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TITLE

# MORE THAN A CO-RECEPTOR: NEW PERSPECTIVES OF NEUROPILIN-1 FUNCTION IN ENDOTHELIUM AND TUMOR CELLS

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Neuropilin (NRP) is a 130- to 140-kDa transmembrane glycoprotein. Fujisawa and colleges first identified NRP in 1987 as the antigen to a monoclonal antibody that specifically bound to particular neuropiles and plexiform layers of the Xenopus tadpole optic tectum. Later, NRP was found to be a receptor for the class 3 semaphorins (SEMA3), a family of chemorepulsive guidance molecules capable of collapsing axonal growth cones and repelling axons of ganglia by Kolodkin's group. The extracellular regions of NRPs are composed of separate subdomains: the a1a2 domain is involved in SEMA3-binding, the b1b2 domain is involved in both SEMA3- and vascular endothelial growth factor (VEGF)-binding (discussed in more detail below), and the c domain is involved in dimerization. Due to its small intercellular domain (39 amino acids), it was thought to be a co-receptor of VEGF or semaphorin receptors. Several years ago our group showed that NRP1 alone can mediate EC migration through its intracellular domain and it's the three amino acids at the C-terminus (SEA-COOH) are essential for the process. The C terminus of RGS-GAIP-interacting protein (GIPC also known as synectin) conveys neuropilin-1 mediated signaling during angiogenesis. Recently, we also demonstrated that NRP-1/synectin axis modulates p53/Caspases axes to promote endothelial cell survival. Interestingly in the absence of NRP-1, several cancer cells including renal cell carcinoma (RCC) cells express significantly lower levels of MDM-2 and p63 proteins but higher levels of p53, become more drug sensitive, and exhibit reduced migration and invasion. The reduction of Shh production due to NRP-1 knockdown might induce enhanced differentiation of the RCC cells. These results reveal an important role for NRP-1 in RCC tumorigenesis and establish a potential link for the generation and maintenance of the dedifferentiation state of cancer initiating cells.