APOBEC induced mutations are strongly enriched on the lagging strand during replication in human cancers

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ABSTRACT

Mutagenesis induced by deaminases of the APOBEC family is prevalent in many cancers. A fraction of APOBEC mutations is clustered around DSBs, however vast majority of them are dispersed over the genome[1,2]. Since APOBEC mutates specifically single stranded DNA (ssDNA)[1,3–6] we hypothesized that lagging DNA strand which exists in single strand state during DNA replication may be a frequent target for APOBEC mutations. Knowing the direction of replication fork progression in human genome we were able predict for each genomic region which of the two DNA strands is lagging during replication[7,8]. We observed that APOBEC mutations exhibit a strong 1.96 fold bias towards lagging strand, suggesting that this is the major mechanism of generation of APOBEC mutations explaining more than 1/3 of cases. Additionally we report the 2.3 fold preference of APOBEC mutations for non-methylated cytosines then for 5-methylcytosine; and nearly complete absence of enrichment of APOBEC and non-APOBEC mutations in patients with APOBEC signature in late replication time. This research provides novel insights into the APOBEC mutagenesis and suggests mechanistic explanations for a considerable fraction of APOBEC induced mutations.