

CRYSTAL STRUCTURE OF THE ANTI-VIRAL APOBEC3G CATALYTIC DOMAIN (CD2) AND ITS FUNCTIONAL IMPLICATIONS

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APOBEC3G restricts the replication of HIV, Hepatitis B Virus (HBV) and retroelements via cytidine deamination on ssDNA or RNA binding. Here we present the high-resolution crystal structure of the C-terminal deaminase domain of APOBEC3G (Apo3G-CD2). The Apo3G-CD2 structure has a five-stranded β -sheet core that is common to all known deaminase structures and closely resembles the structure of another APOBEC protein, Apo2. A structural comparison of Apo3G-CD2 with other deaminase structures reveals a structural conservation of the active-site loops that are directly involved in substrate binding. Additionally, these Apo3G active-site loops in the X-ray structure form a continuous "substrate groove" around the active center. We have introduced mutations around the groove, and identified residues involved in substrate specificity, ssDNA binding, and deaminase activity. We also compared the deamination properties of Apo3G-CD2 to the full length (fl) Apo3G. The fl-Apo3G exerts a 3'→5' deamination bias while processively deaminating cytidines whereas the Apo3G-CD2 exhibits an approximate 2-fold decrease in processivity and no 3'→5' deamination bias. These results provide a basis for understanding the underlying mechanisms of substrate specificity and processivity for the APOBEC family.