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Comparative analysis of the antiretroviral activity of APOBEC3G and APOBEC3F from primates

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Abstract

APOBEC3G and APOBEC3F exhibit antiretroviral activity primarily as a consequence of their ability to deaminate cytidines in retroviral DNA. Here, we compare the properties of APOBEC3F and APOBEC3G from human, macaque, and African green monkey (AGM). While all APOBEC proteins tested exhibited anti-HIV-1 activity, human APOBEC3F was, surprisingly, 10- to 50-fold less potent than human APOBEC3G. However, similar discrepancies in antiviral potency were not found when pairs of proteins from macaque and AGM were compared. Intrinsic differences in the ability of each APOBEC protein to induce hypermutation, rather than differences in packaging efficiency, partially accounted for variable antiretroviral activity. Each of four primate lentivirus Vif proteins reduced human and AGM APOBEC3F expression and antiviral activity, but all were only partially effective and species-specific effects were relatively minor. Overall, highly efficient and species-specific neutralization of APOBEC3G, and less efficient neutralization of APOBEC3F, appears to be a general property of Vif proteins.
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Keywords: HIV-1; Vif; APOBEC3G; APOBEC3F; Hypermutation

Introduction

Intrinsic cellular defenses against retroviral infection include at least two cytidine deaminases, APOBEC3G and APOBEC3F, that modify nascent minus-strand retroviral DNA during reverse transcription (Bishop et al., 2004; Liddament et al., 2004; Sheehy et al., 2002; Wiegand et al., 2004; Zheng et al., 2004) The uracil-containing minus-strand DNA that results from deamination is either degraded, presumably due to recognition by cellular DNA repair enzymes, or survives to become integrated into the host genome in a hypermutated form (Harris et al., 2003; Lecossier et al., 2003; Mangeat et al., 2003; Yu et al., 2004b; Zhang et al., 2003). Although cytidine deamination occurs during the early phases of the retrovirus life cycle, antiviral activity is observed as a consequence of the packaging of cytidine deaminases into viral particles during assembly. (Mariani et al., 2003; Sheehy et al., 2002). Human APOBEC3G packaging requires nucleocapsid and RNA but appears to be a rather nonspecific process, in that it can be packaged into retroviral particles that bear little or no sequence homology (Alce and Popik, 2004; Cen et al., 2004; Douaisi et al., 2004; Khan et al., 2005; Mariani et al., 2003; Schafer et al., 2004; Svarovskaia et al., 2004; Zennou et al., 2004). Thus, it should be difficult for retroviruses to acquire resistance to the antiviral effects of APOBEC3G or APOBEC3F. While murine leukemia virus appears to have acquired the ability to avoid packaging murine APOBEC3, this property does not extend to human APOBEC3G (Doehle et al., 2005a, 2005b), which can be packaged by all retroviruses that have been examined thus far. Most lentiviruses counteract APOBEC3G activity by expressing Vif proteins that prevent its incorporation into virions. This is achieved primarily by inducing its degradation by proteasomes (Conticello et al., 2003; Kao et al., 2003; Liu et al., 2004; Marin et al., 2003; Mehle et al., 2003; Sheehy et al., 2003; Stopak et al., 2003; Yu et al., 2003) and perhaps by additional mechanisms (Mariani et al., 2003; Stopak et al., 2003).

Human APOBEC3G and APOBEC3F differ slightly in their substrate preference (Bishop et al., 2004; Liddament et al., 2004; Wiegand et al., 2004; Zheng et al., 2004). For human

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APOBEC3G, deamination of cytidines in single-stranded DNA appears to be most efficient if another cytidine is present at the-1 position relative to the deaminated base. Thus, the principal effect of APOBEC3G mutagenesis of nascent retroviral DNA during reverse transcription is the accumulation of G-to-A mutations on the plus-strand, in the context of GG dinucleotides (which are changed to AG). However, mutations in other contexts, particularly GA-to-AA, also occur at lower frequency. Conversely, human APOBEC3F deamination is more efficient if a thymidine is present at the −1 position, and therefore, the 'footprint' of APOBEC3F mutagenesis is primarily GA to AA substitutions. Aside from their distinguishable substrate specificities, other reported differences between human APOBEC3G and APOBEC3F proteins are the potency with which they inhibit HIV-1 infectivity and in their relative sensitivity to HIV-1 Vif. Specifically, human APOBEC3F has been reported to be marginally less inhibitory and marginally less sensitive to HIV-1 Vif than is APOBEC3G (Liddament et al., 2004; Wiegand et al., 2004).

