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ANTIBODY RESPONSES

Deamination unlocks diversity

It looks like an RNA editor, but it seems that the B-cell-specific activation-induced cytidine deaminase (AID) might, in fact, work directly on DNA. A new study published in *Nature* shows that AID can deaminate deoxycytidine (dC) — an event that could precipitate antibody gene diversification according to the authors.

AID is essential for all three types of antibody gene diversification — somatic hypermutation (SHM), in which single base-pair changes are introduced into the antigen-binding variable (*V*) regions; gene conversion, in which sequence changes are copied from upstream *V* pseudogenes; and class-switch recombination (CSR), in which recombination between 'switch' sequences leads to a change of antibody isotype. But, the function of AID is unknown and its physiological role in these different processes has been the subject of much speculation.

AID is homologous to APOBEC1, a cytidine deaminase that specifically edits APOB messenger RNA. Therefore, it has been suggested that AID might similarly edit the mRNA of an unidentified mutator enzyme. However, Neuberger and colleagues suggest that SHM, gene conversion and CSR could all be initiated by the direct action of AID on DNA to deaminate dC, resulting in a U–G mismatch lesion.

The authors envisage 4–5 ways in which such a lesion could be resolved, assuming that it is not corrected fully by base-excision repair. First, the mismatch is not repaired at all, and DNA replication leads to C→T (and G→A) transitions. Second, base-excision repair is initiated and the uracil is excised; replication over this abasic site will lead to the C (and G) being replaced by any of the other three bases (thereby allowing transversions at C and G). Third, the U–G lesion undergoes mismatch repair, possibly involving error-prone polymerases, which corresponds to the second phase of SHM. Fourth, the lesion undergoes template-mediated repair on an upstream *V* pseudogene, which results in gene conversion. Finally, if the lesion occurs in a switch site, repair that involves another switch region would lead to CSR.

But, can AID act directly on DNA? To test this, human *AID* was expressed in *Escherichia coli*, and the frequency of acquisition of rifamycin resistance — which normally occurs at low levels — was used as a measure of the frequency of mutation. The bacteria that were transformed with *AID* mutated at an increased frequency, and sequencing revealed that there was a strong bias towards C→T and G→A mutations, which is consistent with the deamination of dC by AID. If this is the case, then AID-transformed bacteria that are deficient for uracil-DNA glycosylase, which is involved in the repair of such mutations, should have an increased mutation rate. This was, indeed, found to be the case.

So, this study strongly supports a DNA-deamination mechanism of antibody diversification. Just how AID specifically targets antibody genes remains an important question for future study.

Jennifer Bell

References and links

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