

Metabolic control of asymmetric division

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Asymmetric division in CD8 T cells produces two daughter cells expressing different levels of c-Myc with distinct metabolic profiles. Manipulating this asymmetric partitioning of c-Myc skews T cell responses and potentially allows the development of more effective vaccines and cancer immunotherapies.

Cell division is often perceived to be a symmetric process by which one cell gives rise to two identical daughter cells. Throughout development, however, cell division can produce two daughter cells with different protein content, cell size, and developmental potential, that ultimately adopt distinct fates in a process termed asymmetric cell division [1]. One of the salient characteristics of the adaptive immune systems is the ability of a single antigen-specific T cell to proliferate and to differentiate into two distinct classes of daughter cells in responding to microbial infection, namely the terminal effector cells that mediate acute protection and the memory cells that provide long-term protective immunity. Work over the years has shed light on how this process occurs *in vivo*. One potential explanation is the asymmetric division of cytotoxic CD8 T cells. Specifically, the daughter cell proximal to the antigen-presenting cell (APC) is marked by higher expression of CD8 (CD8^{high}) and is more likely to differentiate into effector-like T cells. The distal daughter cell expresses a lower level of CD8 (CD8^{low}) and is more likely to differentiate into memory-like T cells [2]. Several transcription factors, including T-bet and TCF-1, have been shown to contribute to the phenotypic and functional differences between the

daughter cells [3, 4]. There is emerging evidence suggesting a role for PI3K signaling and nutrient sensing in dividing T cell fates [4]. Nevertheless, whether there exist metabolic programs that orchestrate asymmetric division in T cells and whether this process can be manipulated for therapeutic purposes remain incompletely understood.

In a recent paper in *Nature*, Verbist *et al.* [5] elegantly demonstrate that c-Myc, a major transcription factor that drives metabolic reprogramming necessary for T cell activation and proliferation [6], is asymmetrically partitioned between the two daughter cells during the first division of activated T cells in mice [5]. Specifically, CD8^{high} daughter cells have higher c-Myc compared with CD8^{low} cells. Furthermore, c-Myc^{high} daughter cells are more activated and glycolytic, and thus more readily differentiate into terminal effector cells, whereas c-Myc^{low} cells are more persistent and can proliferate upon secondary challenge (Figure 1). Mechanistically, the authors show that several amino acid transporters including CD98 and the neutral amino acid transporter SLC1A5 are more highly expressed in c-Myc^{high} daughter cells. This may contribute to the increased amino acid content, and thus the higher activity of mammalian target of rapamycin complex 1 (mTORC1) in these cells. Most importantly, depletion of the amino acid pool or inhibition of mTORC1 activity with rapamycin abolishes the asymmetric partitioning of c-Myc in daughter cells. Using T cell specific loss of Tsc1, which is a crucial negative regulator of mTORC1 activity, the authors further show that hyperactive mTORC1 signaling abrogates the

asymmetric partitioning of c-Myc, as well as the proliferative potential differences between the two daughter cells. This genetic manipulation demonstrates the role of mTORC1 in mediating metabolic reprogramming, which ultimately contributes to the distinct fates of two daughter cells. The findings from this study are consistent with a recent publication from the Powell group [7]. They demonstrated that the asymmetric partitioning of mTORC1 activity in activated CD8 T cells results in the generation of two daughter T cells with differential metabolic profiles and ultimately adopt distinct immune functions.

The study adds to a growing number of reports demonstrating the crucial roles of metabolic reprogramming in T lymphocyte proliferation, differentiation, and function. The importance of nutrient sensing and amino acid concentrations in asymmetric cell division demonstrated from this study is especially intriguing and further highlights the intricate link between metabolism and the immune system. These findings reveal the exciting potential of manipulating the asymmetric division process to skew T cell responses in a direction that is beneficial for vaccine development or antitumor therapy. Nevertheless, they also raise the questions of what are the key players that control asymmetric distribution of mTORC1 activity and the various metabolic components such as amino acid transporters and what happen if this regulation is disturbed? It is known that complete loss or hyperactivation of mTORC1 activity is detrimental for the development of potent effector T cells or functional memory T cells, respectively

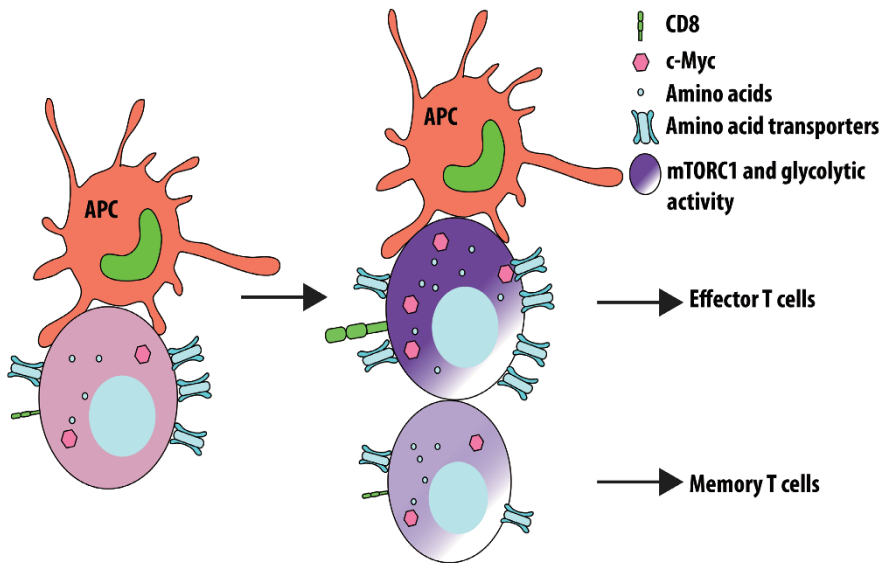


Figure 1 Metabolic control of asymmetric cell division in CD8 T lymphocytes. Proximal daughter cells have higher intracellular amino acid concentrations associated with increased distribution of amino acid transporters and mTORC1 activity, as well as higher c-Myc levels. Proximal daughter cells differentiate readily into effector T cells whereas distal daughter cells have memory-forming potential.

[8, 9]. Thus, the challenge remains to identify the regulatory elements that control the asymmetric partitioning of

the metabolic machinery and to develop strategies that timely and precisely target the mTORC1-c-Myc axis in

such a way that would yield the most therapeutic benefit.

Mytrang H Do^{1, 2},
Ming O Li¹

¹Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA;
²Weill Cornell/Rockefeller/Sloan Kettering Tri-Institutional MD-PhD Program, New York, NY 10065, USA

Correspondence: Ming O Li
E-mail: lim@mskcc.org

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