Tumour angiogenesis and the control of splicing.

Tumours require the development of new blood vessels (angiogenesis). Angiogenesis is regulated by cancers primarily through by the Vascular Endothelial Growth Factor (VEGF) family of proteins and receptors. Like many other cancer pathways, VEGF is alternatively spliced, and there is a stark contrast in mRNA splice variant repertoire (and translated isoform expression) between normal and malignant tissue. This is a novel avenue for the development of anti-cancer therapeutics compared with a strategy simply based on inhibition of gene expression/protein activity alone – since splicing control would benefit from the synthetic capacity of a tumour but direct it towards the production of tumour inhibiting, rather than tumour supporting isoforms of the same genes. The choice of isoforms is regulated by a small number of proteins (signalling molecules & splicing factors) whose identification can provide novel understanding of the phenotypic traits acquired by tumour cells. This project will test the general hypothesis that the splicing pattern of specific isoforms of VEGF is regulated in tumours as they become more angiogenic, and that this alteration in splicing can be driven both by oncogenic processes, and the tumour microenvironment (e.g. hypoxia). You will investigate the Serine-Arginine Protein Kinase 1(SRPK1)-SR Splicing Factor-1 (SRSF1) pathway as a mechanism for VEGF splicing regulation, and use genome-wide approaches to understand networks of splicing control that drive this process. You will combine low-throughput, mechanistic studies on in vivo angiogenesis, focussing on melanoma and colon cancer, with high-throughput RNAseq, to elucidate regulation of angiogenesis. This could lead to the development of novel inhibitors of splicing pathways can be developed that provide proof-of-concept for a new class of anti-angiogenic drug – the alternative-splicing inhibitor.

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