Methods for Inhibiting the Expression of MDM2 to Block Progression of Leukemia

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Technology description

Researchers at UC San Diego have shown that in malignant leukemia progenitors, A-to-I editing of an miRNA binding site within the 3′ UTR region (A-to-I editing prevents miRNA from binding) stabilizes Mouse Double Minute 2 (MDM2) transcripts (MDM2 inhibits or represses expression of the p53 tumor suppressor protein), thereby enhancing blast crisis chronic myeloid leukemia progenitor propagation (i.e., non-edited miRNA binding sites within the 3′ UTR region bind miRNA, resulting in de-stabilizing MDM2 transcripts, decreasing the amount of MDM2, increasing the amount of p53 tumor suppressor, decreasing e.g., leukemia cell, e.g., blast crisis chronic myeloid leukemia progenitor cell, propagation). Moreover, malignant deregulation of ADAR1-mediated RNA editing has been linked to progression and therapeutic resistance of at least twenty types of human cancer. The researchers have developed methods and reagents for ameliorating a cancer by inhibiting the expression or activity of MDM2 by addition of a miRNA which inhibits or destabilizes MDM2 thereby inhibiting the propagation of a cancer cell.

RNA-editing proteins are an important class of proteins that regulate key steps in post-transcriptional RNA processing. One of the most common and best characterized is the Adenosine-to-Inosine editing (A-to-I editing) process. The cell translating machinery recognizes inosine as guanosine and A-to-I editing is accomplished by adenosine deaminase acting on RNA (ADAR) enzyme family that includes ADAR1, ADAR2, and ADAR3. While ADAR3 appears to inhibit ADAR2 editing within coding regions, ADAR1 edits primarily within double stranded RNA (dsRNA) loops formed by inverted primate-specific Alu repetitive elements. Atypical RNA editing can result in the alteration of non-coding RNAs such as miRNAs which can be present in different cancers and play a role in their development.

Application area

The researchers have developed methods and reagents which would be used for ameliorating cancer.

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