CDB SEMINAR

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Novel mechanistic insight into how the Spindle Assembly Checkpoint prevents premature anaphase

Summary
The Spindle Assembly Checkpoint (SAC) is a surveillance mechanism to maintain genome stability by preventing premature anaphase (chromosome mis-segregation) during mitosis. Attachment of the mitotic spindle to kinetochores is a key step to accomplish equal chromosome segregation and the SAC is activated at 'unattached' kinetochores that generate diffusible 'wait anaphase' signal throughout a cell. One of the most striking aspects of the checkpoint is that a single unattached kinetochore is sufficient to delay anaphase. Mitotic Checkpoint Complex (MCC) is an essential effecter for the SAC to inhibit Cdc20, whose activity is required for metaphase-anaphase transition via activation of the Anaphase Promoting Complex/Cyclosome (APC/C). Several biochemical and structural studies have revealed that Cdc20 activity is inhibited by its binding to SAC proteins Mad2 and BubR1. Although several studies on the dynamics of SAC components have been performed, how the MCC prevents APC/C-Cdc20 activation in the cell is poorly understood.
In this talk, we will present data of the consequences of stabilising the interaction between Cdc20 and SAC proteins, which altered properties of the MCC in human cells. We also introduce biochemical assays using purified recombinant human MCC. These data indicate that the MCC inhibits two molecules of Cdc20: both the Cdc20 bound to Mad2 and BubR1 in the complex (in cis) and a Cdc20 that already bound to the APC/C (in trans). This evidence would provide a simple model about how the MCC inhibits APC/C-Cdc20 in the cell, where diffusive the MCC is able to prevent activation of both free form of Cdc20 and APC/C bound Cdc20.

References
(1) Mad2 and the APC/C compete for the same site on Cdc20 to ensure proper chromosome segregation. Izawa D, Pines J. J Cell Biol. 2012
(2) How APC/C-Cdc20 changes its substrate specificity in mitosis.
Izawa D, Pines J. Nat Cell Biol. 2011

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