Neuropilin 1 (NRP1) conveys SEMA3A signals to restrict physiological angiogenesis

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Neuropilin 1 (NRP1) is a transmembrane receptor for the angiogenic vascular endothelial growth factor VEGFA and repulsive axon guidance cue semaphorin SEMA3A. While the importance of NRP1 in mediating proangiogenic signalling is largely described, the role of SEMA3A-NRP1 interaction in vessel morphogenesis is still unclear. In mouse embryos SEMA3A and its signalling through NRP1 are dispensable for brain angiogenesis and lack of SEMA3A does not affect intersomitic vessel (ISV) formation in the trunk. On the contrary, Sema3a was reported to restrict vascular sprouting in the zebrafish embryo trunk via Plxnd1 by regulating the alternative splicing of the VEGFA decoy receptor Flt1, even though the involvement of zebrafish NRP1 orthologues, termed Nrp1a and Nrp1b, in zebrafish embryo angiogenesis was questioned by conflicting knockdown and knockout studies. To resolve contradictory information on the vascular roles of NRP1 and SEMA3A, we have refined prior morpholino knockdown strategy and generated mutant zebrafish embryos lacking both NRP1 orthologues to show that Nrp1 genetically interacts with Sema3a to prevent intersomitic blood vessels overgrowth in the zebrafish embryo trunk independently of soluble Flt1. In agreement, human endothelial cells are repelled by SEMA3A in a NRP1-dependent fashion. Together, these findings for the first time demonstrate that NRP1 can serve as a receptor for endogenous SEMA3A repulsive cues in endothelial cells to shape physiological vascular morphogenesis, in analogy to SEMA3A's role in restricting axon growth via NRP1 during nervous system development.