Angiopoietin-like 4 (ANGPTL4), a secreted protein of the angiopoietin-like family, is induced by hypoxia in both tumor and endothelial cells. It is highly expressed in tumor cells from conventional renal carcinoma and in hypoxic perinecrotic areas of numerous types of human tumors (1).

We previously showed that ANGPTL4, through its action on both vascular and tumor cells, prevents metastases through inhibition of vascular permeability as well as tumor cell motility and invasiveness. In vivo, using both Lewis Lung carcinoma cells as well as melanoma B16 cells, we showed ANGPTL4 inhibits both intravasation extravasation of tumor cells. Using Miles assay, ANGPTL4 inhibited the histamine-induced vascular permeability in electrotransferred mice overexpressing ANGPTL4 compared to control mice (2).

More recently, Padua et al. revealed a clinical association between TGFbeta activity in primary tumors and risk of distant recurrence, specifically for estrogen receptor negative breast tumors with lung metastasis but not bone metastasis. In vivo, lung metastasis seeding from mammary tumors depends on TGFbeta receptors, Smad function and ANGPTL4 expression (3).

Both groups therefore report ANGPTL4 as a key regulator of vascular permeability. Nevertheless, better insights are needed in order to precisely characterize its role during tumor angiogenesis and subsequent metastases in various organs, namely lungs and bones. The aim of the present study is to address the in vivo role of ANGPTL4 in modulating vascular integrity, using Lewis Lung carcinoma cells xenografted in ANGPTL4KO mice. Inhibition of tumor growth is observed in KO mice compared to WT mice (1207+/−105 mm3 versus 3053±569 mm3 at day 26, p=0.002). At day 33, tumor growth is observed in KO mice compared to WT mice (1207+/−120 mm3 versus 7053±569 mm3 at day 26, p=0.002). Furthermore, 10 μm curcumin inhibited significantly (52%, P=0.001) VEGF-induced HUVEC migration similarly to the selective PDE2 inhibitor (0.1 μm BAY-60-7550, 69%, P=0.003) and the selective PDE4 inhibitor (10 μm rolipram, 41%, P=0.006). These results, showing for the first time that curcumin inhibits PDE activities, suggest that curcumin present in food might inhibit angiogenesis at endothelial cell level by inhibiting PDE activities.