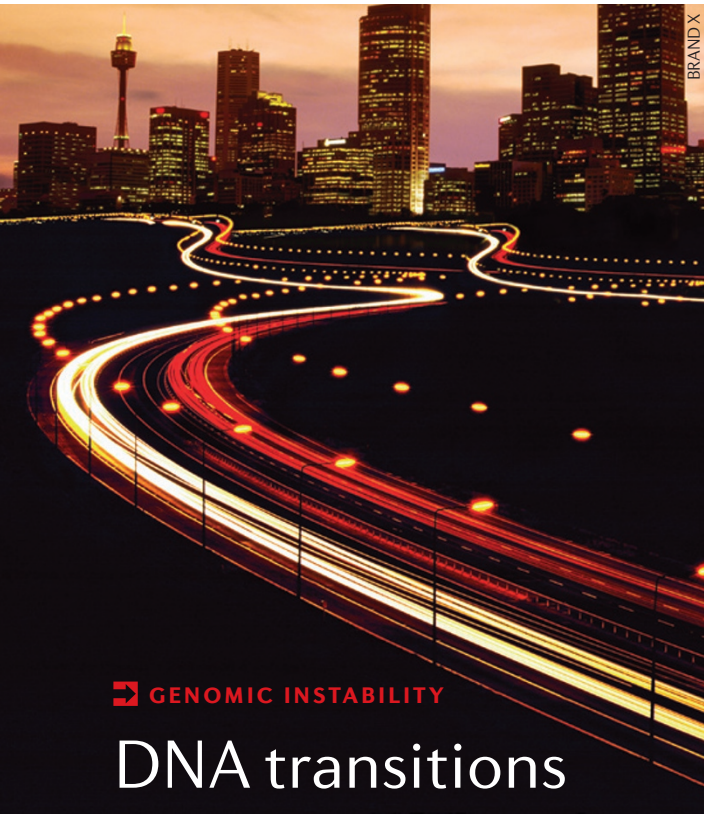
Nature Reviews Cancer | AOP, published online 14 March 2013; doi:10.1038/nrc3490



GENOMIC INSTABILITY

DNA transitions

> APOBEC3B may be an important DNA 'mutator' in cancer

Somatic mutations that have been identified in human breast tumours are predominantly C-to-T transitions. Cytosine can be hydrolysed, resulting in deamination, to produce uracil. Uracil in genomic DNA can either be repaired by potentially mutagenic DNA repair pathways, or it can persist and may result in C-to-T transitions. The cytosines that seem to be prone to C-to-T transition in breast tumours are mostly unmethylated, and deamination of these residues is energetically disfavoured, indicating that enzymatic activity is occuring. Therefore, Burns, Lackey and colleagues investigated whether members of the cytosine deaminase family are responsible for these mutations in breast cancer.

The authors found that *APOBEC3B* mRNA was the only upregulated cytosine deaminase in several breast cancer cell lines. They then expressed enhanced green fluorescent protein (eGFP)-tagged APOBEC3B in three breast cancer cell lines and found that it was expressed in the nucleus, which is consistent with its proposed activity on genomic DNA. Furthermore, the authors found that nuclear fractions of breast cancer cell lines expressing APOBEC3B induced C-to-U editing in an *in vitro* assay, and that this was abrogated when APOBEC3B was knocked down.

Is APOBEC3B important for somatic C-to-T transitions in breast cancer? The authors found that, in breast cancer cell lines endogenously overexpressing APOBEC3B, knockdown of APOBEC3B resulted in substantially reduced levels of genomic uracil. The authors also found that breast cancer cell lines overexpressing APOBEC3B had substantially more mutations than controls, indicating that genomic uracil is mutagenic. Moreover, *TP53* and *MYC* had increased C-to-T transitions in breast cancer cell lines expressing endogenously high levels of APOBEC3B, whereas *CDKN2B* did not, indicating that genomic context may affect the activity of APOBEC3B.

Having found evidence for APOBEC3B inducing C-to-T transitions in breast cancer cell lines, the authors investigated whether the deaminase can also affect other processes. They induced the expression of APOBEC3B, or a catalytically inactive APOBEC3B mutant, in HEK293 cells and found that APOBEC3B activity induced γH2AX (an early event in DNA damage response signalling) and DNA fragmentation, and also reduced cell viability.

Is APOBEC3B relevant to human breast tumours? The authors further demonstrated that *APOBEC3B* was the only cytosine deaminase family member that was overexpressed in human breast tumour samples compared with matched normal tissues. Having established the sequence context preferred by APOBEC3B as 5′-TCA-3′, they analysed the occurrence of C-to-T transitions in breast cancer DNA sequences from three independent data sets and found that C-to-T transitions mostly occurred at these trinucleotides. Furthermore, they found that mutation rates were doubled in tumours expressing high levels of APOBEC3B.

Therefore, APOBEC3B may be an important DNA 'mutator' in cancer that could result in alterations that drive tumour progression and that might contribute to tumour heterogeneity. It remains unclear what regulates APOBEC3B expression in tumours, or exactly how genomic uracil preferentially results in transition mutations. Clearly, further investigation is required to characterize this pathway.

Gemma K. Alderton

ORIGINAL RESEARCH PAPER Burns, M. B. *et al.* APOBEC3B is an enzymatic source of mutation in breast cancer. *Nature* **494**, 366–370 (2013)