Integration of Cln3 determines G1 length in Saccharomyces cerevisiae

Xili Liu[1,2], Xin Wang[1,3] and Chao Tang[1,2,*]

It is usually regarded that Cln3 serve as an on-off switch in Saccharomyces cerevisiae during Start transition. i.e. when Cln3 below threshold, cell awaits at G1 phase. Once Cln3 surpass threshold, cell get through Start quickly. In our study, however, we found there is a quantitative inverse correlation between G1 phase and Cln3 concentration once Cln3 above threshold. An integral of Cln3 concentration rather than Cln3 concentration itself serve as the switch for Start transition. We analyze from both experimental and theoretical aspect to illustrate the underlying mechanism which leads to this quantitative inverse correlation.

***Keywords* — G1 phase, Cln3, Saccharomyces cerevisiae, inverse relation, Cell cycle, Systems biology**

I. INTRODUCTION

It is well known that Start transition is an event of paramount significance in budding yeast cell cycle. For its own fate, every cell judges from every aspect (e.g. nutrient condition, hormone environment) to make such choice prudently. Once Start transition is initiated, serials of irreversible events follows. [1] The most important goalkeeper for Start transition, as we concerned, is Cln3 protein. Previous view shows that Cln3's concentration corresponds to on-off switch for Start transition. When Cln3 below threshold, cell wait at G1 phase. Once Cln3 surpass threshold, cell quickly get through Start transition. [2]

However, under such scenario, Start transition would vary in a wide range since the increase of Cln3's concentration is merged in a biological system influenced by all sources of noise. This contradicts with people's intuition since such an important transition should be robustly organized. Confounded by this puzzle, we tried both theoretical and experimental methods to unveil the underlying mechanism. An illuminating mechanism may put like this: It is the integral of Cln3 rather than Cln3's concentration itself that serve as the goalkeeper. As integral diminishes noise and reflects cell's global condition over a period, it is more reasonable to take on the goalkeeper task.

[1]Center for Theoretical Biology, Peking University, Beijing, People's Republic of China

[2] The State Key Laboratory for Artificial Microstructures and Mesoscopic Physics, School of Physics, Peking University, Beijing, People's Republic of China

[3]Academy for Advanced Interdisciplinary Studies,Peking University, Beijing, People's Republic of China

[*]Correspondence: *tangc@pku.edu.cn*

II. SUMMARY OF RESULTS

In our experimental studies, we regulate Cln3's concentration rigorously by controlling IPTG induced Cln3 in $\mathrm{cln3}\Delta\,\mathrm{bck2}\Delta$ Saccharomyces cerevisiae. G1 length can then be measured correspondently under different Cln3's concentration A obvious inverse relation has been found although merged with some extent level of noise. G1 length shortens from several hours to 6 minutes as Cln3 level increase above threshold.

Modeling simulation is carried out both deterministically and stochastically of good match with experimental data with the following information discovered :

Whi5 phosphorylation is the key process determine time scale range of G1 phase

Cln3 activates Start transition through phosphorylating Whi5[3]. The correlation between G1 length and Cln3 concentration can be described by equation(*):

$$A = \left(G1 - G1_0\right)\cdot\left(C\ln 3 - C\ln 3_0\right) \qquad (*)$$

A is a global parameter for G1 and cln3's relation, constant in each experimental cell, which inversely proportional to Whi5's phosphorylation speed. $C\ln 3_0$ means the threshold value for cell to integrate while $G1_0$ means the minimum bound of G1 length.

Equation (*) shows that G1 and Cln3 are in inverse ratio demonstrating that Cln3 integration governs G1 length .

Positive feedback loop facilitates and accelerates Start transition in low Cln3 concentration

Extrinsic noises are the main source of noise in this biological system

III. CONCLUSION

A clear inverse relation between G1 length and Cln3 demonstrates integral of Cln3 rather than Cln3 itself is paramount in Budding Yeast's choice of Start transition.

REFERENCES

[1] David O Morgan. (2007)The Cell Cycle: Principles of Control (New Science Press, London.

[2] David Stuart, Curt wittenberg (1995)CLN3,not positive feedback, determines the timing of CLN2 transcription. Genes Dev 9 2459-2469.

[3] Michael Costanzo.et.al.(2004) CDK Activity Antagonizes Whi5, an Inhibitor of G1/S Transcription in Yeast. Cell 7,25, 899–913