased in microglia after experimental intracerebral hemorrhage to activate galectin-9 and TLR4 signaling pathways, causing neuroinflammation and microglia polarization which induced secondary brain injury in rats (Chen et al., 2019).

In patients with aneurysmal subarachnoid hemorrhage, higher admission plasma galectin-3 levels were correlated with poorer admission clinical grades and 6-month outcomes (Liu et al., 2016), and plasma galectin-3 levels on days 1–3 predicted the development of delayed cerebral infarction with or without cerebral vasospasm (Nishikawa et al., 2018b). In a mouse model of subarachnoid hemorrhage by endovascular perforation, galectin-3 was upregulated in brain capillary endothelial cells, and pharmacological blockage of galectin-3 attenuated BBB disruption associated with inactivation of TLR4, ERK1/2, signal transducer and activator of transcription-3 and MMP-9, and the consequent preservation of a tight junction protein (Nishikawa et al., 2018a) (Fig. 1).

2.5. Thrombospondin

The thrombospondin family consists of 5 members that are divided into two subgroups, subgroup A assembled as trimers (thrombospondins-1 and -2) and subgroup B assembled as pentamers (thrombospondins-3, -4, and -5) (Wu et al., 2017). Thrombospondins-1–4 are expressed in the brain, and are implicated in synaptogenesis, angiogenesis, and inflammation (Wu et al., 2017).

In patients with acute ischemic stroke, plasma levels of thrombospondins-2 were increased at admission, and those of thrombospondins-1 were increased at 2 h after the treatment with tissue plasminogen activator (Navarro-Sobrino et al., 2011). Another clinical study reported that plasma thrombospondin-1 levels at admission were elevated and an independent predictor of 6-month poor outcomes of ischemic stroke (Gao et al., 2015). In a transient MCA occlusion model in rats, thrombospondin-1 showed a biphasic expression before the peak of angiogenesis: thrombospondin-1 was induced in endothelial cells in the leptomeninges covering the ischemic cortex at the first peak at 1 h, while the cellular origins of the second peak at 72 h were endothelial, glial, neuronal, and macrophage cells in the penumbral region (Lin et al., 2003). Thrombospondin-2 was upregulated in the penumbral region from the peak of angiogenesis to the period when angiogenesis had completely resolved in a monophasic manner, peaking at 2 weeks post-ischemia (Lin et al., 2003). Thrombospondin-1 is considered to induce caspase-3-dependent endothelial cell apoptosis, and the expression of thrombospondins-1 and -2, especially thrombospondin-2 might contribute to the termination of post-ischemic angiogenesis (Lin et al., 2003). In a permanent MCA occlusion model in mice, thrombospondins-1 and -2 were increased and colocalized mostly to astrocytes, and deficiency of thrombospondins-1 and -2 caused impaired recovery irrespective of similar size of cerebral infarction mainly due to the inhibition of synapse formation and axonal outgrowth (Liauw et al., 2008). In another study using a rat permanent MCA occlusion model, the treatment with thrombospondin-4-overexpressing bone marrow stromal cells improved regeneration of blood vessels in the ischemic boundary zone and neurological function post-stroke associated with increased expression of von Willebrand factor, vascular endothelial growth factor, angiopoietin-1, MMP-9, and MMP-2 possibly by the paracrine function of thrombospondin-4-overexpressing bone marrow stromal cells and the activation of transforming growth factor (TGF)-β/Smad2/3 signaling pathway (Zhang et al., 2019).

In patients with intracerebral hemorrhage, increased plasma thrombospondin-1 levels were correlated with the severity of intracerebral hemorrhage and independently predicted 6-month poor outcomes (Dong et al., 2015). In a rat intracerebral hemorrhage model, thrombospondins-1 and -2 were expressed in cerebral endothelial cells peaking at 4 and 14 days post-hemorrhage, respectively: thrombospondins-1 and -2-immunoreactive microvessels existed surrounding the hematoma by about 7 days and then extended into the hematoma (Zhou et al., 2010). Thrombin was an inducer of thrombospondins, which induced angiogenesis in the model (Yang et al., 2012).

In patients with aneurysmal subarachnoid hemorrhage, thrombospondin-1 in lumbar cerebrospinal fluid increased at days 1–3 and then decreased as time passed: higher thrombospondin-1 levels at days 1–3 and days 5–7 post-hemorrhage predicted the development of cerebral vasospasm and 3-month poor outcome (Chen et al., 2016). Higher plasma thrombospondin-1 levels at admission were also associated with more severe clinical status, subsequent development of cerebral vasospasm and 6-month poorer outcomes (Shen et al., 2015). In subarachnoid hemorrhage rats by double blood injections into the cisterna magna, the treatment with leucine-serine-lysine-leucine peptide, a small molecular peptide and a competitive antagonist for TGF-β1, inhibited thrombospondin-1-mediated TGF-β1 activity and therefore subarachnoid fibrosis, resulting in the prevention of the development of chronic hydrocephalus and the improvement of neurocognitive function (Liao et al., 2016).

2.6. Secreted protein acidic and rich in cysteine (SPARC)

SPARC, also known as osteonectin and basement-membrane protein 40, is one of 4 groups of the SPARC family (Jayakumar et al., 2017), and its ortholog is SPARC-like 1, synaptic cleft-1 (SC1), or hevin (Lloyd-Burton et al., 2013). SPARC is predominantly expressed in astrocytes and microglia in the adult central nervous system, possibly playing a role in the maintenance of extracellular matrix integrity, synaptic stability and cortical lamination (Jayakumar et al., 2017; Lloyd-Burton et al., 2013).

In patients with ischemia stroke, admission serum SC1 levels were increased and correlated with the severity of stroke (Ambrosius et al., 2018). In a rat model of transient global cerebral ischemia, SPARC from the vascular basal lamina, endothelial cells and perivascular astrocytes decreased associated with BBB disruption, which was prevented by a mild post-ischemic hypothermia with the maintenance of SPARC levels (Baumann et al., 2009). In photothrombotic cortical ischemia in mice, SPARC was lost in reactive and phagocytic microglia in and adjacent to the lesion, but upregulated in reactive astrocytes and blood vessels surrounding the ischemic core, while SPARC knockout increased microgliosis and enhanced functional recovery: the loss of microglial SPARC may allow microglia to proliferate after ischemia, and the concurrent upregulation of SPARC in reactive astrocytes may keep astrocytic scar proliferation in check (Lloyd-Burton et al., 2013). SC1 was also upregulated in the portions of axonal injury surrounding stroke lesions, and SC1 expression peaked at 1 and 3 days after intracerebral hemorrhage and at 7 days after transient focal ischemia in young-adult and aged rats (Lively and Schlichter, 2012). However, the information in hemorrhagic stroke is limited, and further clinical or experimental data are unavailable.

2.7. Plasminogen activator inhibitor (PAI)-1

PAI-1 is the primary inhibitor of fibrinolysis by antagonizing intrinsic plasminogen activation, and also regulates vascular fibrosis and endothelial cell senescence (Chapin and Hajjar, 2015; Chan et al., 2018). Circulating PAI-1 is considered to be a mediator of cellular aging including vascular endothelial cells and therefore a marker of aging (Chan et al., 2018). Circulating PAI-1 is increased in hypertension through angiotensin type-1 receptor activation, and impairs microvascular perfusion (Chan et al., 2018).