While human, macaque, and AGM APOBEC3G proteins have each been shown to reduce the infectivity of human, macaque, and AGM lentiviruses, they differ markedly in their propensity to be excluded from virions by certain Vif proteins (Mariani et al., 2003). In particular, HIV-1 and SIV_{AGM} Vif proteins act specifically on APOBEC3G proteins from the species in which the parental virus is found, but HIV-1 Vif is ineffective against AGM APOBEC3G and SIV_{AGM} Vif is ineffective against human APOBEC3G (Mariani et al., 2003). A single amino acid difference at position 128 of the human and AGM APOBEC3G proteins is a critical determinant of this difference (Bogerd et al., 2004; Mangeat et al., 2004; Schrofelbauer et al., 2004; Xu et al., 2004). The resistance of human APOBEC3G to SIV_{AGM} Vif may, in part, be responsible for the failure of SIV_{AGM} strains, which are highly prevalent in relatively abundant African primates, to colonize humans. Conversely, Vif proteins from the HIV-2/SIV_{MAC}/SIV_{SM} primate lentivirus lineage appear somewhat more promiscuous in that they are active against both human and AGM APOBEC3G proteins (Bogerd et al., 2004; Schrofelbauer et al., 2004). Perhaps as a result, viruses from this lineage are able to replicate efficiently in at least four relatively divergent primate species, namely sooty mangabeys, macaques, baboons, and humans.

Thus, while APOBEC3G and APOBEC3F are known to be inhibitors of primate lentivirus replication and APOBEC3G has clear species-specific properties that likely affect the ability of lentiviruses to cross-species, there has been no previous characterization of nonhuman primate APOBEC3F proteins. Therefore, to determine whether species-specific differences in APOBEC3F might contribute to species-specific primate lentivirus tropism, we compared the anti-HIV-1 activity and Vif sensitivity of human, rhesus macaque, and AGM APOBEC3F and APOBEC3G proteins. We found surprising species-specific differences in the relative potency with which APOBEC3F and APOBE3G inhibited HIV-1 infectivity. Conversely, the marked species-specific differences in the sensitivity of APOBEC3G proteins to primate lentivirus Vif proteins were much less evident when APOBEC3F proteins were compared. Thus, in the case of humans, rhesus monkeys, and AGMs, APOBEC3F appears a significantly less potent barrier to cross-species transmission than does APOBEC3G.

Results

APOBEC3F from macaques and African green monkeys

cDNAs encoding APOBEC3F were amplified from a human cell line (CEM), a rhesus macaque cell line (221), and an AGM cell line (CV-1). An alignment of the amino acid sequences that these cDNAs encode is shown in Fig. 1. Macaque and AGM APOBEC3F proteins were 93% identical to each other, and 87% and 88% identical to human APOBEC3F respectively. Sequence differences among the APOBEC3F variants were

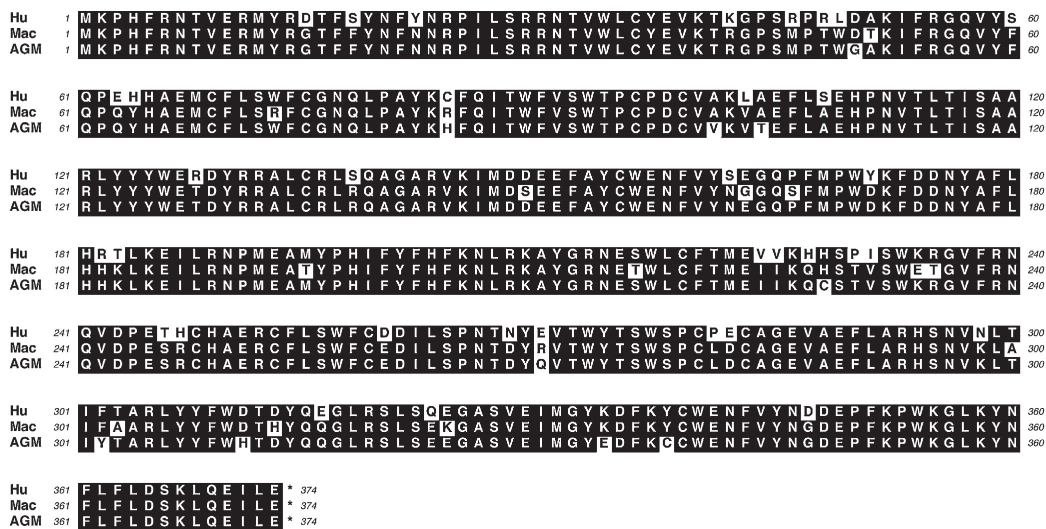

Fig. 1. Alignment of APOBEC3F amino acid sequences from human CEM cells (Hu), rhesus macaque 221 cells (Mac), and African green monkey CV1 cells (AGM).

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