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DISSERTATION TITLE: *Regulation of Cdk activity in the cell cycle*

Cell division is one of the most fundamental processes in all living organisms. The events leading to cell division are coordinated in the cell cycle, which is carefully regulated to ensure that each daughter cell is equipped with a complete set of chromosomes. Consequently, malfunction in cell-cycle regulation might result in inappropriate cell division and abnormal cell growth such as found in cancer. Key enzymes regulating cell-cycle progression are cyclin-dependent kinases (Cdks). Their activity is crucial for the two most important stages of the cell cycle: Doubling of the DNA content in S phase and segregation of the DNA to new daughter cells in mitosis. In this work, we have investigated how Cdk activity is regulated in different stages of the cell cycle.

In the first part, we show that the Wee1 kinase is an important regulator of S-phase Cdk activity. Loss of Wee1 leads to increased Cdk activity concomitant with altered regulation of replication. The increased Cdk activity in the *wee1*$^{-}$ mutant results in more ongoing replication which makes the cells more vulnerable to replication stress. We show further that the inhibitory effect of Wee1 on Cdk activity in S phase is counteracted by Cdc25 phosphatase.

Cell-cycle checkpoints are crucial for the integrity of the genome. They block cell-cycle progression by inhibiting Cdk activity and thereby provide time to repair DNA damage or allow completion of a cell-cycle phase. The DNA-damage checkpoint in G2 phase ensures that cells enter mitosis without any damage. Cancer cells often carry mutations in DNA-damage checkpoints and depend on alternative pathways to delay entry into mitosis. In the second part of this study, we show the existence of a checkpoint-independent pathway that arrests cells in G2 phase. Further, we propose that the mechanism of the novel pathway is the selective downregulation of cyclin B translation which leads to reduced Cdk activity and delays entry into mitosis.