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The SMX tri-nuclease: Making it safe to play with knives

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Statement of the Problem: Structure-selective endonucleases recognize and cleave branched DNA structures that arise during DNA replication and repair. In eukaryotes, the SLX1-SLX4, MUS81-EME1, and XPF-ERCC1 endonucleases are essential for genome stability because they remove various types of branched DNA structures that would otherwise impede DNA replication and/or chromosome segregation. Examples of such structures include stalled replication forks and covalently linked, four-stranded recombination intermediates called Holliday junctions (HJs). Human SLX4 provides the scaffold for a tri-nuclease complex called SMX, comprised of SLX1-SLX4, MUS81-EME1, and XPF-ERCC1 (Fig.1). The assembly of SMX is temporally regulated throughout the cell cycle: SMX is largely restricted to cells entering mitosis. How SLX4 co-ordinates three different nucleases to cleave specific DNA substrates is of great interest to researchers studying DNA repair and macromolecular complexes.

Methodology & Theoretical Orientation: We use a multi-pronged approach, including biochemistry and molecular biology, to study the molecular mechanisms underpinning SMX assembly and activity.

Findings: SMX is a promiscuous endonuclease that cleaves a broad range of branched DNA structures *in vitro*. This tri-nuclease complex is required for DNA repair and accurate chromosome segregation *in vivo*. Within the context of HJs, the SLX4 scaffold brings together the SLX1 and MUS81-EME1 active sites to catalyze HJ resolution. However, within the context of replication fork structures, SLX4 stimulates MUS81-EME1 to cleave these structures by relaxation of its substrate specificity.

Conclusion & Significance: Elucidating the functional interplay between SMX proteins has provided the first mechanistic details for this unique tri-nuclease complex. These data also provide important insights into understanding how the potentially damaging power of SMX is directed to safeguard genome stability.

Biography

Haley Wyatt began her postgraduate studies in cancer biology after obtaining a Bachelor of Science Honours in chemistry and biochemistry from the University of Regina. Dr Wyatt received her Doctoral degree in biochemistry and molecular biology in 2009 at the University of Calgary and Southern Alberta Cancer Research Institute. With a strong basic and translational research background from Calgary, she was well prepared to pursue her interests in genome stability. She completed her postdoctoral fellowship with Dr Stephen West at the prestigious Clare Hall Laboratories in the UK. Her studies elucidated the biochemical mechanisms of nuclease complexes in DNA recombination and repair, defined new paradigms, and resolved many outstanding questions in these fields. In April 2017, she established her own research lab in the Department of Biochemistry at the University of Toronto. Dr Wyatt's lab uses biochemical and cellular biology approaches to study the assembly and activation of nuclease complexes.

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