PAI-1 is encoded by the serine proteinase inhibitor family E member 1 gene, of which functional polymorphisms can result in an increase in PAI-1 levels, being implicated with poor outcome in ischemic stroke (Hendrix et al., 2017). According to meta-analysis studies, the rs1799889 polymorphism was significantly associated with the risk of cerebral infarction (Liu et al., 2018b), and PAI-1 4G/5G polymorphism was significantly associated with increased risks of adult but not pediatric ischemic stroke in Asians (Hu et al., 2017). In addition, a risk of ischemic stroke was increased with -844G/A but not 11,053 T > G polymorphism, while PAI-1 4G/5G polymorphism tended to reduce a risk of hemorrhagic stroke (Hu et al., 2017). Higher plasma PAI-1 levels before thrombolysis may predict symptomatic intracranial hemorrhage, but the results have been conflicting in the clinic (Wang et al., 2015b). After transient MCA occlusion in mice, messenger ribonucleic acid levels of PAI-1 (237 folds) and PAI-2 (19 folds) increased in ischemic brain and peaked at 24 h post-ischemia associated with increased PAI-1 plasma activity: brain infarct volume was significantly reduced in PAI-1-deficient mice, but not in PAI-2-deficient mice (Griemert et al., 2018). Inflammatory responses after cerebral ischemia may induce PAI-1, which impairs the fibrinolytic system by binding to endogenous tissue-type plasminogen activator and promotes stable fibrin clot formation, leading to the obstruction of microvessels in the ischemic zone (Griemert et al., 2018). Pharmacological inhibition of PAI-1 also increased reperfusion and decreased infarct volume by reducing fibrin deposition in a mouse transient MCA occlusion model (Denorme et al., 2016), and by increasing collateral perfusion and dilating leptomeningeal anastomotic arterioles via nitric oxide in a rat transient MCA occlusion model (Chan et al., 2018).

There are no clinical studies as to PAI-1 in intracerebral hemorrhage. In experimental intracerebral hemorrhage, PAI-1 was upregulated mainly in neurons and astrocytes around the hematoma possibly by thrombin-induced inflammatory reactions and peaked at the first day (Hua et al., 2002). The upregulation of PAI-1 may be neuroprotective against thrombin-induced toxicity (Hua et al., 2002).

In patients with subarachnoid hemorrhage, PAI-1 levels in cerebrospinal fluid and plasma were higher around 7 days in poorer clinical grade and associated with cerebral vasospasm (Ikeda et al., 1997; Ji et al., 2014). As to gene polymorphisms, patients with the AA genotype of rs2227631 and 4G/4G genotype had higher risks of delayed cerebral ischemia, while those with the GG genotype of rs7242 and AA genotype of rs2227684 had lower risks for poor outcomes (Hendrix et al., 2017). There are no experimental studies as to subarachnoid hemorrhage.

2.8. Glypican

Glypican is a heparin sulphate binding glycoprotein bound to the external surface of the plasma membrane, and 6 members (glypicans 1–6) have been identified in mammals (Jayakumar et al., 2017). Glypicans are implicated as a regulator of cell signaling pathways including Wnt and Hedgehog, fibroblast growth factor, and bone morphogenic protein, and are considered to play a role in axonal pathfinding, synaptogenesis, and structural plasticity (Jayakumar et al., 2017).

As to the relationships between glypicans and stroke, only one paper has been published. In a rat permanent MCA occlusion model, direct infusion of glypican into the infarct cavity from 7 days to 14 days post-ischemia reduced glial fibrillary acidic protein-immunoreactive glial scar and increased microtubule-associated protein-2 immunoreactivity in the peri-infarct region associated with neurobehavioral improvement possibly by increasing fibroblast growth factor-2 (Hill et al., 2012).

2.9. Fibulin

The human fibulin family includes 7 glycoproteins originally characterized as components of elastic fibers in connective tissues (Obaya et al., 2012).

Serum levels of fibulin-1, which stabilizes extracellular matrix integrity surrounding the vascular smooth muscle and is related with arterial stiffness, were higher at 7 years after ischemic stroke compared with monozygotic twins with no history of ischemic stroke (Vadgama et al., 2019). In a rat transient MCA occlusion model, overexpression of fibulin-5, which is secreted by various vascular cells including vascular smooth muscle cells, fibroblasts and endothelial cells, exerted anti-apoptotic effects on neurovascular endothelium and prevented BBB disruption by inhibiting the production of reactive oxygen species, activating Rac-1 pathway and suppressing MMP-9 upregulation, resulting in improved neurological outcomes, although infarction volume was unchanged (Guo et al., 2016). Limb remote ischemic postconditioning-induced elevation of fibulin-5 reduced cerebral infarction and prevented BBB disruption in the same rat model (Zhang et al., 2017).

In hemorrhagic stroke, serum fibulin-5 levels at admission were correlated with the disease severity in terms of neurological status and hematoma volume, as well as 3-month outcomes in patients with intracerebral hemorrhage (Hu et al., 2016). Other data are unavailable as to hemorrhagic stroke.

2.10. Small leucine-rich proteoglycan

The small leucine-rich proteoglycan family currently consists of 17 members in 5 classes (Dellett et al., 2012). Among the members, decorin and biglycan are expressed in normal adult rat brain, and contribute to the maintenance of the nervous system through the regulation of adult neural stem and the responses to central nervous system injuries, in addition to the roles in embryonic neural development (Dellett et al., 2012). After tissue injuries in the central nervous system, decorin and biglycan are upregulated in astrocytes, and may play roles in the recovery or the glial scar formation, respectively (Dellett et al., 2012).

Available data about small leucine-rich proteoglycans are very limited in stroke, and only 4 papers have been published. Decorin rs516115 genotypes TC/CC were associated with higher serum glucose and a higher frequency of cerebrovascular diseases compared to the TT genotype (Kunnas et al., 2016). In patients with acute ischemic stroke (within 7 days of onset), plasma decorin levels were significantly decreased, particularly in the large-artery atherosclerotic stroke, and were positively correlated with plasma MMP-2 levels (Xu et al., 2012b). Plasma decorin levels gradually decreased and were the lowest at 7–14 days after ischemic stroke in a clinical setting: lower decorin levels were associated with poorer outcomes (Xu et al., 2012a). In a rat two-hemorrhage injection model into the cisterna magna, the treatment with recombinant decorin inhibited the upregulation of TGF-β1, phosphorylated Smad2/3, connective tissue growth factor, collagen I and pro-collagen I C-terminal propeptide after subarachnoid hemorrhage, resulting in less subarachnoid fibrosis, less frequency in chronic hydrocephalus and better neurocognitive function (Yan et al., 2016a).

2.11. Pigment epithelium-derived factor (PEDF)

PEDF is a glycoprotein of a non-inhibitory member of the serine protease inhibitor gene family, and is expressed in neurons and astrocytes in the cerebral cortex and striatum in adult rat brain (Sanagi et al., 2008).

