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Review

DNA Editing by APOBECs: A Genomic Preserver and Transformer

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Information warfare is not limited to the cyber world because it is waged within our cells as well. The unique AID (activation-induced cytidine deaminase)/APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide) family comprises proteins that alter DNA sequences by converting deoxycytidines to deoxyuridines through deamination. This C-to-U DNA editing enables them to inhibit parasitic viruses and retrotransposons by disrupting their genomic content. In addition to attacking genomic invaders, APOBECs can target their host genome, which can be beneficial by initiating processes that create antibody diversity needed for the immune system or by accelerating the rate of evolution. AID can also alter gene regulation by removing epigenetic modifications from genomic DNA. However, when uncontrolled, these powerful agents of change can threaten genome stability and eventually lead to cancer.

Trends

APOBECs, a family of C-to-U DNA deaminases, are an enzymatic source of mutations.

DNA editing by AID/APOBECs serves in diverse biological functions.

APOBECs defend the genome from viruses and retrotransposons.

Genomic DNA editing by APOBEC3A and APOBEC3B increases mutation loads in cancer.

DNA editing of retrotransposons accelerates evolution by increasing genomic sequence diversity.

DNA Editing: Challenging the Read-Only Dogma

Traditionally, genomic data is considered to be 'read only'. A considerable part of our proteome is devoted to preserving, reading, and executing the genomic blueprint. This program is supposed to be identical for all cells within an organism. However, a family of proteins challenges the read-only dogma by rewriting DNA content. This family, the **AID/APOBECs** (or 'APOBECs'; see Glossary), can alter DNA sequence by enzymatically deaminating deoxycytidine, converting it to deoxyuridine, a process coined **DNA editing**. A well-studied member of the APOBEC family is AID. Taking advantage of DNA deamination, AID orchestrates the process of antibody affinity maturation and diversification in the immune system. The first function ascribed to DNA editing by the APOBEC branch of the family is retroviral inhibition. APOBECs, primarily APOBEC3 (A3), edit retroviral DNA during reverse transcription, typically inducing its degradation. In addition to retroviruses, A3s are potent restrictors of a variety of other viruses and **retrotransposons**. The latter, also known as retroelements, are retrovirus-like DNA sequences that are a major constituent of vertebrate genomes. Through a copy-and-paste mechanism they propagate throughout the genome and threaten its stability and function. A3s are key players in restricting these genomic parasites and can inflict lethal mutations in their DNA, as they so efficiently do in retroviruses. In some cases, retroelements enter the genome despite the hypermutation induced by DNA editing. Such events, when occurring in germline cells, can accelerate genome evolution by introducing divergent sequences that have undergone many mutations in a single generation. Although DNA editing is primarily a means for genome defense, the ability to rewrite DNA is a two-edged sword. Uncontrolled activity in somatic cells can lead to mutations in the genome and eventually result in cancer. Indeed, APOBECs are now established as a major source of mutation in multiple types of cancer and have been associated with poor outcome. The fields of AID and APOBEC research have been rapidly advancing, with new functions being assigned to the family

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on a regular basis. Previous reviews have discussed in detail the role of APOBECs in innate immunity [1–4], cancer [5–8], epigenetics [9–11], and evolution [12]. We attempt here to present a concise review that synthesizes all APOBEC functions and discusses the contribution of DNA editing to these functions, highlighting the evolutionary aspects of APOBEC3s and DNA editing (Figure 1, Key Figure).

The APOBEC Protein Family

Emergence of the APOBECs

The APOBEC family of cytidine deaminases has expanded and diverged throughout vertebrate evolution and contemporarily consists of AID and five APOBECs, numbered 1 to 5 (abbreviated

