Mouse Model to Study Gene Cluster in Chronic Lymphocytic Leukemia and Cell Cycle Progression

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Chronic Lymphocytic Leukemia (CLL) Studies Focus on Chromosomal Region Associated with Genetic Aberrations Chronic lymphocytic leukemia (CLL) pathogenesis has been associated with many genetic aberrations. The most common is the deletion of chromosomal region 13q14, which encodes the DLEU2 gene (deleted in leukemia 2), and the miR15-a/16-1 microRNA cluster. A conditional knockout of this entire region was generated simultaneously and was shown to recapitulate the full spectrum of human CLL disease pathogenesis (IR 2807-MDR TechBrief). However, it was unclear whether DLEU2, a gene with unknown function, or the miR15-a/16-1 cluster was mediating the phenotypes. Furthermore, work from other researchers using in vitro cell culture systems have implicated this cluster as a negative regulator of cell proliferation and programmed cell death. However, the in vivo role of this microRNA cluster in cell cycle progression and CLL pathogenesis requires further characterization.

Mouse Model Generated with Deleted Gene Cluster for Valuable Research Tool A conditional knockout mouse was generated that specifically deletes the miR15-a/16-1 cluster. The microRNA cluster is flanked with sites for a recombinase, which allows for in vivo deletion of the intervening microRNA cluster, while maintaining the integrity of the surrounding genes, in particular DLEU2. This allows the investigator to tease the functional contribution of both the microRNA cluster and DLEU2 in CLL pathogenesis. Furthermore, it provides a mouse model to study the role of miR15-a/15-1 in cell cycle control in other cell types.

Applications: • Mouse model to assess the contribution of the miR15-a/16-1 cluster in CLL pathogenesis. • Mouse model to test computer predicted miR15-a/16-1 target genes. • Mouse model to study the role of miR15-a/16-1 cluster in cell cycle progression.

Advantages: • Conditional deletion allows the researcher to breed with mouse lines that have the recombinase under pharmacological and/or cell-type or tissue specific promoters for temporal and spatial deletion of the microRNA cluster to determine when and where this cluster is of importance. • Can be crossed with mouse lines containing reporter constructs of predicted miR15-a/16-1 target genes to demonstrate in vivo regulation by miR-15a/16-1. • Strain can also be crossed to mouse lines containing knockouts of miR15-a/16-1 target genes to determine the contribution of each target gene to the miR15-a/16-1 knockout phenotype. • Unlike in vitro cell culture systems, the mouse model allows investigators to study the microRNA’s functional role under physiological settings.

Chronic Lymphocytic Leukemia (CLL) Studies Require Mouse Model with Full Spectrum of Disease Pathogenesis Chronic lymphocytic leukemia (CLL) is the most common B-cell derived malignancy in adults.
However, the etiology of CLL has remained obscure due to lack of evidence that genetic alterations observed in human CLL cases actually contribute to its pathogenesis. The current mouse models used to study CLL are mouse models that over-express the TCL1 gene, an event not seen in human B cell malignancies, or an inbred mouse strain in which multiple loci have been implicated. While these mouse models are useful tools, they do not recapitulate the genetic lesions observed in human CLL cases or provide mechanistic insight that could be used for translational approaches. Therefore, the field needs a faithful mouse model that recapitulates the full spectrum of disease pathogenesis and can also provide insights into the molecular mechanism of pathogenesis.

Mouse Model Generated with Most Common Genetic CLL Alteration for Valuable Research Tool The inventors generated a conditional knockout mouse that recapitulates the most common genetic alteration observed in CLL, deletion of chromosome region 13q14. The mouse line was genetically engineered to put the minimal deleted region (MDR), which contains the DLEU2 gene (deleted in leukemia 2) gene, and the miR15-a/16-1 microRNA cluster within sites that can be recognized by a recombinase, and therefore deleted in vivo. The mouse model displays the full spectrum of CLL-associated phenotypes: monoclonal B cell lymphocytosis (MBL); classical CLL/small lymphocytic lymphoma (SLL); and non-Hodgkins lymphoma. Furthermore, another hallmark feature of human CLL, the observance of a clonal B cell population with almost identical B-cell receptors is observed. In summary, the B-cell malignancies generated by this mouse model are phenotypically similar to human CLL cases. This is a valuable research tool to understand CLL pathogenesis and generate translational treatments.

Applications: • Mouse model that recapitulates the full spectrum of disease pathogenesis in human CLL. • Mouse model that can be used in trials to test therapeutics targeted against CLL. • Tool to study the etiology and molecular mechanisms underlying CLL pathogenesis.

Advantages: • Conditional deletion allows for partial or complete deletion of the loci (one or two alleles). • Mouse strain can be crossed to mouse lines where the recombinase is under different cell-type or tissue specific promoters to study the role of this deletion in different cell types. • Mouse line can be bred to any other mouse background (knockout or transgenic) to determine the role of other genes implicated in CLL pathogenesis.

Patent Status: Patent Pending

Licensing Status: Available for Licensing


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