Editorial

Stem Cell INVESTIGATION

Lineage choice decisions in B-cell development and leukemia

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Every tissue in the body is founded by a particular type of cell that is termed stem cell. These cells are generally presumed to be tissue-specific and, as such, are also responsible for maintenance of the tissue throughout the lifespan of an organism. There are two fundamental aspects to the regular behaviour of tissues during their genesis and thereafter. The offspring of stem cells divide in a manner that is controlled to the social benefit of the organism to generate/ensure the bulk of tissue that is required. These dividing cells mature: they acquire individual characteristics to enable them to perform a unique function within the tissue. Within cancer cells aspects of this normal physiology are distorted. This means the many strands to understanding of the behaviour of normal cells cannot be loosened from the strands of efforts to unravel what goes wrong in cancer.

For many years, the blood cell system has provided a model system that has been used by many researchers to investigate how a stem cell can give rise to a wide variety of mature cell types. The principles that emerged to developmental biology have been applied to the structure of tissues throughout the body. However, many of the principles have been challenged by findings over a number of years. This has led to revision to the way we view blood cell development. In turn, this has impacted on our understanding of the origin and nature of leukemias, and cancer in general. "Classic" bifurcating tree maps for the development of the various blood and immune cells depict a single route to each of the mature cell types and strict compartments to haematopoietic stem cells (HSCs) and haematopoietic progenitor cells (HPCs). This model led to the notion that decision-making occurs much earlier than previously thought and within HSCs. However, developing HSCs and HPCs are much more versatile than described in the classic model. To directly address the versatility of HSCs and HPCs, Zhang *et al.* [2018] designed an initial screen to identify candidate transcription factors mainly expressed in HSCs and HPCs but not in lineage-committed cells (1). Within the 15 transcription factors identified, only forced expression of Hoxb5 factor was able to reprogram committed progenitors of B cells into distinct subsets of T lymphocytes. The authors performed then an elegant series of experiments examining the basis for the selective regulation of Hoxb5-mediated B-cell reprogramming potential. The authors showed that the constitutive expression of Hoxb5 in all hematopoietic cells, including T lymphocytes, had a minimal effect on hematopoiesis. However, transient expression of Hoxb5 in precursor B cells was sufficient for stable conversion of B cells into T cells *in vivo*, and sustained expression of Hoxb5 was dispensable

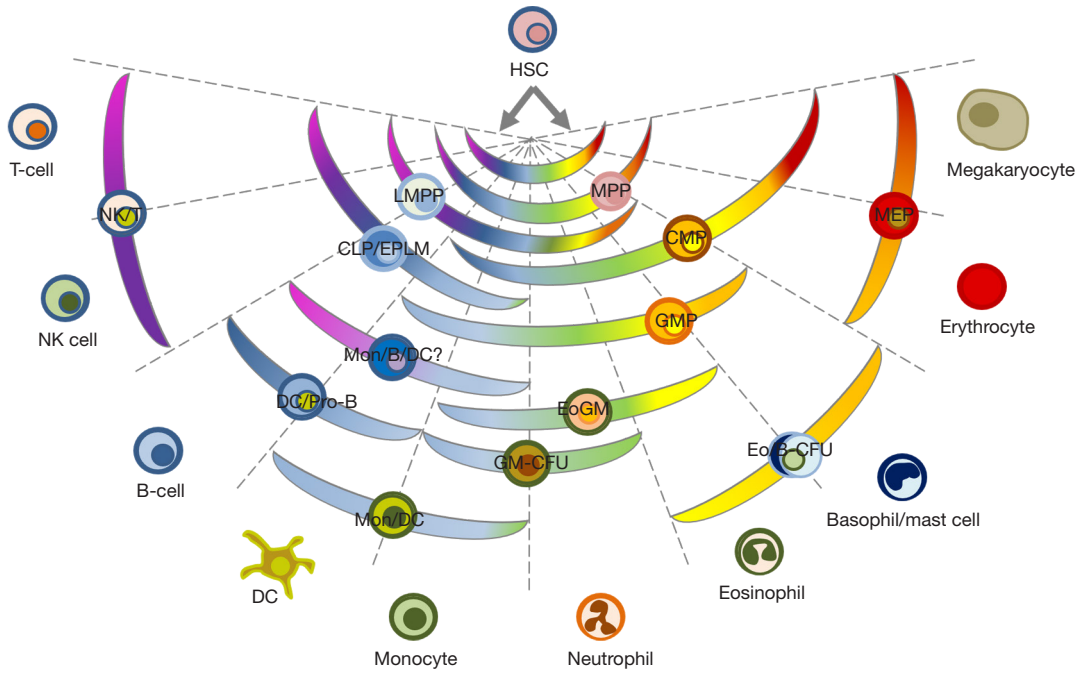

Figure 1 The pair-wise model of hematopoiesis. Differentiation options are envisaged as a series of invariant pair-wise developmental relationships with cells becoming gradually biased from the hematopoietic stem cell stage of development towards producing one cell type or another. The close relationship between cell lineages is inferred from the incomplete sets of lineage options within known progenitor cells (partial arcs in the figure). HSC, haematopoietic stem cell; LMPP, lymphoid primed multipotent progenitor; MPP, multipotent progenitor; CLP, common lymphoid progenitor; EPLM, early progenitors with lymphoid and myeloid potential; CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; NK, natural killer cell; EoGM, eosinophil-granulocyte-macrophage; GM-CFU, granulocyte-macrophage progenitor-colony forming unit; DC, dendritic cell; MEP, megakaryocyte-erythroid progenitor.

