Insights into cell-cycle progression under basal conditions and during adaptation to stress

Abstract

Many key insights into general principles of cell-cycle control came from investigations in yeast. Our recent studies have revealed that in budding yeast the vacuole/lysosome plays an essential role in cell-cycle progression, specifically during progression through early G1 phase. In addition, we discovered conditions where re-entry from a paused cell-cycle requires a non-canonical cyclin-dependent kinase.

During vegetative growth, vacuole inheritance ensures that the bud receives a vacuole. Moreover, mutants with defects in vacuole inheritance rapidly generate a new vacuole via a biogenesis pathway. Indeed, mutation of some genes required for vacuole biogenesis are synthetically lethal with a mutation in vacuole inheritance. We discovered that this synthetic lethality is due to an arrest in cell-cycle progression. Moreover, we discovered that the role of the vacuole in cell-cycle progression is due in part to signaling from TORC1-Sch9 and likely also requires the Fab1 lipid signaling pathway.

In a parallel project we discovered that when yeast recover from stress, they require a non-canonical cyclin dependent kinase to re-enter the cell cycle. Stress causes an arrest of the cell cycle via downregulation CDK1/Cdc28, the main cyclin-dependent kinase (CDK). Under basal conditions CDK1/Cdc28 facilitates progression from early G1 phase via phosphorylation of the transcriptional inhibitor Whi5, the yeast analog of RB1/retinoblastoma. Here we report that during recovery from stress, Pho85-Pho80 (Cdk5/p35), which is not critical during the basal cell-cycle, initiates the restart of the cell cycle. We show that Pho85-Pho80 directly phosphorylates Sch9, which in turn directly phosphorylates Whi5, which promotes release of the G_1 phase arrest. These findings provide insight into how cells re-enter the cell cycle during recovery from stress and reveal that a non-canonical CDK has a major role in the cell cycle, and transiently acts instead of CDK1.