Asymmetric cell division regulates the transcriptional balance controlling memory fate decisions in T cells

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The asymmetric cell division is an evolutionary acquisition strategy of multicellular organisms that enable the pluripotent cells to produce two daughter cells with distinct cellular fates. This characteristic is responsible for originating all the embryonic leaflets and tissues of the Metazoan Phyla in which stem cells divide asymmetrically to give rise to two different daughter cells, one preserving the original stem cell pluripotency (self-renewal) and the other daughter, committed to a further differentiation program, into specialized cell types with non-stem cell fate (1). The mechanisms through which the asymmetric cell divisions are conferred to dividing daughter cells are inherently acquired at the time of division of the mother cell. In multicellular organisms, this response is triggered by the polarization of the mother cell and the consequent alignment of the mitotic spindle with the axis of polarity during mitotic division (1).

In *C. elegans*, asymmetric cell divisions occurring in the embryo are critical in establishing the axes of the body plan (2). In *Drosophila melanogaster*, this mechanism plays a crucial role in neural development, via regulation of the Notch signaling pathway and transcription factors (3). The protein regulator, Prospero, and the transcription factor, Numb, are both synthesized in the neuroblast progenitor cells and segregate into only the ganglion-committed cells under differentiation from mother cells during mitotic divisions. Numb is a suppressor of Notch, and its asymmetric segregation to differentiating ganglion mother cell results in a distinct cell fate from the neuroblast progenitors. This neural differentiation program requires the role of Prospero for gene regulation of ganglion cells. Asymmetric cell division balances self-renewal proliferation of progenitor cells with cell cycle exit and differentiation of dividing daughter cells (3).

A number of different genes have been demonstrated to play a role in the pluripotency of stem cells, such as Bmi-1, Wnt and Notch. These genes are critical to the self-renew capacity of dividing progenitor stem cells. Their abnormal expression during stem cell differentiation leads to an impairment of asymmetric cell division in dividing cells that is thought to play a role in the tumorigenic transformation of progenitor cells (4). The unequal distribution of transcription factors along the division of progenitor cells, and their differentiation into tissue-specialized committed cells, have also been shown to play important roles in the immune system. It has recently been demonstrated that asymmetric cell division is responsible for the dichotomy between the generation of memory T cells and effector cells from a common precursor activated by antigenic recognition in the context of an antigen-presenting cell (5).

The antigenic-specific priming of T cells, triggers the asymmetric cell division program in which dividing cells proximal to the antigen-presenting cell are prone to undergo commitment to effector differentiation, while the distal dividing blasts are likely to acquire a memory T cell phenotype (5). This is possible due to the asymmetric distribution through dividing daughter lymphocytes of the transcription factor c-Myc, a cell cycle regulator of the mitotic proliferative activity of T cell blasts. This asymmetric sort of c-Myc is associated with the distinct cell fates governing memory versus effector T cells (5). Investigations into how intrinsic factors are asymmetrically

distributed along the T cell lineage commitment should clarify our understanding of the optimal long-term memory generation of protective immunity and coordinate our efforts in the search for prospective strategies to design immunotherapies against cancer and infectious diseases.

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Footnote

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