TRIM5αがウイルスの増殖を阻害する過程でであう宿主因子を得る事は可能である。今回のデータより得られた候補の一つ vimentin はHIV-1 のアクセサリータンパク質 Vpr、Vif との結合が報告されている。特に Vpr はウイルス粒子中に Gag-p6 を介して取り込まれる事が明らかとなっており、ウイルス産生阻害への関与が期待された。実際に Vimentin のドミナントネガティブ変異体を用いることで、HIV-1 産生は大きく低下したが、RhT5αとの関与を示す事はできなかった。CRN1C はアクチンフィラメント上での輸送に関わるモータータンパク質であると考えられ、ウイルス感染時、コアが侵入してくる段階で関与している可能性と pr55Gag の細胞膜への輸送へ関与している可能性が考えられたが CRN1C のノックダウンによって RhT5αの HIV-1 産生阻害への影響を認めることはできなかった。

組み替えタンパク質の大腸菌からの発現は成功したが大腸菌内から得られたタンパク質の多くが分解、切断を受けていた。精製に用いる GST タグは His タグと同じ N 末端についているが、C 末端側には S-タグが付加してあり、これらを用いて２段階の精製を行う事で全長タンパク質のみの回収・精製を予定していた。しかしながら、発現が確認された GST を融合させた組替え TRIM5αタンパク質のグルタチオンビーズとの結合が認められなかった。この点に関してレトロウイルス関連の国際会議等で、多数の経験豊富な研究者と Discussion を行ったが、TRIM5αと GST を連結させることでタンパク質の立体構造が不安定となり、グルタチオンと結合できなくなることが強く予想されている。GST との融合タンパク質作製、精製はごく一般的な方法であったものの、この方法で TRIM5αの安定したタンパク質精製を実現するのは困難であり、実験系の大きな変更を余儀なくされた。一方で、本実験は当初の研究計画に含まれていない予備的な実験系であることから、以後本研究のタンパク質間相互作用の解析は主に共免疫沈降法を用いて行った。

本研究成果より SOCS1 は RhT5αを非プロテアソーム系で分解誘導しており、その発現を抑えることで RhT5a は TE671 細胞内でも HIV-1 産生阻害活性を発揮できることが明らかとなった。また、以前の我々による研究結果から RhT5αは同様に Gag の非プロテアソーム系での分解を誘導している。残念ながらこれらの詳細は未だ明らかにできていないが、これらの事実は三者が同じパスウェイの中で相互作用を持つという仮説を支持する。

本研究において副次的に発見された変異体ではあるが、RhT5αのリンカー領域をヒト化することで、サイトプラズミックボディ形成は行うが抗ウイルス活性を失った変異体を同定した。この領域の重要性は今まで報告されておらず、新規の変異体を構築したと言え、また、ウイルスのライフサイクルの前期課程における効果も報告されていないことから、RhT5αが二つの異なるメカニズムによって HIV-1 の感染と産生を抑制していることが強く支持された。

HuT5αのSNP間で抗HIV-1活性に違いが認められた。この違いを生じた詳細なメカニズムは不明であるが、今回最も強かった H43Y はRINGドメインの変異であるためE3ユビキチンライゲース活性の亢進によるものと予想される。同様にして、それぞれ相手となる宿主因子とのアフィニティや酵素活性の強弱により SNP 間で活性の違いが生じたと考えられる。このことはHuT5αのパートナーとなる宿主因子を探し、そのアフィニティを増大する、もしくは酵素活性を増強することで、HuT5αに抗 HIV-1 産生活性を付与できる可能性を支持する。

本研究開始時に挙げた目標は以下の 2 点であった。

- HuT5αがなぜ HIV-1 産生を抑制できないのかを明らかにする。
- 得られた知見に基づき HuT5αによるHIV-1 複製阻害活性の誘導を試みる。

本研究成果より SOCS1 の発現レベルをコントロールすることで HuT5αの活性を誘導できる可能性が示唆された。また、詳細な機序は未解明ではあるが HuT5αの抗 HIV-1 活性を増強する可能性の高い宿主因子も同定することができた。HIV-1 粒子内より同定され、ウイルス増殖に、また RhT5αによる HIV-1 産生阻害に重要な宿主因子のリストに関しては現状で97種の宿主因子を同定し、更に他の実験データと組み合わせることで多面的に評価したことで、一定の成果を得ることができたと考えている。

