Collaborative Research Project - Faculty of Medicine, Nursing and Health Sciences, Monash University, the Peter MacCallum Cancer Centre and the Italian Institute for Genomic Medicine

Characterisation of the complex interplay between transcriptional and chromatin modifying enzymes to regulate gene expression.

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Tightly controlled gene expression is essential for normal cellular development and homeostasis, and the dysregulation of gene expression is a universal feature of human disease and a hallmark of cancer.

RNA polymerase II (Pol II) transcription is regulated across multiple distinct yet interconnected layers, including a) the 3D organisation of the genome, b) global and localised modification of histone proteins and DNA (epigenetic regulation), and c) the coordinated activities of the multi-subunit Pol II complex, general and specific transcription factors, RNA processing modules (including splicing, cleavage, and polyadenylation factors) at individual genes. At each gene Pol II must complete a 'transcription cycle' progressing through distinct phases to produce mRNA transcripts. Progression through transcription cycle stages is controlled by a family of transcriptional cyclin-dependent-kinase/cyclin complexes (tCDKs), with roles described for CDK8 (recruitment), CDK7 (initiation), CDK9 (pausing/release, termination), and CDK12/CDK13 (elongation). Moreover, we have identified the PP2A-integrator complex as a phosphatase-containing complex that opposes the activity of CDK9 and potentially other CDKs to fine tune transcription in a highly dynamic manner. Interestingly, environmental conditions (such as nutrient availability) have a profound impact on these events and regulate the activity of PP2A, though the mechanistical implications remain largely unknown.

There remain many gaps in our fundamental knowledge of the complex molecular relationships that influence gene expression, including interactions between distinct tCDKs operating at different phases of Pol II transcription cycles, and potential regulatory networks between tCDKs and epigenetic regulators that shape the broader epigenetic landscape. We are interested to understand how transcriptional CDKs, PP2A and other transcription/chromatin regulatory proteins are dynamically recruited to or evicted from chromatin in response to different endogenous or exogenous stimuli.

This research area offers opportunities for conducting research projects, which will use complementary genetic and pharmacological systems, molecular biology and biochemistry experimental approaches to study the dynamic localisation of transcriptional regulatory proteins to decipher how oncogenic and normal transcription programs are related in a highly coordinated and dynamic manner.

Main references:

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