

Structural Basis for RNA editing by ADARs

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RNA undergoes many different types of modifications and edits after being transcribed by RNA polymerase. These post-transcriptional alterations regulate many biological processes and aberrant RNA modification is linked to many phenotypes and diseases. One class of modification is called RNA editing, which changes the transcript's genomically-encoded sequence by inserting, deleting, or chemically altering nucleotides. The most abundant type of RNA editing is the enzymatically catalyzed deamination of Adenosine to Inosine (A-to-I), which is observed in millions of human RNA transcripts. Because Inosine base-pairs with Cytosine, the cellular machinery interprets this base as Guanosine. These A-to-I edits therefore can alter RNA secondary structure, splicing events, and re-code specific mRNA codons.

Adenosine deaminases acting on RNA (ADARs) are editing enzymes that catalyze the hydrolytic deamination of the 6-amino group of Adenosine to generate Inosine. ADAR proteins are modular with two or three N-terminal double-stranded RNA (dsRNA)-binding domains (dsRBDs) and a C-terminal catalytic or deamination domain comprising roughly 400 amino acids, which regulates much of the RNA sequence specificity. ADARs can only edit adenosines in regions of dsRNA. We recently determined the X-ray crystal structures of various human ADAR2 constructs bound to different dsRNA substrates with natural and unnatural nucleotide analogs to better understand the ADAR reaction mechanism, the origin of editing-site selectivity, and the effect of mutations on diseases. These structures, together with structure-guided mutagenesis experiments, explain the basis of the ADAR deaminase domain's dsRNA specificity, its targeted base-flipping mechanism, and its nearest-neighbor preferences. In addition, the structures revealed that ADARs can bind to dsRNA substrates as an asymmetric dimer, uncovering a previously unknown dimerization interface, which was shown to be biologically significant.