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Sialic acid associated to VEGFR2 of the endothelial cell surface is implicated in VEGF-dependent angiogenesis

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Sialic acid (NeuAc) is a major anion on the endothelial cell (EC) where, by governing different molecular interactions it modulates important processes including angiogenesis. NeuAc is usually associated to N-glycan linked to various receptors, including the vascular endothelial growth factor receptor-2 (VEGFR2), the main pro-angiogenic receptor on ECs. By means of complementary approaches including computational analysis, surface plasmon resonance, immunoprecipitation, enzymatic digestion, immunofluorescence, cross-linking experiments with sugar-binding lectins and SiRNA targeting sialyltransferases (STs), we demonstrate that VEGFR2 bears both α,1-fucose and α(2,6)-linked sialic acid (NeuAc). However, only the latter is required for VEGF binding to VEGFR2 and consequent VEGF-dependent VEGFR2 activation and motogenic response in ECs. Accordingly, among the various lectin assayed, only the α(2-6)-NeuAc-binding lectin Sambucus nigra (SNA) prevents VEGF-dependent VEGFR2 autophosphorylation, EC motility, proliferation motogenesis. Also, it inhibits VEGF-dependent angiogenesis in the chick-embryo chorioallantoic membrane neovascularization assay and mouse matrigel plug assay in vivo. Interestingly, downregulation of ST6Gal-1 expression by siRNA transduction inhibits VEGFR2 α(2,6)-NeuAc sialylation that is paralleled by an increase of ST3Gal-1 expression that results in an ex-novo α(2,3)-NeuAc sialylation of the receptor that functionally rescues VEGF/VEGFR2 interaction. Since these data point to VEGFR2 sialylation as a target for the treatment of angiogenesis-dependent diseases, we have started an integrated approach made up of in silico, biochemical and biological methodologies to speed up the process of discovery of compounds able to bind the common structural framework involved in catalysis shared by the different STs implicated in the sialylation of VEGFR2, to be evaluated for their anti-angiogenic potential..

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