CONTEXT-DEPENDENT MODULATION OF CELL EXTRAVASATION FROM BLOOD VESSELS BY ANGPTL4

M. DURAND 1, E. GOMEZ 1, A. CAZES 1, M. LESAGE 1, J. PHILIPPE 1, A. GALAUP 1, S. GERMAIN 1
1 Inserm U833 — Collège de France, Paris, France
2 Service d’Hématologie Biologique A, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

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+/-305 mm3 versus 3053+/-569 mm3, p=0.002). Furthermore, 10μm curcumin inhibited significantly (52%, P=0.001) VEGF-induced HUVEC migration similarly to the selective PDE2 inhibitor (0.1μm BAY-60-7550, 69%, P=0.003) and the selective PDE4 inhibitor (10μm 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.

REFERENCES

THE POLYPHENOL CURCUMIN INHIBITS IN VITRO ANGIOGENESIS AND CYCLIC NUCLEOTIDE PHOSPHODIESTERASES (PDES) ACTIVITIES SIMILARLY TO PDE INHIBITORS

A. ABUSNINA 1, T. KERAVIS, 1, C. LUGNIER 1
1 Gilbert laustralt, faculté de pharmacie, Illkirch, France

VEGF, by stimulating endothelial cells to migrate, proliferate and differentiate, plays a major role in angiogenesis. Increase in intracellular cAMP is known to inhibit basal as well as VEGF-induced endothelial cell proliferation. Cyclic nucleotide phosphodiesterases (PDEs) play a key role in signal transduction by hydrolyzing specifically cyclic nucleotides.

Our team has previously reported that PDE2 and PDE4 up-regulations (activity, protein and mRNA) in human umbilical vein endothelial cells (HUVECs) are implicated in VEGF-induced angiogenesis and that inhibition of PDE2 and PDE4 isozyme activities prevents the development of angiogenesis by increasing cAMP level, by inhibiting cell proliferation, cell migration and cell cycle progression (Favot et al., Thromb Haemost 2003, 90: 334 and 2004, 92: 634). On another hand, we have shown that polyphenols inhibit PDEs (Orallo et al., Naunyn Schmiedebersgs Arch Pharmacol 2004, 370: 452; Planta Med 2005, 71: 99; Alvarez et al., Br J Pharmacol. 2006, 147: 269).

The polyphenol curcumin, isolated from the plant Curcuma longa, is present in curry powder, and is known to have anti-inflammatory, anti-oxidant and anti-cancer properties. The anti-carcinogenic properties of curcumin have been demonstrated in animals by its ability to inhibit tumor initiation and tumor progression. Therefore, this study was aimed to investigate the participation of PDEs in anti-angiogenic properties of curcumin.

The effect of curcumin on PDE activities was assessed by the determination of IC50 values on the five isozymes PDE1-PDE5 purified from vascular tissues. Curcumin was able to inhibit PDE1, PDE2, PDE3 and PDE4 with IC50 values in the range of 10 to 20μm, and PDE5 with an IC50 value of 35μm.

Curcumin at a concentration of 10μm inhibited both basal and VEGF-stimulated HUVEC proliferation (58% and 54% respectively, P<0.003). Furthermore, 10μm curcumin inhibited significantly (52%, P=0.001) VEGF-induced HUVEC migration similarly to the selective PDE2 inhibitor (0.1μm BAY-60-7550, 69%, P<0.003) and the selective PDE4 inhibitor (10μm rolipram, 41%, P<0.006).

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