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Upregulation of angiopoietin-like 4 by viral G protein-coupled receptor promotes angiogenesis and vascular permeability in Kaposi's sarcoma

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Background

Kaposi's sarcoma (KS) is an enigmatic vascular tumor thought to be a consequence of dysregulated expression of the human herpesvirus-8 (HHV-8 or KSHV)-encoded G protein-coupled receptor (vGPCR) [1]. Both human and vGPCR experimental KS lesions are characterized by prominent angiogenesis and vascular permeability attributed to the paracrine release of angiogenic mediators, most notably vascular endothelial growth factor (VEGF). To date, the relative contribution of these paracrine mediators to the angiogenic and exudative phenotype of KS lesions remains unclear. Here we show that vGPCR upregulated angiopoietin-like 4 (ANGPTL4) (Figure 1A, 1B, 1C) plays a prominent role in promoting the angiogenesis and increasing vascular permeability in this tumor. Inhibition of ANGPTL4 effectively blocks vGPCR promotion of angiogenesis and vascular permeability in vitro and tumorigenesis in vivo (Figure 1D , 1E, 1F, 1G , 1H).

Conclusion

These observations suggest that ANGPTL4 is a previously unrecognized target for the treatment of patients with KS. As angiogenesis and increased vessel permeability are common themes in all solid tumors, these results may have a broad impact on our understanding and treatment of cancer.

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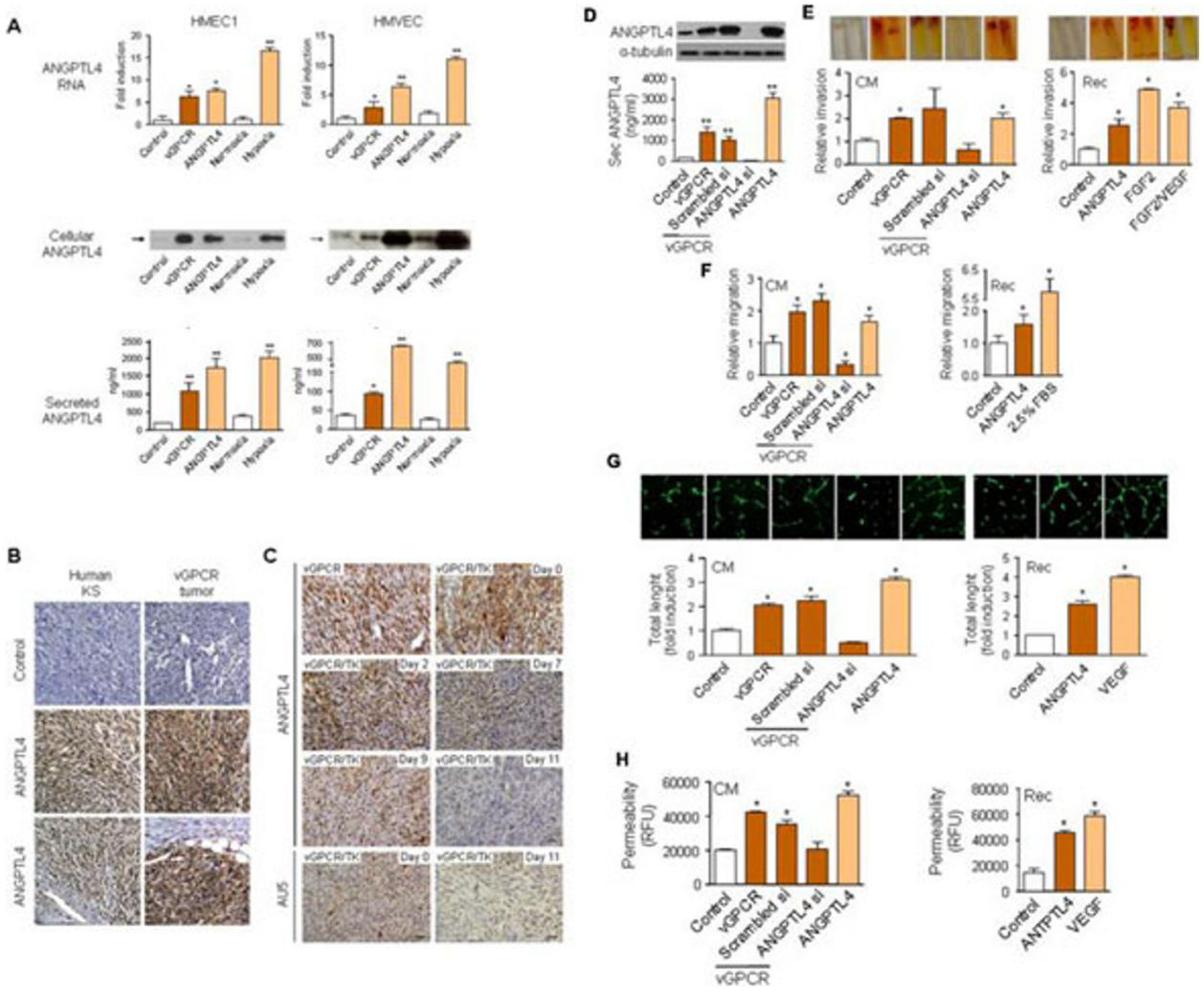

Figure 1 (*A*) Analysis of ANGPTL4 mRNA levels (qRT-PCR), cellular ANGPTL4 (WB) and secreted ANGPTL4 (ELISA) of HMEC1 or HMVEC transfected with pCEFL Tet REV TA and pBIG AU5 vGPCR. (*B*) ANGPTL4 expression in murine vGPCR tumors and human AIDS-KS. An isotype-matched control antibody (Control) or an ANGPTL4 antibody (ANGPTL4) was used. Similar results were found in all murine vGPCR [2] and all human lesions tested [2]. (*C*) (Control) vGPCR and vGPCR/TK allografts were generated [3]. Treatment of vGPCR/TK tumors with ganciclovir (50 mg/kg) lead to complete loss of all (AU5) vGPCR-expressing cells. Sections were stained with an ANGPTL4 antibody, showing progressive decreased expression. Magnification x 20 (*C* and *D*). (*D*) HMEC1s were transfected with Scrambled (Scrambled si), ANGPTL4 (ANGPTL4 si) or no siRNA and then with pCEFL Tet REV TA and pBIG AU5 vGPCR. Cells were left untreated (Control) or treated with (1 μg/ml) Dox for 24h (vGPCR). Levels of ANGPTL4 in cellular extracts and conditioned media are shown. Overexpression of ANGPTL4 served as control (*E*) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce blood vessel development within basement membrane extract (BME)-filled angioreactors (shown in figure) implanted in nude mice (DIVAA assay). Recombinant FGF2, FGF2/VEGF served as controls. (*F*) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce migration of HMEC1s, using Boyden-chamber assay. 2.5% serum (FBS) was used as a control. (*G*) Conditioned media (CM) or hrANGPTL4 (5μg/ml) was used to induce tubule formation of HMVECs in matrigel. hrVEGF (50 ng/ml) served as control. (H) HMEC1s were transfected with Scrambled (Scrambled si), ANGPTL4 (ANGPTL4 si) or no siRNA and then with pCEFL Tet REV TA and pBIG AU5 vGPCR. Cells were left untreated (Control) or treated with (1 μg/ml) Dox for 24h (vGPCR). Conditioned media from these cells (CM) or hrANGPTL4 (5μg/ml) was used to measure FITC–dextran permeability in mature HMVEC monolayers. Treatment (30 min) with VEGF (50 ng/ml) was used as a control.