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Review article

The role of a transcription factor LYL1 in leukemogenesis

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Abstract

A number of transcription factors were revealed in the study of chromosomal translocation associated with T cell acute lymphoblastic leukemia. LYL1 is one of the examples of such transcription factors. LYL1 is a member of the class II basic helix-loop-helix transcription factors and aberrantly expressed in a fraction of human T cell acute lymphoblastic leukemia. The mechanism of leukemogenesis by LYL1 has been studied in transgenic mouse ubiquitously overexpressing LYL1 using a construct expressing full-length cDNA driven by a human elongation factor 1α promoter. 30% of these transgenic mice developed malignant lymphoma with an average latent period of 352 days. Lymphomas developed are both B and T cell lymphomas. LYL1 forms a heterodimer with another basic helix-loop-helix protein E2A. Overexpressed LYL1 inhibits the E2A/HEB heterodimer formation, thus inactivates the physiological function of E2A, which might be the essential step to leukemogenesis.

Key words: LYL1, lymphoma, basic helix-loop-helix transcription factor, E2A, transgenic mice, two-hybrid assay

LYL1 belongs to the class II basic helix-loop-helix transcription factor family. It was first identified at chromosomal translocation loci [t(7; 19)(q35; p13)] from a human T cell leukemia cell line, and ectopic expression of LYL1 observed in a fraction of human T cell acute lymphoblastic leukemia (ALL) (Mellentin et al.,1989; Ferrando et al.,2002; Ferrando and Look, 2003). The basic helix-loop-helix sequence of LYL1 shows remarkable similarity with those of TAL1 (also known as SCL) and TAL2. TAL1 and TAL2 were also identified at the breakpoints of chromosomal translocation of T cell acute lymphoblastic leukemia. Biological role of LYL1 remains largely unknown but it can bind to another basic helix-loop-helix protein E2A. The expression of LYL1 is restricted to hematopoietic cells, especially mature B lymphocytes (Visvader et al., 1991; Kuo et al., 1991).

In order to know the leukemogenic mechanism of LYL1, transgenic mice which were overexpressing LYL1 has been made (Zhong et al., 2007). In these mice, the human elongation factor 1α promoter (EF-1α) drove the expression of LYL1 ubiquitously. Unlike wild-type mice, the expression of LYL1 in thymus was observed in these transgenic mice. These mice exhibited short kinked tails and a loss of hair. Thirty percent of the transgenic mice developed both B cell and T cell lymphoma after relatively long latent period (average 352 days).

E2A forms a heterodimer with overexpressed LYL1, which inhibits the normal function of E2A

E2A is another basic helix-loop-helix protein which has an essential role in normal development of lymphocytes. In T lymphocytes, E2 A interacts with HEB, a member of Class I basic helix-loop-helix family and activates target genes (like CD4). On the other hand, in B lymphocytes, E2A functions through the formation of a homodimer to regulate downstream genes (Lazorchak et al., 2005; Murre, 2005). Because LYL1 can interact with E2A protein, Overexpressed LYL1 can form a heterodimer with E2A, thus inhibit the physiological function of E2A in the normal

development of lymphocytes. Zhong et al. studied the effect of LYL1 on dimerization of E2A using mammalian two-hybrid assay. In this study, the formation of both E2A homodimer and E2A/HEB heterodimer was blocked by LYL1 in a dose-dependent manner (Zhong et al., 2007). Because E2A knock-out mice produce T cell lymphoma (Bain et al., 1997; Yan et al., 1997), inhibition of E2A function seems to lead to the leukemogenesis. Therefore, it is possible to consider that overexpressed LYL1 partially disrupt the normal function of E2A, which lead to the development of lymphoma.

LYL1 also inhibits regulatory function of E2A/HEB heterodimer. E2A regulates the expression of target genes through binding to an E-box consensus sequence. For exam-

