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## THE CONTRIBUTION OF THE RHO PROTEIN PATHWAY TO THE TUMOUR VASCULAR DISRUPTING ACTION OF CA-4-P

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The vascular disrupting agent, combretastatin A-4- phosphate (CA-4-P), activates GTPase Rho A and Rho kinase in endothelial cells in vitro. The aim was to investigate whether this pathway contributes to vascular shutdown by CA-4-P in vivo. Colorectal carcinoma SW1222 cells were subcutaneously implanted into SCID mice and treated i.p. with CA-4-P (30 or 100 mg/kg) alone or in combination with Y-27632 (50mg/kg), a Rho kinase inhibitor. One or 3 hours post-treatment, mice were injected with fluorescein labelled lectin (i.v.) for endothelial labelling of perfused vessels, and tumours removed 5 minutes later for subsequent staining for endothelial CD31. Control tumour blood vessels had 38.5% effective perfusion (percentage of lectin relative to CD31 staining). CA-4-P (100mg/kg) significantly reduced perfusion at 3 hours to 11.8%, and this was elevated to 20.5% with Y-27632 pre-treatment. These data suggest that Rho kinase is involved in the mechanism of action of CA-4-P. Another inhibitor, dibutyryl cAMP (dbcAMP), which phosphorylates and inactivates Rho via activating protein kinase A, was also used. In vitro, dbcAMP blocked CA-4-P action in human umbilical endothelial cells. When used in vivo, dbcAMP alone significantly increased perfusion of tumour blood vessels relative to controls. Further studies using laser doppler flowmetry are in progress to confirm this response. The data taken together imply that the Rho protein pathway is involved in the relative perfusion of tumour vessels, and this pathway may contribute to the vascular disrupting action of CA-4-P.

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