[5] J.E. Schmitz, M.J. Kuroda, S. Santra, V.G. Sasseville, M.A. Simon, M.A. Lifton, P. Racz, K. Tenner-Racz, M. Dalesandro, B.J. Scallon, J. Ghrayeb, M.A. Forman, D.C. Montefiori, E.P. Rieber, N.L. Letvin, K.A. Reimann, Control of viremia in simian immunodeficiency virus infection by $CD8^+$ lymphocytes, Science 283 (1999) 857–860.
[6] A.J. McMichael, T. Hanke, HIV vaccines 1983–2003, Nat. Med. 9 (2003) 874–880.
[7] S.M. Sumida, D.M. Truitt, A.A.C. Lemckert, R. Vogels, J.H.H.V. Custers, M.M. Addo, S. Lockman, T. Peter, F.W. Peyerl, M.G. Kishko, S.S. Jackson, D.A. Gorgone, M.A. Lifton, M. Essex, B.D. Walker, J. Goudsmit, M.J.E. Havenga, D.H. Barouch, Neutralizing antibodies to adenovirus serotype 5 vaccine vectors are directed primarily against the adenovirus hexon protein, J. Immunol. 174 (2005) 7179–7185.
[8] A.T. Catanzaro, R.A. Koup, M. Roederer, R.T. Bailer, M.E. Enama, Z. Moodie, L. Gu, J.E. Martin, L. Novik, B.K. Chakrabarti, B.T. Butman, J.G. Gall, C.R. King, C.A. Andrews, R. Sheets, P.L. Gomez, J.R. Mascola, G.J. Nabel, B.S. Graham, Phase 1 safety and immunogenicity evaluation of a multiclade HIV-1 candidate vaccine delivered by a replication-defective recombinant adenovirus vector, J. Infect. Dis. 194 (2006) 1638–1649.
[9] F.H. Priddy, D. Brown, J. Kublin, K. Monahan, D.P. Wright, J. Lalezari, S. Santiago, M. Marmor, M. Lally, R.M. Novak, S.J. Brown, P. Kulkarni, S.A. Dubey, L.S. Kierstead, D.R. Casimiro, R. Mogg, M.J. Dinubile, J.W. Shiver, R.Y. Leavitt, M.N. Robertson, D.V. Mehrotra, E. Quirk, Safety and immunogenicity of a replication-incompetent adenovirus type 5 HIV-1 clade B gag/pol/nef vaccine in healthy adults, Clin. Infect. Dis (2008). Epub ahead of print.
[10] T. Matano, M. Kano, H. Nakamura, A. Takeda, Y. Nagai, Rapid appearance of secondary immune responses and protection from acute CD4 depletion after a highly pathogenic immunodeficiency virus challenge in macaques vaccinated with a DNA prime/Sendai virus vector boost regimen, J. Virol. 75 (2001) 11891–11896.
[11] M. Kano, T. Matano, A. Kato, H. Nakamura, A. Takeda, Y. Suzaki, Y. Ami, K. Terao, Y. Nagai, Primary replication of a recombinant Sendai virus vector in macaques, J. Gen. Virol. 83 (2002) 1377–1386.
[12] T. Matano, M. Kobayashi, H. Igarashi, A. Takeda, H. Nakamura, M. Kano, C. Sugimoto, K. Mori, A. Iida, T. Hirata, M. Hasegawa, T. Yuasa, M. Miyazawa, Y. Takahashi, M. Yasunami, A. Kimura, D.H. O'Connor, D.I. Watkins, Y. Nagai, Cytotoxic T lymphocyte-based control of simian immunodeficiency virus replication in a preclinical AIDS vaccine trial, J. Exp. Med. 199 (2004) 1709–1718.
[13] Y. Nagai, Paramyxovirus replication and pathogenesis. Reverse genetics transforms understanding, Rev. Med. Virol. 9 (1999) 83–99.
[14] M.H. Skiadopoulos, S.R. Surman, J.M. Riggs, W.R. Elkins, M. St Claire, M. Nishio, D. Garcin, D. Kolakofsky, P.L. Collins, B.R. Murphy, Sendai virus, a murine parainfluenza virus type 1, replicates to a level similar to human PIV1 in the upper and lower respiratory tract of African green monkeys and chimpanzees, Virology 297 (2002) 153–160.
[15] M. Kato, H. Igarashi, A. Takeda, Y. Sasaki, H. Nakamura, M. Kano, T. Sata, A. Iida, M. Hasegawa, S. Horie, E. Higashihara, Y. Nagai, T. Matano, Induction of Gag-specific T-cell responses by therapeutic immunization with a Gag-expressing Sendai virus vector in macaques chronically infected with simian-human immunodeficiency virus, Vaccine 23 (2005) 3166–3173.
[16] T. Matano, M. Kano, T. Odawara, H. Nakamura, A. Takeda, K. Mori, T. Sato, Y. Nagai, Induction of protective immunity against pathogenic simian immunodeficiency virus by a foreign receptor-dependent replication of an engineered avirulent virus, Vaccine 18 (2000) 3310–3318.
[17] A. Kato, K. Kiyotani, Y. Sakai, T. Yoshida, Y. Nagai, The paramyxovirus, Sendai virus, V protein encodes a luxury function required for viral pathogenesis, EMBO J. 16 (1997) 578–587.
[18] T. Matano, M. Kano, A. Takeda, H. Nakamura, N. Nomura, Y. Furuta, T. Shioda, Y. Nagai, No significant enhancement of protection by Tat-expressing Sendai viral vector-booster in a macaque AIDS model, AIDS 17 (2003) 1392–1394.
[19] H.O. Li, Y.F. Zhu, M. Asakawa, H. Kuma, T. Hirata, Y. Ueda, Y.S. Lee, M. Fukumura, A. Iida, A. Kato, Y. Nagai, M. Hasegawa, A cytoplasmic RNA vector derived from nontransmissible Sendai virus with efficient gene transfer and expression, J. Virol. 74 (2000) 6564–6569.
[20] M. Yoshizaki, T. Hironaka, H. Iwasaki, H. Ban, Y. Tokusumi, A. Iida, Y. Nagai, M. Hasegawa, M. Inoue, Naked Sendai virus vector lacking all of the envelope-related genes: reduced cytopathogenicity and immunogenicity, J. Gene. Med. 8 (2006) 1151–1159.
[21] K.S. Slobod, J.L. Shenep, J. Lujan-Zilbermann, K. Allison, B. Brown, R.A. Scroggs, A. Portner, C. Coleclough, J.L. Hurwitz, Safety and immunogenicity of intranasal murine parainfluenza virus type 1 (Sendai virus) in healthy human adults, Vaccine 22 (2004) 3182–3186.

