Angiopoietin-like 4 as promoter of angiogenesis and vascular permeability

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Angiopoietin-like 4 *(ANGPTL4)*, a member of the *ANGPTL* family, is involved in many pathological disorders, including cardiac and lung diseases, cancer, retinal diseases, diabetes, atherosclerosis and nephrotic syndrome. This cytokine is a circulating multifunctional protein, which undergoes post-translational modifications (glycosylation) and subsequent proteolytic processing by membrane proprotein convertases, upon secretion of the full-length gene product. ANGPTL4 N-terminal domain *(nANGPTL4)* acts as an adipokine, inhibiting lipoprotein lipase (LPL) and causing hydrolysis of circulating triglycerides (TG) into free fatty acids, under conditions of fasting and exercise. Alternatively, *ANGPTL4* C-terminal domain *(cANGPTL4)* has an important role in anoikis resistance, altered redox regulation, tumorigenesis, and angiogenesis. Compelling evidence suggests a role of *cANGPTL4* in solid tumors, including melanoma, breast carcinoma, hepatocellular carcinoma, renal cell carcinoma and colorectal cancer. The overexpression of *ANGPTL4* in tumors appears to be associated with poor prognosis and poor disease-free survival rates. In our lab, we observed that *ANGPTL4* is a pro-angiogenic factor in Kaposi's sarcoma (KS), a vascular tumor caused by infection with human herpesvirus 8 or KS-associated herpesvirus (HHV-8/KSHV), and a common type of oral cancer in immunocompromised individuals. We observed upregulation of *ANGPTL4* in both oral KS lesions and KS animal models because of the expression of the HHV8/KSHV G protein-coupled receptor (vGPCR), a constitutively-active viral GPCR homolog to CXCR2. The mechanism by which vGPCR induces *ANGPTL4* gene expression includes the activation of Hypoxia Inducible Factor 1 (HIF1). Interestingly, we found that vGPCR-induced *ANGPTL4* upregulation promotes angiogenesis in KS by the potent induction of endothelial cell migration. We also found that *ANGPTL4* promotes vessel hyperpermeability, disrupting both adherens and tight endothelial junctions, an effect that contributes to the profuse edema seen in this tumor. Our results suggest that *ANGPTL4* may be a novel therapeutic target for KS and other disorders associated with pathologic angiogenesis and vascular hyperpermeability.

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