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Editorial

Tracking Down the Origin of Stem Cell Programs in Cancer Cells

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Editorial

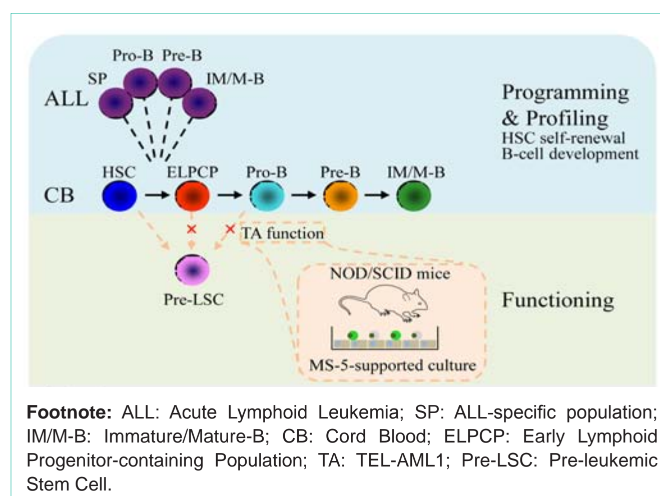
Cancer stem cells (CSCs) are cells that possess stem cell properties, particularly the ability to propagate cancer. The origin of the stem cell program of cancer cells is a key issue elucidating carcinogenesis. It is possibly retained from stem cells or cancerously reprogrammed from progenitor and even mature cells. Studies on leukemia have provided pivotal observations, particularly the identification of initiating pre-malignant cells, namely, pre-leukemic stem cells (pre-LSCs) [1] or pre-leukemic hematopoietic stem cells (HSCs) in leukemogenesis [2].

Initiating pre-malignant cells are difficult to identify because of lack of feasible approaches to determine healthy individuals who carried the cells. Genetic analysis has provided opportunities in this endeavor. For the first time, we identified initiating pre-malignant stem cells in leukemia by using the unique genetic background of a pair of monochorionic twins [1]. In our study, a 2-year-old twin acquires acute lymphoblastic leukemia (ALL), whereas the other twin remains healthy. Molecular analysis of the blood cells of the twins revealed the existence of an identical leukemic fusion, namely, TEL-AML1. The fusion was considered prenatal in origin, that is, it occurred *in utero* in one twin and then spread to the other twin through their shared placenta. TEL-AML1 has been presumed as the initiating genetic lesion in associated leukemia [3]. Immunophenotypic analysis of blood cells of the healthy twin revealed a population containing markers for stem cells ($CD34^+$ and $CD38^-$) and B-cells ($CD19^+$). This population does not exist in normal blood samples. Subsequently, the population was replicated in our disease models by inducing TEL-AML1 in human cord blood (CB) cells, followed by xenotransplantation in NOD-SCID mice or inoculation in cultures with mouse stromal cells, MS5. The results showed the self-renewal potential of the population in both experimental systems and thus demonstrated the population contained pre-LSCs [1].

Modern advanced genetic techniques, including deep sequencing, have been used to determine founder mutations that may generate a pre-malignant ancestral cell of cancer. Pre-leukemic HSCs have been recently identified in acute myeloid leukemia (AML) after the initiating mutation $DNMT3A^{mut}$ was determined [2].

We investigated the early reprogramming process of leukemogenesis by obtaining samples from pre-malignant cells and subjecting them to RNA array analysis. We determined that modeled pre-LSCs were located at the differentiation stage between HSCs ($CD19^-$, $CD34^+$, and $CD38^-$) and pro-B cells ($CD34^+$ and $CD19^+$). Functional assay results showed that pre-LSCs were primed with multi-lineage potential; hence, stem cell programs in pre-LSCs may be retained from HSCs, rather than converted from B progenitor cells. This assumption was proven by the results of leukemogenesis targeting experiments, in which only cells that possess self-renewal potential (that is, HSCs) are the suitable target of TEL-AML1 (Figure 1) [4].

To consolidate previous findings, we investigated samples of patients with TEL-AML1-associated ALL; these samples were functionally confirmed to have stem cell properties and contain leukemic stem cells (LSCs) within different immunophenotypic fractions. We comparatively profiled a refined program in cells of the immunophenotypic populations of human ALL and CB cells of normal counterparts at different differentiation stages; this program, which was termed as HSCB program, was edited from functional genes essential to HSC self-renewal and B-cell development. Bioinformatic analysis showed that ALL populations were loosely clustered and located close to the normal population, which contains stem and primitive progenitor cells (Figure 1). This result confirms that stem cell programs in leukemic lymphoblast's are retained from stem cells, rather than introduced on progenitor cells by leukemogenic molecules, such as TEL-AML1 [4].



Footnote: ALL: Acute Lymphoid Leukemia; SP: ALL-specific population; IM/M-B: Immature/Mature-B; CB: Cord Blood; ELPCP: Early Lymphoid Progenitor-containing Population; TA: TEL-AML1; Pre-LSC: Pre-leukemic Stem Cell.

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Methylation analysis of self-renewal genes was conducted to investigate the mechanism underlying the retention of stem cell programs in pre-LSCs and LSCs. The results showed that these genes are active and exhibit a low methylation level in HSCs and become hypermethylated and inactive in progenitor cells; by contrast, these genes consistently present a low methylation level in leukemic cells with stem cell properties. Furthermore, this maintenance of the stem cell program may occur in specific niches because TEL-AML1-expressed cells tend to localize closely along the endosteum in bone marrow (BM) (unpublished data) [5].

The machinery of self-renewal differs between fetal HSCs and BM HSCs, and childhood leukemia may have a prenatal or postnatal origin [6]. Future studies must investigate the mechanism underlying the conversion of fetal self-renewal machinery to a postnatal one when HSCs migrate to BM after birth. Findings of such studies are crucial in elucidating the mechanism through which stem cell programs are cancerously reprogrammed to trace down the origin of leukemia. Factors such as niche adaption, epigenetic alteration, and genetic mutation may be mutually involved in the process [5]. The developed concept and experimental paradigm used may be applicable for exploring similar issues in other types of cancers in various tissues.

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