The Gift of Gab1 (Grb-2-Associated Binder 1)

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Ischemia-induced neovascularization is critical for blood flow recovery and tissue repair in hypoxic conditions. It occurs via extension or remodeling of existing blood vessels, observed throughout development and into adulthood. The angiogenic process is driven by growth factors emanating from the zone of ischemia, leading to the activation, proliferation, and migration of endothelial cells (ECs), which lie at the forefront of the expanding vasculature (Figure). Angiogenesis is involved in many physiological and pathological settings, such as ischemia, atherosclerosis, diabetes, and cancer, making it an attractive therapeutic target.

Gab1 belongs to the scaffolding adaptor protein family. It has an N-terminal pleckstrin homology domain, as well as multiple tyrosine-based motifs and proline-rich sequences, which are potential binding sites for Src homology 2 and 3 domains, respectively. Gab1 undergoes tyrosine phosphorylation upon cell stimulation with various growth factors, cytokines, G protein-coupled receptor agonists, and immunoregulatory agents. Tyrosine-phosphorylated Gab1 provides docking sites for Src homology 2 domain–containing signaling molecules, such as the protein-tyrosine phosphatase protein tyrosine phosphatase, non receptor type II (SHP2), phosphatidylinositol 3-kinase regulatory subunit p85, phospholipase C-γ, Crk, and Ras GTPase-activating protein.

Gab1 can be recruited to activated receptors through direct or indirect mechanisms. Direct recruitment has been demonstrated only for interactions between Gab1 and c-Met (the receptor for HGF). However, Gab1 has been shown to interact indirectly with a number of receptor tyrosine kinases relevant to the cardiovascular system, such as the ErbB receptors of neuregulin-1β, and VEGF receptor 2. Gab1 has also been involved in shear stress–dependent activation of protein kinase A, upstream of endothelial nitric oxide production.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Zhao et al directly demonstrate a role for Gab1 in regulating postnatal angiogenesis in vivo and in vitro. In fact, the authors of this article and 2 other groups simultaneously generated Gab1–endothelial cell-specific Gab1 knockout mice using an endothelial-specific cre-lox approach. The animals are viable and have no obvious vascular defects, indicating that endothelial Gab1 is not involved in developmental vasculogenesis. All 3 groups demonstrated that Gab1-ecKO mice have inadequate angiogenesis after hindlimb ischemia: 2 weeks after the femoral artery resection, blood flow and capillary density in the gastrocnemius muscle remain low compared with wild-type mice, which is associated with limb necrosis.

The dramatic decrease in capillary density in Gab1-ecKO mice suggested that EC survival may be compromised. Indeed, Zhao et al report that apoptotic ECs are more abundant in the gastrocnemius muscle from Gab1-ecKO mice than in wild-type mice after ischemia. VEGF and HGF are potent prosurvival factors, and Zhao et al observed that levels of both growth factors are increased in ischemic hindlimb muscles. However, the viability of Gab1-deficient ECs cannot be maintained by either growth factor in vitro, whereas wild-type cells are protected from death. One possible explanation is supplied by Shioyama et al. They demonstrated that in ECs overexpressing Gab1, HGF specifically upregulates the mRNA and protein expression of Krüppel-like factor 2. Krüppel-like factor 2 is an important antiapoptotic agent, acting in part through endothelial nitric oxide synthase activation.

A thorough understanding of signaling pathways underlying postnatal angiogenesis is crucial in designing new treatment for human ischemic diseases. Zhao et al demonstrated that Gab1 is necessary for HGF-induced Akt and extracellular signal-regulated kinase (ERK) 1/2 phosphorylation through phosphatidylinositol 3-kinase and SHP2 activation, respectively. Shioyama et al completed those findings, showing that ERK5 is also activated downstream of Gab1-SHP2 after HGF stimulation. Furthermore, Lu et al found that Gab1 is also required for Akt activation in VEGF-induced angiogenesis and identified an important protein kinase A–dependent pathway for VEGF-induced endothelial nitric oxide synthase activation.

Taken together, the evidence provided by 3 different groups shows that endothelial Gab1 is crucial for HGF- and VEGF-induced postnatal angiogenesis. These studies sug-
ggested a possible cross-talk between VEGF and HGF, both growth factors using Gab1 as a signaling intermediate to activate ERK1/2 and Akt. These are key pathways involved in EC stabilization and migration and could account for the dramatic impairment of angiogenic processes in Gab1−/−KO mice. A logical follow-up question will be to address the role of Gab1 in matrix metalloproteinase activation and vascular remodeling, which are required for EC detachment from extracellular matrix and migration in angiogenesis.

References


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