ADAM-Mediated Shedding, A New Flavor in Angiogenesis Regulation

Lena Claesson-Welsh

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis (ie, blood vessel formation). VEGF acts by binding to the VEGF receptor 2 (VEGFR2) tyrosine kinase, expressed on endothelial cells. In healthy individuals, the vasculature is quiescent; invasion of vascular sprouts into the surrounding tissue during angiogenesis is tightly regulated by the Notch family of ligands and receptors. VEGF is also a critical regulator of vascular permeability, which involves disruption of endothelial adherens junctions through disengagement of vascular endothelial (VE) cadherin.

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Both Notch family receptors and VE-cadherin belong to a wide range of molecules known to be posttranslationally modified by shedding through “a disintegrin and metalloproteinase” (ADAM) proteins, which form the ADAM family of sheddases. The ADAMs are cell surface–localized transmembrane enzymes that act to release ectodomains of membrane proteins, leading to removal of membrane receptors and potentially to creation of fragments with biological activities distinct from the mother protein. In addition, ADAM family members can modify adhesion of cells by binding via their disintegrin domain to integrins, often by presenting the classic R-G-D binding motif. Consequently, it is likely that the ADAMs contribute to both positive and negative regulation of many cellular processes.

By using a yeast–2-hybrid screen, Donners and colleagues have now identified ADAM10 as a binding partner for VEGFR2. They show that VEGF regulates both expression and maturation of ADAM10, which, in turn, promotes shedding of both VEGFR2 and VE-cadherin. Pharmacological inhibition of ADAM10 was accompanied by decreased vascular permeability, at least in vitro (Figure).

Several molecules with potential functions in the vasculature are cleaved by ADAM10, such as VE-cadherin (an adherens junction protein) collagen IV (present in the vascular basement membrane), cMet (a receptor tyrosine kinase and an angiogenic regulator), and interleukin 6 (an inflammatory cytokine). Moreover, gene targeting of ADAM10 underscores its important role in the developing vasculature.

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From the Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden.

Correspondence to Lena Claesson-Welsh, PhD, Department of Genet-
ics and Pathology, Uppsala University, Rudbeck Laboratory, Dag Ham-
marskjölds väg 20, 751 85 Uppsala, Sweden. E-mail Lena.Welsh@g
enpat.uu.se

Editorial


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ADAM10 expression and whether ADAM10 may either serve as a biomarker or be exploited as a therapeutic target. The fact that endothelial cell-specific gene targeting of ADAM17 leads to decreased retinal damage in oxygen-induced retinopathy and to decreased tumor growth supports the notion that ADAM proteins are clinically relevant.

Disclosures

None.

References


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