今回得られたリストに関しては RhT5αの作用機序に注目した場合のものであり、粒子内全ての宿主因子を評価可能なものではない。本研究計画を通じて得た HIV-1 粒子の精製、濃縮、内部タンパク質構成の解析方法・技術を用いて、PBMC で増幅した HIV-1、可能であれば HIV-1 感染者の血中から濃縮したHIV-1 の構成タンパク質を調べることで、新規抗HIV-1戦略を開発していく上で重要な知見につながると考えている。

E.結論

本研究計画の最終年度として、申請時に予想された成果の一つであるウイルス粒子内より検出されHIV-1のライフサイクルに重要な宿主タンパク質に関する情報を得ることはできたと考えている。また、当該因子をノックダウンすることで HuT5αによる HIV-1 産生阻害を認めるもの同定されており、更なる精査、解析は必要であるものの本研究の目的は最低限達することができたと考えている。一方で、得られた因子の解析は完了したとは言えず、また詳細に解析を進めた因子の論文での発表も期間内には終了しなかった。本報告書にもある SOCS1 に関しては近日中に成果をまとめて投稿する予定であり、S3 タンパク質に関しても少々の追加実験の後投稿予定である。その他の因子に関しても解析を継続する予定であり順次報告し続けていくことで、研究成果を還元していきたい。

G. 研究発表

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HIV-1 の増殖に重要な新規宿主因子の同定

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HIV-1 産生阻害におけるアカゲザル TRIM5a の細胞内動態の解析

助川明香、佐久間龍太、大嶺青河、池田靖弘、山岡昇司

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ヒト CPSF6 の C 末欠損帯は HIV-1 感染後の逆転写効率に影響を及ぼす因子である

堀恭徳、武内寛明、佐久間龍太、山岡昇司

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HIV-1 の増殖に重要ない新規宿主因子の同定

佐久間龍太、助川明香、武内寛明、山岡昇司

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武内寛明、佐久間龍太、山岡昇司

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アカゲザル TRIM5α(RhT5α)による HIV-1 の感染・産生阻害に重要な宿主因子の探索

鹿間さおり、助川明香、佐久間龍太、山岡昇司

日本エイズ学会　平成 23 年 12 月 1 日　（東京）

アカゲザル TRIM5α (RhT5α)による HIV-1 産生阻害活性の細胞特異性における SOCS1 の役割

助川明香、佐久間龍太、大嶺青河、池田靖弘、山岡昇司

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Involvement of Actin Binding Protein Coronin 1C in HIV-1 Replication and Rhesus Macaque TRIM5α-Mediated Restriction

Saori Shikama, Ryuta Sakuma, Sayaka Sukegawa, Shoji Yamaoka

IUMS2011　平成 23 年 9 月 14 日　（北海道）

Suppressor of Cytokine Signaling 1 is a Possible Cause of the Cell Line Dependency of the Rhesus Macaque TRIM5α-Mediated Late Restriction

Sayaka Sukegawa, Ryuta Sakuma, Seiga Ohmine, Yasuhiro Ikeda, Shoji Yamaoka

IUMS2011　平成 23 年 9 月 13 日　（北海道）

The Role of Suppressor of Cytokine Signaling 1 in Rhesus Macaque

TRIM5a-Mediated Late Restriction and its Cell Line Dependency
Ryuta Sakuma, Sayaka Sukegawa, Seiga Ohmine, Yasuhiro Ikeda and Shoji Yamaoka
CSH Retrovirus meeting 平成23年5月26日 (NY, USA)

無し

アカゲザルTRIM5α(RhT5α)によるHIV-1産生阻害に対するSOCS1タンパク質の影響
助川明香、佐久間龍太、大嶺青河、池田靖弘、山岡昇司 (演題番号:O2-2-07)
平成22年11月8日