after the target cells committed to lineage conversion. These results convincingly showed that forced expression of Hoxb5 in precursor (pro/pre) B cells was sufficient to convert mouse B cells into T cells *in vivo*. However, the efficiency of Hoxb5-induced B cell-to-T cell conversion was very low, indicating that a minority of precursor B cells overexpressing Hoxb5 were reprogrammed into T cells *in vivo*, but the majority were able to differentiate normally into B cells. This cell-fate conversion was the consequence of Hoxb5-mediated repression of genes encoding B cell master regulators, activation of genes encoding T cell regulators and regulation of genes encoding chromatin and epigenetic modifiers and remodelers. Thus, they further found that Hoxb5 directly targeted Ebf1, Pax5, Bcl11a, Foxp1 and Foxo1, consistent with published reports that repression of Pax5 and Ebf1 is crucial for the B cell-to-T cell conversion (2,3). Likewise, Hoxb5 directly targeted transcription factors with important roles in the regulation of T cell fate as Lmo2, Nfatc1, Tcf12, Prdm1 and Runx2.

The results are both attractive and provocative in equal measure. On one hand, the conversion of precursor B-cells into T cells indicates that, after having selected a cell lineage, they can still "step sideways" to adopt alternative, closely related, fates. Thus, these findings are a clear support for the pair-wise model of hematopoiesis proposed by Brown and Ceredig (4-6). Notably, the pair-wise model does not prescribe a single route from HSCs to each of the end cell types. Instead, the model envisages a spectrum of options arranged in a particular manner (*Figure 1*). According to this model, differentiation options are envisaged as a series of invariant pair-wise developmental relationships with cells becoming gradually biased from the hematopoietic stem cell stage of development towards producing one cell type or another. This major change to our understanding of haematopoiesis is supported by the *in vivo* conversion of precursor B-cells into T cells and impacts on how we view leukemia development (*Figure 2*).

During leukemogenesis a normal cell acquires a new but

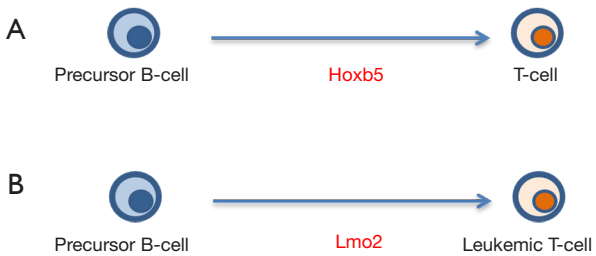

Figure 2 Conversion of precursor B-cells into either normal T cells by the reprogramming capacity of Hoxb5 (A) or into leukemic T cells by the reprogramming capacity of Lmo2 (B).

inappropriate (malignant) identity to give rise to a clonal aberrant population. This is only possible if the oncogenic event initiating cancer had an inherent reprogramming capacity, to be able to lead to the change in cellular identity (7,8). *LMO2* is one of the most frequent drivers of childhood T-cell acute lymphoblastic leukemia (T-ALL) (9) and has been identified as one of the transcription factors regulated by Hoxb5 during the *in vivo* conversion of precursor B-cells into T cells (1). Likewise, recent findings have shown that *LMO2* functions as a "hit-and-run" oncogene that acts at an early stage of T-cell leukemogenesis to reprogram hematopoietic stem/progenitor cells (HS/PCs) for T-cell malignancy, showing that activity of the *Lmo2* oncogene restricted to HS/PCs can induce malignancies in mice that are of a T-cell stage of differentiation (10,11). However, the permissiveness for development of T-ALL seems to be associated with wider windows of differentiation than previously appreciated. Restricted Cre-mediated activation of *Lmo2* at different stages of B-cell development, including pro-pre B cells, induced systematically and unexpectedly T-ALL that closely resembled those of their natural counterparts (10). Biological barriers exist to prevent cells from changing their identity in this manner in order to avoid the risk of malignant transformation (7,8,12,13). In B-cell malignancies it has been shown that loss of p53 is a frequent occurrence and facilitates the pathological reprogramming to a malignant B-cell phenotype (14,15). Similarly, a significant proportion of T-ALL in all our murine models carried *p53* loss-of-function mutations facilitating pathological reprogramming to a malignant T-cell phenotype (10). It will be worthy to see if *p53* is also a biological barrier for Hoxb5-mediated B-cell reprogramming potential (*Figure 2A*). These findings led us to propose that T-ALL is the result of an inappropriate lineage-decision making process occurring via a reprogramming-like mechanism which can even start within a B-cell (*Figure 2B*). Nonetheless, the observation that transient expression of Hoxb5 was sufficient for stable conversion of precursor B cells into T cells *in vivo* raises a potential new avenue for the full understanding of hematopoietic development and the genesis of leukemia.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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