Key Figure

Diverse Functions of DNA Editing by APOBECs

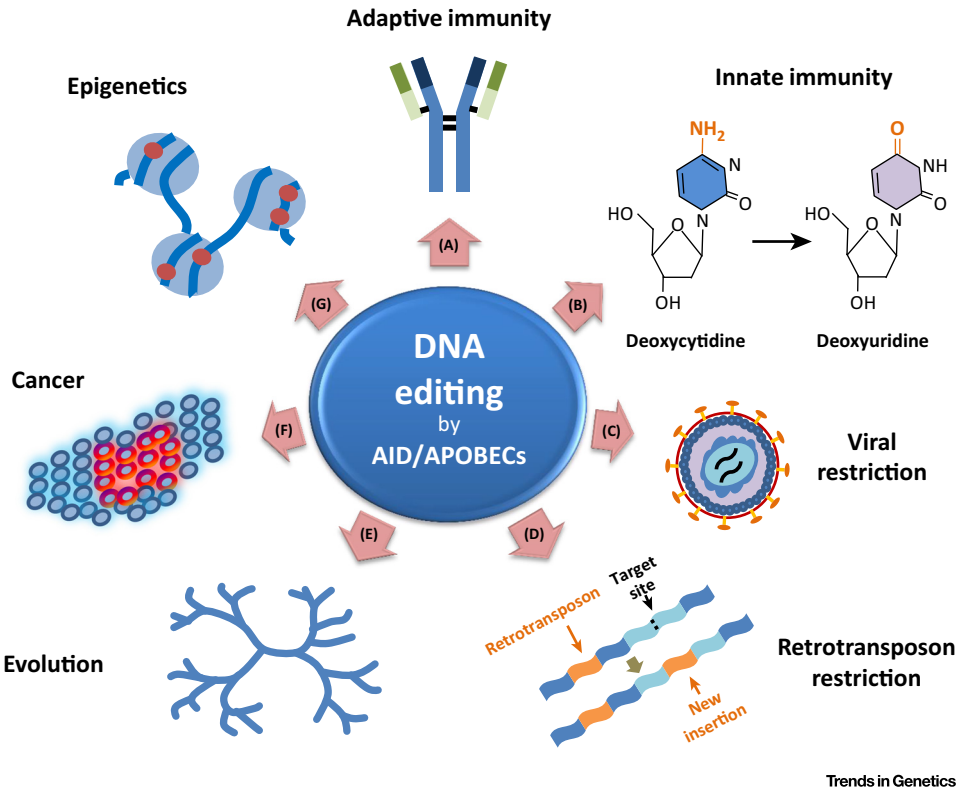

Figure 1. Cytidine deamination, the ability to convert deoxycytidine to deoxyuridine in DNA, is the claim to fame of the APOBEC family. (A,B) Through such DNA editing, this vertebrate-specific family plays key roles in both adaptive and innate immunity, preventing a variety of infectious diseases. AID, one of the first APOBECs to emerge, is essential for antibody diversification in B-cells. (C) The ability of APOBECs to hypermutate DNA enables them to restrict viral (primarily retroviral) propagation. (D) Using the same mechanism, they restrict retrotransposons, which are retroviral-like genetic elements present in high copy-number throughout the genome, and by doing so prevent deleterious mutation. (E) In some cases, DNA-edited retroelements escape degradation and successfully enter the genome. This results in the introduction of novel hypermutated sequences into the genome, enabling the latter to make use of them for new or modified function. When occurring in the germline, DNA editing of retrotransposons accelerates evolution. (F) APOBECs, although usually tightly regulated to avoid off-target activity, have been shown to target nuclear DNA and cause cancer. (G) In epigenetics, AID may mediate so-called active demethylation by deamination of methylated deoxycytidines, which has the potential to alter gene expression.

Glossary

Activation-induced cytidine deaminase (AID): a C-to-U DNA-editing enzyme, which is essential for antibody affinity maturation and diversification.

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide (APOBEC): a family of C-to-U DNA editors that have a role in diverse biological functions. AID is also a member of the family, which is sometimes referred to as the AID/APOBEC family. By increasing mutation loads in retroelements and DNA the APOBECs can accelerate evolution and promote cancer.

APOBEC3s: a placental mammal specific member of the APOBEC family that plays an important role in innate immunity by restricting the propagation of viruses and genomic retroelements.

C-to-U DNA editing: conversion of deoxycytidine to deoxyuridine in DNA by the AID and APOBEC enzymes through the process of deamination (removal of an amine group).

Retrotransposons: transposable genetic elements that are also known as retroelements and comprise a large fraction of eukaryote genomes. They propagate throughout the genome by a copy-and-paste mechanism that involves reverse transcription. These parasites are a potential source of mutation and a threat to genome integrity, and therefore must be restricted (e.g., by APOBECs). By contrast, they are agents of change in the genome, which spread novel sequences throughout the genome, thus driving evolution.