Johns Hopkins University

Department of Biology Seminar Series

Thursdays, 4:00pm

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Mudd Room 100 - October 31st, 2024

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Host: Yumi Kim

A Glance at the Meiotic DSB Machinery

The initiation of homologous recombination during meiotic prophase critically depends on the precise regulation of DNA double-strand breaks (DSBs), facilitated by the transesterase Spo11 and its accessory partners. Despite Spo11's essential role, its structural and activation mechanisms remain incompletely understood due to limited structural and biochemical studies. We present cryo-EM structures of the yeast Spo11 (ySpo11) core complex, resolved at up to 3.3 Å, revealing interactions with the DNA backbone and providing insights into DNA end-binding specificity and cleavage preferences, potentially capturing a post-cleavage regulatory state. Our biochemical studies on the mouse SPO11 (mSPO11) core complex show its activity in generating both nicks and DSBs, contrasting with the inactivity of its yeast counterpart. Mutations in the catalytic tyrosine and magnesium binding sites abolish this cleavage activity in mSPO11, but dual mutations restore nicking without enabling full DSB formation, suggesting that active mSPO11 functions as a dimer. Additionally, we explore the role of the Rec114- Mei4 complex, which forms nucleoprotein condensates essential for proper DSB regulation. Our findings suggest these condensates facilitate the recruitment and activation of the DSB machinery, potentially by aiding Spo11 core complex dimerization and activation. Together, our structural and biochemical data offer significant insights into the regulatory mechanisms of Spo11 core complexes, advancing our understanding of the molecular interplay critical for ensuring precise DSB regulation during meiosis.