3. その他
Retroviral Host Cell Factors: TRIM5, APOBEC3G and Cyclophilins
Ryuta Sakuma and Hiroaki Takeuchi
HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies, ISBN: 978-953-307-665-2

H. 知的財産権の出願・登録状況
1. 特許取得
現在、特許等を申請できる状況には無いが、新規宿主因子の探査であり、研究計画実施中に頂いた審査時の審査員の助言に従い、特許取得が可能な状態を維持する形での慎重な研究活動・成果報告を心がけたい。

2. 実用新案
無し
3. その他

III. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Ryuta Sakuma and Hiroaki Takeuchi	Retroviral Host Cell Factors: TRIM5, APOBEC3G and Cyclophilins	Nancy Dumais	HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies	InTech	Croatia	2011	183-192

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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SIV replication in human cells

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Current human immunodeficiency virus type 1 pandemic is believed to originate from cross-species transmission of simian immunodeficiency virus (SIV) into human population. Such cross-species transmission, however, is not efficient in general, because viral replication is modulated by host cell factors, with the species-specificity of these factors affecting viral tropism. An understanding of those host cell factors that affect viral replication contributes to elucidation of the mechanism for determination of viral tropism. This review will focus an anti-viral effect of ApoB mRNA editing catalytic subunit, tripartite motif protein 5 alpha, and cyclophilins on SIV replication and provide insight into the mechanism of species-specific barriers against viral infection in human cells. It will then present our current understanding of the mechanism that may explain zoonotic transmission of retroviruses.

Keywords: HIV-1, SIV, APOBEC3G, TRIM5α, cyclophilin A, cyclophilin B

INTRODUCTION

There is significant evidence that the ongoing worldwide acquired immunodeficiency syndrome (AIDS) epidemic was caused by cross-species transmission of simian immunodeficiency viruses (SIVs) into the human population. Replication of primate lentiviruses in their natural hosts is generally non-pathogenic; however, cross-species transmission of these viruses can result in highly pathogenic phenotypes. How and when this transmission occurred is still debated but it is now generally accepted that HIV-2 originated from a sooty mangabeys strain of SIV (SIVsm; Hirsch et al., 1989; Chen et al., 1996) while HIV-1 appears to have originated from a chimpanzee strain of SIV (SIVcpz; Gao et al., 1999). Zoonotic transmission of SIVs, however, is not common and is controlled by host factors that generally prohibit SIV replication in human hosts and many human-derived cell lines.

Viral replication is modulated by host cell factors, with the species-specificity of these factors affecting viral tropism. Some of these host factors can restrict viral replication and the anti-viral systems mediated by such host restriction factors, termed intrinsic immunity, play an important role in determining species-specific barriers against viral infection. For instance, Fv-1 in mice is known to restrict replication of a murine leukemia virus (Rein et al., 1976; Gautsch et al., 1978; Towers et al., 2000) and tripartite interaction motif 5α (TRIM5α) recently has been found to be responsible for restricting HIV-1 but not SIV infection in Old World monkey (OWM) cells (Hatziioannou et al., 2004b; Keckesova et al., 2004; Stremlau et al., 2004; Yap et al., 2004; Song et al., 2005; Ylinen et al., 2005). Restriction of retroviral replication by these host cell factors takes place after viral entry, but before the integration step, and the viral determinants for this type of restriction have been mapped to the capsid (CA) protein (Gautsch et al., 1978; Kozak and Chakraborti, 1996; Towers et al., 2000; Goff, 2004; Stremlau et al., 2006). Two recent studies showed that the cellular protein SAMHD1 is myeloid-lineage cell-specific HIV-1 restriction factor counteracted by Vpx proteins from HIV-2 and SIVsm (Hrecka et al., 2011; Laguette et al., 2011). Restriction of lentivirus infection by SAMHD1 is likely to take place at the reverse transcription step. Another anti-retroviral protein, tetherin (also referred to as BST-2, CD317, or HM1.24) inhibits retrovirus release and is antagonized by HIV-1 Vpu protein, Nef protein of many SIVs, or Env protein of HIV-2 (Neil et al., 2008; Le Tortorec and Neil, 2009; Zhang et al., 2009). Understanding how host cell factors affect viral replication, positively or negatively, would contribute to elucidating the molecular mechanism that determines viral tropism. Here, we discuss an anti-viral effect of ApoB mRNA editing catalytic subunit (APOBEC), TRIM5α, and cyclophilins (Cyps) on SIV replication.

