External vs. Internal Control of Cell Growth and Division

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We designed an experimental approach to systematically dissect the signaling elements controlling cell growth and division as a function of detected Glucose in yeast. The key conceptual element is the design of yeast strains in which the expected/external growth signal is de-coupled from the actual internal Glucose signal. This artificial creation of conflict situations allows the dissection of signaling events i) initiating and ii) executing cell division. Given the dual role of Glucose as a nutrient and as a growth factor for yeast, this set of strains constitutes a model system for the systematic investigation of both cell growth control and nutrient homeostasis regulation.

We systematically investigated the contribution of Glucose sensing and glucose uptake in *S.Cerevisiae* to cell growth and division. For this, we constructed a series of strains in which Glucose sensing and uptake are decoupled. That is, whereas in a wildtype situation, where a certain influx matches the externally sensed glucose concentration, in our strains we can impose a Glucose uptake rate that is independent of the externally sensed glucose [1].

We systematically exposed these strains to various scenarios of external and internal glucose concentrations, and used life video-microscopy in combination with a microfluidics device to identify the contribution of each of the two signals on cell size and cell division rate. Of particular interest are the situations in which the 'expected' influx (due to external sensing) differs from the 'actual' influx (due to imposed transporter expression).

We found that in situations where the 'expected' influx is higher than the actual influx, cells set their cell size according to external glucose which leads to enlarged cells. Further, division rate is maximal in situations where the expected influx matches actual influx, but not necessarily when internal glucose is highest. That is, even if both external and internal glucose increase, the division rate may go down because of the increased mismatch of the two signals. If two main glucose sensors, Snf3 and Rgt2, are deleted, external glucose loses its ability to suppress cell division, suggesting that these sensors halt the cell-cycle if the internal Glucose does not match the externally sensed glucose.

In contrast to high external glucose, we found that in zero or very low external Glucose cells undergo significant cell division, in a way that is independent of transporter expression, and hence glucose influx.

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REFERENCES

[1] Youk H, van Oudenaarden A, Growth landscape formed by perception and import of glucose in yeast. *Nature* **462** (2009)