Abrupt sister chromatid splitting in anaphase without obligatory positive feedback

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***Short Abstract* — Major transitions within the cell cycle are implemented with positive feedback loops in their regulatory pathways, which ensures that they occur quickly and are irreversible. Chromosome splitting in anaphase is abrupt and synchronous, and it seemed natural to assume that the regulation involves positive feedback. We now show in fission yeast that feedback happens, if at all, far upstream, but not at the level of the direct regulators. Hence, sister chromatid separation, being already irreversible by nature, may be one of the few major cell cycle transitions that can operate without positive feedback.**

***Keywords* — Cell cycle, mitosis, feedback regulation.**

I. Introduction

THE sudden splitting of sister chromatids at anaphase is visually one of the most remarkable transitions in the cell cycle. Anaphase is initiated when the protease separase cleaves cohesin, a protein complex that holds sister chromatids together. Prior to anaphase, separase is inhibited by securin (Nasmyth et al., 2000). Securin degradation proceeds over 4 - 20 min, depending on the organism, but separation of all chromosomes is typically a magnitude faster.

To explain the sudden onset of sister chromatid separation, a switch-like increase in separase activity has been suggested (Hellmuth et al., 2014; Holt et al., 2008; Shindo et al., 2012; Yaakov et al., 2012). Positive feedback is one of the regulatory mechanisms that can induce such switch-like changes and operates at many cell cycle transitions (Ferrell, 2013; Kapuy et al., 2009). A candidate positive feedback loop for sister chromatid separation has been identified in budding yeast (Holt et al., 2008), but it remains unclear whether it is physiologically important and functionally conserved across eukaryotes.

To address this question, we characterized the kinetics of both sister chromatid separation and the underlying securin degradation in fission yeast cells. Combining our quantitative results with computational models suggests that synchronous sister chromatid separation occurs without positive feedback regulation.

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II. Findings

A. Perturbation experiments do not support the presence of feedback regulation

We find that synchronicity of sister chromatid separation strongly correlates with securin degradation kinetics. Our findings makes positive feedback downstream of separase release highly unlikely.

B. Mechanisms for abrupt anaphase without feedback regulation

Using computational modeling, we show that simple assumptions about securin-separase association or securin degradation are sufficient to explain rapid separase release. These mechanisms ensure a high synchronicity of sister chromatid separation, even without positive feedback.

C. Chromosomes show a tendency to separate in a certain order

Although there is no absolute order, there is a slight tendency of ordered separation. We show how this behavior can theoretically be explained.

III. Conclusion

Although positive feedback loops are ubiquitous in the cell cycle, such regulation may not be necessary for sister chromatid separation. Irreversibility is already ensured thermodynamically through loss of cohesion and the switch-like increase in separase activity can be accomplished by mechanisms other than positive feedback.

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