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 the HIV-1 accessory gene product, Vif (standing 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; Fan and Peden, 1992; Gabuzda et al., 1992; Blanc et al., 1993; Sakai et al., 1993; von Schwedler et al., 1993; Borman et al., 1995). Recently, some cytidine deaminases were identified as a new class of host restriction factors that target retroviruses such as HIV-1 or SIV (Harris and Liddament, 2004; Cullen, 2006). 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. Apo3G is also a host factor that restricts replication of human and simian lentiviruses in their respective target cells. Unlike TRIM5α or Fv-1, Apo3G does not exert its anti-viral activity by targeting the viral CA 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 a subsequent infection step. HIV-1 counteracts Apo3G with Vif expression. During the production of progeny virions, Vif binds to Apo3G and induces Apo3G's proteasomal degradation, resulting in the decreased steady-state levels of human Apo3G (hApo3G; Yu et al., 2003).

There are several anti-retroviral mechanisms of Apo3G against HIV-1 infection. First, Apo3G-containing virus can accumulate in a large number of substitutions that register as cytidine (C) to deoxyuridine (dU) 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 hypermutation" (Harris et al., 2003; Lecossier et al., 2003; Mangeat et al., 2003; Mariani et al., 2003; Zhang et al., 2003; Yu et al., 2004b). Second, Apo3G can inhibit tRNA annealing or tRNA processing during reverse transcription (Guo et al., 2006, 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 anti-retroviral activity of APOBEC family because APOBEC proteins from non-human species can also inhibit HIV-1 infection (Mariani et al., 2003; Bishop et al., 2004a,b; Wiegand et al., 2004; Cullen, 2006), the Vif-Apo3G interaction is thought to be species-specific (Simon et al., 1998; Mariani et al., 2003). 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 (Mariani et al., 2003; Bogerd et al., 2004; Mangeat et al., 2004; 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 (Takeuchi et al., 2005). 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).

Moreover, two independent groups showed that the different APOBEC3 family members function to neutralize specific lentiviruses (Yu et al., 2004a; Dang et al., 2006). One report from the lab of Dr. Nathaniel R. Landau showed that APOBEC3B and APOBEC3C were potent inhibitors of SIV (Yu et al., 2004a). Both enzymes were efficiently encapsidated by HIV-1 and SIV. Another report from the lab of Dr. Yong-Hui Zheng demonstrated that APOBEC3DE blocked the replication of both HIV-1 and SIV but not that of MLV (Dang et al., 2006) and APOBEC3H inhibited the replication of HIV-1 by a cytidine deamination-independent mechanism (Dang et al., 2008). These findings raise the possibility that the various APOBEC3 family members protect against different lentiviruses and point to a possible role in the zoonotic transmission of SIV.

TRIM5α: FV-1-TYPE HOST FACTOR RESTRICTING HIV-1 IN PRIMATE CELLS

The host protein which dictates Ref1 activity was identified as an α-isoform of rhesus macaque TRIM5 protein by the laboratory of Dr. Joseph Sodroski (Stremlau et al., 2004). TRIM5 is a member of the 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 primate homologs of TRIM5α were shown to restrict retroviruses, such as N-MLV, and equine infectious anemia virus (Hatziioannou et al., 2004b; Keckesova et al., 2004; Perron et al., 2004; Yap et al., 2004; Song et al., 2005; Ylinen et al., 2005; Si et al., 2006). Rhesus monkey TRIM5α (rhTRIM5α) has strong anti-HIV-1 activity but only modestly restricts SIV isolated from a macaque monkey (SIVmac) and does not block MLV infection, whereas its human homolog does not restrict HIV-1 infection.