In a rat permanent MCA occlusion model, PEDF was downregulated at an early stage and was upregulated by a peroxisome proliferator-activated receptor-γ agonist, thus causing the downregulation of NF-κB and MMP-9 and a decrease in neurological deficits, brain edema and infarct volume (Zhu et al., 2012). In a rat transient MCA occlusion model, PEDF was upregulated in reactive astrocytes at 7 days post-ischemia, and had neuroprotective effects by increasing an inducible antioxidant enzyme manganese superoxide dismutase, facilitating glutamate clearance via the upregulation of glutamate transporters, attenuating pro-inflammatory gene expression, preventing the development of brain edema via the downregulation of water channel aquaporin 4, and inhibiting the degeneration of glial cells (Sanagi et al., 2008). Exosomes from PEDF-modified adipose-derived mesenchymal stem cells ameliorated cerebral ischemia-reperfusion injury by activating autophagy and suppressing neuronal apoptosis in a rat MCA occlusion model (Huang et al., 2018).

In hemorrhagic stroke, no studies have been reported as to the roles of PEGF.

2.12. Other matricellular proteins

Autotaxin, the CCN (cysteine-rich angiogenic protein 61, connective tissue growth factor and nephroblastoma overexpressed gene) family of proteins, R-spondins, hemicentin, and βig-h3 (also known as keratoepithelin, RGD-CAP, or TGF-β-induced protein) are known as matricellular proteins, but their roles in ischemic and hemorrhagic strokes remain unknown.

3. Perspectives

Alterations in expressions of various matricellular proteins may be

Table 2
Matricellular proteins as potential biomarkers in stroke.

Matricellular protein	Cerebral infarction	Intracerebral hemorrhage	Subarachnoid hemorrhage
Tenascin-C	ND	Peripheral blood: - Increase at admission → Poor outcome	Cerebrospinal fluid: - Increase at days 1–3 → Angiographic VSP, DCI, chronic HCP, poor outcome Peripheral blood: - Increase at days 4–6 → angiographic VSP, DCI
Periostin	Peripheral blood: - Higher values → Correlation with 6–28-day poorer outcome	Peripheral blood: - Increase at admission → Poor outcome	Peripheral blood: - Increase at admission → DCI, poor outcome - Increase at days 4–6 → DCI with/without angiographic VSP
Osteopontin	Peripheral blood: - Higher thrombin-cleaved osteopontin N-terminal at admission → Differentiation of atherothrombotic stroke - Increase at day 7 → Poor outcome	Peripheral blood: - Increase within 24 h post-onset → Unknown significance	Peripheral blood: - Increase at days 4–6 → Poor outcome
Galectin	Peripheral blood: - Higher galectin-3 at days 1 and 6 → Poor outcome - Increase of galectin-9 at day 6 and galectin-1 in the 4th week → No relation with outcome	Peripheral blood: - Higher galectin-3 at admission → Poor outcome	Peripheral blood: - Increase at admission → Poor outcome - Increase at days 1–3 → Delayed cerebral infarct with/without angiographic VSP
Thrombospondin	Peripheral blood: - Admission higher thrombospondin-1 → Poor outcome - Admission higher thrombospondin-2 → Unknown significance	Peripheral blood: - Higher thrombospondin-1 → Poor outcome	Cerebrospinal fluid: - Higher thrombospondin-1 at days 1–3 and 5–7 → Cerebral VSP, poor outcome Peripheral blood: - Higher thrombospondin-1 at admission → Cerebral VSP, poor outcome
Secreted protein acidic and rich in cysteine (SPARC)	Peripheral blood: - Admission higher SC1 (ortholog of SPARC) → Stroke severity	ND	ND
Plasminogen activator inhibitor-1	Peripheral blood: - Higher values → Post-thrombolytic intracranial bleeding (with conflicting reports), poor outcome	ND	Cerebrospinal fluid Peripheral blood - Increase around day 7 → Cerebral VSP
Glypican	ND	ND	ND
Fibulin	Peripheral blood - Increase of fibulin-1 at 7 years post-stroke → Unknown significance	Peripheral blood: - Admission higher fibulin-5 → Poor outcome	ND
Small leucine-rich proteoglycan (decorin and biglycan)	Peripheral blood - Prolonged decrease of decorin (lowest, days 7–14 post-stroke) → Poor outcome	ND	ND
Pigment epithelium-derived factor	ND	ND	ND

DCI, delayed cerebral ischemia; HCP, hydrocephalus; ND, no data; SC1, synaptic cleft-1; VSP, vasospasm.

critically implicated in the pathophysiology of ischemic and hemorrhagic strokes, and can cause, suppress or repair brain injuries depending on the surrounding situations and the characteristics of the protein. Recent clinical application of machine learning analysis also demonstrated the importance of some matricellular proteins as a determinant on outcome measures in hemorrhagic stroke (Tanioka et al., 2019). As some of matricellular proteins including tenascin-C, galectin-3, decorin and biglycan belong to damage-associated molecular patterns and therefore are ligands of pattern recognition receptors such as TLR4, they may be important initiators and enhancers of post-stroke intrinsic inflammatory reactions under sterile conditions (Suzuki, 2019). In addition, as matricellular proteins such as tenascin-C and periostin are products of TLR4, which is a representative of pattern recognition receptors that induces maximal inflammatory reactions among the TLR family, matricellular protein–TLR4–matricellular protein pathways may lead to a vicious spiral that further augments inflammatory reactions and aggravates brain injuries after stroke (Okada et al., 2019). Functional or direct interactions among matricellular proteins including tenascin-C, periostin, osteopontin and galectin-3 have also been reported (Liu et al., 2017; Suzuki et al., 2018a) (Fig. 1). Although the information regarding the roles of matricellular proteins in stroke is still limited, it may be a therapeutic option to block the expression and function of a harmful matricellular protein whereas to augment the expression and function of a protective matricellular protein. The studies reporting the usefulness of matricellular proteins as a prognostic biomarker are also increasing (Table 2): in fact, matricellular proteins may be suitable as biomarkers because they are stable, relatively easily measurable, and prompt response proteins to brain insults (Suzuki et al., 2018c). We expect that a better understanding of the roles of matricellular proteins in stroke will provide valuable insights into the pathogenesis and the intrinsic protective mechanisms, ultimately leading to the improvement of therapeutic outcomes in patients with stroke. Now, molecular targeted drugs against some of matricellular proteins are being developed (Jayakumar et al., 2017; Suzuki et al., 2018a). We are waiting for these drugs to be clinically available after meticulous translational researches (Suzuki and Nakano, 2018).

Funding

This work was supported by a grant-in-aid for Scientific Research from Japan Society for the Promotion of Science (grant number 17K10825).

Declaration of Competing Interest

None.

Acknowledgements

We thank Chiduru Yamamoto-Nakamura (Department of Neurosurgery, Mie University Graduate School of Medicine) for her assistance with administrative support.

References

Acar, A., Cevik, M.U., Arikanoglu, A., Evliyaoglu, O., Basarili, M.K., Uzar, E., Ekici, F., Yucel, Y., Tasdemir, N., 2012. Serum levels of calcification inhibitors in patients with intracerebral hemorrhage. Int. J. Neurosci. 122, 227–232. https://doi.org/10.3109/00207454.2011.642039.

