The molecular mechanisms of RNA Polymerase II termination

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Project description:

Transcription defines every aspect of biology and its misregulation can lead to the broadest and most devastating range of diseases, from autoimmunity and cancer to neurodegeneration. Transcription also drives biological complexity, as complex programmes of gene expression enable cells to change identity during development and respond to environmental changes. The Cheung and West labs want to understand how our genomes are transcribed, how it influences an organisms' growth, and why it goes wrong in diseases such as cancer.

Transcription by RNA Polymerase II (Pol II) is especially important, as produces the messenger RNAs that are translated into proteins. Like all RNA polymerases, Pol II undergoes a transcription cycle which delineates mRNA production into initiation, elongation and termination phases. The transition of Pol II through each phase is carefully regulated to ensure protein-coding genes are transcribed at the right time and at the appropriate levels. Whilst initiation and elongation are well studied, termination is more mysterious; the molecular mechanisms that enable Pol II to dissociate from the genome at the correct time and location are not known. This is vital as Pol II must be released from the genome to complete the transcription cycle and allow generation of new transcripts. Similarly, premature or failed termination can lead to formation of spurious RNA transcripts which disrupts regulation of adjacent genes, and be deleterious for health. Although the factors that stimulate termination are known, the molecular mechanism of how they enable Pol II release from the genome are yet to be determined.

This project will explore how these termination factors modify Pol II for release of its bound DNA and RNA. We will establish biochemical and biophysical assays to measure Pol II termination and use cryo-electron microscopy to directly visualise the structural basis of termination. These in-vitro studies will be complemented by in-vivo studies using CRISPR-Cas9 to genetically manipulate human cell lines to perturb and dissect the termination mechanism.