GENETICS

APOBEC—A DOUBLE-EDGED SWORD

Enzymes of the family apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) cytidine deaminases, which inhibit retroviruses by converting cytosine residues to uracil, have been implicated in at least six cancer types. This helpful immunological function mediates deleterious somatic mutations in breast, bladder, cervical, head-and-neck and lung (adenocarcinoma and squamous-cell carcinoma) cancers, with one family member—APOBEC3B—being responsible for the majority of cytosine mutations.

“The cytosine mutation bias in several cancer genome studies suggested a role for enzymatic deamination,” explains lead investigator Reuben Harris. Given this bias, Harris’s team were interested in probing cancer genomes to assess whether the levels of DNA deaminase expression correlated with cancer. Their initial study in breast cancer supported a role for the enzymes in mutagenesis. In their latest report, the researchers analysed 4,800 exomes and 1,000,000 somatic mutations in 19 cancer types, showing APOBEC3B is upregulated and its preferred target sequence is mutated in five other cancers.

Another study, led by Dmitry Gordenin, also showed a strong correlation between APOBEC expression and mutagenesis with cancer. Studying hundreds of thousands of mutations from >2,000 exomes from 14 cancers from The Cancer Genome Atlas project, the researchers showed that the APOBEC mutation pattern is prominent in six cancer types. Importantly, HER2 expression was enriched in breast cancers with the APOBEC mutation pattern, which suggests a role for the enzyme in tumorigenesis.

“For cancer types where APOBEC mutagenesis prevails, we must identify the genetic and environmental factors that facilitate mutagenesis,” suggests Gordenin. Harris agrees: “since cancer depends on mutation for every stage of development, one would predict that cancers with APOBEC3B mutagenesis will be more heavily mutated, more heterogeneous and more prone to metastasis and resistance to therapy. Of course, the question of clinical impact is very important, and this possible relationship needs to be rigorously tested with large clinical studies.”

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Original articles Burns, M. B. *et al.* Evidence for APOBEC3B mutagenesis in multiple human cancers. *Nat. Genet.* doi:10.1038/ng.2701 | Roberts, S. A. *et al.* An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat. Genet.* doi:10.1038/ng.2702