An RNA editing / dsRNA binding-independent gene regulatory mechanism of ADARs and its clinical implication in cancer

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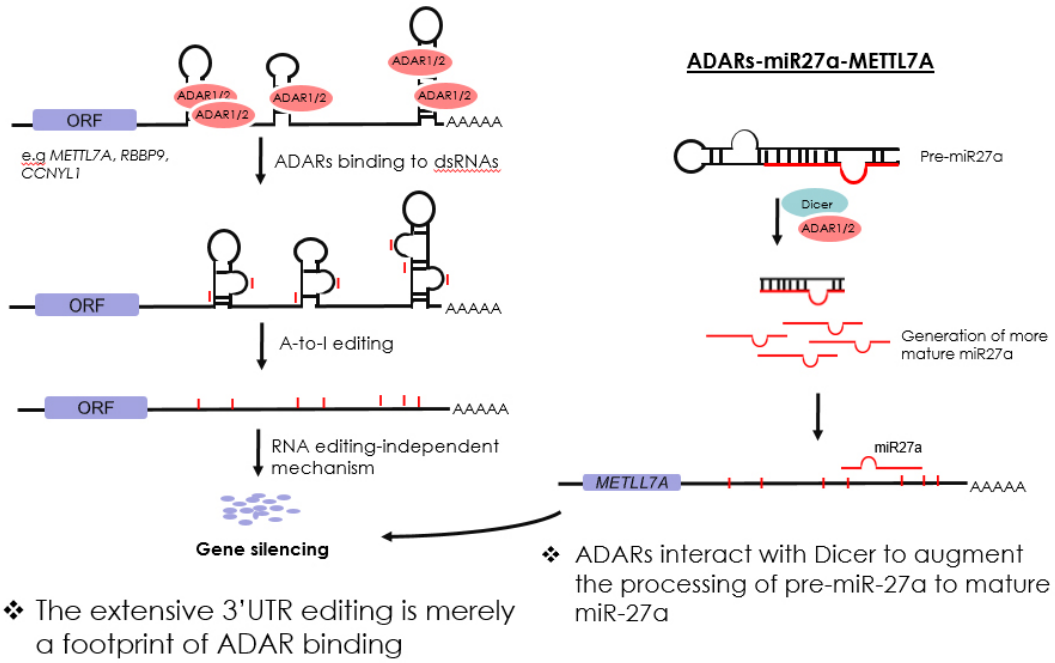
ABSTRACT

Adenosine-to-inosine (A-to-I) RNA editing, catalyzed by Adenosine DeAminases acting on doublestranded RNA(dsRNA) (ADAR), occurs predominantly in the 3_ untranslated regions (3_UTRs) of spliced mRNA. Here we uncover an unanticipated link between ADARs (ADAR1 and ADAR2) and the expression of target genes undergoing extensive 3_UTR editing. Using METTL7A (Methyltransferase Like 7A), a novel tumor suppressor gene with multiple editing sites at its 3_UTR, we demonstrate that its expression could be repressed by ADARs beyond their RNA editing and double-stranded RNA (dsRNA) binding functions.

ADARs interact with Dicer to augment the processing of pre-miR-27a to mature miR-27a. Consequently, mature miR-27a targets the METTL7A 3_UTR to repress its expression level. In sum, our study unveils that the extensive 3_UTR editing of METTL7A is merely a footprint of ADAR binding, and there are a subset of target genes that are equivalently regulated by ADAR1 and ADAR2 through their non-canonical RNA editing and dsRNA binding-independent functions, albeit maybe less common. The functional significance of ADARs is much more diverse than previously appreciated and this gene regulatory function of ADARs is most likely to be of high biological importance beyond the best-studied editing function. This non-editing side of ADARs opens another door to target cancer.



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