Project Summary: Oncoprotnet: Dynamic protein interaction networks in cancer

Scientific Findings This research project studies interactions between proteins in cancer cells. The main interest is in discovering which interactions occur in cancer cells, and how these interactions between proteins alter the behaviour of the cell in a tumour. The main experimental techniques are molecular biological techniques in cultured human cancer cells and a technique called proteomics is used to identify which proteins are present in the cells, and which are different between cancer and normal cells. Our specific interest is to identify interactions between proteins that function in a signalling pathway in colorectal cancer call the Wnt signalling pathway.

This award has enabled two important outcomes in this area:

(1) Identification of a protein interaction in colorectal cancer cells that occurs between two very important oncoproteins (proteins that drive the formation of tumours). We discovered this interaction and analysed how and where the interaction occurs in the cell. This finding is of significance because previously it was not known that these proteins interacted. The finding may also be significant for efforts to identify new targets for therapeutics. Specifically this interaction occurs between Beta-catenin and DNA Methyltransferase I, a protein that regulates the patterns of DNA methylation in human cells. Our study identifies a link between signalling which communicates information to the cell from its exterior and the process of gene-expression regulation through DNA methylation (Song et al, Molecular Cancer Research, 2015)

(2) We have used these proteomics techniques in conjunction with transcriptomics and constructed a network model of Wnt/Beta-catenin signalling in cancer cells. The novelty of this project is that the network model integrates different types of molecular data, and has enabled the identification of new processes and pathways involved in Wnt regulation in cancer cells (Ewing et al, *paper submitted*).

Impact Both Wnt signalling and DNA methylation are fundamental cellular processes that have been implicated in many different cancers. Wnt signalling is typically inappropriately activated, and altered DNA methylation leads to over-expression or silencing of oncogenes and tumour suppressors across diverse tumour types. This project investigates the synergism between these two important cellular processes, and the project may identify new therapeutic targets. As an example, inhibiting the protein-protein interaction between Beta-catenin and DNA methyltransferase I might destabilize these two oncogenic proteins, and could be a new anti-cancer therapeutic. Future cancer patients may benefit from these findings. Patients with tumours that exhibit elevated Wnt signalling and DNA methyltransferase activity (for example colon and breast) could benefit significantly in the future from an inhibitor as it would disrupt a fundamentally important oncogenic mechanism. Certain classes of cancer patients currently benefit from epigenetic therapies which target DNMT1 (e.g. azacytidine). However, despite great interest in developing cancer therapies that target the Wnt pathway, none are yet available in the clinic (although several are in clinical trials). In addition to anti-cancer researchers, our work will also impact the stem cell and regenerative medicine communities. The Wnt pathway is widely implicated in the control of stem cell proliferation and differentiation, and uncovering a mechanism through with the epigenetic status of stem cells might be controlled will be of interest to these communities. Many applications in regenerative medicine involve the creation, culture and maintenance of pluripotent stem cells. Uncovering mechanisms that regulate the behaviour of stem cells will be of significant interest to biotech companies in this area.

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