The PP2A phosphatase counteracts the function of the 9-1-1 axis in checkpoint activation

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Abstract:

DNA double-strand breaks (DSBs) are highly cytotoxic lesions that must be repaired to avoid loss of genetic information or chromosome rearrangements.

Eukaryotic cells can repair DSBs by two main mechanisms: non-homologous end-joining (NHEJ) and homologous recombination (HR). At the same time, DNA damage elicits a checkpoint response depending on the Mec1/ATR kinase, which detects the presence of single-stranded DNA and activates the effector kinase Rad53/CHK2.

In *Saccharomyces cerevisiae*, one of the signalling circuits leading to Rad53 activation involves the evolutionarily conserved 9-1-1 complex, which acts as a platform for the binding of Dpb11 and Rad9 (referred to as the 9-1-1 axis) to generate a protein complex that allows Mec1 activation.

By examining the effects of both loss-of-function and hypermorphic mutations, here, we show that the Cdc55 subunit of the PP2A phosphatase counteracts activation of the 9-1-1 axis. The lack of this inhibitory function results in DNA-damage sensitivity and sustained checkpoint-mediated cell-cycle arrest.

This PP2A anti-checkpoint role depends on the capacity of Cdc55 to interact with Ddc1 and to counteract Ddc1-Dpb11 complex formation by preventing Dpb11 recognition of Ddc1 phosphorylated on Thr602.