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Asymmetric Inheritance

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Editorial

Asymmetric inheritance of cell fate determinants in developing organisms is known to play a major role in cellular differentiation, and it is a fundamental process in generating cellular diversity. Due to the crucial role that epigenetic mechanisms play in regulating cell identity and function, it has been a long-standing question whether and how stem cells maintain their epigenetic memory through many cell divisions. In the lab, we found that during asymmetric cell division of Drosophila male germ line stem cell (GSC), histone H3 (H3) becomes asymmetrically segregated-the "old" H3 is retained in the GSC while the "new" H3 is enriched in the differentiating daughter cell [1]. Recently, we also found that randomized H3 segregation pattern correlates with both GSC loss and progenitor germ line tumor phenotypes, suggesting that asymmetric H3 inheritance is required for both GSC maintenance and proper differentiation [2]. We propose that old and new H3 are asymmetrically deposited to sister chromatids during DNA replication, and mitotic machinery recognizes this asymmetry for differential segregation.

The processes of DNA replication and cell division allow the genetic material of a cell to be duplicated and transferred faithfully to its daughter cells. However, if DNA replication and cell division were always carried out in a symmetric manner, it would lead in a cluster of tumor cells instead of a multicellular organism. Therefore, understanding of any complex living organism depends on learning how cells become different during cell division while faithfully maintaining the same genetic material. In 1975, John Cairns proposed the "immortal strand" hypothesis, suggesting that the stem cell continually inherits the old DNA strands to minimize accumulation of random DNA replication errors that could change cell fate [3]. However, the immortal strand hypothesis has not been widely accepted owing to the lack of solid supporting in vivo evidence. Two similar (and more accepted) models, named the "strand-specific imprinting and selective chromatid segregation" [4] and "silent sister chromatid" [5] hypotheses suggest epigenetic differences between sister chromatids are required to direct the asymmetric outcomes during asymmetric cell division.

It is well recognized that the distinct epigenetic information of a cell type defines its unique gene expression pattern. Nevertheless, how epigenetic information contained in the parental cell is either maintained or changed during cell division and faithfully transferred into the daughter cells remains largely unknown. Our primary goal is to understand how differential epigenome generated on sister chromatids in stem cell during DNA replication and how mitotic machinery distinguishes them during mitosis for cell fate determination. To understand this, we are using high-resolution live cell imaging microscopy technique, such as light-sheet microscopy and spinning disk confocal microscopy, to visualize spatial and temporal regulation of asymmetric sister chromatids segregation in GSCs. In addition, we are also using super resolution microscopy technique, such as STORM, PALM, and STED, to achieve a high spatial resolution to understand local asymmetry in epigenetic during DNA replication.

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