Ninjurin1
– A Novel Regulator of Angiogenesis Mediated by Pericytes –
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Angiogenesis, the growth of new capillary from existing blood vessels, is an important natural process that is central to various pathophysiological processes in the body, not only during fetal development but also in postnatal tissue repair and disease development. Angiogenesis is a hallmark of wound healing, cancer development, ischemic and inflammatory diseases.1–3

The formation of new sprouts is dynamic and requires a large number of highly orchestrated processes. Three different types of endothelial cells (ECs), comprising tip, stalk and phalanx cells, have been suggested to be involved in sprouting angiogenesis. Attracted by proangiogenic signals, ECs degrade cell-cell junctions, including VE-cadherin and ZO-1, so that basement membrane and pericytes detach, allowing a tip cell to migrate in response to guidance signals. Following the migration of tip cells, stalk cells proliferate and form a lumen to maintain the integrity and perfusion of the growing vascular bed. Tip cells from neighboring sprouts meet and anastomose to form a perfused branch. Upon the initiation of blood flow, ECs become quiescent phalanx cells. Deposition of basement membrane and recruitment of mural cells stabilize the new connection. A fundamental feature of vessel maturation is the recruitment of the mural cells, pericytes and vascular smooth muscle cells that coat small capillaries and larger vessels, respectively.3 During angiogenesis, bidirectional pericyte-EC signaling is critical for capillary sprout formation. Observations of pericytes leading capillary sprouts also imply their role in EC guidance. As such, pericytes have recently emerged as a therapeutic target to promote or inhibit angiogenesis.4 The prominent signaling pathways that regulate endothelial-mural cell-cell communication are platelet-derived growth factor-β (PDGF-β)/PDGF receptor-β, angiopoietin 1 (Ang1)/Tie2 and transforming growth factor β, which control mural cell recruitment, EC viability and mural cell differentiation, respectively.3–6 However, the mechanisms which regulate their actions in microvascular physiology have been largely underinvestigated.

Nerve injury-induced protein 1, or Ninjurin-1 (Ninj1), is a cell-surface protein and an adhesion molecule. Ninj1 was originally discovered during the identification of molecules related to nerve injury and is known to be upregulated in neuronal and Schwann cells after sciatic nerve injury.7 The Ninj1 gene contains an open reading frame of 152 amino acids (aa), which encodes a predicted 16-kDa polypeptide. Ninj1 has 2 hydrophobic transmembrane domains (72–100 aa, and 118–139 aa) and a putative N-glycosylation site.7 In addition, the 12-residues on the N-terminal ectodomain of Ninj1 are crucial for its hemophilic binding activity (Figure).8 In mammals, there are 2 types of Ninjurin, Ninj1 and Ninj2, which share conserved hydrophobic regions for their transmembrane domains but differ in adhesion motifs and they do not interact with each other.8 Furthermore, the tissue distribution of Ninjurs

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Ninj1 negatively regulates angiogenesis by mediating the interaction between PCs and EC tubes. Although the physiological or pathological significance of Ninj1 in angiogenesis and the precise mechanism of EC-PC interaction via Ninj1 remain unclear, these findings may open new avenues to treating ischemic diseases and pericyte-associated diseases, including cancer, diabetes and neurodegenerative disorders, by targeting the Ninj1-related pathways in capillary cells.

**Disclosures**

The authors have no conflict of interest directly relevant to the content of this article.

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