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B-1 progenitor acute lymphoid leukemia

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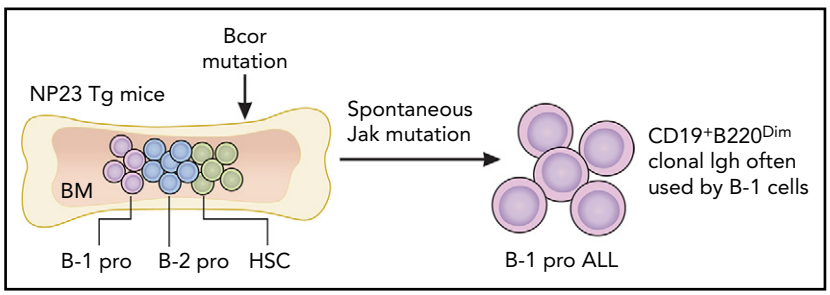
In this issue of *Blood*, Yin et al demonstrated that engineered BCL6 interacting corepressor protein (*Bcor*) mutation in hematopoietic stem/progenitor cells of sensitized mice induced acute lymphoid leukemia (ALL) of B-1 progenitor phenotype,[1] which has been recently identified by them.[2] The intriguing aspect of this report is the complete penetrance of B-1 progenitor leukemia by *Bcor* mutation, which selectively developed among other various progenitors in the bone marrow (BM).

B-1 progenitor ALL or B-1 cells may be unfamiliar terms for many researchers and hematologists. B-1 cells are a unique B-cell subset that is well characterized in mice but not in humans. Unlike conventional adaptive immune B cells (B-2 cells), innate immune-like B-1 cells reside mainly in the pleural and peritoneal cavities. B-1 cells spontaneously secrete natural immunoglobulin M antibodies with stereotypic usage of immunoglobulin heavy chains (Igh), independent of T-cell help. These cells play important roles in the first line of defense against infections.

B-1 cells are unique in their developmental origins. They are mostly derived from progenitors in the fetal liver and neonatal BM and are developmentally different from conventional B-2 cells that are differentiated from hematopoietic stem cells (HSCs) through B-2 progenitors (such as prepro-B, pro-B, and pre-B cells) in the BM.[3,4] B-1–specific progenitors, $sIg^-AA4.1^+CD19^+B220^{lo/-}$ (CD19 single positive) population has been identified in the fetal liver and neonatal BM, and the number of the B-1–specific progenitors in the postnatal BM declines with mouse age.[5,6] B-1–specific progenitors are segregated from conventional B-2 progenitors, $sIg^-AA4.1^+CD19^-B220^+$ (B220 single positive) population. Both the progenitors mature into $sIg^-CD19^+B220^+$ (CD19B220 double positive) pre-B cells, and thus, after the pre-B-cell stage, one cannot distinguish B-1 progenitors from B-2 progenitors, and B-1 progenitors are a very small population in the adult BM. Importantly, the human counterpart of mouse B-1 cells has been controversial.

Almost all acute leukemias of B-progenitor phenotype in mouse models are thought to be the B-2 progenitor-derived, expressing surface markers of pro-B/pre-B cells (B220 single-positive or CD19B220 double-positive cells). However, the B-progenitor leukemia induced by *Bcor* mutation in NUP98-PHF23 (NP23) transgenic (Tg) mice, reported by Yin et al, displayed a CD19 single-positive B-1–specific progenitor phenotype, accompanied by a spontaneous *Jak* mutation (see figure).



Yin et al engineered a *Bcor* mutation in BM cells or fetal liver cells from NP23 Tg mice and injected them into lethally irradiated mice. All the recipient mice developed leukemia with B-1 progenitor phenotype and the same Igh usage with B-1 cells. B-1 pro, B-1 progenitors; B-2 pro, B-2 progenitors.

NP23 is a chromatin-modifying oncoprotein, associated with human acute myeloid leukemia (AML). Previously, it has been reported that all NP23 Tg mice develop leukemia, including AML, T-cell ALL, and B-cell ALL, by 14 months of age.[2,7] B-1 progenitor leukemia, with spontaneous mutations of *Bcor* and *Jak*, was found in ~10% of these leukemic mice. Intriguingly, not only the surface markers but also the clonal Igh usage of B-1 progenitor leukemic cells are similar to fetal liver–derived B-1 cells.[2] Based on these results, Yin et al engineered a *Bcor* mutation by Cas9 in lineage-negative hematopoietic progenitors from the BM and the fetal liver of NP23 Tg mice and transplanted them into irradiated mice. Surprisingly, B-1 progenitor leukemia developed in all recipient mice. B-1 progenitors are a very small population among other progenitors in the BM, including HSCs, myeloid progenitors, common lymphoid progenitors, and B-2 pro/pre-B progenitors (see figure). Why do only B-1 progenitors develop leukemia when *Bcor* mutation was engineered in total NP23 Tg BM cells? It is generally considered that leukemogenic events are not sufficient to induce leukemia in all blood cells; rather, they need to occur in the selective hematopoietic lineage and at a specific progenitor stage in order to develop leukemia.[8] Therefore, the results by Yin et al suggest that there must be an underlying mechanism through which *Bcor* mutation selectively induced B-1 progenitor leukemia with spontaneous *Jak* mutation.

An animal model of acute leukemia with B-1 progenitor phenotype has not been reported before. There is a report showing that B-1 progenitors developed more aggressive ALL with shorter latency compared with B-2 progenitors when the BCR-ABL gene was overexpressed in B-1 and B-2 progenitors and the cells were transplanted into immunodeficient mice.[9] The BCR-ABL leukemic cells in recipient mice displayed CD19B220 double-positive pre-B-cell phenotype regardless of the B-1 or B-2 progenitor origin. Because both B-1 and B-2 progenitors become CD19B220 double-positive cells during maturation, this result suggests that CD19B220 double-positive pre-B leukemia may include both B-1 and B-2 progenitor cell origins. In this sense, the report by Yin et al supports the possibility that B-lymphoid leukemia of B-1 progenitor origin may be underappreciated.

Another important aspect of this and their previous report is that we may be able to connect mouse B-1 progenitor leukemia with the human counterpart. The *Bcor* mutation in human B-ALL is very rare; however, a correlation between mouse B-1 progenitor ALL in NP23 Tg and human B-progenitor ALL with *Jak* mutation and cytokine receptor like factor 2 (CRLF2) overexpression has been indicated by gene expression signature and the preference for Igh usage.[2] CRLF2 encodes a receptor for thymic stromal lymphopoietin, an important cytokine receptor for B-1 cell development. Therefore, the B-1 progenitor ALL mouse model could be a great tool to identify the human counterpart of B-1 progenitors and related leukemias. Because the cell surface markers are quite different between mice and human, identifying the human counterpart of B-1 cells has been challenging and still controversial. Elucidating the underlying mechanism via which B-1 progenitors selectively develop leukemia would be a key to resolve this long-standing question in the field.

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

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