Ambrosius, W., Michalak, S., Kazmierski, R., Lukasik, M., Andrzejewska, N., Kozubski, W., 2018. The association between serum matricellular protein: secreted protein acidic and rich in cysteine-like 1 levels and ischemic stroke severity. J. Stroke Cerebrovasc. Dis. 27, 682–685. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.060.

Baliga, S.S., Merrill, G.F., Shinohara, M.L., Denhardt, D.T., 2011. Osteopontin expression during early cerebral ischemia-reperfusion in rats: enhanced expression in the right cortex is suppressed by acetaminophen. PLoS One 6, e14568. https://doi.org/10.1371/journal.pone.0014568.

Baumann, E., Preston, E., Slinn, J., Stanimirovic, D., 2009. Post-ischemic hypothermia attenuates loss of the vascular basement membrane proteins, agrin and SPARC, and the blood-brain barrier disruption after global cerebral ischemia. Brain Res. 1269, 185–197. https://doi.org/10.1016/j.brainres.2009.02.062.

Bonsack, F., Sukumari-Ramesh, S., 2019. Differential cellular expression of galectin-1 and galectin-3 after intracerebral hemorrhage. Front. Cell. Neurosci. 13, 157. https://doi.org/10.3389/fncel.2019.00157.

Burguillos, M.A., Svensson, M., Schulte, T., Boza-Serrano, A., Garcia-Quintanilla, A., Kavanagh, E., Santiago, M., Viceconte, N., Oliva-Martin, M.J., Osman, A.M., Salomonsson, E., Amar, L., Persson, A., Blomgren, K., Achour, A., Englund, E., Leffler, H., Venero, J.L., Joseph, B., Deierborg, T., 2015. Microglia-secreted galectin-3 acts as a toll-like receptor 4 ligand and contributes to microglial activation. Cell Rep. 10, 1626–1638. https://doi.org/10.1016/j.celrep.2015.02.012.

Carbone, F., Vuilleumier, N., Burger, F., Roversi, G., Tamborino, C., Casetta, I., Seraceni, S., Trentini, A., Padroni, M., Dallegri, F., Mach, F., Fainardi, E., Montecucco, F., 2015. Serum osteopontin levels are upregulated and predict disability after an ischaemic stroke. Eur. J. Clin. Invest. 45, 579–586. https://doi.org/10.1111/eci.12446.

Chan, S.-L., Bishop, N., Li, Z., Cipolla, M.J., 2018. Inhibition of PAI (plasminogen activator inhibitor)-1 improves brain collateral perfusion and injury after acute ischemic stroke in aged hypertensive rats. Stroke 49, 1969–1976. https://doi.org/10.1161/STROKEAHA.118.022056.

Chapin, J.C., Hajjar, K.A., 2015. Fibrinolysis and the control of blood coagulation. Blood Rev. 29, 17–24. https://doi.org/10.1016/j.blre.2014.09.003.

Chen, Q., Ye, Z.N., Liu, J.P., Zhang, Z.H., Zhou, C.H., Wang, Y., Hang, C.H., 2016. Elevated cerebrospinal fluid levels of thrombospondin-1 correlate with adverse clinical outcome in patients with aneurysmal subarachnoid hemorrhage. J. Neurol. Sci. 369, 126–130. https://doi.org/10.1016/j.jns.2016.08.017.

Chen, Z.Q., Yu, H., Li, H.Y., Shen, H.T., Li, X., Zhang, J.Y., Zhang, Z.W., Wang, Z., Chen, G., 2019. Negative regulation of glial Tim-3 inhibits the secretion of inflammatory factors and modulates microglia to antiinflammatory phenotype after experimental intracerebral hemorrhage in rats. CNS Neurosci. Ther. 25, 674–684. https://doi.org/10.1111/cns.13100.

Dellett, M., Hu, W., Papadaki, V., Ohnuma, S., 2012. Small leucine rich proteoglycan family regulates multiple signalling pathways in neural development and maintenance. Dev. Growth Differ. 54, 327–340. https://doi.org/10.1111/j.1440-169X.2012.01339.x.

Denorme, F., Wyseure, T., Peeters, M., Vandeputte, N., Gils, A., Deckmyn, H., Vanhoorelbeke, K., Declerck, P.J., De Meyer, S.F., 2016. Inhibition of thrombin-activatable fibrinolysis inhibitor and plasminogen activator inhibitor-1 reduces ischemic brain damage in mice. Stroke 47, 2419–2422. https://doi.org/10.1161/STROKEAHA.116.014091.

Dong, X.Q., Yu, W.H., Zhu, Q., Cheng, Z.Y., Chen, Y.H., Lin, X.F., Ten, X.L., Tang, X.B., Chen, J., 2015. Changes in plasma thrombospondin-1 concentrations following acute intracerebral hemorrhage. Clin. Chim. Acta 450, 349–355. https://doi.org/10.1016/j.cca.2015.09.013.

Doyle, K.P., Yang, T., Lessov, N.S., Ciesielski, T.M., Stevens, S.L., Simon, R.P., King, J.S., Stenzel-Poore, M.P., 2008. Nasal administration of osteopontin peptide mimetics confers neuroprotection in stroke. J. Cereb. Blood Flow Metab. 28, 1235–1248. https://doi.org/10.1038/jcbfm.2008.17.

Fujimoto, M., Shiba, M., Kawakita, F., Liu, L., Shimojo, N., Imanaka-Yoshida, K., Yoshida, T., Suzuki, H., 2016. Deficiency of tenascin-C and attenuation of blood-brain barrier disruption following experimental subarachnoid hemorrhage in mice. J. Neurosurg. 124, 1693–1702. https://doi.org/10.3171/2015.4.JNS15484.

Fujimoto, M., Shiba, M., Kawakita, F., Liu, L., Shimojo, N., Imanaka-Yoshida, K., Yoshida, T., Suzuki, H., 2018. Effects of tenascin-C knockout on cerebral vasospasm after experimental subarachnoid hemorrhage in mice. Mol. Neurobiol. 55, 1951–1958. https://doi.org/10.1007/s12035-017-0466-x.

Gao, J.B., Tang, W.D., Wang, H.X., Xu, Y., 2015. Predictive value of thrombospondin-1 for outcomes in patients with acute ischemic stroke. Clin. Chim. Acta 450, 176–180. https://doi.org/10.1016/j.cca.2015.08.014.

Gong, L., Manaenko, A., Fan, R., Huang, L., Enkhjargal, B., McBride, D., Ding, Y., Tang, J., Xiao, X., Zhang, J.H., 2018. Osteopontin attenuates inflammation via JAK2/STAT1 pathway in hyperglycemic rats after intracerebral hemorrhage. Neuropharmacology 138, 160–169. https://doi.org/10.1016/j.neuropharm.2018.06.009.

Griemert, E.V., Recarte Pelz, K., Engelhard, K., Schafer, M.K., Thal, S.C., 2018. PAI-1 but not PAI-2 gene deficiency attenuates ischemic brain injury after experimental stroke. Transl. Stroke Res. https://doi.org/10.1007/s12975-018-0644-9.

