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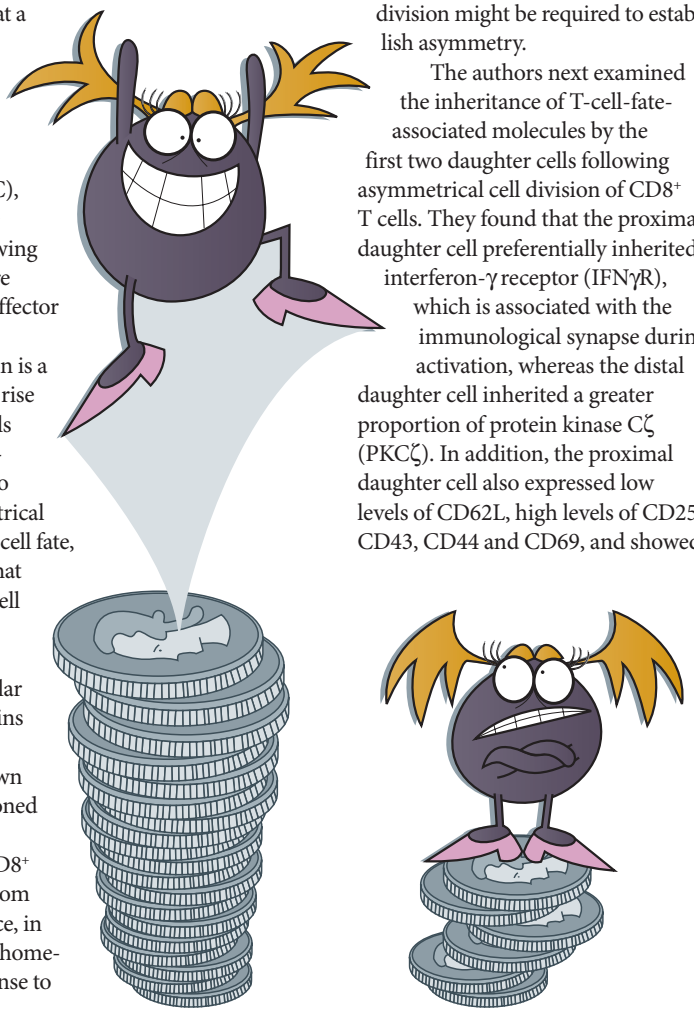
LYMPHOCYTE ACTIVATION

Unequal inheritance initiates T-cell diversity

The adaptive immune response is associated with the development of pathogen-experienced effector and memory T cells. But how is this heterogeneity initiated? Steven Reiner and colleagues now show that a dividing T cell undergoes asymmetrical cell division, which is coordinated by the prolonged interaction between the T cell and an antigen-presenting cell (APC), in response to infection. The first two daughter cells following asymmetrical cell division are differentially fated towards effector and memory lineages.



Asymmetrical cell division is a process by which a cell gives rise to two different daughter cells through the unequal inheritance of specific molecules. To determine whether asymmetrical cell division is involved in T-cell fate, the authors isolated T cells that were preparing for the first cell division from mice infected with *Listeria monocytogenes* and examined their subcellular characteristics *ex vivo*. Proteins associated with polarity and synapse formation were shown to be asymmetrically partitioned perpendicular to the mitotic spindle in both $CD4^+$ and $CD8^+$ T cells. By contrast, T cells from uninfected lymphopenic mice, in which T cells undergo acute homeostatic proliferation in response to self antigen, had a diffuse distribution of these proteins. These findings indicate that the prolonged interaction between an APC and a T cell that occurs during infection prior to cell division might be required to establish asymmetry.

The authors next examined the inheritance of T-cell-fate-associated molecules by the first two daughter cells following asymmetrical cell division of $CD8^+$ T cells. They found that the proximal daughter cell preferentially inherited interferon-γ receptor (IFNγR), which is associated with the immunological synapse during activation, whereas the distal daughter cell inherited a greater proportion of protein kinase Cζ (PKCζ). In addition, the proximal daughter cell also expressed low levels of CD62L, high levels of CD25, CD43, CD44 and CD69, and showed greater expression of the genes encoding IFNγ and granzyme B. These characteristics are consistent with the effector T-cell lineage. By contrast, the distal daughter cell expressed high levels of CD62L, low levels of CD25, CD43, CD44 and CD69, and expressed higher amounts of interleukin-7 receptor-α (*CD127*) mRNA, all of which are characteristics of early memory T-cell precursors.

But do these phenotypic characteristics have functional relevance? Proximal and distal daughter cells were isolated from infected mice, sorted and transferred to naive recipients that were then challenged immediately or 30 days later with *L. monocytogenes*. Proximal daughter cells provided equal or better protection following immediate challenge, than distal daughter cells. However, distal daughter cells provided significantly greater protection following challenge 30 days after T-cell transfer. These results indicate that the functional properties of proximal and distal daughter cells reflect the phenotypic markers of effector and memory T-cell precursors, respectively.

The data indicate that asymmetrical cell division in T cells in response to infection results in the generation of daughter cells with distinct cell fates. The differentiation of both effector and memory precursor cells from a single responding T cell ensures the intraclonal diversity necessary to maintain an efficient immune response.

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