RNA binding proteins that control tumour growth by regulating blood vessel growth.

Cancers require a blood supply if they are to grow beyond a few millimetres across and to invade into other areas of the body. This blood vessel growth is driven by the production of proteins that stimulate existing blood vessels to invade into the cancer tissues, providing nutrients and removing waste. One of the most important proteins that drives this growth is called VEGF, a naturally occurring protein that is normally tightly controlled by normal cells. This natural protein is required for many healthy tissues to function normally, and is made in two forms that balance each other. An imbalance of these two forms results in aggressive and uncoordinated blood vessel growth, and cancers stimulate this imbalance by altering the way the protein is generated - a process called splicing. VEGF can be spliced to form either a survival type, termed VEGF165b, or a growth type, termed VEGF165. The difference between these two types depends on how splicing as a process is controlled. We have identified a key regulator of VEGF splicing, a protein called TIA-1. This protein itself can be generated as multiple forms by different splicing, and in cancers (but not normal tissues) there is a variant form that is hyperactive, resulting in strong production of VEGF165 in tumour cells. This project intends to find out how important this mutant TIA1 protein is in cancer cells, what else it controls other than VEGF, and whether it could be a valid target for new cancer therapies. Alternative splicing is now being recognised as a new paradigm for cancer development, and an attractive target for new cancer drugs. However, very few cancer specific proteins that regulate splicing have yet been discovered, and this may be a key to unlocking a new front in the development of cancer drugs. Specifically we aim to find out if TIA-1 alternative splicing is a common event in colon cancer, whether the alternatively spliced sTIA-1 blocks the normal TIA1, whether sTIA-1 gains function independent of normal TIA-1, determine if the different TIA-1 forms control blood vessel growth in colon carcinoma and find out whether reduced cancer growth in TIA-1 expressing cells is through inhibition of VEGF mediated blood vessel growth by altering VEGF splicing

Primary Supervisor: Prof David Bates

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