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Retroviral Host Cell Factors: TRIM5, APOBEC3G and Cyclophilins

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1. Introduction

The conventional innate and adaptive immune systems are very effective at viral infections. However, for retroviral infections, there is another immune system that can recognize at multiple levels e.g. expression of internal host factors with antiviral activity. This is a component of viral recognition and subsequent restriction that has been called "intrinsic immunity"(Bieniasz, 2004). Intrinsic immunity can distinguish from innate and adaptive immunity, and it does not need to be induced by viral infections. Retrovirus replication has many steps in common with other retroviruses. Upon entry into the cytoplasm of target cells, some host factors are required for efficient retroviral replication cycle, and others act as restriction factors that block reverse transcription and ligation of viral cDNA to chromosomal DNA. Recently, several host factors have been identified such as the proline isomerase cyclophilin A (CypA), ApoB mRNA editing catalytic subunit (APOBEC) and tripartite motif protein 5 alpha (TRIM5α) against retrovirus infection. This review will focus on how these host factors modulate retroviral activity. It will then present our current understanding of the mechanism that may explain zoonotic transmission of retroviruses.

1.1 Fv1 and Fv4: Restriction factors that block infection by Friend-MLV in murine cells

The most intensively studied anti-cellular gene is Friend virus susceptibility (Fv) gene in laboratory mice. Fv1 and Fv4 were of special interest in Fv alleles because cultured murine cells containing them were resistant to infection by Friend murine leukemia virus (MLV)(Gardner et al., 1980; Hartley et al., 1970; Pincus et al., 1971; Rasheed and Gardner, 1983; Suzuki, 1975). Fv1-mediated restriction of MLV, for instance, is a well-studied representative of a class of restriction factors that act after membrane fusion, are highly virus-specific (Goff, 2004). Fv1 has two alleles, $Fv1^n$ and $Fv1^b$, targeting B- and N-tropic MLV, respectively (Rein et al., 1976). Fv4 was shown to encode an ecotropic MLV-like *env* gene and recent report showed that Fv4 inhibits infection by exerting dominant negative effect on MLV Env (Takeda and Matano, 2007). Although the precise mechanism of Fv1 restriction remains unclear, the important point is that the viral determinants for this type of restriction have been mapped to the capsid protein (MLV amino acid 110) and as a target of host factors that can modulate retroviral life cycle (Gautsch et al., 1978; Kozak and Chakraborti, 1996).

1.2 Ref1 and Lv1: Fv1-type restriction factors in human or primate cells

A host factor that belongs to the same category of Fv1-type restriction factors is Ref1 (restriction factor 1). Ref1 is expressed in human and other non-murine cells and imposes a similar restriction of Fv1 that is controlled by relationship between the same capsid residue (MLV CA 110) and Fv1 (Towers et al., 2000). The difference between Ref1 and Fv1 function is that Ref1 restricts retroviral replication at a step prior to reverse transcription while Fv1 seems to impose a post-reverse transcription block (Goff, 2004). Another restriction factor, lentivirus susceptibility factor 1 (Lv1), was found to be responsible for restricting HIV-1 and N-tropic MLV but not rhesus macaque simian immunodeficiency virus (SIVmac) replication in Old World monkey cells (Besnier et al., 2002; Cowan et al., 2002; Munk et al., 2002).

1.3 TRIM5α: Fv1-type host factor restricting HIV-1 in primate cells

Recently, the host protein which dictates Ref1 activity was identified as an α-isoform of rhesus macaque TRIM5α protein by the laboratory of Dr. Joseph Sodroski (Stremlau et al., 2004). TRIM5 is a member of the tripartite motif (TRIM) family of proteins, and has RING, B-box 2 and coiled-coil as common and conserved domains among the family and B30.2(PRYSPRY) domain on its c-terminal region (Nisole et al., 2005). Subsequently, the human and non-human primates homologues of TRIM5α were shown to explain restriction activity against retroviruses, N-MLV, and equine anemia virus (Hatziioannou et al., 2004b; Keckesova et al., 2004; Perron et al., 2004; Si et al., 2006; Song et al., 2005; Yap et al., 2004; Ylinen et al., 2005). Rhesus monkey TRIM5α has strong anti-HIV-1 activity, only modest restriction against SIVmac, and does not block MLV infection, whereas its human homologue does not active against HIV-1 infection.