Guo, J., Cheng, C., Chen, C.S., Xing, X., Xu, G., Feng, J., Qin, X., 2016. Overexpression of fibulin-5 attenuates ischemia/reperfusion injury after middle cerebral artery occlusion in rats. Mol. Neurobiol. 53, 3154–3167. https://doi.org/10.1007/s12035-015-9222-2.

He, X.W., Li, W.L., Li, C., Liu, P., Shen, Y.G., Zhu, M., Jin, X.P., 2017. Serum levels of galectin-1, galectin-3, and galectin-9 are associated with large artery atherosclerotic stroke. Sci. Rep. 7, 40994. https://doi.org/10.1038/srep40994.

He, X., Bao, Y., Shen, Y., Wang, E., Hong, W., Ke, S., Jin, X., 2018. Longitudinal evaluation of serum periostin levels in patients after large-artery atherosclerotic stroke: a prospective observational study. Sci. Rep. 8, 11729. https://doi.org/10.1038/s41598-018-30121-5.

Hendrix, P., Foreman, P.M., Harrigan, M.R., Fisher 3rd, W.S., Vyas, N.A., Lipsky, R.H., Lin, M., Walters, B.C., Tubbs, R.S., Shoja, M.M., Pittet, J.F., Mathru, M., Griessenauer, C.J., 2017. Association of plasminogen activator inhibitor 1 (SERPINE1) polymorphisms and aneurysmal subarachnoid hemorrhage. World Neurosurg. 105, 672–677. https://doi.org/10.1016/j.wneu.2017.05.175.

Hill, J.J., Jin, K., Mao, X.O., Xie, L., Greenberg, D.A., 2012. Intracerebral chondroitinase ABC and heparan sulfate proteoglycan glypican improve outcome from chronic stroke in rats. Proc. Natl. Acad. Sci. U. S. A. 109, 9155–9160. https://doi.org/10.1073/pnas.1205697109.

Hu, L., Dong, M.X., Zhao, H., Xu, G.H., Qin, X.Y., 2016. Fibulin-5: a novel biomarker for evaluating severity and predicting prognosis in patients with acute intracerebral haemorrhage. Eur. J. Neurol. 23, 1195–1201. https://doi.org/10.1111/ene.13013.

Hu, X., Zan, X., Xie, Z., Li, Y., Lin, S., Li, H., You, C., 2017. Association between plasminogen activator inhibitor-1 genetic polymorphisms and stroke susceptibility. Mol. Neurobiol. 54, 328–341. https://doi.org/10.1007/s12035-015-9549-8.

Hua, Y., Xi, G., Keep, R.F., Wu, J., Jiang, Y., Hoff, J.T., 2002. Plasminogen activator inhibitor-1 induction after experimental intracerebral hemorrhage. J. Cereb. Blood Flow Metab. 22, 55–61. https://doi.org/10.1097/00004647-200201000-00007.

Huang, X., Ding, J., Li, Y., Liu, W., Ji, J., Wang, H., Wang, X., 2018. Exosomes derived from PEDF modified adipose-derived mesenchymal stem cells ameliorate cerebral ischemia-reperfusion injury by regulation of autophagy and apoptosis. Exp. Cell Res. 371, 269–277. https://doi.org/10.1016/j.yexcr.2018.08.021.

Ikeda, K., Asakura, H., Futami, K., Yamashita, J., 1997. Coagulative and fibrinolytic activation in cerebrospinal fluid and plasma after subarachnoid hemorrhage. Neurosurgery 41, 344–350. https://doi.org/10.1097/00006123-199708000-00002.

Ishibashi, S., Kuroiwa, T., Sakaguchi, M., Sun, L., Kadoya, T., Okano, H., Mizusawa, H., 2007. Galectin-1 regulates neurogenesis in the subventricular zone and promotes functional recovery after stroke. Exp. Neurol. 207, 302–313. https://doi.org/10.1016/j.expneurol.2007.06.024.

Jayakumar, A.R., Apeksha, A., Norenberg, M.D., 2017. Role of matricellular proteins in disorders of the central nervous system. Neurochem. Res. 42, 858–875. https://doi.org/10.1007/s11064-016-2088-5.

Ji, Y., Meng, Q.H., Wang, Z.G., 2014. Changes in the coagulation and fibrinolytic system of patients with subarachnoid hemorrhage. Neurol. Med. Chir. (Tokyo) 54, 457–464. https://doi.org/10.2176/nmc.oa2013-0006.

Ji, W.J., Chou, X.M., Wu, G.Q., Shen, Y.F., Yang, X.G., Wang, Z.F., Lan, L.X., Shi, X.G., 2017. Association between serum periostin concentrations and outcome after acute spontaneous intracerebral hemorrhage. Clin. Chim. Acta 474, 23–27. https://doi.org/10.1016/j.cca.2017.09.002.

Kanamaru, H., Kawakita, F., Asada, R., Suzuki, H., 2019a. The role of periostin in brain injury caused by subarachnoid hemorrhage. OBM Neurobiology 3, 15. https://doi.org/10.21926/obm.neurobiol.1903035.

Kanamaru, H., Kawakita, F., Nakano, F., Miura, Y., Shiba, M., Yasuda, R., Toma, N., Suzuki, H., pSEED group, 2019b. Plasma periostin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Neurotherapeutics 16, 480–490. https://doi.org/10.1007/s13311-018-00707-y.

Kawakita, F., Suzuki, H., 2020. Periostin in cerebrovascular disease. Neural Regen. Res. 15 (1), 63–64. https://doi.org/10.4103/1673-5374.264456.

Kudo, A., 2017. Introductory review: periostin-gene and protein structure. Cell. Mol. Life Sci. 74, 4259–4268. https://doi.org/10.1007/s00018-017-2643-5.

Kunnas, T., Solakivi, T., Määttä, K., Nikkari, S.T., 2016. Decorin genotypes, serum glucose, heart rate, and cerebrovascular events: the Tampere adult population cardiovascular risk study. Genet. Test. Mol. Biomarkers 20, 416–419. https://doi.org/10.1089/gtmb.2016.0049.

Ladwig, A., Walter, H.L., Hucklenbroich, J., Willuweit, A., Langen, K.-J., Fink, G.R., Rueger, M.A., Schroeter, M., 2017. Osteopontin augments M2 microglia response and separates M1- and M2-polarized microglial activation in permanent focal cerebral