TRIM5α recognizes incoming viral cores, but not a monomeric CA protein, thorough its B30.2 (PRYSPRY) domain. B-box 2 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 the core into cytoplasm. To restrict HIV-1 infection and to recognize viral core, TRIM5α must oligomerize through its B-box 2 and coiled-coil domains (Mische et al., 2005; Li and Sodroski, 2008). Its RING domain has E3 ubiquitin ligase activity. It self-ubiquitination occurs TRIM5α is quickly degraded (Diaz-Griffero et al., 2006). This rapid degradation of TRIM5α is not required for post-entry restriction since replacement of TRIM5α RING domain with the corresponding domain of TRIM21, which has lower self-ubiquitination activity and a longer half-life than TRIM5α did not alter the anti-viral activity (Kar et al., 2008). Recently, the laboratory of Dr. Mark Yeager discussed a novel architecture made with dimers of TRIM5-21R. TRIM5α-21R forms a dimer through its B-box 2 and coiled-coil domains, and these dimers form six-sided rings on CA lattices to promote rapid core disassembly (Ganser-Pornillos et al., 2011). Overexpression of TRIM5α leads to the formation of cytoplasmic bodies and is believed to be required for its anti-viral activity (Stremlau et al., 2006; Campbell et al., 2008). During TRIM5α-mediated post-entry restriction, disassembly of viral cores is induced too quickly and the accumulation of viral RT-products is reduced (Stremlau et al., 2006). On the other hand, MG132 treatment inhibited quick-disassembly, yet HIV-1 infectivity was still 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 rapid 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. Previous report showed that TRIM5α alleles did not cluster by species between rhesus macaques and sooty mangabeys and none of the alleles from either species restricted SIV, suggesting that there is little effect of rhTRIM5α on transmission of SIVsm within species (Newman et al., 2006). Recently, Pacheco et al. (2010) reported that New World monkey (NWM) TRIM5α restricts foamy virus infection. Another consideration is the clinical significance of TRIM5α against 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 (van Manen et al., 2008; Cagliani et al., 2010; Takeuchi et al., 2012). Thus, TRIM5α-mediated restriction may be a multi-step process 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 ubiquitin–proteasome-independent manner. This TRIM5α-mediated late-restriction is still controversial (Zhang et al., 2008), yet it is conceivable that TRIM5α restricts HIV-1 infection and production in two distinct mechanisms. Although TRIM5α restricts HIV-1 infection in a broad range of cells, its late restriction involved transient overexpression (Sakuma et al., 2007).

Here is another notable class of the TRIM family called TRIM-Cyp isolated from NWM. A report from the laboratory of Dr. Jeremy Luban demonstrated that owl monkey cells express TRIM-Cyp that restricts HIV-1 infection (Sayah et al., 2004). Although TRIM-Cyp has a cyclophilin A (CypA) 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 overexpressed rhesus TRIM-Cyp restricts HIV-1 infection and production (Newman et al., 2006; Brennan et al., 2008; Wilson et al., 2008; Dietrich et al., 2010).

Unlike other restriction factors, there is no known accessory gene product of HIV-1 to antagonize TRIM5α-mediated restrictions. Indeed, human TRIM5α has only a modest restriction activity against HIV-1 infection. TRIM5 proteins from several NWM species restrict infection by SIVmac and SIVagm (Song et al., 2005). This suggests that TRIM5α could be a key molecule of the species-species barrier.

CYCLOPHILINS: HOST FACTORS INVOLVED IN RETROVIRUS REPLICATION

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 CsA to CypA inhibits this isomerase activity (Takahashi et al., 1989). In retrovirus replication, CypA was found to bind HIV-1 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 (Zhao et al., 1997; Bosco et al., 2002), 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 *cis–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 remains unclear.

It has been well established that CypA promotes an early step of HIV-1 infection in human cells (Franke et al., 1994; Thali et al., 1994; Braaten et al., 1996a,c; Franke and Luban, 1996; Braaten and Luban, 2001; Sokolskaja et al., 2004; Hatziioannou et al., 2005). 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 (Franke et al., 1994; Thali et al., 1994; Ott et al., 1995; Braaten et al., 1996a; Bukovsky et al., 1997; Ackerson et al., 1998; Braaten and Luban, 2001). It is still unclear how CypA is efficiently packaged into HIV-1 virion, but several reports showed that both dimerization of CA and multimerization of CypA are required for efficient interaction (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 infected target cells rather than during HIV-1 budding from the virion producer cells, indicating that target cell CypA promotes HIV-1 infectivity (Kootstra et al., 2003; Towers et al., 2003; Sokolskaja et al., 2004).

