

P030 Inhibition of PI3K sensitizes the tumour neovasculature to TNF

Leander Huyghe, An Goethals, Jeroen Hostens and Peter Brouckaert

Department of Molecular Biomedical Research, VIB/Ghent University, Technologiepark 927, B-9052 Zwijnaarde, Belgium

Tumor Necrosis Factor(TNF) is used in the clinic with high efficacy to treat regional tumours of the limbs via isolated limb perfusion. Severe shock-inducing side-effects, however, preclude systemic treatments. Previous work in our research group has established that the tumour endothelial cells are the main target cells for the tumour-destructive effects of TNF. In the present study, we demonstrate that inhibition of the PI3K-Akt pathway sensitizes these cells to TNF. When C57BL/6J mice bearing an established tumour were treated with TNF in combination with the selective PI3K inhibitors wortmannin or LY294002, complete tumour regression could still be obtained with a 10-fold lower dose of TNF. In groups where higher doses of TNF were used, the irreversible PI3K inhibitor wortmannin, but not LY294002 increased the toxicity of TNF. At lower doses no increase in toxicity was observed. Similar results were obtained with rapamycin, an inhibitor of the downstream target mTOR. In a perfusion experiment with Hoechst33342 we could demonstrate that the combination of TNF and wortmannin completely blocked the blood flow through the tumour as early as 6h after injection. Taken together, we have shown that inhibition of the PI3K-Akt pathway allows a significant reduction of the therapeutic dose of TNF.