TRIM5α recognizes incoming viral core, but not a monomeric capsid protein, thorough its B30.2(PRYSPRY) domain. B-box2 and coiled-coil domains are required for TRIM5α multimerization, and both coiled-coil and B30.2(PRYSPRY) domains are essential for viral core binding (Reymond et al., 2001; Stremlau et al., 2006). TRIM5α captures HIV-1 core at a very early step(s) after infection, immediately after the release of core into cytoplasm. To restrict HIV-1 infection and to recognize viral core, TRIM5α must be oligomerized through its B-box 2 and coiled-coil domains. Its RING domain has E3 ubiqutin ligase activity, and self-ubiqutination is occurred, then TRIM5α is quickly degraded. This quick degradation of TRIM5α is not necessary for post-entry restriction, since replacement of TRIM5α RING domain with the corresponding domain of TRIM21 which has lower self-ubiqutination activity and longer half life than TRIM5α didn't alter the antiviral activity. When TRIM5α was over expressed, cytoplasmic body is formed, and the cytoplasmic body is supposed to be required for its antiviral activity. During TRIM5α-mediated post-entry restriction, disassembly of viral core is induced too quickly and the accumulation of viral RT-products is reduced. MG132 treatment inhibits to induce quick-disassembly, but still HIV-1 infectivity was restricted. Two reports showed that TRIM5α could block not only viral cDNA accumulation but also the nuclear import of viral cDNA (Berthoux et al., 2004; Wu et al., 2006). Thus TRIM5α-mediated post-entry restriction is thought to have at least two phases: (i) TRIM5α induces quick-disassembly of viral core in a proteasome dependent manner and (ii) TRIM5α degrades HIV-1 cDNAs in a proteasome independent manner. The determinant of specificity and magnitude of the post-entry restriction lies on B30.2(PRYSPRY) domain. Recently, Pacheco *et al.* reported that new world monkey TRIM5α restricts foamy virus

infection (Pacheco et al., 2010). Another consideration is the clinical significance of TRIM5α against acquired immunodeficiency syndrome (AIDS) in human. Moreover several reports showed that the efficacy of TRIM5α-mediated suppression of HIV-1 replication might interfere with disease progression of AIDS in humans (Cagliani et al., 2010; van Manen et al., 2008). Thus, TRIM5α-mediated restriction may occur multi step in retrovirus replication with the relationship between other host factor(s).

Recently, the lab of Dr. Yasuhiro Ikeda reported that rhesus macaque TRIM5α also inhibits HIV-1 production by inducing the degradation of a viral precursor Gag protein (Sakuma et al., 2007). To restrict HIV-1 production, amino acid residues in B-box 2 and coiled-coil domains dictated the specificity of the restriction. In the late restriction, the accumulation of HIV-1 RNA was not affected but the accumulation of precursor Gag was inhibited in an ubiqutine-proteasome independent manner. This TRIM5α-mediated late-restriction is still controversial (Zhang et al., 2008), yet it is presumable that TRIM5α restricts HIV-1 infection and production in two distinct mechanisms. Although TRIM5α restricts HIV-1 infection in broad range of cells, its late restriction depends on a cell line (Sakuma et al., 2007).

Here is another notable class of the TRIM family called TRIM-Cyp isolated from new wold monkeys (NWM). A report from the laboratory of Dr. Jeremy Luban demonstrated that owl monkey has TRIM-Cyp that restricts HIV-1 infection (Sayah et al., 2004). Although TRIM-Cyp has a cyclophilin A sequence in its C-terminal region instead of B30.2(PRYSPRY) domain that dictates the specificity and the magnitude of post entry restriction in OWM-TRIM5α-mediated post-entry restriction, it recognizes incoming core structure and restricts HIV-1 infection (Stremlau et al., 2006). Recently, TRIM-Cyp mRNA was also detected in a rhesus macaque cell, and over-expressed rhesus TRIM-Cyp restricts HIV-1 infection and production (Brennan et al., 2008; Dietrich et al., 2010; Sakuma et al., 2010; Wilson et al., 2008).

