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TITLE
Catalytic activity of Dnmt3b is dispensable for mouse development but critical to prevent hematologic malignancies.

HYPOTHESIS:
We hypothesize that methyltransferase activity (MTA) of Dnmt3b is critical for normal mouse development and to prevent malignant hematopoiesis.

BACKGROUND/AIMS:
Cytosine methylation in mammalian cells is catalyzed by four DNA methyltransferases (Dnmts) 1, 3a, 3b and 3c. Loss of Dnmt3b results in impaired mouse embryogenesis at day E13.5. In humans, mutations of the Dnmt3b gene were identified in ICF syndrome, a rare autosomal recessive disorder characterized by immunodeficiency, centromeric instability and facial anomalies. In addition, mutations affecting MTA of Dnmt3b were identified in human hematologic malignancies including Sezary syndrome (27%), Hairy cell leukemia (5%) and Diffused Large B-cell lymphoma (4%). Here, we investigated the importance of Dnmt3b’s MTA on mouse embryonic development and prevention of malignant hematopoiesis.

METHODS:
We generated cohorts of myc Dnmt3b\textsuperscript{ki/ki} mice harboring conventional knockin allele lacking MTA activity. Protein levels of Dnmt3b were determined by Western blot. Mouse skeleton was stained in Alizarin Red for 3 days. Bone marrow transplant utilizing MLL-AF9 was used to generate MLL in WT and Dnmt3b\textsuperscript{ki/ki} mice. Normal and malignant cell populations were identified by FACS based analysis.

RESULTS & CONCLUSIONS
We show that Dnmt3b’s MTA is dispensable for mouse embryonic development, however, Dnmt3b\textsuperscript{ki/ki} mice develop ICF-like syndrome with symptoms including mild facial dysmorphism, growth retardation and immunodeficiency observed as reduction in total B-cells in spleen and bone marrow. Impaired B-cell development is observed also in mice reconstituted with Dnmt3b\textsuperscript{ki/ki} BM cells. In addition to impaired hematopoiesis, monoallelic loss of Dnmt3b’s MTA results in B-cell malignancies in cohort of mice. Myc-induced T-cell lymphoma is accelerated in the absence of Dnmt3b’s MTA. Finally, MLL induced by MLL-AF9 overexpression is enhanced in the absence of Dnmt3b’s MTA. Altogether, our data suggest that Dnmt3b’s MTA is dispensable for mouse development but critical to prevent hematologic malignancies.