MicroRNA-9 Promotes Proliferation of Leukemia cells in Adult CD34 Positive Acute Myeloid Leukemia with normal karyotype by Down-regulation of Hes1

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Running Title: role of microRNA-9 in AML with normal karyotype

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Abstract

Acute myeloid leukemia (AML) is a group of heterogeneous hematopoietic malignancies sustained by leukemic stem cells (LSCs) that can resist treatment. Previously, we found that low expression of Hes1 was a poor prognostic factor for AML. However, the activation status of Hes1 and its regulation in LSCs and leukemic progenitors (LPs) as well as normal hematopoietic stem cells (HSCs) in Hes1-low AML patients has not been elucidated. In this study, the expression of Hes1 in LSCs and LPs was analyzed in adult $CD34^+$ Hes1-low AML with normal karyotype and the upstream miRNA regulators were screened. Our results showed that the level of either Hes1 or p21 was lower in LSCs or LPs than that of HSCs whereas the level of miR-9 was highest in LPs and lowest in HSCs. An inverse correlation was observed in the expression of Hes1 and miR-9. Furthermore, we validated miR-9 as one of the regulators of Hes1 by reporter gene analysis. Knockdown of miR-9 by lentivirus infection suppressed the proliferation of AML cells by the induction of G0 arrest and apoptosis *in vitro*. Moreover, knockdown of miR-9 resulted in decreased circulating leukemic cell counts in peripheral blood and bone marrow, attenuated splenomegaly, and prolonged survival in a xenotransplant mouse model. Our results indicate that the miR-9 plays an important role in supporting AML cell growth and survival by down-regulation of Hes1 and that miR-9 has potential as a therapeutic target for treating AML.

Keywords: acute myeloid leukemia, Hes1, microRNA-9, hematopoietic stem cells, leukemic stem cells, leukemic progenitors