Not like other restriction factors, the counter part of TRIM5α-mediated restrictions is not accessory gene product of HIV-1, and human TRIM5α has just a modest restriction activity. NWM cell doesn't have TRIM5α, yet even without B30.2(PRYSPRY), TRIM5-Cyp can be a defense against viral infection. These evidences suggest that TRIM5α could be a key molecule to explain the species-species barrier. And if so, TRIM5α's dual antiviral activities can block the viral transmission even from closer species like to human from monkeys.

1.4 APOBEC: Enzymatic restriction factor that target retroviruses

Replication of HIV-1 in primary CD4+ T cells, monocyte and some immortalized T cell lines depends on the presence of HIV-1 accessory gene product, Vif (stands for virus infectivity factor)(Fisher et al., 1987; Strebel et al., 1987), and it works in a host cell-specific manner. Vif is required for enhanced HIV-1 replication in some cell types called non-permissive cells, in contrast HIV-1 replication is Vif-independent in permissive cells (Akari et al., 1992; Blanc et al., 1993; Borman et al., 1995; Fan and Peden, 1992; Gabuzda et al., 1992; Sakai et al., 1993; von Schwedler et al., 1993). Recently, some cytidine deaminases were identified as a new class of host restriction factors that target retroviruses such as HIV-1 or SIV (Cullen, 2006; Harris and Liddament, 2004). APOBEC3G (Apo3G), a member of the APOBEC family of cytidine deaminases, is the first identified enzymatic restriction factor and the determinant that makes cells permissive or non-permissive. Unlike TRIM5α nor Fv1, Apo3G does not exert its antiviral activity by targeting the viral capsid protein, but it has to be incorporated into a newly synthesized virion during a production step, and then inhibits virus replication

by targeting single-stranded viral cDNA during an infection step. HIV-1 counteracts Apo3G with Vif expression. During the production of progeny virions, Vif binds to Apo3G and induces Apo3G's proteosomal degradation, resulting in the decreased steady-state levels of human Apo3G (hApo3G) (Yu et al., 2003).

There are several antiretroviral mechanisms of Apo3G against HIV-1 infection. First, Apo3G-containing virus can be resulted in a large number substitution that register as cytidine (C) to thymine (T) in a virus minus-strand during reverse transcription, resulting guanine (G) to adenine (A) mutations in a viral plus strand, known as 'G to A hypermutaion'(Harris et al., 2003; Lecossier et al., 2003; Mangeat et al., 2003; Mariani et al., 2003; Yu et al., 2004; Zhang et al., 2003). Second, Apo3G can inhibit tRNA annealing or tRNA processing during reverse transcription (Guo et al., 2006; Guo et al., 2007; Mbisa et al., 2007). Third, Apo3G inhibits DNA strand transfer or integration (Li et al., 2007; Luo et al., 2007; Mbisa et al., 2007). Although Apo3G has the most potent anti-HIV-1 activity among the APOBEC family of proteins, another member of the family, APOBEC3F (Apo3F) was shown to inhibit HIV-1 infection in the absence of Vif (Bishop et al., 2004a; Liddament et al., 2004; Wiegand et al., 2004; Zheng et al., 2004), whereas APOBEC3B (Apo3B) can inhibit HIV-1 infection in both the presence and absence of Vif (Bishop et al., 2004a; Doehle et al., 2005; Rose et al., 2005).

Although we can imagine the broad range of antiretroviral activity of APOBEC family because APOBEC proteins from non-human species can also inhibit HIV-1 infection (Bishop et al., 2004a; Bishop et al., 2004b; Cullen, 2006; Mariani et al., 2003; Wiegand et al., 2004), the Vif-Apo3G interaction is thought to be species specific (Mariani et al., 2003; Simon et al., 1998). Accordingly, hApo3G is insensitive to SIVagm Vif while african green monkey Apo3G (agmApo3G) is insensitive to HIV-1 Vif and the determinant of this species specificity depends on amino acid 128 of hApo3G and agmApo3G (Bogerd et al., 2004; Mangeat et al., 2004; Mariani et al., 2003; Schrofelbauer et al., 2004; Xu et al., 2004). However, such species specificity is not strictly controlled, for example a report from the laboratory of Klaus Strebel demonstrated that SIVagm Vif supported replication of SIVagm virus in the hApo3G-positive human A3.01 T cell line. Replication of *vif*-defective SIVagm in A3.01 cells was severely restricted, resulted in an accumulation of cytidine deaminase-induced G-to-A mutations in SIVagm genome (Takeuchi et al., 2005). Therefore, it is probable that SIV Vif has evolved to counteract hApo3G restriction and this might contribute zoonotic transmission of SIV.

