Mouse was obtained to generate Mll models. Mll-PTD and Flt3-ITD single mutant mice expressing either FLT3-ITD or MLL-PTD were embryonic lethal. Mll-PTD and Flt3-ITD/WT mice have a poor prognosis. Mll-PTD mice succumb to bone marrow failure soon after induction. Flt3-ITD/WT is found in 30-35% of AML patients. A subset of AML patients have a poor prognosis.

Acute Myeloid Leukemia (AML) is a blood cancer arising mostly in older adults. MLL-partial tandem duplication (MLL-PTD) is present in 5-7% of cyogenetically normal AML patients. FLT3-internal tandem duplication (FLT3-ITD) is found in 30-35% of AML patients. A subset of AML patients with both FLT3-ITD and MLL-PTD have a poor prognosis.

Single mutant mice expressing either Mll-PTD or Flt3-ITD independently do not develop leukemia; however, a double mutant mouse expressing Mll-PTD and Flt3-ITD develops AML with a long latency and mimics human AML phenotypically and molecularly.

Mll-PTD expression is silenced in both human samples and mouse models of MLL-PTD+AML. Germ-line absence of Mll-WT in Mll-PTD+ Mll+/−Flt3/FLOX dile mice is embryonic lethal, whereas Mll−/− conditional knockout mouse was obtained to generate Mll+/−Flt3/FLOX mice.

Objective 1: Does Mll-PTD maintain gain-of-function in the absence of Mll-WT?

Objective 2: Is Mll-WT a tumor suppressor in an Mll+ WT+ AML murine model?

Mll-PTD;Flt3-ITD cooperate to induce fatal acute leukemia

Mll-PTD:Flt3-ITD mice with AML develop splenomegaly

Mll-PTD acts as a gain-of-function mutation in the absence of Mll-WT

Mll-PTD:Flt3-ITD murine acute leukemia is similar to human AML

Mll-WT vs. Mll-PTD Expression

MIll-WT and Mll-PTD mice do not succumb to BM failure after deletion of Mll-floxed allele.

RT-PCR data demonstrates silencing of Mll-WT expression in leukemic Mll+/−Flt3/FLOX and Mll−/− mice.

Mll-WT drives HOX9 expression in single and double mutant murine model.

Objective 1: Does Mll-PTD function without Mll-WT?

Objective 2: Is Mll-WT a tumor suppressor in Mll-PTD+ AML?

References


The following OSUCCC Shared Resources were used to conduct these studies: Nucleic Acid, Flow Cytometry, Comparative Pathology and Mouse Phenotyping. This work was supported by National Cancer Institute grants to MAC (CA089341; CA093333; GM122015), to MAC and GM (CA102031), to MAC and GM (CA140158) to NAZ (T32 GM008341; T32 GM008333; GM122015), to MAC and GM (CA011618) to NAD (T32 GM12453; OSU College of Medicine Fellowship and Pelotonia Graduate Fellowship), to KMB (T32 CA009338), and to DB, DY and RS (Pelotonia Undergraduate Fellowship).

Acknowledgements

The James

Role of MLL-Wild Type in hematopoiesis and leukemia transformation in MLL-Partial Tandem Duplication mouse models

Background

Role of MLL-Wild Type in hematopoiesis and leukemia transformation in MLL-Partial Tandem Duplication mouse models

Acute Myeloid Leukemia (AML) is a blood cancer arising mostly in older adults. MLL-partial tandem duplication (MLL-PTD) is present in 5-7% of cyogenetically normal AML patients. FLT3-internal tandem duplication (FLT3-ITD) is found in 30-35% of AML patients. A subset of AML patients with both FLT3-ITD and MLL-PTD have a poor prognosis.

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Objective 1: Does Mll-PTD function without Mll-WT?

Objective 2: Is Mll-WT a tumor suppressor in Mll-PTD+ AML?

Mll-PTD acts as a gain-of-function mutation in the absence of Mll-WT

Summary

Future Directions to analyze Mll-PTD+ AML in acute leukemia models

1. Evaluate whether loss of Mll-WT hypomorph and/or as a tumor suppressor in Mll+PTD+AML decreases latency of leukemogenesis in an Mll-PTD:Flt3-ITD mouse model of AML.

2. Evaluate expression of oncogenic HoxA9 and Mael in Mll+ PTD+ Flt3-ITD+ mouse model pre- and post-conditional knockout.

3. Monitor disease progression by flow cytometry based immunophenotyping.

References


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