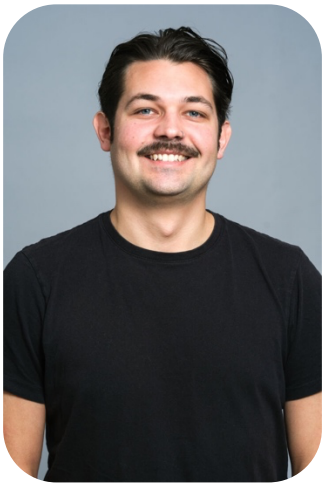
IQB Seminar

No advance registration is required.

How MYC modulates TOP2A diffusion to regulate activity – the tip of the iceberg?



Donald Cameron Ph.D.

Senior postdoctoral researcher

Dept. of Cell & Molecular Biology,

Karolinska Institutet, Sweden

Abstract:

Topoisomerases (TOPs) are essential enzymes which relieve DNA supercoiling through a process of cleaving, unwinding, and resealing DNA strands. Regulation of TOP abundance and activity is critical to prevent genomic instability and facilitate nuclear processes. Our prior research has indicated that the oncoprotein MYC can recruit and stimulate TOPs to remove supercoils generated by oncogenic transcription[1]. Understanding the mechanism behind this process could reveal strategies to block MYC stimulation of TOPs, thus decoupling oncogenic signalling from transcription.

The aim of this study was to dissect how TOP2A is regulated in the cell and how MYC can hijack this regulation. We demonstrate that TOP2A maintains a dynamic equilibrium between inactive sequestration in the nucleolus, substrate searching in transcription hubs and actively engaged on the chromatin. This equilibrium is highly responsive to changes in supercoil burden of the cell and can regulate TOP2A abundance in the nucleoplasm. Recognizing that the nucleolus and transcription hubs are phase-separated condensates and that TOP2A can form droplets *in vitro*[2], we sought to investigate how MYC can affect these condensates.

Although MYC alone cannot form condensates, our findings show that it promotes the formation of TOP2A condensates and reduces their density, potentially to favour greater protein diffusivity. Indeed, using single molecule tracking techniques, we observed that MYC depletion decreases TOP2A diffusivity in live cells. Our preliminary data suggest that the biophysical properties of MYC enable it to disrupt self-oligomerization of its target proteins, freeing them to interact with their substrates. This mechanism is consistent with MYC's known function as a global transcription amplifier[3]. While this project has focussed on MYC's impact on TOP2A, we have identified other nuclear transcription factors that possess similar properties to MYC, which in turn could regulate a broad range of proteins like TOP2A. Our continued investigation of this phenomenon will hopefully elucidate the mechanisms behind transcriptional regulation and potentially reveal novel methods to target tumour proliferation.

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Organizer
Laboratory of Genome Structure and Function,
Institute for Quantitative Biosciences, The University of Tokyo