Although the antiviral activity of Apo3G is clearly correlated with its deaminase activity (Iwatani et al., 2006; Mangeat et al., 2003; Navarro et al., 2005; Opi et al., 2006; Shindo et al., 2003; Zhang et al., 2003), some members of APOBEC family have additional anti-retrovirus activities that do not require catalytically activity of itself (Li et al., 2007; Luo et al., 2007). In fact, several reports showed that deaminase-defective Apo3G and Apo3F have antiviral activity, and some antiviral-inactive mutants of both Apo3G and Apo3F have cytidine deaminase activity (Bishop et al., 2006; Holmes et al., 2007; Newman et al., 2005; Shindo et al., 2003).

However, deaminase-defective Apo3G mutant with C288S/C291A substitutions did not show any anti-viral actibity and over-expression of the mutant could work as a dominant negative agent of wild-type Apo3G, suggesting a tightly-relationship between antiviral and deaminase activities (Miyagi et al., 2007; Opi et al., 2006). Recently, it was demonstrated that hApo3G has an intrinsic immune effect on viral DNA synthesis, which may account for cytidine deaminase-independent antiviral activity of Apo3G, and did not abort replication

steps following reverse transcription (Iwatani et al., 2007). Therefore, precise mechanism of Apo3G-dependent restriction of retroviral infection still remains unclear.

1.5 Cyclophilin A: positive factor against retrovirus replication (or restriction factor?)

Cyclophilins are ubiquitous proteins and first identified as the target of cyclosporine A (CsA), an immunosuppressive reagent (Takahashi et al., 1989). CypA has proline-isomerase activity that catalyzes the cis-trans isomerization of proline residue (Fischer et al., 1989). The binding of cyclosporine A to cyclophilin A inhibits this isomerase activity (Takahashi et al., 1989). In retrovirus replication, CypA was found to bind HIV-1 capsid (CA) in the yeast two-hybrid system (Luban et al., 1993). The sequence Ala88-Gly89-Pro90-Ile91 of CA protein is the major fragment bound to the active site of CypA (Franke et al., 1994; Gamble et al., 1996; Zhao et al., 1997). Interestingly, The peptidyl-prolyl bond between Gly89 and Pro90 of the CA fragment has a trans conformation, in contrast to the cis conformation observed in other known CypA-peptide complexes (Bosco et al., 2002; Zhao et al., 1997), and Gly89 preceding Pro90 has an unfavorable backbone formation usually only adopted by glycine, suggesting that special Gly89-Pro90 sequence but not other Gly-Pro motif is required for the binding of CA protein to CypA. Therefore, CypA might be likely to act as a molecular chaperone but not a cis-trans isomerase (Zhao et al., 1997). However, one report showed that CypA does not only bind CA protein but also catalyzes efficiently cic-trans isomerization of Gly89-Pro90 peptidyl-prolyl bond (Bosco et al., 2002). The relationship between the Gly89-Pro90 bond and catalysis of cis-trans isomerization by CypA still remain unclear.

