Identification of Novel Biomarkers to Detect Chronic Myelogenous Leukemia (CML) Progression

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BACKGROUND

Generally, our current knowledge about cancer is based upon the mutations in protein coding genes, such as tumor suppressors and oncogenes. Recently, with advancements in the deep sequencing arena, focus has turned to the importance of epigenetic and post-transcriptional events in cancer progression and resistance associated with therapeutic treatments. These findings have revealed the complexity of gene expression at the RNA level. To that end, two of the most common RNA modifications are the editing of N^6-methyl adenosines (m^6A) and adenosine-to-inosine (A-to-I). For A-I conversion, Adenosine Deaminases Act on RNA (ADARs) enzymes targeting non-coding sequences and alterations in ADAR expression or activity can lead to cancer, but the pathogenic mechanisms remain under investigation. Furthermore, malignant RNA editing, driven by ADAR1 activation has been shown to be a major contributor to cancer relapse and progression.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have been researching the role of ADAR1 editase-dependent mechanisms governing leukemia stem cell (LSC) generation. They have discovered that in blast crisis (BC) CML, both an increase in JAK2 signaling and an amplification of BCR-ABL1 activate ADAR1. This is consistent with the finding in a humanized BC-CML mouse model, ADAR1 was down-regulated when both JAK2 and BCR-ABL1 were inhibited. Moreover, amplification of BCR-ABL1, a hallmark of BC transformation has been linked to LIN28B upregulation and the inhibition of the tumor suppressive miRNA, Let-7. These data suggest that ADAR1 regulates let-7 miRNA biogenesis in an A-to-I editing-dependent manner, which has a functional impact on BC CML progenitor self-renewal and survival.

APPLICATIONS

The invention identifies a new set of biomarkers to detect leukemia stem cell (LSC) reprograming and chronic myeloid leukemia progression as well as new potential therapeutic targets for treating myelodysplastic syndrome and CML, such as Let-7.

STATE OF DEVELOPMENT

Experiments were performed in a humanized BC CML-mouse model as well as examining $CD34^+$ cord blood cells and K562 cells transduced with ADAR1 wild type or an $ADAR1^{E912A}$ RNA editing deficient mutant.

INTELLECTUAL PROPERTY INFO

A PCT patent has been published and the technology is available for licensing.

RELATED MATERIALS

▶ Maria Anna Zipeto , Angela C.Court, Anil Sadarangani, Nathaniel P. Delos-Santos, Larisa Balaian, Hye-Jung Chun, Gabriel Pineda, Sheldon R.Morris, Cayla N. Mason, Ifat Geron, Christian Barrett, Daniel J.Goff, Russell Wall, Maurizio Pellecchia, Mark Minden, Kelly A. Frazer, Marco A. Marra, Leslie A. Crews, Qingfei Jiang, Catriona H. M. Jamieson. ADAR1 Activation Drives Leukemia Stem Cell Self Renewal by Impairing Let-7 Biogenesis. Cell Stem Cell. Aug 4, 2017. Published online 2016 Jun 9. doi: 10.1016/j.stem.2016.05.004 -

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OTHER INFORMATION

KEYWORDS

ADARs, Adenosine Deaminase Acting on RNA, leukemia, stem cells, RNA editing, CML, blast crisis, let-7 microRNA, JAK2, BCR- ABL1

CATEGORIZED AS

- **Medical**
  - Diagnostics
  - Disease: Cancer
  - Therapeutics

RELATED CASES

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PATENT STATUS

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Additional Patent Pending

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