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Retroviruses under editing crossfire

A second member of the human APOBEC3 family is a Vif-blockable innate antiretroviral factor

The importance of innate intracellular immunity as a mechanism of protection against viruses is increasingly being recognized. For example, the Friend virus susceptibility 1 (*Fv1*) gene restricts the sensitivity of mice to the murine leukaemia virus (MLV; Best *et al*, 1996), and the cytoplasmic body-component tripartite-motif 5α (TRIM5-α) limits the susceptibility of non-human primates to infection by the human immunodeficiency virus (HIV; Stremlau *et al*, 2004). Inevitably, viruses have evolved strategies to overcome these obstacles. The virion-infectivity factor (Vif) protein of lentiviruses counters the antiviral action of the cellular enzyme apolipoprotein B mRNA-editing enzyme catalytic-polypeptide 3G (APOBEC3G; Sheehy *et al*, 2002). APOBEC3G belongs to the cytidine deaminase superfamily, the founding member of which is APOBEC1. Another well-characterized relative is activation-induced deaminase (AID), which is a B-cell protein that has an essential role in antibody diversification through governing somatic hypermutation, gene conversion and class-switch recombination at the immunoglobulin loci (Neuberger *et al*, 2003).

APOBEC3G is expressed notably in T lymphocytes and macrophages, which are the main targets of HIV. In the absence of Vif, it is packaged into virions during viral assembly and acts during reverse transcription to deaminate deoxycytidine residues to deoxyuridine (dU) in the growing minus-strand viral DNA (Sheehy *et al*, 2002; Harris *et al*, 2003; Lecossier *et al*, 2003; Mangeat *et al*, 2003; Zhang *et al*, 2003). These dU-rich transcripts are either degraded or yield G-to-A hypermutated proviruses that are largely non-functional (Fig 1). Vif fends off the attack from the host by binding to the cytidine deaminase, which prevents its virion incorporation and triggers its degradation in proteasomes (Conticello *et al*, 2003; Kao *et al*, 2003; Mariani *et al*, 2003; Marin *et al*, 2003; Sheehy *et al*, 2003; Stopak *et al*, 2003; Yu *et al*, 2003; Liu *et al*, 2004; Mehle *et al*, 2004). In the absence of Vif, APOBEC3G is active against a broad range of retroviruses and can also block the hepatitis B virus (HBV; Harris *et al*, 2003; Mangeat *et al*, 2003; Turelli *et al*, 2004).

Although G-to-A hypermutation, which is the consequence of C-to-U changes in the minus-strand DNA, has been noted in HIV-1 field isolates, not every occurrence can be attributed to APOBEC3G. Indeed, the first G of both GA and GG dinucleotides is commonly mutated, whereas APOBEC3G shows a marked preference for editing the second C of CC but not TC (Beale *et al*, 2004). In the 16 June issue of *The EMBO Journal*, Wiegand and colleagues have explained this conundrum by revealing that human T lymphocytes also produce APOBEC3F, which is a close relative of APOBEC3G (Wiegand *et al*, 2004). This enzyme has similar Vif-blockable anti-HIV properties, but favours TC as its target. In the same month, Zheng and colleagues also reported on the antiviral action of APOBEC3F in the *Journal of Virology*, and showed that APOBEC3F, like its sister protein, undergoes proteasomal degradation in the presence of HIV-1 Vif (Zheng *et al*, 2004). Interestingly, both APOBEC3F and APOBEC3G are expressed in the T-lymphoid cell lines that are most commonly used to study Vif function, which probably explains why RNA-interference-based evidence of the antiviral role of APOBEC3G was still missing from the otherwise prolific literature on this enzyme.

