

Internal Webinar

Deciphering the proteomic profile of active vs. dormant origins of replication in the mammalian system

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Replication of the human genome, which spans more than 3 billion base pairs, is a highly demanding process. To complete this task within a single cell cycle, mammalian cells license tens of thousands of replication origins. However, only a small subset is activated during an unperturbed S phase, while the remaining stay dormant. These dormant origins serve as a backup pool, becoming activated under replication stress to ensure faithful genome duplication. The selective firing of origins provides both efficiency and robustness, yet raises a central question: what mechanisms determine which origins fire and which remain dormant? Despite extensive characterisation of the genomic and epigenomic features associated with replication origin activity, the molecular composition of active and dormant origins and the proteins that contribute to their differential regulation remain poorly understood.

To address this, we present a strategy called Isolation and Differential Enrichment of Active and Latent origin-associated proteome – Mass Spectrometry (IDEAL-MS). The approach combines selective enrichment of the proteome associated with the actively replicating DNA strand, followed by the enrichment of licensed but inactive MCM-containing chromatin to capture proteins associated with dormant origins. Coupling these sequential enrichment steps with quantitative mass spectrometry enables the systematic comparison of the proteomic environments associated with distinct origin states.

This method provides a framework for investigating the molecular differences between active and dormant replication origins and for identifying candidate proteins that may contribute to origin selection, activation, suppression, or maintenance. More broadly, the approach enables the characterisation of origin-associated proteomes and may facilitate a better understanding of the molecular mechanisms underlying the regulation of DNA replication initiation and the cellular response to replication stress.

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