ischemia. Mediators Inflamm. 2017, 1–11. https://doi.org/10.1155/2017/7189421.
Lalancette-Hebert, M., Gowing, G., Simard, A., Weng, Y.C., Kriz, J., 2007. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. J. Neurosci. 27, 2596–2605. https://doi.org/10.1523/JNEUROSCI.5360-06.2007.
Liao, F., Li, G., Yuan, W., Chen, Y., Zuo, Y., Rashid, K., Zhang, J.H., Feng, H., Liu, F., 2016. LSKL peptide alleviates subarachnoid fibrosis and hydrocephalus by inhibiting TSP1-mediated TGF-β1 signaling activity following subarachnoid hemorrhage in rats. Exp. Ther. Med. 12, 2537–2543.
Liauw, J., Hoang, S., Choi, M., Eroglu, C., Choi, M., Sun, G.H., Percy, M., Wildman-Tobriner, B., Bliss, T., Guzman, R.G., Barres, B.A., Steinberg, G.K., 2008. Thrombospondins 1 and 2 are necessary for synaptic plasticity and functional recovery after stroke. J. Cereb. Blood Flow Metab. 28, 1722–1732. https://doi.org/10.1038/jcbfm.2008.65.
Lin, T.N., Kim, G.M., Chen, J.J., Cheung, W.M., He, Y.Y., Hsu, C.Y., 2003. Differential regulation of thrombospondin-1 and thrombospondin-2 after focal cerebral ischemia/reperfusion. Stroke 34, 177–186.
Liu, L., Suzuki, H., 2018. The role of matricellular proteins in experimental subarachnoid hemorrhage-induced early brain injury. In: Lapchak, P.A., Zhang, J.H. (Eds.), Springer Series in Translational Stroke Research: Cellular and Molecular Approaches to Regeneration and Repair. Springer Nature, Cham, MO, pp. 397–407. https://doi.org/10.1007/978-3-319-66679-2_20.
Liu, H., Liu, Y., Zhao, J., Liu, H., He, S., 2016. Prognostic value of plasma galectin-3 levels after aneurysmal subarachnoid hemorrhage. Brain Behav. 6, e00543. https://doi.org/10.1002/brb3.543.
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. https://doi.org/10.1161/STROKEAHA.117.016629.
Liu, L., Fujimoto, M., Nakano, F., Nishikawa, H., Okada, T., Kawakita, F., Imanaka-Yoshida, K., Yoshida, T., Suzuki, H., 2018a. Deficiency of tenascin-C alleviates neuronal apoptosis and neuroinflammation after experimental subarachnoid hemorrhage in mice. Mol. Neurobiol. 55, 8346–8354. https://doi.org/10.1007/s12035-018-1006-z.
Liu, Y., Cheng, J., Guo, X., Mo, J., Gao, B., Zhou, H., Wu, Y., Li, Z., 2018b. The roles of PAI-1 gene polymorphisms in atherosclerotic diseases: a systematic review and meta-analysis involving 149,908 subjects. Gene 673, 167–173. https://doi.org/10.1016/j.gene.2018.06.040.
Lively, S., Schlichter, L.C., 2012. SC1/hevin identifies early white matter injury after ischemia and intracerebral hemorrhage in young and aged rats. J. Neuropathol. Exp. Neurol. 71, 480–493. https://doi.org/10.1097/NEN.0b013e318256901c.
Lloyd-Burton, S.M., York, E.M., Anwar, M.A., Vincent, A.J., Roskams, A.J., 2013. SPARC regulates microglosis and functional recovery following cortical ischemia. J. Neurosci. 33, 4468–4481. https://doi.org/10.1523/JNEUROSCI.3585-12.2013.
Lok, Z.S.Y., Lyle, A.N., 2019. Osteopontin in vascular disease. Arterioscler. Thromb. Vasc. Biol. 39, 613–622. https://doi.org/10.1161/ATVBAHA.118.311577.
Luo, W., Wang, H., Hu, J., 2018. Increased concentration of serum periostin is associated with poor outcome of patients with aneurysmal subarachnoid hemorrhage. J. Clin. Lab. Anal. 32, e22389. https://doi.org/10.1002/jcla.22389.
Nakatsuka, Y., Kawakita, F., Yasuda, R., Umeda, Y., Toma, N., Sakaida, H., Suzuki, H., pSEED group, 2017. Preventive effects of cilostazol against the development of shunt-dependent hydrocephalus after subarachnoid hemorrhage. J. Neurosurg. 127, 319–326. https://doi.org/10.3171/2016.5.JNS152907.
Nakatsuka, Y., Shiba, M., Nishikawa, H., Terashima, M., Kawakita, F., Fujimoto, M., Suzuki, H., pSEED group, 2018. Acute-phase plasma osteopontin as an independent predictor for poor outcome after aneurysmal subarachnoid hemorrhage. Mol. Neurobiol. 55, 6841–6849. https://doi.org/10.1007/s12035-018-0893-3.
Navarro-Sobrino, M., Rosell, A., Hernández-Guillamon, M., Penalba, A., Boada, C., Domingues-Montanari, S., Ribó, M., Alvarez-Sabín, J., Montaner, J., 2011. A large screening of angiogenesis biomarkers and their association with neurological outcome after ischemic stroke. Atherosclerosis 216, 205–211. https://doi.org/10.1016/j.atherosclerosis.2011.01.030.
Nishikawa, H., Suzuki, H., 2017. Implications of periostin in the development of subarachnoid hemorrhage-induced brain injuries. Neural Regen. Res. 12, 1982–1984. https://doi.org/10.4103/1673-5374.221150.
Nishikawa, H., Suzuki, H., 2018. Possible role of inflammation and galectin-3 in brain injury after subarachnoid hemorrhage. Brain Sci. 8https://doi.org/10.3390/brainsci8020030. pii: E30.
Nishikawa, H., Liu, L., Nakano, F., Kawakita, F., Kanamaru, H., Nakatsuka, Y., Okada, T., Suzuki, H., 2018a. Modified citrus pectin prevents blood-brain barrier disruption in mouse subarachnoid hemorrhage by inhibiting galectin-3. Stroke 49, 2743–2751. https://doi.org/10.1161/STROKEAHA.118.021757.
Nishikawa, H., Nakatsuka, Y., Shiba, M., Kawakita, F., Fujimoto, M., Suzuki, H., pSEED group, 2018b. Increased plasma galectin-3 preceding the development of delayed cerebral infarction and eventual poor outcome in non-severe aneurysmal subarachnoid hemorrhage. Transl. Stroke Res. 9, 110–119. https://doi.org/10.1007/s12975-017-0564-0.
Obaya, A.J., Rua, S., Moncada-Pazos, A., Cal, S., 2012. The dual role of fibulins in tumorigenesis. Cancer Lett. 325, 132–138. https://doi.org/10.1016/j.canlet.2012.06.019.
O'Donnell, M.J., Chin, S.L., Rangarajan, S., Xavier, D., Liu, L., Zhang, H., Rao-Melacini, P., Zhang, X., Pais, P., Agapay, S., Lopez-Jaramillo, P., Damasceno, A., Langhorne, P., MJ, M., Rosengren, A., Dehghan, M., Hankey, G.J., Dans, A.L., Elsayed, A., Avezum, A., Mondo, C., Diener, H.C., Ryglewicz, D., Czlonkowska, A., Pogosova, N., Weimar, C., Iqbal, R., Diaz, R., Yusoff, K., Yusufali, A., Oguz, A., Wang, X., Penaherrera, E., Lanas, F., Ogah, O.S., Ogunniyi, A., Iversen, H.K., Malaga, G., Rumboldt, Z., Oveisgharan, S., Al Hussain, F., Magazi, D., Nilanont, Y., Ferguson, J., Pare, G., Yusuf, S., INTERSTROKE investigators, 2016. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 388, 761–775. https://doi.org/10.1016/S0140-6736(16)30506-2.
