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Effect of ADAMTS-2, a metalloproteinase containing a disintegrin domain and thrombospondin type I repeats, during angiogenesis *in vitro* and *in vivo*

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Formation of new blood vessels (angiogenesis) is a key step during the development of various pathologies, including cancer. Enzymes of the ADAMTS family are closely related to MMPs and ADAMs. They further contain specific domains, such as the "Thrombospondin type I" (TSP1) repeats, that are able to strongly repress angiogenesis, as described for thrombospondin-1 and -2, and for ADAMTS-1 and -8. The primary function of ADAMTS-2 is to process collagen type I, II and III precursors into mature molecules by excising the amino-propeptide. We further hypothesized that it could modulate angiogenesis through its TSP1 repeats. This hypothesis was investigated using different *in vitro* experimental models of angiogenesis. Recombinant ADAMTS-2 induced morphological changes in human umbilical vein endothelial cells (HUVEC) and human microvessel endothelial cells (HMEC), and significantly reduced their proliferation, attachment and spreading. Similar effects were observed when using inactive ADAMTS-2 mutated at the Zn^{2+}-binding catalytic site. ADAMTS-2 did not alter the initial steps of formation of capillary-like structures by HUVEC *in vitro*. However, these structures appeared much less stable and were more rapidly disrupted in presence of ADAMTS-2 than in control conditions. ADAMTS-2 was also tested in an *ex vivo* angiogenesis model using aortic rings from rats and mice, wild type or KO for ADAMTS-2. Outgrowth of capillaries was slightly increased from aortas of ADAMTS-2 KO mice (TS2-/-) as compared to aortas from control animals (TS2+/+), while addition of full size recombinant ADAMTS-2 reduced the formation of capillary structures from rat aortas, suggesting its anti-angiogenic activity. Choroidal neovascularization induced in TS2+/+ or TS2-/- mice by LASER burns was used as *in vivo* model to confirm the *in vitro* and *ex vivo* results. Several genes involved in the healing and angiogenesis processes (fibrillar collagens, VEGF, TGF-beta and CTGF) were not differently regulated in TS2+/+ and TS2-/- mice at 5 days.