Research Highlights

Stem Cell INVESTIGATION

RNA editing as an activator of self-renewal in cancer

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Malignant transformation and cancer progression are complex processes caused by dysfunction of genetic programs. It is well established that aberrant posttranscriptional regulation of messenger RNA contributes the pathogenesis of many types of tumors initiation, progression and treatment evasion (1). One such mechanism is the IFN-γ pathway activation of the ADAR1-p150 isoform in chronic myeloid leukemia (CML) progenitors. This pathway was shown to lead to activation of expression of self-renewal genes (2).

The Adenosine deaminase acting on RNA (ADAR1) protein can induce the substitution of adenosine to inosine (A-to-I) in double stranded RNA complexes which tend to form when two repetitive sequences, such as Alu repeats, lie in proximity in opposite directions within an RNA transcript. MicroRNAs (miRNAs) are transcribed from the genome and catalyze both inhibition of translation and degradation of mRNAs through an interaction with Argonaut complexes. miRNAs are transcribed as long transcripts known as primary-miRNAs (pri-miRNAs), which are then cleaved and processed in two steps to yield mature miRNAs that directly interact with Argonaut to target mRNAs.

The *let*-7 family of miRNAs is known to play roles in both developmental timing and cancer through their targets, LIN28A and LIN28B. LIN28A and LIN28B are RNA binding proteins that are known to stabilize mRNAs that code for self-renewal genes (3). Besides regulating expression of various factors of the self-renewal program, LIN28 controls maturation of *let*-7 miRNA family members which in turn target and downregulate LIN28A/B and other transcripts related to developmental timing and cancer such as RAS and MYC.

Since pri-, pre- and mature miRNA are double strand RNAs, they serve as high affinity substrates for ADAR1 A-to-I RNA editing activity, thereby affecting miRNA maturation and activity (4). ADAR1 has also been shown to influence miRNA biogenesis by directly interacting with the RNAi processing machinery proteins (5). Dysregulation of ADAR1 expression and altered A-to-I editing patterns were reported in a number of cancer models. However, the mechanism underlying ADAR1 contribution to cancer and particularly to induction of self-renewal pathways remain poorly understood. In a recent study by Zipeto *et al*. (6), the authors define novel mechanisms by which inflammatory signaling through the JAK2-STAT pathway can induce ADAR1 dependent editing of the *pri-let7d* transcript. This resulted in upregulation of LIN28B expression and the activation LIN28B dependent embryonic-like self-renewal program in CML.

Zipeto *et al*. performed gene expression profiling and found elevated levels of members of the JAK/STAT inflammatory signaling pathway in blast crisis (BC) leukemia cells compared to normal and chronic phase progenitors. This also resulted in upregulation of ADAR1-P150 expression levels. Furthermore, ectopic JAK2 upregulation enhanced the effect of *BCR-ABL1* gene amplification, the hallmark chromosomal abnormality of CML BC transformation. This gene amplification is also known to correlate with downregulation of *let-7a* expression and thereby upregulation of LIN28B (6).

Combined inhibition of ADAR1 and JAK2 restored *let*-7 expression and inhibited self-renewal in leukemia stem cells (LSC). In contrast, ectopic activation of ADAR1 upregulated pluripotency genes, particularly *let*-7 targets. The authors further demonstrated that ADAR1 impairs *let*-7

biogenesis by directly editing *pri-let7-d* transcripts and thus altering secondary structure and preventing their cleavage by DROSHA/DGCR8. Therefore, Zipeto *et al*. uncovered a comprehensive molecular mechanism linking external environmental inflammation signals to activation, aberrant post-transcriptional processing, and to the induction of a self-renewal program that promotes the reprogramming of chronic phase progenitor cells into BC LSCs.

Various types of tumors and transformations undergo changes in ADAR enzyme expression and RNA editing. For example A-to-I mediated conversion of a single nucleotide in the AZIN1 transcript was shown to enhance the pathogenesis of hepatocellular carcinoma (7). Transcriptome analysis of hundreds of distinct cancer samples identified increased A-to-I editing compared to normal tissues, which was also shown to correlate with severity of patient prognosis (8).

Understanding of how cancer initiating cells assume their properties is a major step in developing strategies for dealing with cancer. It has been estimated that about 15% of human tumors exhibit repression of *let*-7 activity and concordant upregulation of LIN28A/LIN28B (9). However, the mechanisms governing this activation of the embryonic like self-renewal program are not well understood. Thus, it is of great importance to further investigate the role of post-transcriptional A-to-I RNA editing of miRNAs, particularly *let-7s* in other cancer models. Since restoration of ADAR1 expression levels correlates with reversal of malignant phenotypes, targeting ADAR1 might prove useful as a therapeutic candidate for treatment of wide range of cancers. Whether ADAR1 and A-to-I editing proven to be of clinical significance or not, Zipeto *et al*. is a significant contribution to our understanding of distinctive gene regulation mechanisms and their role in malignant transformation.

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Footnote

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