It has been well established that CypA promotes an early step of HIV-1 infection in human cells (Braaten et al., 1996a; Braaten et al., 1996c; Braaten and Luban, 2001; Franke and Luban, 1996; Franke et al., 1994; Hatziioannou et al., 2005; Sokolskaja et al., 2004; Thali et al., 1994). CypA is efficiently encapsidated into HIV-1 produced from infected cells through interaction with the CA domains of the Gag polyprotein and disruption of CypA incorporation into virions by CsA or HIV-1 Gag mutants caused a decrease in replication efficiency (Ackerson et al., 1998; Braaten et al., 1996a; Braaten and Luban, 2001; Bukovsky et al., 1997; Franke et al., 1994; Ott et al., 1995; Thali et al., 1994). It is still unclear how CypA is efficiently packaged into HIV-1 virion, but several report showed that both dimerization of CA and multimerization of CypA is required for efficient binding each other (Colgan et al., 1996; Javanbakht et al., 2007). Although CA-CypA interaction is required for infectivity, the important point is that CypA interacts with incoming HIV-1 cores in newly target cells than occurring as core assemble during HIV-1 budding from the virion producer cells, indicated that target cell CypA promotes HIV-1 infectivity (Kootstra et al., 2003; Sokolskaja et al., 2004; Towers et al., 2003).

CypA-dependent virus replication is only limited the retroviruses which encode CA that binds CypA. In fact, only those retroviruses are dependent upon CypA for replication (Braaten et al., 1996c; Franke and Luban, 1996; Franke et al., 1994; Luban et al., 1993; Thali et al., 1994). These observations suggested that CA-CypA interaction might contribute tropism determinants for retroviruses. HIV-1 infection in non-human primate cells inhibits prior to reverse transcription after virus entry (Besnier et al., 2002; Cowan et al., 2002; Hatziioannou et al., 2003; Himathongkham and Luciw, 1996; Hofmann et al., 1999; Munk et al., 2002; Shibata et al., 1995; Towers et al., 2003). This restriction is thought to be the same step in the retrovirus life cycle where CypA works (Braaten et al., 1996b). Indeed, Analysis of CypA-binding region of CA with chimeric viruses of HIV-1 and SIV showed the viral determinant for species-specificity (Berthoux et al., 2004; Bukovsky et al., 1997; Cowan et al., 2002;

Dorfman and Gottlinger, 1996; Hatziioannou et al., 2004a; Hatziioannou et al., 2006; Ikeda et al., 2004; Kamada et al., 2006; Kootstra et al., 2003; Owens et al., 2004; Owens et al., 2003; Sayah et al., 2004; Shibata et al., 1991; Shibata et al., 1995; Stremlau et al., 2004; Towers et al., 2003).

Human CypA is required for efficient HIV-1 infection but not SIV. There is no known role for CypA in SIV infection in human cells. Recently, the first report from the laboratory of Klaus Strebel showed that human CypA acts as restriction factor against SIV infection in human cells, and SIV Vif counteracts a CypA-imposed inhibition against SIV infection with exclusion of CypA from SIV vision (Takeuchi et al., 2007). This phenomenon could distinguish from the function of SIV Vif against hApo3G previously reported from same laboratory (Takeuchi et al., 2005) because they used human cells lacking detectable deaminase activity. This observation raised the possibility that SIV Vif is crucial for zoonotic transmission of SIV from monkey to human.

2. Conclusion

Viral replication requires a lot of host cell factors, whose species specificity may affect viral tropism. On the other hand, there exist host factors that restrict viral replication. The anti-viral system mediated by some of these restriction factors, termed intrinsic immunity, which is distinguished from the conventional innate and adaptive immunity has been indicated to play an important role in making species-specific barriers against viral infection. As discussed in this chapter, we describe the current progress in understanding of such restriction factors against retroviral replication, especially focusing on TRIM5α and APOBEC whose anti-retroviral effects have recently been recognized. Additionally, we mentioned CypA that is essential for HIV-1 replication in human cells and may affect viral tropism. Understanding of these host factors would contribute to identification of the determinants for viral tropism. Finally, understanding of the factors mediating intrinsic immunity may lead to the development of antiviral agents that can boost their potency and thereby lead to treatments for viral disease.

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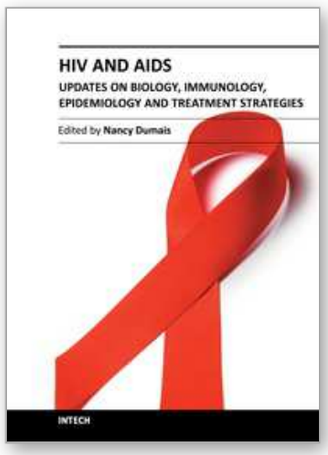

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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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