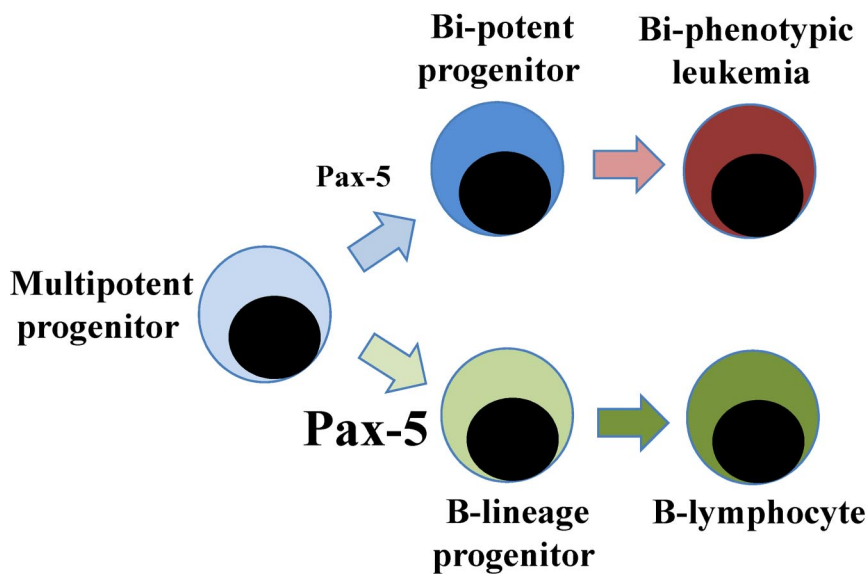


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# Transcription factor dose links development to disease

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In this issue of *Blood*, Simmons et al report that low expression levels of the transcription factor Pax-5 in B-lineage progenitors results in the formation of highly proliferative B220<sup>+</sup>CD11b<sup>+</sup> cells expressing both lymphoid and myeloid genes much in resemblance to cells generated in acute lymphoblastic leukemia (ALL)-like bi-phenotypic acute leukemia (BAL).<sup>1</sup> In contrast, high expression levels of Pax-5 in the progenitors result in expression of CD19 and apparently stable B-lineage commitment, suggesting a critical role for Pax-5 dose in both normal B-cell development and in the generation of leukemia.



Dose-dependent regulation of cell differentiation by Pax-5. The figure shows a schematic drawing of the effect of Pax-5 dose on the differentiation of multipotent progenitors and generation of bi-phenotypic leukemia.

The crucial functions of transcription factor dose have been well recognized in the field of developmental biology through classic examples such as sex determination in *Drosophila melanogaster* where the sex of the embryo is dictated by the functional dose of X-chromosome-encoded transcription factors. Other examples can be found in the hematopoietic system in mice where the dose of the transcription factor PU.1 dictates myeloid versus lymphoid cell fate.<sup>2</sup> Even though lineage-restricted transcription factors have been recognized for their role in leukemia development through chromosomal translocations resulting in fusion proteins or overexpression, the interest in the impact of

reduced transcription factor dose in the oncogenic process has been rather limited. However, the finding that a large portion of childhood acute B-cell leukemias carries inactivation mutations in genes encoding transcription factors involved in B-cell development<sup>3</sup> has sparked an increased interest in this research area. Even though heterozygous mutations could be found in the *TCF-3 (E2A)*, *IKZF-1 (Ikaros)*, and *Ebf-1* genes, the most common change in the pre-B cell leukemia was alterations in the *Pax-5* gene.<sup>3</sup> Pax-5 was initially identified as a transcription factor involved in the regulation of the *CD19* gene; however, subsequent analysis revealed that this protein is crucial for the development of

mature B-lymphocytes. Even though B-cell development is dependent on a network of transcription factors, Pax-5 appears to play a unique role in early B-cell development. In the absence of Pax-5, progenitor cells activate a set of B cell-specific genes; however, this expression is not stable and can be reversed, resulting in a dramatic lineage plasticity of the cells.<sup>4,6</sup> This is reflected in an ability of Pax-5-deficient pro-B cells to adopt alternative cell fates including T-cell, NK-cell, and under some conditions even myeloid cell fates.<sup>4,6</sup> This plasticity can also be observed after deletion of *Pax-5* in mature B-lymphocytes because this results in dedifferentiation giving rise to multipotent progenitors capable of generating cells of other lineages (see figure).<sup>6</sup>

The report by Simmons et al reveals that the functional outcome of Pax-5 expression is highly dependent on the expression levels.<sup>1</sup> High expression induces activation of B-lymphoid genes and apparently stable commitment to B-lineage, while lower levels of expression result in the generation of an abnormal cell population with combined expression of genes normally restricted to either lymphoid or myeloid lineages. In this report, the authors stress the similarity to what can be observed in BAL where one typical characteristic is the combined expression of B-lymphoid and myeloid markers. However, in the light of the frequently detected mutations in Pax-5 in pre-B cell leukemia, their findings are likely to have implications extending beyond that of BAL. Their data show that there are no dramatic phenotypic changes in mice lacking one allele of Pax-5<sup>1</sup> supporting the idea that an inactivating mutation in one allele of Pax-5 per se is not sufficient to give rise to dramatic developmental disturbances or leukemia. Even though this may appear paradoxical, it is crucial to recognize that the functional dose of a transcription factor can be regulated at several different levels. The functional impact of an amorphic allele, as observed in mouse models carrying a null allele of Pax-5 where no protein is produced, may have a largely different impact on transcription factor function than the formation of a hypomorphic allele with reduced function by a point mutation in leukemia. This is because a partially functional protein may act as an antimorph counteracting the function of normal Pax-5 protein by competition for interaction with cofactors or binding to target promoters,

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reducing the functional dose of Pax-5 below that observed for an amorphic allele. Because of that a loss of heterozygosity resulting in combined amorphic mutation of the second allele of Pax-5 would have to be predicted to result in loss of B-lineage identity,<sup>6</sup> the function of Pax-5 in B-cell malignancies is likely an issue of transcription factor dose. Even though we have a developed understanding of the function of Pax-5 in early B-cell development, the exact mechanisms underlying the unique role in the regulation of B-lineage fidelity remains elusive. One possible explanation comes from the finding that Pax-5 and Ebf-1 appear to participate in an auto-regulatory loop of crucial importance for stable B-lineage commitment.<sup>7</sup> An impaired function of Pax-5 could then result in a gradual reduction in

both Pax-5 and Ebf-1 doses enhancing the impact of a heterozygous inactivating mutation in the *Pax-5* gene.

Hence, even though the understanding of how a partial reduction in transcription factor function contributes to the formation of leukemia is still rather poorly developed, the report by Simmons et al adds new links between leukemia and transcription factor dose, bringing developmental biology and clinical oncology closer with potentially large benefit for 2 important areas of modern medicine.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■

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