Glycosaminoglycan modification of Neuropilin-1 modulates VEGFR2 signaling

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Proteoglycan modification of protein is often involved in the interaction between growth factor and its receptors. Neuropilin-1 (NRP1) is a co-receptor for vascular endothelial growth factor (VEGF) that enhances the angiogenic signals cooperatively with VEGFR2. VEGF signaling is essential for physiological and pathological angiogenesis through its effects on vascular endothelial cells (EC) and smooth muscle cells (SMC), but the mechanisms coordinating this response are not well understood. Here we show that a substantial fraction of NRP1 is proteoglycan modified with either heparan sulfate or chondroitin sulfate on a single conserved Ser. The composition of the NRP1 glycosaminoglycan (GAG) chains differs between EC and SMC. Glycosylation increased VEGF binding in both cell types, but the differential GAG composition of NRP1 mediates opposite responsiveness to VEGF in EC and SMC. Finally, NRP1 expression and its GAG modification post-transcriptionally regulate VEGFR2 protein expression. These findings indicate that GAG modification of NRP1 plays a critical role in modulating VEGF signaling, and may provide new insights into physiological and pathological angiogenesis.