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Natural resistance to HIV infection: The Vif–APOBEC interaction

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Abstract

Members of the APOBEC family of cellular polynucleotide cytidine deaminases (e.g., APOBEC3G) are potent inhibitors of HIV infection. Wild type viral infections are largely spared from APOBEC function through the action of the viral Vif protein. In Vif's absence, inhibitory APOBEC proteins are encapsidated by budding virus particles leading to excessive cytidine (C) to uridine (U) hypermutation of negative sense reverse transcripts in newly infected cells. This registers as guanosine (G) to adenosine (A) mutations in plus stranded cDNA. Because the functions of Vif and APOBEC proteins oppose each other, it is likely that fluctuations in the Vif/APOBEC balance can influence the natural history of HIV infection. Experimental support for this notion would further justify and stimulate drug discovery initiatives in this area. ***To cite this article: M.H. Malim, C. R. Biologies 329 (2006).***

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1. Intrinsic, cell-mediated resistance to HIV-1 infection

Like all viruses, the pathogenic retrovirus human immunodeficiency virus type-1 (HIV-1) participates in multiple interactions with the infected host cell during replication. Such intra-cellular interactions have generally been viewed as benefiting HIV-1 growth and, therefore, are considered as facilitators of infection and transmission. Recent discoveries, however, have revealed that human (and non-human primate) cells harbour at least two intrinsic (or non-immune) intracellular resistance mechanisms that can suppress HIV-1 infection. The first is mediated by members of the APOBEC (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like) family of polynucleotide cytidine deaminases and was discovered through efforts to understand the role of the HIV-1 accessory/regulatory protein, Vif, during viral infection [1]. The second is mediated by TRIM (tripartite interaction motif) proteins and was revealed through studies of species-specific post-entry blocks to HIV and simian immunodeficiency virus (SIV) infections [2]. The mechanisms of action of these anti-HIV factors are clearly distinct from each other, as well as being unrelated to the anti-viral activities of type-1 interferons.

2. APOBEC3G and cytidine deamination during HIV-1 replication

The first APOBEC protein found to inhibit HIV-1 was APOBEC3G (initially called CEM15). The gene was isolated on the basis of its ability to inhibit in-

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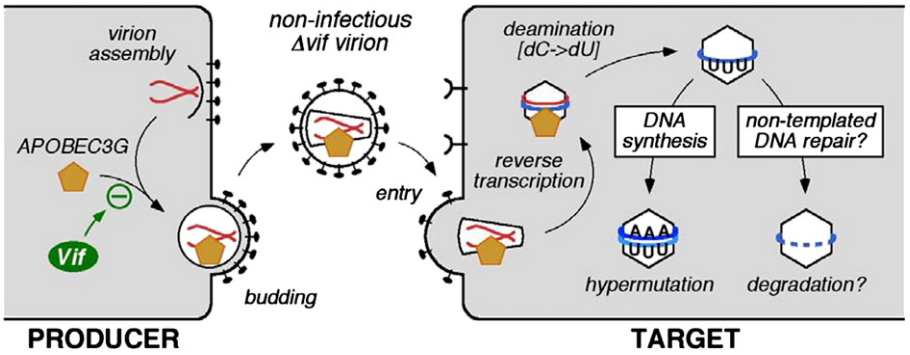

Fig. 1. Effects of APOBEC3G-mediated cytidine deamination on HIV-1 infection. APOBEC3G is incorporated into nascent virus particles and mediates C-to-U deamination of first-strand reverse transcripts in target cells. This results in G-to-A hypermutation of the coding strand and is associated with premature cDNA degradation.

fection by, and replication of, *vif*-deficient (Δ*vif*) mutant strains of HIV-1 [1]. Specifically, ectopic expression of APOBEC3G in cells that otherwise do not express this enzyme, converts these cells to the phenotype in which productive HIV-1 infection is Vif-dependent. Since then, it has been demonstrated that APOBEC3G is a polynucleotide (i.e., DNA or RNA) cytidine deaminase that is incorporated into Δ*vif* virions as they are assembled in virus producing cells [3–6]. The enzyme is then carried forward into challenged target cells where it catalyses excessive cytidine-to-uridine (C-to-U) editing of nascent (mostly) minus strand (or first strand) reverse transcripts: such mutations are therefore registered as guanosine (G) to adenosine (A) transitions in plus stranded DNA (Fig. 1). Because mutational frequencies can exceed 10% of all G residues, this phenomenon is usually called *hypermutation*. The minus strand is targeted for deamination because APOBEC3G can only utilise single-stranded templates, and the plus strand exists almost entirely as double-stranded DNA [7,8]. In addition to the obvious inactivation of viral genes and genetic elements through hypermutation, the presence of APOBEC3G also results in reduced accumulations of viral cDNAs during infection by Δ*vif* viruses [5,9]. Though the mechanistic link between hypermutation and deficits in cDNA levels awaits elucidation, it has been proposed that recognition of U-containing viral DNA by cellular DNA repair enzymes could trigger their degradation (Fig. 1) [10].

3. Cytidine deamination independent effects of APOBEC3G

Unexpectedly, two recent and independent lines of evidence have indicated that APOBEC3G can also exert anti-viral effects(s) in the absence of detectable viral cDNA editing. First, a structure-function analysis of APOBEC3G revealed that certain amino acid substitutions in the C-terminal cytidine deaminase 'core' domain of APOBEC3G (this particular APOBEC family member has two such domains) can give rise to mutant proteins that have lost the ability to mutate DNA, yet have retained anti-viral function in transfection-based assays [11]. Second, Greene and colleagues [12] have shown that suppressing APOBEC3G expression in target cells through RNA interference (RNAi) based methods can alleviate the restricted HIV-1 infection of cultured, quiescent primary T cells. Here, the majority of viral cDNAs that were recovered from untreated resting T cells (which express APOBEC3G) had not been subjected to editing, suggesting that the barrier to infection is attributable to an alternative (hypermutation-independent) mechanism. The molecular basis for each of these inhibitory effects is unknown, as is the degree to which they are related to each other.

4. Vif inhibits APOBEC3G function by inducing proteasomal degradation and preventing virion incorporation

The viral Vif protein protects wild-type HIV-1 from the anti-viral activity of APOBEC3G. It has now been established that Vif interacts with APOBEC3G and thereby serves as an 'adapter' to recruit APOBEC3G to a cullin5 ECS E3 ubiquitin ligase [13]. Formation of this complex results in the polyubiquitination and subsequent proteasome-mediated degradation of APOBEC3G in virus producing cells [13–17]. The intra-cellular levels of APOBEC3G are correspondingly reduced, resulting in the inhibition of packaging into virions and the preservation of viral infectivity. There is also limited evidence that Vif may also help exclude APOBEC3G from virions by a more direct mechanism,