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CDK modulation coordinates G_1 events after S phase

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To maintain genome stability during fluctuating environmental conditions, cells have adapted mechanisms to regulate cell cycle events. For unicellular organisms, such as budding yeast, this response is essential for the survival of the organism. For example, under conditions of nutrient limitation, diploid budding yeast cells enter meiosis and package the meiotic products into spores.[1] The spores are able to survive adverse conditions. Once nutrients return, spores germinate and proliferate mitotically. Interestingly, if nutrients become available prior to the cell reaching an established commitment point in meiosis, the cell exits meiosis and returns to mitosis.[2] This developmental switch from meiosis to mitosis allows the cells to abort the energy-consuming processes of meiosis and sporulation with the restoration of favorable conditions.

The remarkable capability of budding yeast to switch from meiosis to mitosis raises the question of how cell cycle events are regulated to maintain genome stability. This question is especially intriguing for cells that return to mitosis from meiotic prophase I, the stage in which homologous chromosomes pair and initiate recombination. The coordination of cell cycle events in cells that return to mitosis from prophase I is different than that of a normal mitosis (**Fig. 1**). In a normal mitosis, cells form a bud in G_1, replicate their DNA in S-phase, and then divide their nucleus in M-phase. Cells that return to mitosis from prophase I have already replicated their DNA in pre-meiotic S phase; the cells then form a bud and divide their nucleus without an intervening DNA replication.[2,3]

In a recent study, we asked how CDK activity is modulated to coordinate cell cycle events during the return to mitosis from prophase I.[4] In budding yeast, a single CDK, Cdk1, is regulated by 9 different cyclins, each restricted to the appropriate cell cycle stage (G_1-CDK, S-CDK, and M-CDK) and important for events in that stage.[5] Cells in prophase I have S-CDK activity; therefore, we hypothesized that cells that return to mitosis utilize S-CDK activity for budding instead of G_1-CDK activity, as utilized in a normal mitosis. To investigate this hypothesis, we developed a microfluidics assay to monitor individual cells first exposed to nutrient-limiting medium to initiate meiosis and then nutrient-rich medium to induce the return to mitosis.[4] We deleted the G_1 cyclins singularly and in combinations and did not observe a delay in budding during the return to mitosis from prophase I. However, depletion of an S-phase cyclin resulted in a loss of budding or a lengthy delay in budding. These results suggest that the S-phase cyclins, not the G_1 cyclins, are utilized for budding during the return to mitosis from prophase I. The persistance of S-CDK activity from prophase I to mitosis provides a mechanistic rationale for why cells do not re-replicate their DNA between bud formation and nuclear division during the return to mitosis; the cells do not return to a stage with low CDK activity, which is required for origin licensing and DNA replication.[4,5]

Morever, we found that the G_2/M checkpoint kinase Swe1 (Wee1 homolog) is essential for coordinating cell cycle events during the return to mitosis from prophase I.[4] In a normal mitosis, Swe1 phosphorylates and inhibits Cdk to prevent cells from entering M phase if they are too small, or if a bud has not formed.[6] We found that *swe1*Δ cells that exit prophase I undergo a mitotic nuclear division without first forming a bud.[4] This aberrant division creates a multi-nucleate cell. Furthermore, deletion of the mitotic cyclin Clb2 rescues this aberrant division. Our results suggest the following model: cells that return to mitosis from prophase I require Swe1 to inhibit M-CDK and block nuclear division. The cell utilizes S-CDK for budding, and once a bud forms, the inhibitory phosphorylation on M-CDK is removed, and cells undergo a nuclear division.

There is currently a long-standing debate in the field about the coordination of cell cycle events. The two competing models are the quantitative model for CDK control of the cell cycle and the cyclin specificity model.[7] In the quantitative model for CDK control, the increasing activity of CDK results in an orderly progression of the cell cycle, with low CDK activity driving S phase and high CDK activity driving M phase. In the cyclin specificity model, different cyclin–CDK complexes recognize specific substrates to coordinate cell cycle transitions. Cells that return to mitosis from meiotic prophase seem to coordinate mitotic events utilizing both the quantitative control of CDK and cyclin specificity. Our work shows that M-CDK activity must be downregulated by Swe1 to allow budding prior to a nuclear division.[4] These results support the quantitative model of CDK control of the cell cycle, in that cells modulate the levels of CDK

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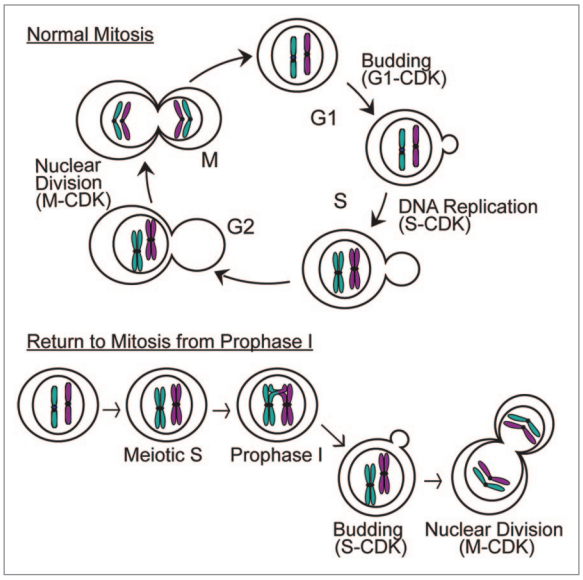

Figure 1. The order of cell cycle events of a normal mitosis compared with the return to mitosis from prophase I.

to accommodate the different order of cell cycle events. However, budding likely requires a specificity of cyclins. Although the specification of budding by CDK is somewhat promiscuous in that both S-CDK and G_1-CDK can fulfill this role, M-CDK blocks polarized bud growth.[6] This suggests that budding substrates are specified by S-CDK and quantitative lowering of M-CDK alone will not permit budding. Therefore, to accommodate cell cycle changes in response to fluctuating environmental conditions, the cell has evolved mechanisms to quantitatively modulate CDK levels and specify substrates.

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