Commentary

An adequate human T cell repertoire from a single T cell progenitor: Lessons from an experiment of nature

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The study of human T cell development is hampered by the lack of genetic tools that have been successfully used in mice. In both mice and humans, T lymphocytes develop in the thymus from progenitors that originate in the bone marrow. In mice, targeted mutations (“knockout” mice) and transgenics have provided a better understanding of T cell development [1,2]. Mostly descriptive studies exist for human T cell development, although patients with rare genetic defects, such as SCID patients have been instrumental in obtaining insight into this intricate process.

A healthy human immune repertoire includes billions of T cells with different T cell receptors (TCRs) to help recognize and respond to virtually any pathogenic invasion. During T cell development, this diverse repertoire is generated by gene recombination of V, (D), and J TCR segments. Progenitors from hematopoietic stem cells (HSCs) in the bone marrow migrate to the thymus where they proliferate and differentiate into mature T cells. Surprisingly, only a subset of these progenitors is needed to reconstitute a diverse repertoire of human T cells in immune-deficient mice [3]. Partially due to data from mouse studies, it is generally assumed that an early thymocyte progenitor has lost the long-term self-renewal potential, but whether a self-renewing T cell progenitor exists in humans is not known.

In the last issue, Kury et al describe an intriguing X-linked SCID case [4], reporting a somatic reversion of the IL2RG mutation in all T cells but not in other immune cells. As such an event is extremely rare, the authors hypothesise that this reversion did not happen in more than one progenitor cell. The rescue of T cell development is illustrated by the presence of a functioning, albeit limited T cell repertoire. Surprisingly, only a subset of these progenitors is needed to reconstitute a diverse repertoire of human T cells in immune-deficient mice [3]. Partially due to data from mouse studies, it is generally assumed that an early thymocyte progenitor has lost the long-term self-renewal potential, but whether a self-renewing T cell progenitor exists in humans is not known.

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transplantation. The T cell progenitor will likely not be identified solely by the existing surface markers since they have been used extensively and not led to early novel progenitor subsets. Instead, epigenetic studies or single-cell sequencing in combination with single-cell functional studies may provide a better chance at identifying the subtle differences between various lineage-biased multipotent progenitors that appear similar on the surface. A potential alternative is the in vitro generation of T cell progenitors using the Notch ligand DLL4, as has been proposed [10] and is now tried in clinical studies.

Collectively, the careful analysis of unique patients such as the one reported by Kury and colleagues remains invaluable for a better understanding of human lymphopoiesis.

Fig. 1. Potential origin of the T cell progenitor (in red) with long-term self-renewal ability.

Declarations of Interests

Authors have nothing to disclose.

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