

ABSTRACT

DBF4 COORDINATES DNA REPLICATION, CHROMOSOME SEGREGATION, AND CHECKPOINT SIGNAL TRANSDUCTION

By

Ying-Chou Chen

Faithful transmission of genetic information not only requires accuracy in DNA synthesis and chromosome segregation, but also surveillance mechanisms that respond to various stresses in order to coordinate repair and cell-cycle progression. Recent evidence suggests that the Dbf4-dependent Cdc7 kinase (DDK), a two-subunit kinase essential for eukaryotic DNA replication, plays such a role in genomic maintenance. In this study, we demonstrated that Dbf4 inhibits Cdc5 (yeast Polo-like kinase) to prevent premature exit from mitosis. It also regulates late origin firing during replication stress by a direct interaction with the Rad53 checkpoint kinase (the ortholog of mammalian Chk2). Dbf4 is able to simultaneously associate with Cdc7, Cdc5, and Rad53, suggesting that Dbf4 serves as a molecular scaffold to mediate DNA replication, chromosome distribution, and checkpoint responses. We further performed a genomewide synthetic lethal screen using a *dbf4* mutant, which is defective in binding both Cdc5 and Rad53, to explore the biological relevance of these physical interactions. We globally mapped the genetic interactions of DBF4 and defined the functional categories for these interactions. These data provide insights into the role of Dbf4 in the convergence of checkpoint signaling and mitotic regulation and prompt us to re-evaluate the role of Dbf4 in cell-cycle regulation.