To act as antiretrovirals, APOBEC3F and APOBEC3G must be incorporated into particles. The determinants of this event are not yet known, but the fact that they apply to both of these proteins might facilitate their identification. In addition, the two antiviral APOBEC3 proteins will be able to provide information on the mechanism of Vif action. Aspartate at position 128 of APOBEC3G is crucial for Vif binding and constitutes an important barrier to the

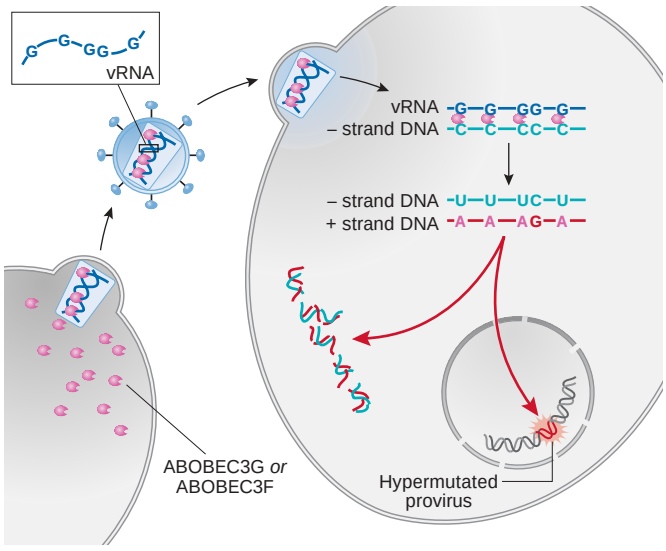

Fig 1 | Innate immunity by deamination. Apolipoprotein B mRNA-editing enzyme catalytic-polypeptide 3G (APOBEC3G) and APOBEC3F are incorporated into nascent retroviral particles through as yet unknown mechanisms. During reverse transcription, they deaminate deoxycytidine residues to deoxyuridine (dU) in the minus-strand viral DNA. These dU-rich transcripts are either degraded by DNA-repair pathways or yield hypermutated proviruses. In the presence of Vif, the antiviral factors are sequestered and degraded in virus-producing cells.

cross-species transmission of lentiviruses. Indeed, this is the binding site for Vif from HIV-1 and HIV-2, but not from simian immunodeficiency virus from the African green monkey (SIV_{AGM}), so this virus is restricted to human cells. Reciprocally, APOBEC3G from the African green monkey, which harbours a lysine at position 128, is recognized by Vif from SIV_{AGM} but not HIV; it therefore inhibits the latter but not the former virus. Residue 128 in APOBEC3F is glutamate, and if this amino acid is introduced into APOBEC3G, it is compatible with HIV-1 but not SIV_{AGM} Vif binding (Schrofelbauer *et al*, 2004). Like APOBEC3G, APOBEC3F must therefore contribute to the species-specific tropism of primate lentiviruses.

In the mouse, there is only one APOBEC3 orthologue and it is endowed with antiretroviral activity (Mariani *et al*, 2003). In humans, the APOBEC3 family has seven members (designated APOBEC3A through to APOBEC3G), which are clustered next to each other in the same orientation on chromosome 22 and probably evolved through consecutive duplications of a common ancestor (Jarmuz *et al*, 2002). APOBEC3E seems to be a pseudogene, whereas the other members of the family are expressed in various tissue-restricted ways. APOBEC3G and APOBEC3F are located some 25,000 base pairs apart and seem to be largely co-regulated, possibly through the sharing of common transcriptional control elements.

APOBEC1 edits the apolipoprotein B mRNA at a precise position, whereas the other APOBEC family members that have been characterized so far—including AID—target single-stranded DNA and act in a less sequence-specific manner. With these new studies, substrates have now been identified for two members of the human APOBEC3 group and in both cases, these substrates are of viral origin. The full extent of the APOBEC3F antiviral potential remains to be determined; however, an even more interesting question is whether either of these two cytidine deaminases can also edit cell-derived sequences. The fact that they are constitutively expressed rather than being virus induced suggests that this is the case. Considering their affinity for reverse transcripts, they might act on endogenous retroelements. These elements, whether endogenous retroviruses or non-long terminal repeat (LTR) retrotransposons, constitute up to 40% of the human genome. Although their contribution as facilitators of genome evolution is unquestionable, it is plausible that their retrotransposition activity is limited by innate mechanisms of the host. However, such a function would not fit with the narrow tissue distributions of APOBEC3F and APOBEC3G, which are expressed mainly in immune cells such as T and B lymphocytes and, at least for APOBEC3G, macrophages. This raises the intriguing possibility that there is an editing substrate that is essential for the function of all three of these cellular arms of the immune response. This warrants efforts aimed at identifying the cellular targets of APOBEC3G and APOBEC3F, and at determining whether these antiviral cytidine deaminases have a role beyond the blockade of exogenous retroelements.

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