Session II

Csi1p recruits alp7p/TACC to the spindle pole bodies for bipolar spindle formation

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Accurate chromosome segregation requires timely bipolar spindle formation during mitosis. The transforming acidic coiled-coil (TACC) family proteins and the ch-TOG family proteins are key players in bipolar spindle formation. They form a complex to stabilize spindle microtubules, mainly dependent of their localization to the centrosome (the spindle pole body/SPB in yeast). The molecular mechanism underlying the targeting of the TACC-ch-TOG complex to the centrosome remains unclear. Here, we show that the fission yeast Schizosacchromyces pombe TACC ortholog alp7p is recruited to the SPB by csi1p. The csi1p interacting region lies within the conserved TACC domain of alp7p while the carboxyl-terminal domain of csi1p is responsible for interacting with alp7p. Compromised interaction between csi1p and alp7p impairs the localization of alp7p to the SPB during mitosis, thus delaying bipolar spindle formation and leading to anaphase B lagging chromosomes. Hence, our study establishes that csi1p serves as a linking molecule tethering spindle stabilizing factors to the SPB for promoting bipolar spindle assembly.

Functions of BCL-2 family in mitotic cell death

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Antimitotic drugs such as Taxanes are some of the most effective anticancer agents. By interfering the function of mitotic apparatus or antagonizing crucial components of the mitotic machinery, these drugs can inhibit mitotic progression in cancer cells and further induce apoptosis after prolonged mitotic arrest. However, abnormal mitotic exit mechanisms including mitotic slippage and multipolar division occurred in antimitotic drug-treated cells and are strongly linked to drug resistance. Therefore, it is important to unravel the question of how mitotic cell death occurs at the molecular level. The BCL-2 (B-cell lymphoma 2) protein family regulates apoptosis by controlling mitochondria outer membrane integrity. In this systematic study, the whole BCL-2 family was screened to identify members that may be involved in antimitotic drug-induced mitotic cell death. The effects of downregulation of individual BCL-2 family members in HeLa and HCT116 cells were evaluated by time-lapse live cell imaging. Through analyzing the kinetics of mitotic cell death, these studies indicated that multiple anti-apoptotic members, including BCL-B, BCL-W, BCL-XL and MCL1, were involved in Paclitaxol-induced mitotic cell death. Overexpression of these proteins partially repressed the mitotic cell death induced by paclitaxel or nocodazole. The expression of BCL-XL, BCL-W and MCL1 were modified during the prolonged mitotic arrest, indicating that the active roles of BCL-2 proteins in mitotic cell death may be carried out by mitotic-specific regulations. Since BCL-2 inhibitors are being evaluated as potential anticancer agents, this study highlighted the potential and molecular basis of synergism between BCL-2 inhibitors and antimitotic drugs.