Okada, T., Suzuki, H., 2017. Toll-like receptor 4 as a possible therapeutic target for delayed brain injuries after aneurysmal subarachnoid hemorrhage. Neural Regen. Res. 12, 193–196. https://doi.org/10.4103/1673-5374.200795.
Okada, T., Kawakita, F., Nishikawa, H., Nakano, F., Liu, L., Suzuki, H., 2019. Selective toll-like receptor 4 antagonists prevent acute blood-brain barrier disruption after subarachnoid hemorrhage in mice. Mol. Neurobiol. 56, 976–985. https://doi.org/10.1007/s12035-018-1145-2.
Ozaki, S., Kurata, M., Kumon, Y., Matsumoto, S., Tagawa, M., Watanabe, H., Ohue, S., Higaki, J., Ohnishi, T., 2017. Plasma thrombin-cleaved osteopontin as a potential biomarker of acute atherothrombotic ischemic stroke. Hypertens. Res. 40, 61–66. https://doi.org/10.1038/hr.2016.110.
Rabenstein, M., Hucklenbroich, J., Willuweit, A., Ladwig, A., Fink, G.R., Schroeter, M., Langen, K.J., Rueger, M.A., 2015. Osteopontin mediates survival, proliferation and migration of neural stem cells through the chemokine receptor CXCR4. Stem Cell Res. Ther. 6, 1–12. https://doi.org/10.1186/s13287-015-0098-x.
Rahimian, R., Lively, S., Abdelhamid, E., Lalancette-Hebert, M., Schlichter, L., Sato, S., Kriz, J., 2019. Delayed galectin-3-mediated reprogramming of microglia after stroke is protective. Mol. Neurobiol. https://doi.org/10.1007/s12035-019-1527-0.
Rogall, R., Rabenstein, M., Vay, S., Bach, A., Pikhovych, A., Baermann, J., Hoehn, M., Couillard-Despres, S., Fink, G.R., Schroeter, M., Rueger, M.A., 2018. Bioluminescence imaging visualizes osteopontin-induced neurogenesis and neuroblast migration in the mouse brain after stroke. Stem Cell Res. Ther. 9, 1–12. https://doi.org/10.1186/s13287-018-0927-9.
Roll, L., Faissner, A., 2019. Tenascins in CNS lesions. Semin. Cell Dev. Biol. 89, 118–124. https://doi.org/10.1016/j.semcdb.2018.09.012.
Sanagi, T., Yabe, T., Yamada, H., 2008. Gene transfer of PEDF attenuates ischemic brain damage in the rat middle cerebral artery occlusion model. J. Neurochem. 106, 1841–1854. https://doi.org/10.1111/j.1471-4159.2008.05529.x.
Shen, Y.F., Wang, W.H., Yu, W.H., Dong, X.Q., Du, Q., Yang, D.B., Wang, H., Jiang, L., Du, Y.F., Zhang, Z.Y., Zhu, Q., Che, Z.H., Liu, Q.J., 2015. The prognostic value of plasma thrombospondin-1 concentrations after aneurysmal subarachnoid hemorrhage. Clin. Chim. Acta 448, 155–160. https://doi.org/10.1016/j.cca.2015.06.024.
Shiba, M., Suzuki, H., 2019. Lessons from tenascin-C knockout mice and potential clinical application to subarachnoid hemorrhage. Neural Regen. Res. 14, 262–264. https://doi.org/10.4103/1673-5374.244789.
Shimamura, M., Taniyama, Y., Katsuragi, N., Koibuchi, N., Kyutoku, M., Sato, N., Allahtavakoli, M., Wakayama, K., Nakagami, H., Morishita, R., 2012. Role of central nervous system periostin in cerebral ischemia. Stroke 43, 1108–1114. https://doi.org/10.1161/STROKEAHA.111.636662.
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. https://doi.org/10.1038/hr.2014.36.
Sun, L., Qiang, R., Yang, Y., Jiang, Z.-L., Wang, G.-H., Zhao, G.-W., Ren, T.-J., Jiang, R., Xu, L.-H., 2014. L-Serine treatment may improve neurorestoration of rats after permanent focal cerebral ischemia potentially through improvement of neurorepair. PLoS One 9, e93405. https://doi.org/10.1371/journal.pone.0093405.
Suzuki, H., 2019. Inflammation: a good research target to improve outcomes of poor-grade subarachnoid hemorrhage. Transl. Stroke Res. https://doi.org/10.1007/s12975-019-00713-y.
Suzuki, H., Nakano, F., 2018. To improve translational research in subarachnoid hemorrhage. Transl. Stroke Res. 9, 1–3. https://doi.org/10.1007/s12975-017-0546-2.
Suzuki, H., Kinoshita, N., Imanaka-Yoshida, K., Yoshida, T., Taki, W., 2008. Cerebrospinal fluid tenascin-C increases preceding the development of chronic shunt–dependent hydrocephalus after subarachnoid hemorrhage. Stroke 39, 1610–1612. https://doi.org/10.1161/STROKEAHA.107.505735.
Suzuki, H., Hasegawa, Y., Chen, W., Kanamaru, K., Zhang, J.H., 2010a. Recombinant osteopontin in cerebral vasospasm after subarachnoid hemorrhage. Ann. Neurol. 68, 650–660. https://doi.org/10.1002/ana.22102.
Suzuki, H., Kanamaru, K., Suzuki, Y., Aimi, Y., Matsubara, N., Araki, T., Takayasu, M., Kinoshita, N., Imanaka-Yoshida, K., Yoshida, T., Taki, W., 2010b. Tenascin-C is induced in cerebral vasospasm after subarachnoid hemorrhage in rats and humans: a pilot study. Neurol. Res. 32, 179–184. https://doi.org/10.1179/174313208X355495.
Suzuki, H., Kanamaru, K., Shiba, M., Fujimoto, M., Imanaka-Yoshida, K., Yoshida, T., Taki, W., 2011. Cerebrospinal fluid tenascin-C in cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J. Neurosurg. Anesthesiol. 23, 310–317. https://doi.org/10.1097/ANA.0b013e31822aa1f2.
Suzuki, H., Kanamaru, K., Shiba, M., Fujimoto, M., Kawakita, F., Imanaka-Yoshida, K., Yoshida, T., Taki, W., 2015. Tenascin-C is a possible mediator between initial brain injury and vasospasm–related and –unrelated delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Acta Neurochir. Suppl. 120, 117–121. https://doi.org/10.1007/978-3-319-04981-6_20.
Suzuki, H., Fujimoto, M., Kawakita, F., Liu, L., Nakatsuka, Y., Nakano, F., Nishikawa, H., Okada, T., Kanamaru, H., Imanaka-Yoshida, K., Yoshida, T., Shiba, M., 2018a. Tenascin-C in brain injuries and edema after subarachnoid hemorrhage: findings from basic and clinical studies. J. Neurosci. Res. https://doi.org/10.1002/jnr.24330.
Suzuki, H., Nakatsuka, Y., Yasuda, R., Shiba, M., Miura, Y., Terashima, M., Suzuki, Y., Hakozaki, K., Goto, F., Toma, N., 2019. Dose-dependent inhibitory effects of cilostazol on delayed cerebral infarction after aneurysmal subarachnoid hemorrhage. Transl. Stroke Res. 10 (4), 381–388. https://doi.org/10.1007/s12975-018-0650-y.
Suzuki, H., Nishikawa, H., Kawakita, F., 2018c. Matricellular proteins as possible biomarkers for early brain injury after aneurysmal subarachnoid hemorrhage. Neural Regen. Res. 13, 1175–1178. https://doi.org/10.4103/1673-5374.235022.