CypA-dependent virus replication is only limited to retroviruses which encode CA that binds CypA. In fact, only those retroviruses are dependent upon CypA for replication (Luban et al., 1993; Franke et al., 1994; Thali et al., 1994; Braaten et al., 1996c; Franke and Luban, 1996). These observations suggested that CA–CypA interaction might contribute tropism determinants for retroviruses. HIV-1 infection in non-human primate cells is blocked prior to reverse transcription after virus entry (Shibata et al., 1995; Himathongkham and Luciw, 1996; Hofmann et al., 1999; Besnier et al., 2002; Cowan et al., 2002; Munk et al., 2002; Hatziioannou et al., 2003; 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 (Shibata et al., 1991, 1995; Dorfman and Gottlinger, 1996; Bukovsky et al., 1997;

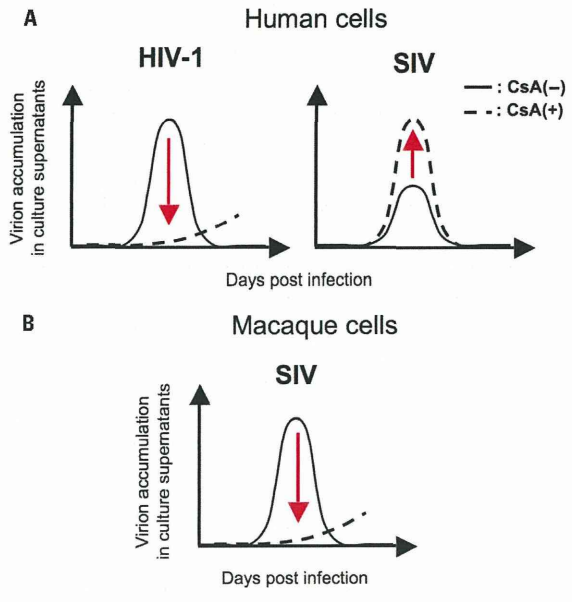

FIGURE 1 | A schema for the effect of CsA on HIV/SIV replication in human/macaque cells. (A) CsA treatment impairs the replication of HIV-1 (left panel) but enhances SIV replication (right panel) in human cells. **(B)** CsA treatment inhibits SIV replication in macaque cells. The solid line indicates virion accumulation of culture supernatant in the absence of CsA and the broken line indicates that of culture supernatant in the presence of CsA.

Cowan et al., 2002; Kootstra et al., 2003; Owens et al., 2003, 2004; Towers et al., 2003; Berthoux et al., 2004; Hatziioannou et al., 2004a, 2006; Ikeda et al., 2004; Sayah et al., 2004; Stremlau et al., 2004; Kamada et al., 2006).

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 the infection of two SIVs (SIVmac and SIVagm) in human cells, and Vif protein of two SIVs counteracts a CypA-imposed inhibition against the infection of two SIV strains with exclusion of CypA from SIV virion (Takeuchi et al., 2007). This phenomenon is different from the function of SIVagm Vif against hApo3G previously reported from the same laboratory (Takeuchi et al., 2005) because they used human cells lacking detectable deaminase activity.

Moreover, a recent report showed a species-specific effect of CsA, a peptidyl-prolyl *cis–trans* isomerase (PPIase) inhibitor, on SIV replication, implying a possible contribution of Cyps to the determination of SIV tropism (**Figure 1**; Takeuchi et al., 2012). They demonstrated a host species-specific effect of CypA on SIV replication: CypA affects the replication of two SIVs (SIVmac and SIVagm) negatively in human cells but positively in macaque cells (**Figure 1**). Further analysis indicated that the infection of two SIVs was not significantly affected by CypA but inhibited by cyclophilin B (CypB), another PPIase, in human cells (**Figure 2A**; Takeuchi et al., 2012). In contrast, CypA is likely to have positive

