学位論文審査結果の要旨

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（学位論文審査結果の要旨）

Bahcc1 is critical for the aberrant epigenetic program in a mouse model of *MLL-ENL*-mediated leukemia

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

In leukemogenesis, genotoxic stress in hematopoietic stem and progenitor cells (HSPCs) drives individual context-dependent programs of malignant transformation. In light of the various differentiation stages of HSPCs based on a recently revised definition using CD150/CD48, our analyses showed that a subpopulation of long-term-repopulating HSCs was most susceptible to *MLL-ENL*-mediated transformation. An analysis of the molecular mechanism identified *Bromo-adjacent homology domain and coiled-coil containing 1* (*Bahcc1*), which encodes a reader molecule of trimethylated histone H3 lysine 27 (H3K27me3), as a candidate gene involved in distinct susceptibility to leukemic transformation. Interestingly, *Bahcc1* was previously reported to be highly expressed in acute myeloid leukemia (AML) with an unfavorable prognosis, including some cases of *MLL*-rearranged AML. We found that MLL-ENL upregulated *Bahcc1* through binding to its promoter, and that Bahcc1 was involved in *MLL-ENL*-mediated immortalization at least partly through repression of H3K27me3-marked *Cdkn1c*. Analyses using bone marrow transplantation in mice showed that depletion of *Bahcc1* suppressed the leukemogenic activity of *MLL-ENL*. These findings shed light on the distinct immortalization potential of HSPCs and suggest a novel *MLL-fusion-Bahcc1* axis, which may lead to development of molecular

targeted therapy against *MLL-fusion*-mediated leukemia.

本論文は、マウスモデル *MLL-ENL* 関連白血病において *Bahcc1* の発現上昇がエピジェネティクス異常の原因として重要であること、また、ヒト白血病細胞株においても同様のことを証明し、将来的に *BAHCC1* が *MLL-ENL* 関連白血病の分子標的治療のターゲットになる可能性を示した論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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