Editorial

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.1

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.2 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 colleagues3 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 ADAM10,4 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).4 Moreover, gene targeting of ADAM10 underscores its important role in the developing vasculature5.

Figure. Regulation of angiogenesis and vascular permeability by ADAM10. The boxed 1 indicates binding of VEGF to VEGFR2 expressed on endothelial cells, leading to activation of the VEGFR2 tyrosine kinase (red) and (boxed 2) upregulation of ADAM10 expression level and activity (red activity arrow). This, in turn, leads to (boxed 3) cleavage of VEGFR2 and VE-cadherin, located at endothelial cell junctions. Combined, the modification of VEGFR2 and VE-cadherin and other proteins regulates angiogenesis and permeability. PM indicates plasma membrane.

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embryos die at embryonic day 9.5 with multiple developmental defects in the vasculature and other organs. The data from Donners et al3 strongly implicate ADAM10 in pathological angiogenesis. A comparison of normal vessel wall samples with those of ruptured human atherosclerotic plaques showed marked upregulation of ADAM10 immunostaining in the ruptured samples. Similarly, there was increased expression of ADAM10 in the microvasculature in human colorectal cancer.

The details of the complex formation between ADAM10 and VEGFR2, described by Donners and coworkers,3 is unclear. ADAM10 does not possess any known motif for interaction with receptor tyrosine kinases, such as Src homology 2 domains. The recent literature has provided many examples of unorthodox protein-protein interactions (not mediated by known protein interaction domains) (ie, between VEGFR2 and platelet-derived growth factor receptor-β).6 These interactions may reflect high-density colocalization of signaling components in plasma membrane structures, such as lipid rafts. ADAM10 is probably not the only ADAM family member that, under certain circumstances, may associate with VEGFR2 or serve to regulate angiogenesis. Pharmacological inhibition of ADAM10 or combined inhibition of ADAM10 and ADAM17, as tested by Donners and coworkers, often showed a more potent effect when inhibiting both ADAM10 and ADAM17.

Several diseases are accompanied by excess angiogenesis, such as cancer and chronic inflammation, resulting in a strong interest in suppressing angiogenesis for therapeutic purposes. Thus, it is tempting to use targets that are expressed more or less exclusively in “pathological” blood vessels. ADAM10 can be added to the list of proteins that are upregulated in pathological processes. It will be interesting to know whether physiological angiogenesis is accompanied by increased

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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\textsuperscript{7} supports the notion that ADAM proteins are clinically relevant.

**Disclosures**

None.

**References**


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