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REVIEW

Host factors involved in resistance to retroviral infection

Hiroaki Takeuchi and Tetsuro Matano

International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan

ABSTRACT

Viral replication requires the help 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, which is termed intrinsic immunity and is distinguished from conventional innate and adaptive immunity, has been described as playing an important role in making species-specific barriers against viral infection. Here, we describe the current progress in understanding of such restriction factors against retroviral replication, focusing on TRIM5α and APOBEC, whose anti-retroviral effects have recently been recognized. Additionally, we mention cyclophilin A, which 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.

Key words apolipoprotein B mRNA-editing enzyme-catalytic subunit, cyclophilin A, retrovirus, tripartite interaction motif 5 α.

Among host factors exerting inhibitory effects on viral replication, the *Fv-1* and the *Fv-4* loci have been known to confer resistance to Friend virus infection in mice and their restriction mechanisms have been intensively investigated (1–5). The latter, *Fv-4*, corresponds to a defective endogenous provirus with an ecotropic MLV-like *env* gene. Entry of ecotropic MLV into cells expressing *Fv-4* is inhibited by binding of the *Fv-4 env* gene product, Fv-4 Env, to the ecotropic MLV receptor, and this receptor interference has been reported to play a central role in resistance to Friend virus infection (6). Additionally, it has recently been suggested that the Fv-4 Env-mediated dominant negative effect on MLV Env function contributes to efficient resistance in *Fv-4*-expressing mice (7). On the other hand, MLV restriction mediated by the *Fv-1* gene product, Fv-1, occurs after viral entry into the cells but before the integration step during the viral replication cycle (8). The two main alleles of *Fv-1*, *Fv-1*^{n} and *Fv-1*^{b}, confer resistance to replication of B-tropic and N-tropic MLV respectively (9). Although the precise mechanism of Fv-1-mediated restriction remains unclear, comparison of viral genome sequences between B-tropic and N-tropic MLV has indicated the 110th amino acid in Gag CA as the viral determinant for the tropism, suggesting that MLV Gag CA is the target for the host factor involved in this restriction (10, 11).

Ref-1, which shows a similar pattern of inhibition of retroviral replication with Fv-1, is known as a restriction factor in mammalian cells apart from murine cells. The viral determinant for Ref-1-mediated restriction has been

Correspondence
Hiroaki Takeuchi and Tetsuro Matano, International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
Tel: +81 3 6409 2078; Fax: +81 3 6409 2076; email: htake@ims.u-tokyo.ac.jp and matano@m.u-tokyo.ac.jp

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List of Abbreviations: A, adenine; agmApo3G, African green monkey Apo3G; Ala, alanine; Apo3G, APOBEC3G; APOBEC, apolipoprotein B mRNA-editing enzyme-catalytic subunit; CA, capsid; CypA, cyclophilin A; CsA, cyclosporine A; G, guanine; Gly, glycine; hApo3G, human Apo3G; HIV-1, human immunodeficiency virus type 1; Ile, isoleucine; Lv-1, lentivirus susceptibility factor 1; MLV, murine leukemia virus; OWM, old world monkey; Pro, proline; Ref-1, restriction factor 1; SIVagm, African green monkey simian immunodeficiency virus; SIVmac, simian immunodeficiency virus mac; TRIM5, tripartite interaction motif 5; TRIM5α, tripartite interaction motif 5 α; Vif, virus infectivity factor.

reported to be at the Gag CA residue, corresponding to the 110th in MLV Gag CA involved in Fv-1-mediated restriction (12). Ref-1 and Fv-1 both show viral restriction post-viral entry in the early phase of the retroviral replication cycle, but the exact point of restriction has been indicated to be different: the former, Ref-1-mediated restriction, occurs at the step prior to reverse transcription, while the latter, Fv-1 mediated restriction, is considered to occur post-reverse transcription (8). Further, restriction of HIV-1 replication post-viral entry has been reported in OWM cells that support efficient replication of SIVmac, and the existence of a restriction factor, Lv-1, responsible for this resistance of non-human primate cells to HIV-1 replication has been suggested (13–15).