Tanioka, S., Ishida, F., Nakano, F., Kawakita, F., Kanamaru, H., Nakatsuka, Y., Nishikawa, H., Suzuki, H., pSEED group, 2019. Machine learning analysis of matricellular proteins and clinical variables for early prediction of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Mol. Neurobiol. https://doi.org/10.1007/s12035-019-1601-7.

Vadgama, N., Lamont, D., Hardy, J., Nasir, J., Lovering, R.C., 2019. Distinct proteomic profiles in monozygotic twins discordant for ischaemic stroke. Mol. Cell. Biochem. 456, 157–165. https://doi.org/10.1007/s11010-019-03501-2.

Wang, X., Louden, C., Yue, T.-L., Ellison, J.A., Barone, F.C., Solleveld, H.A., Feuerstein, G.Z., 1998. Delayed expression of osteopontin after focal stroke in the rat. J. Neurosci. 18, 2075–2083. https://doi.org/10.1523/jneurosci.18-06-02075.1998.

Wang, J., Xia, J., Zhang, F., Shi, Y., Wu, Y., Pu, H., Liou, A.K., Leak, R.K., Yu, X., Chen, L., Chen, J., 2015a. Galectin-1-secreting neural stem cells elicit long-term neuroprotection against ischemic brain injury. Sci. Rep. 5, 9621. https://doi.org/10.1038/srep09621.

Wang, W., Li, M., Chen, Q., Wang, J., 2015b. Hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke: mechanisms, models, and biomarkers. Mol. Neurobiol. 52, 1572–1579. https://doi.org/10.1007/s12035-014-8952-x.

Wang, L.G., Huangfu, X.Q., Tao, B., Zhong, G.J., Le, Z.D., 2018. Serum tenascin-C predicts severity and outcome of acute intracerebral hemorrhage. Clin. Chim. Acta 481, 69–74. https://doi.org/10.1016/j.cca.2018.02.033.

Wei, D., Xiong, X., Zhao, H., 2015. Tim-3 cell signaling and iNOS are involved in the protective effects of ischemic postconditioning against focal ischemia in rats. Metab. Brain Dis. 30, 483–490. https://doi.org/10.1007/s11011-014-9543-2.

Wu, X., Luo, X., Zhu, Q., Zhang, J., Liu, Y., Luo, H., Cheng, Y., Xie, Z., 2017. The roles of thrombospondins in hemorrhagic stroke. Biomed. Res. Int. 2017, 8403184. https://doi.org/10.1155/2017/8403184.

Xu, Y.-Z., Yang, Z.-G., Zhang, Y.-H., Zhang, Y.-W., Hong, B., Liu, J.-M., 2012a. Dynamic reduction of plasma decorin following ischemic stroke: a pilot study. Neurochem. Res. 37, 1843–1848. https://doi.org/10.1007/s11064-012-0787-0.

Xu, Y.-Z., Zhao, K.-J., Yang, Z.-G., Zhang, Y.-H., Zhang, Y.-W., Hong, B., Liu, J.-M., 2012b. Decreased plasma decorin levels following acute ischemic stroke: correlation with MMP-2 and differential expression in TOAST subtypes. Mol. Med. Rep. 6, 1319–1324. https://doi.org/10.3892/mmr.2012.1108.

Yan, Y.-P., Lang, B.T., Vemuganti, R., Dempsey, R.J., 2009. Persistent migration of neuroblasts from the subventricular zone to the injured striatum mediated by osteopontin following intracerebral hemorrhage. J. Neurochem. 109, 1624–1635. https://doi.org/10.1111/j.1471-4159.2009.06059.x.

Yan, H., Chen, Y., Li, L., Jiang, J., Wu, G., Zuo, Y., Zhang, J.H., Feng, H., Yan, X., Liu, F., 2016a. Decorin alleviated chronic hydrocephalus via inhibiting TGF-β1/Smad/CTGF pathway after subarachnoid hemorrhage in rats. Brain Res. 1630, 241–253. https://doi.org/10.1016/j.brainres.2015.11.004.

Yan, X.J., Yu, G.F., Jie, Y.Q., Fan, X.F., Huang, Q., Dai, W.M., 2016b. Role of galectin-3 in plasma as a predictive biomarker of outcome after acute intracerebral hemorrhage. J. Neurol. Sci. 368, 121–127. https://doi.org/10.1016/j.jns.2016.06.071.

Yang, A.L., Zhou, H.J., Lin, Y., Luo, J.K., Cui, H.J., Tang, T., Yang, Q.D., 2012. Thrombin promotes the expression of thrombospondin-1 and -2 in a rat model of intracerebral hemorrhage. J. Neurol. Sci. 323, 141–146. https://doi.org/10.1016/j.jns.2012.09.002.

Zhang, W., Wang, Y., Bi, G., 2017. Limb remote ischaemic postconditioning-induced elevation of fibulin-5 confers neuroprotection to rats with cerebral ischaemia/reperfusion injury: activation of the AKT pathway. Clin. Exp. Pharmacol. Physiol. 44, 656–663. https://doi.org/10.1111/1440-1681.12742.

Zhang, W., Cui, Y., Gao, J., Li, R., Jiang, X., Tian, Y., Wang, K., Cui, J., 2018. Recombinant osteopontin improves neurological functional recovery and protects against apoptosis via PI3K/Akt/GSK-3β pathway following intracerebral hemorrhage. Med. Sci. Monit. 24, 1588–1596. https://doi.org/10.12659/msm.905700.

Zhang, Q., Zhou, M., Wu, X., Li, Z., Liu, B., Gao, W., Yue, J., Liu, T., 2019. Promoting therapeutic angiogenesis of focal cerebral ischemia using thrombospondin-4 (TSP4) gene-modified bone marrow stromal cells (BMSCs) in a rat model. J. Transl. Med. 17, 111. https://doi.org/10.1186/s12967-019-1845-z.

Zhou, H.J., Zhang, H.N., Tang, T., Zhong, J.H., Qi, Y., Luo, J.K., Lin, Y., Yang, Q.D., Li, X.Q., 2010. Alteration of thrombospondin-1 and -2 in rat brains following experimental intracerebral hemorrhage: laboratory investigation. J. Neurosurg. 113, 820–825. https://doi.org/10.3171/2010.1.JNS09637.

Zhu, C., Zhang, X., Qiao, H., Wang, L., Zhang, X., Xing, Y., Wang, C., Dong, L., Ji, Y., Cao, X., 2012. The intrinsic PEDF is regulated by PPARγ in permanent focal cerebral ischemia of rat. Neurochem. Res. 37, 2099–2107. https://doi.org/10.1007/s11064-012-0831-0.

Zhu, Q., Luo, X., Zhang, J., Liu, Y., Luo, H., Huang, Q., Cheng, Y., Xie, Z., 2017. Osteopontin as a potential therapeutic target for ischemic stroke. Curr. Drug Deliv. 14, 766–772. https://doi.org/10.2174/1567201814666161116162148.