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A critical role for RhoA-GTPase signaling in the tumour vascular disrupting action of combretastatin A4-phosphate *in vivo*

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Background

Tubulin binding microtubule depolymerising agents form a growing group of tumour vascular disrupting agents (VDAs) in clinical trial, with combretastatin A-4-phosphate (CA4P) the lead compound. Signalling through RhoGTPase/ROCK-dependent pathways is central to CA4P-induced effects on endothelial cells *in vitro* (Kanthou C. & Tozer GM, 2002, *Blood* 99: 2060-2069). Here, we tested the hypothesis that RhoGTPase/ROCK signalling is also important *in vivo*.

Method

SW1222 human colorectal carcinoma cells were grown as solid sub-cutaneous tumours in SCID mice. The Rho kinase (ROCK) inhibitor, Y-27632 (50 mg/kg) or saline control, was administered intraperitoneally (i.p.), 5 minutes prior to 100 mg/kg CA4P or saline i.p.. Laser Doppler flowmetry was used to assess tumour vascular response from 0 – 2h post-treatment. Intravenous administration of fluorescent tomato lectin was used for assessing tumour perfusion at 1, 3, 6 and 24 hours post-treatment. Necrosis (H&E) and leukocyte infiltration (immunohistochemistry) were assessed at 24h.

Results

Y-27632 alone did not significantly increase necrosis at 24 hours (17±4% versus 10±3% of tumour sectional area). However, prior administration of Y-27632 significantly reduced CA4P-induced tumour necrosis from 61±5% to 35±7%, accompanied by a decrease in staining for the myeloid markers, myeloperoxidase and GR-1. Y-27632 pre-treatment did not affect laser Doppler and perfused vascular volume measurements in the first few hours after CA4P but significantly reduced the effect of CA4P on perfused vascular volume measured at 6 and 24 hours.

Conclusion

Our data indicate that RhoGTPase/ROCK-dependent signalling is a critical factor in determining extent of tumour necrosis induction by CA4P and suggest that ROCK inhibition is acting downstream from initial vascular shut-down, potentially via modulation of myeloid cell recruitment. These mechanisms also have significance for similar VDAs in development.

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