Cell Cycle Commitment

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IN yeast, the G1 checkpoint *Start* determines if a cell enters the mitotic cycle or engages the mating program, but never both since the aims of the two programs are diametrically opposed: mating produces one cell from two, while mitosis produces two cells from one. This dichotomy is reflected in the antagonistic relationships between the underlying signaling molecules.

When a mitotic cell cycle is selected, the upstream cyclin-Cdk complex (Cln3-Cdc28) initiates a transcriptional positive feedback loop of two more G1 cyclins (Cln1 and Cln2). In the presence of mating factor, a MAPK pathway activates Far1, which inhibits G1 cyclins to prevent cell cycle progression. We show that the inhibition of both Far1 and the MAPK scaffold protein Ste5 by Cln1 and Cln2 completes a double negative feedback system that is bistable. In this context, bistability is an effective way to generate mutually exclusive cell fates: if G1 cyclin activity is below threshold, pheromone-induced signaling drives it lower and the mating program ensues; however, if G1 cyclin activity (through positive feedback) is above threshold, pheromone-induced signaling is inhibited.

We use quantitative fluorescence microscopy coupled with microfluidics to precisely determine the commitment point in individual cells that are abruptly exposed to a step increase in pheromone concentration. In WT cells, this occurs just after the initiation of the G1 cyclin positive feedback loop. The removal of Ste5 inhibition has no effect on the commitment point, but resulted in a fatal mixed cell fate. Thus, our analysis reveals a surprising degree if modularity at the cell cycle-MAPK interface.