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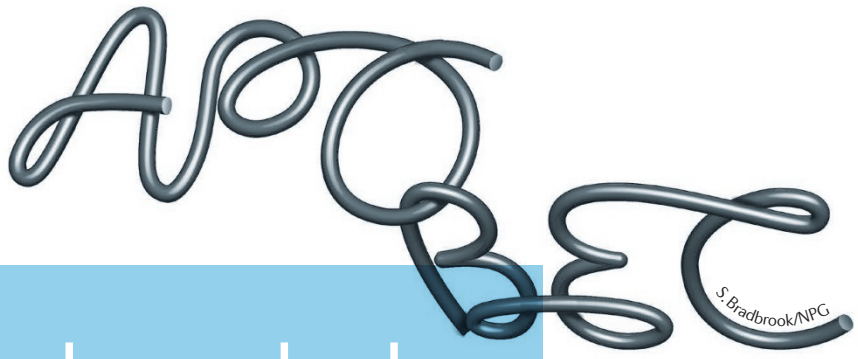

GENETICS

APOBEC conundrum solved

Cytosine mutations within TCA and TCT motifs, which are caused by the APOBEC cytosine deaminases, are common in tumours described in The Cancer Genome Atlas (TCGA). Genetic studies have identified associations with cancer risk for common germline variants close to a gene cluster that encodes enzymes from the APOBEC3 protein family. Now, two research teams have comprehensively explored the connection between germline variants associated with cancer risk in the *APOBEC3* region and APOBEC mutagenesis.

Reuben Harris and colleagues had previously demonstrated a role of APOBEC3B in mutagenesis in breast and several other cancers. In the latest study, published in *Nature Communications*, they took advantage of the fact that a complete deletion of the *APOBEC3B* gene occurs in some human cancers. They were "very surprised to find that an 'APOBEC mutation signature' was clearly evident in breast tumours from patients who lacked this enzyme." This prompted Harris and co-workers to postulate that if APOBEC3B had been the sole contributor to APOBEC signature mutations in breast cancer, then the signature should have been completely absent from these tumours. The team investigated which of the related APOBEC enzyme was responsible for this signature, with genetic, biochemical, cellular data all pointing toward APOBEC3H-I as the culprit. "This result was surprising because many research labs had considered this particular *APOBEC3H* variant as inactive," explains Harris. His team showed that the APOBEC signature is evident only in breast tumours with APOBEC3H-I, but completely absent from breast tumours with any other APOBEC3H variant. A single amino acid polymorphism in APOBEC3H-I is, most likely, the mechanism that destabilizes a cytoplasmic retention process and permits this enzyme to enter the nuclear compartment.

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As Harris highlights, "the major implication is that APOBEC3B and APOBEC3H-I are together responsible for the entire APOBEC mutation signature", and future cancer research should focus on these two enzymes. Harris comments: "in particular, one can envisage a novel class of inhibitors that target these enzymes specifically to slow tumour evolution, and make many existing anticancer drugs work better by decreasing the problem of adaptive drug resistance."

In the second study published in *Nature Genetics*, Ludmila Prokunina-Olsson *et al.* explored the contribution of two common germline variants in the *APOBEC3* region to cancer. The first variant is a single-nucleotide polymorphism (SNP), rs1014971, associated with bladder cancer risk, and the second is a 30 kb deletion that eliminates APOBEC3B, to create a APOBEC3A–APOBEC3B chimera associated with an elevated risk of breast cancer. They showed that carriers of the risk allele of the SNP have a significant genetic predisposition for developing bladder tumours enriched with APOBEC-signature mutations. By contrast, the 30 Kb deletion was associated with APOBEC mutagenesis in breast tumours owing to the activity of the APOBEC3A enzyme. They showed that environmental exposures to DNA-damaging agents or viral infections strongly influence the expression of *APOBEC3A* and *APOBEC3B in vitro*, which might indicate increased cancer risk in individuals with specific germline variants who are exposed to environmental triggers.

In TCGA, high levels of *APOBEC* signature mutations or homozygosity for the cancer-associated SNP rs1014971 near APOBEC3B, was associated with better survival in patients with muscle-invasive bladder cancer, a highly aggressive tumour type. Prokunina-Olsson emphasizes, "our work offers some explanation about the source of APOBEC mutagenesis contributed by germline variants and environmental exposures. Our findings should be tested in the clinic to predict survival and, possibly, treatment response, at least for bladder cancer, in which the effect of these factors was strong."

Lisa Hutchinson

ORIGINAL ARTICLES Starrett, G. J. *et al.* The DNA cytosine deaminase *APOBEC3H* haplotype likely contributes to breast and lung cancer mutagenesis. *Nat. Comms.* http://www.nature.com/articles/ncomms12918 (2016) | Middlebrooks, C. D. *et al.* Association of germline variants in the *APOBEC3* region with cancer risk and enrichment with APOBEC-signature mutations in tumors. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3670 (2016)