GENE REGULATION

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Precise and responsive gene regulation directs development, immune responses and organ function. In cancer cells, gene regulatory mechanisms become altered resulting in the acquisition of deleterious features. 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 pathway and how this impacts on gene expression and cell function, in health and disease. 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 is key to understanding their role in tumours and in the development of therapeutic targeting approaches. We investigate the biochemical functions of the RNA capping enzymes and how they are regulated by cellular signalling pathways through post-translational modifications and co-factors. This year we have reported that the cap methyltransferase, CMTR1, is recruited to its target genes via an interaction with RNA polymerase II at the initiation of transcription. We found that CMTR1 has gene-specific impacts on transcription, regulating key genes involved in DNA replication and protein synthesis. Thus, CMTR1 is critical for cell proliferation. Furthermore, we found that CK2, a kinase widely upregulated in a spectrum of tumours, phosphorylates CMTR1, increasing its interaction with RNA polymerase II. Phosphorylation of CMTR1 increases RNA capping, gene expression and cell proliferation. We are investigating the impact of this pathway in tumours and innate immune responses. We continue to collaborate with Owen Sansom to investigate the role of the RNA capping enzymes in 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.

How do the RNA capping enzymes influence T cell function?

T cells are key cells of the adaptive response to infections and cancer. When T cells interact with cognate antigens, gene expression and cellular metabolism increase massively, permitting rapid proliferation and the production of cell populations required to target infection and cancer. We investigate how the RNA capping enzymes are upregulated during T cell activation and the role they play in proliferation and differentiation. The different RNA capping enzymes have distinct roles in gene expression during T cell activation, and as a consequence, have distinct roles in T cell function and fate decisions. Recently, we discovered that the RNA cap methyltransferase, RNMT is upregulated during T cell activation, resulting in upregulation of mRNAs and snoRNAs involved in ribosomal protein and RNA production and processing. As a result, RNMT upregulation increases ribosome production during T cell activation, a process critical to produce effector populations. We are now investigating the role of CMTR1 during T cell activation, specifically defining its role in cell fate decisions. We are collaborating with Ed Roberts to understand the role of the RNA capping enzymes in T cell responses to cancer.

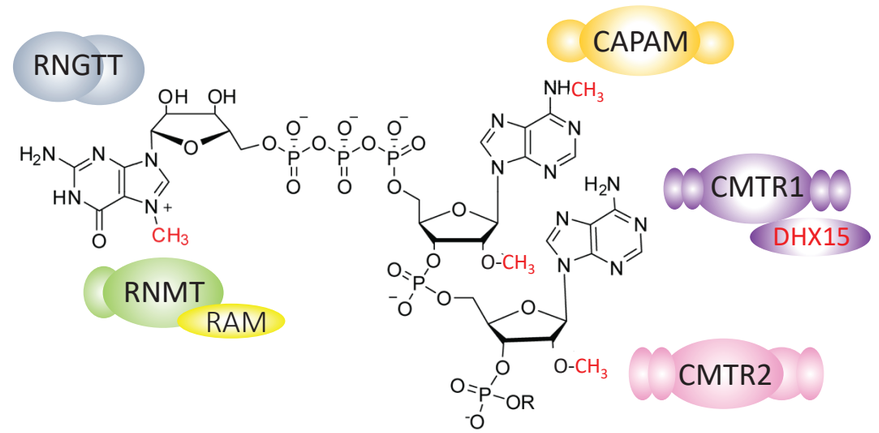

Figure 1
An RNA cap structure and capping enzymes

How do the RNA capping enzymes co-ordinate gene regulation programmes during differentiation?

The RNA cap methyltransferases have a common methyltransferase core, but this is flanked by domains which differ in each enzyme, allowing them to be independently regulated by co-factors and post-translational modifications. We discovered that the RNA capping enzymes RNMT and CMTR1 are differentially regulated as embryonic stem cells differentiate; RNMT is repressed and CMTR1 is activated. RNMT and CMTR1 have distinct target genes. Therefore, distinct regulation of these enzymes during differentiation allows co-ordinate regulation of key genes during changes in cell identity. RNMT repression is required for loss of pluripotency genes during differentiation and CMTR1 upregulation is required for histones and ribosomal protein genes, and associated DNA replication and protein synthesis. These findings are relevant to development but also have parallels in tumour initiation and progression, during reprogramming of gene expression.

Are the RNA capping enzymes viable therapeutic targets?

The RNA cap methyltransferases have influential roles in gene expression and cell proliferation. We investigate whether inhibiting these enzymes can have selective roles in inhibiting the growth and proliferation of cancer cells. We aim to identify cancer genotypes which sensitise cells to inhibition of RNA capping. We continue to collaborate with the Dundee Drug Discovery Unit and external partners to develop tool compounds .

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