IMS Seminar

Date: April 26th 2023
Time: 11:00-12:00
Place: Zoom, and Conference room, 6F North Research Building

Distinguished Professor and Chair, Department of Microbiology & Molecular Genetics
Co-leader Molecular Oncology Program UC Davis Comprehensive Cancer Center

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Recombination and Genome Instability:
Multi-invasion-mediated rearrangements during non-allelic homologous recombination

Abstract

Punctuated bursts of structural genomic variations (SVs) have been described in various organisms, but their etiology remains incompletely understood. Homologous recombination (HR) is a template-guided mechanism of repair of DNA double-strand breaks and stalled or collapsed replication forks. We recently identified a DNA break amplification and genome rearrangement pathway originating from the endonucleolytic processing of a multi-invasion (MI) DNA joint molecule formed during HR. Genome-wide sequencing approaches confirmed that multi-invasion-induced rearrangement (MIR) frequently leads to a cascade of repeat-mediated SVs and aneuploidies. Using molecular and genetic analysis, and a novel, highly sensitive proximity ligation-based assay for chromosomal rearrangement quantification, we further delineate two MIR sub-pathways. MIR1 is a universal pathway occurring in any sequence context, which generates secondary breaks and frequently leads to additional SVs. MIR2 occurs only if recombining donors exhibit substantial homology, and results in sequence insertion without additional break or SV. The most detrimental MIR1 pathway occurs late on a subset of persisting DNA joint molecules in a PCNA/Pol□-independent manner, unlike recombinational DNA synthesis. This work provides a refined mechanistic understanding of these HR-based SV formation pathways and shows that complex repeat-mediated SVs can occur without displacement DNA synthesis. Sequence signatures for inferring MIR1 from long-read data are proposed.

Keywords: Genome Rearrangement Cascade, Structure-Selective Endonucleases, Translocation

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