GENE REGULATION

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[1]Wellcome Trust Investigator Award
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Precise and responsive gene regulation directs development, organ function and immune responses. Common oncogenic mutations result in deregulation of gene expression which can result in the acquisition of deleterious cellular behaviours and escape from growth control. We aim to understand how gene expression is regulated through the RNA cap, a potent structure formed on RNA polymerase II transcripts which impacts on transcription, RNA processing and translation. We investigate how the RNA capping enzymes are regulated by cellular signalling pathways and how they impact on gene expression and cell function. We explore the therapeutic value of targeting the RNA capping methyltransferases, identifying oncogenic pathways which render cells sensitive to inhibition of these enzymes.

How do the RNA capping enzymes function in health and disease?

Defining the mechanisms by which the RNA capping enzymes function and respond to cellular signalling pathways is key to understanding their role in tumour initiation and progression. We investigate the biochemical functions of the RNA capping enzymes and how they are regulated by post-translational modifications and co-factors. The development of therapeutic targeting approaches requires an understanding of RNA capping enzyme structure and interaction with ligands. We collaborate with Danny Huang to determine how RNA cap structures interact with proteins. We collaborate with Jo Birch (School of Cancer Sciences, University of Glasgow) to investigate the regulation of the RNA capping enzymes in Glioblastoma and Owen Sansom to investigate the role of the RNA capping enzymes in intestinal tumour initiation and progression. A key aim is to define the genetic alterations which increase sensitivity to RNA capping inhibition, thus indicating disease areas in which to target these enzymes.

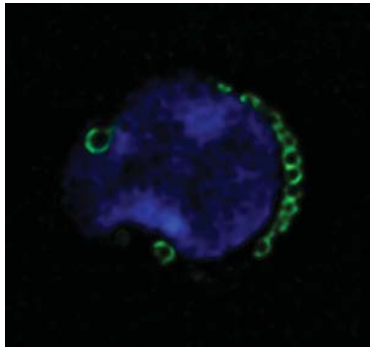


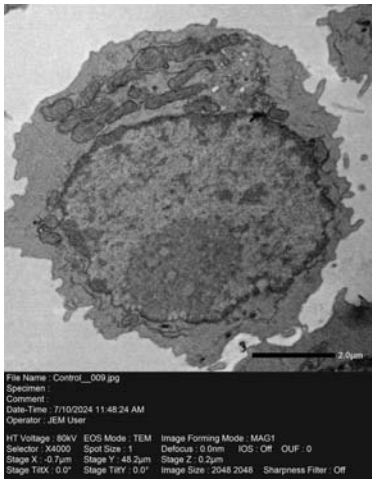
Figure 1. Murine T Cells. IF analysis of TOMM20.

How do the RNA capping enzymes influence T cell function?

T cells are critical cells in the adaptive response to cancer and infection. When T cells interact with cognate antigens, gene expression and cellular metabolism increase massively, permitting rapid proliferation and the production of effector T cell populations required to target infection and cancer. We investigate how the RNA capping enzymes are upregulated during T cell activation, directing cell proliferation, differentiation and effector functions. The different RNA capping enzymes have distinct roles in gene expression during T cell activation and consequently have distinct roles in T cell function and fate decisions. In a tumour, the microenvironment influences RNA capping enzyme function as metabolites become limited. We collaborate with Ed Roberts to understand the role of the RNA capping enzymes in T cell responses in tumours.

Figure 2. Dopaminergic neurons derived from induced pluripotent stem cells. Cells engineered to express phospho-defective RNMT (mid panel) and phospho-mimic RNMT (right panel).

Image credit: Rajaei Almohammed, CRUK Scotland Institute.



How does RNA cap regulation co-ordinate gene regulation during differentiation?

Regulation of the RNA capping enzymes during differentiation co-ordinates the expression of genes associated with cell identity. During development and in the adult, regulation of the RNA cap methyltransferases has important roles in cell differentiation and cell function. These same mechanisms are re-used in tumour initiation and progression, influenced by metabolites in the tumour microenvironment. This year we have been investigating the role of RNA cap regulation in neuron development, function and in glioblastomas. The RNA cap methyltransferases have specific roles in neurons and glioblastomas with impact on proliferation, morphology and migration. In order to understand the gene-specificity of the RNA cap methyltransferases we analyse nucleotide-enzyme interactions using molecular biology and biophysical techniques. Our aim is to develop bespoke targeting strategies for the RNA cap methyltransferases for use in cancer and regenerative medicine.

Are the RNA capping enzymes viable therapeutic targets?

The RNA cap methyltransferases have influential roles in gene expression, cell proliferation, and pluripotency and differentiation. Targeting the RNA cap methyltransferases has selective roles in inhibiting the growth and proliferation of cancer cells. We are identifying oncogenic mutations in cancer models which sensitise cells to inhibition of RNA capping. We collaborate with Cancer Research Horizons to target RNA cap metabolism in colorectal cancer models. We collaborate with the Dundee Drug Discovery Unit and external partners to develop tool compounds to inhibit the RNA cap methyltransferases and use these to probe target disease areas.

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