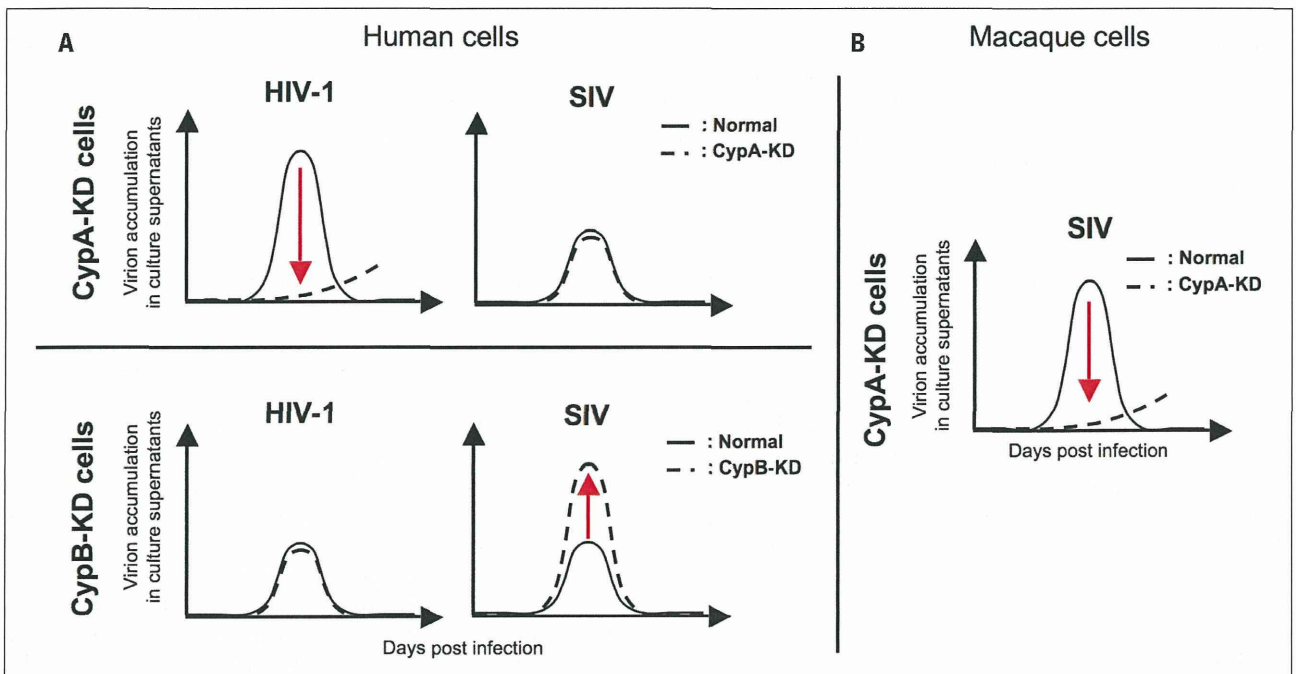

FIGURE 2 | A schema for the effect of cyclophilin A and cyclophilin B on HIV/SIV replication in human/macaque cells. (A) CypA knock-down (CypA-KD) impairs the replication of HIV-1 (upper left panel). In contrast, SIV replication is not reduced but rather enhanced by CypA knock-down (upper right panel). CypB knock-down (CypB-KD) shows no significant effect on HIV-1 replication (lower left panel) but enhances the replication of SIV (lower right panel). **(B)** CypA-KD inhibits SIV infection. The solid line indicates virion accumulation of culture supernatant produced from normal cells and the broken line indicates that of culture supernatant produced from CypA or CypB knock-down cells.

effects on the infection of two SIVs in macaque cells (**Figure 2B**; Takeuchi et al., 2012). These results suggest that Cyps might have a host species-specific effect of Cyps on SIV replication and provide insight into the mechanism of species-specific barriers against viral infection.

CONCLUDING REMARKS

Viral replication is modulated by host cell factors. Many of these factors function in a species-specific manner. On the other hand, there exist host factors that restrict viral replication. The antiviral 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 review, 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 a host species-specific effect of Cyps including CypA and CypB on SIV replication. Such restriction factors would play an important role in determining species-specific barriers against viral infection.

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7

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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