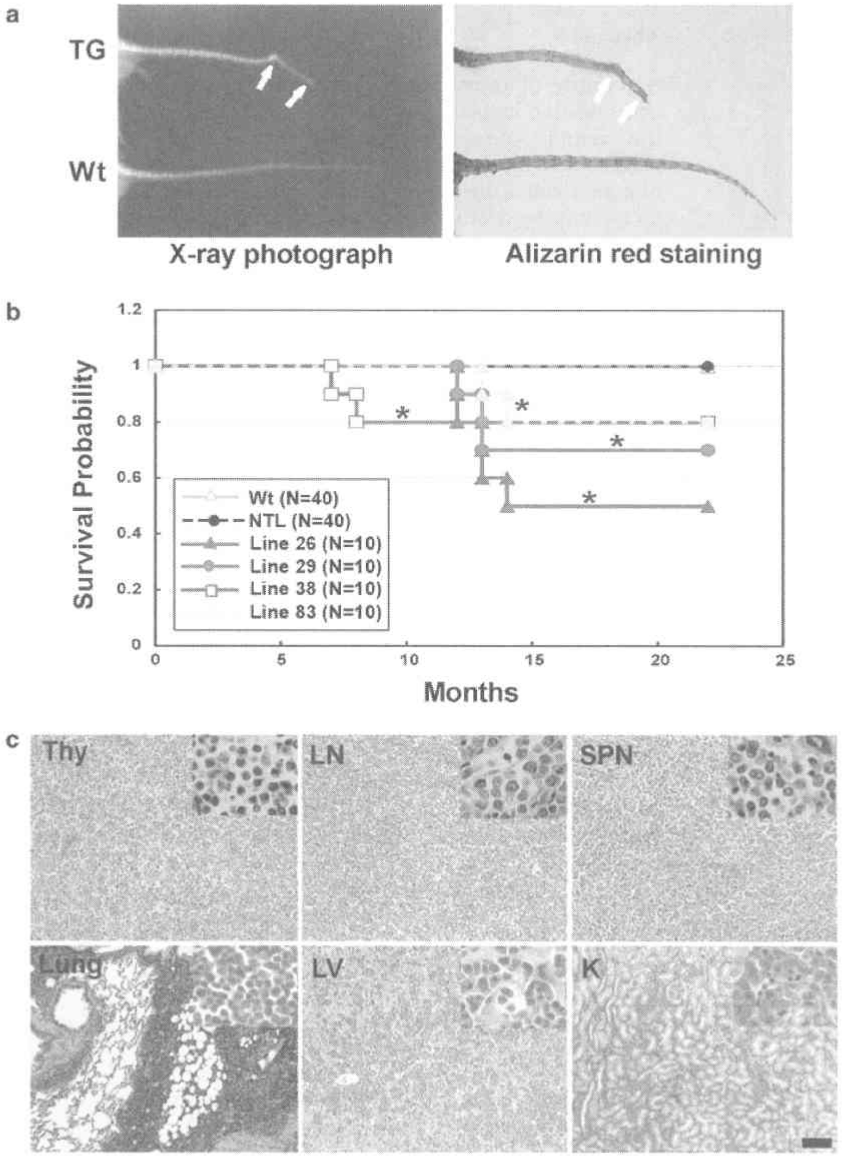

Fig. 1 Development of malignant lymphoma in LYL1 transgenic mice
(a) Representative X-ray photograph (left) and Alizarin red staining (right) of tail. TG, transgenic mice of 11 months; Wt, wild type of 11 months; white arrows, misformed vertebrae. (b) Survival curve for the offspring of four independent lines of LYL1 transgenic mice and wild type control (Wt, wild type; NTL, non-transgenic littermates; $^{*}P<0.001$ with Kaplan Meiyer analysis). (c) Histology of involved organs in case of T-cell lymphoma (#2644). Thy, thymus; LN, lymph node; SPN, spleen; LV, liver; K, kidney (Bar=100μm; 25μm at the inset).

ple, CD4 transcription is activated by E2A, which forms a complex with HEB and binds to the E-box element of the CD4 enhancer (Sawada and Littman, 1993). Zhong et al. studied the effect of LYL1 on the regulatory activity of E2A/HEB. A firefly luciferase reporter vector driven by a CD4 enhancer-promoter was transfected into 293T cells with vectors expressing LYL1, E2A, TAL1 or HEB in various combinations. The luciferase activity was activated mostly when the reporter vector was transfected with the combination of E2A and HEB. It was suppressed when HEB was substituted by LYL1 or TAL1.

Conclusion

LYL1 has a function to form malignant lymphomas when it is expressed in transgenic mouse. Although the direct target genes of LYL1 are not revealed at present, it developed B- and T-cell lymphoma by inhibiting the role of another basic helix-loop-helix protein E2A. Identification of LYL1 target genes is the most important step to fully understand the real leukemogenic function of LYL1.

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