

VASCULAR NORMALIZATION IN REGULATOR OF G PROTEIN SIGNALLING 5-DEFICIENT TUMOURS PROMOTES IMMUNE DESTRUCTION

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The vasculature of solid tumours displays an aberrant morphology characterized by dilated and fragile vessels, intensive vessel sprouting, and loss of hierarchical architecture. Due to ongoing angiogenesis, immune effector cells generated *in vivo*, or supplied *ex vivo*, are often unable to migrate into established tumour parenchyma in sufficient numbers to exert an anti-tumour effect. We identified regulator of G protein signalling (RGS) 5 as a master gene responsible for the abnormal morphology of tumour vessels. In a transgenic mouse model for spontaneous insulinomas, RGS5 is a marker for progenitor perivascular cells which wrap around endothelial cells and regulate vessel stability and vascular survival. We established RGS5-deficient, tumour-bearing mice and show here that in the absence of RGS5, tumour vessels are more mature and predominantly covered with differentiated pericytes. Blood vessels are more regularly shaped and less dilated thus exhibiting features of a normalized tumour vasculature. Consequently, tumour hypoxia and vessel leakiness are drastically reduced. These changes have a dramatic effect on tumour immunotherapy by enhancing influx of immune effector cells into tumours leading to their destruction. These findings establish an association between vessel normalization and an increased anti-tumour immune response. It is also the first demonstration of reduced angiogenic activity and improved therapeutic outcome upon loss of gene function *in vivo*.