TRIM5α: A HOST FACTOR RESTRICTING HIV-1 REPLICATION POST-VIRAL ENTRY IN PRIMATE CELLS

Recently, two independent groups have identified the α-isoform of TRIM5, TRIM5α, as a restriction factor responsible for resistance of monkey cells to HIV-1 infection and shown that restriction of HIV-1 replication by TRIM5α derived from rhesus and owl monkeys but not efficiently from humans (16, 17) (Fig. 1). Subsequent studies have revealed virus-specific restriction activities by TRIM5α and its homologues derived from humans and non-human primates (18–24). For instance, restriction by rhesus monkey TRIM5α is efficient against HIV-1 but inefficient against SIVmac and undetectable against MLV (Fig. 1).

TRIM5α is a trimeric cytoplasmic protein (25, 26) consisting of RING finger, B-box, coiled-coil, and SPRY (B30.2) domains (27, 28). The coiled-coil domain is indispensable for TRIM5α multimerization, and both the coiled-coil and the SPRY domains are required for its binding to the virion core (28, 29).

TRIM5α-midiated restriction of HIV-1 replication is considered to occur after viral entry in the early phase of the viral replication cycle, but its precise mechanism remains unclear and several possibilities have been proposed. First, it has been suggested that binding of TRIM5α to the virion CA after viral entry may accelerate or abrogate the process of its uncoating and disruption, resulting in inhibition of HIV-1 replication (29). Second, involvement of ubiquitin in TRIM5α-mediated restriction has been suggested by recent reports showing that a mutation in its RING finger domain decreases the restriction ability of TRIM5α (16, 30–32) and that recovery from the restriction occurs in the presence of proteosome inhibitors (32, 33), although this is controversial (29, 31, 32). Furthermore, some reports have shown TRIM5α-mediated

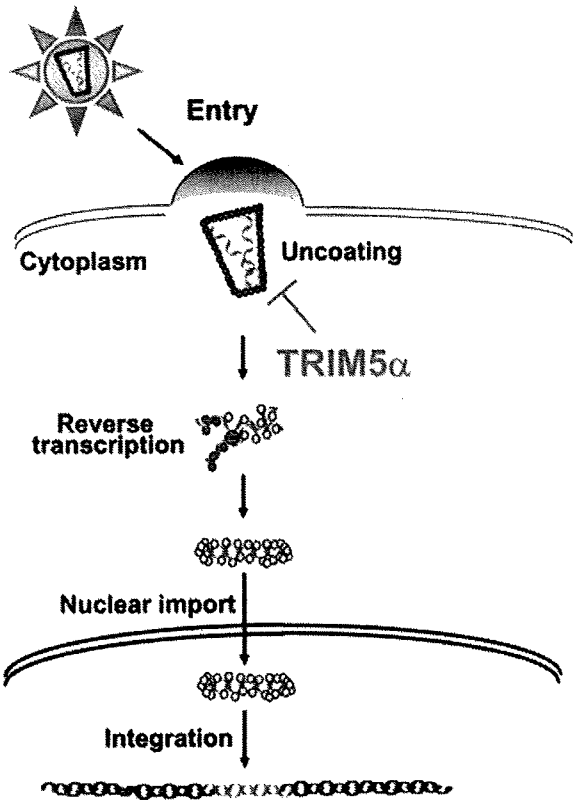

Fig. 1. A schema for TRIM5α-mediated restriction of HIV-1 replication in OWM cells. Recognition of HIV-1 CA by TRIM5α results in restriction of HIV-1 replication at the step after viral entry into the cytoplasm.

inhibition of viral cDNA nuclear import as well as viral cDNA synthesis (34, 35). In addition to restriction at the early phase of retroviral replication cycle, TRIM5α has recently been shown to inhibit virus production by accelerating degradation of viral Gag protein (36).

APOBEC: AN ENZYMATIC HOST FACTOR RESTRICTING RETROVIRAL REPLICATION

HIV-1 replication in primary CD4$^+$ T lymphocytes and monocytes is dependent on the presence of an HIV-1 accessory protein, Vif, which has been reported to work in a host cell-specific manner (37, 38). Vif is required for infectious HIV-1 production from some immortalized human T cell lines such as CEM (termed non-permissive) but not in others such as CEM-SS (termed permissive), and the existence of a restriction factor whose anti-retroviral activity can be abrogated by Vif has been suggested in the case of the non-permissive cells (39–45). Comparison of the non-permissive and permissive cells has

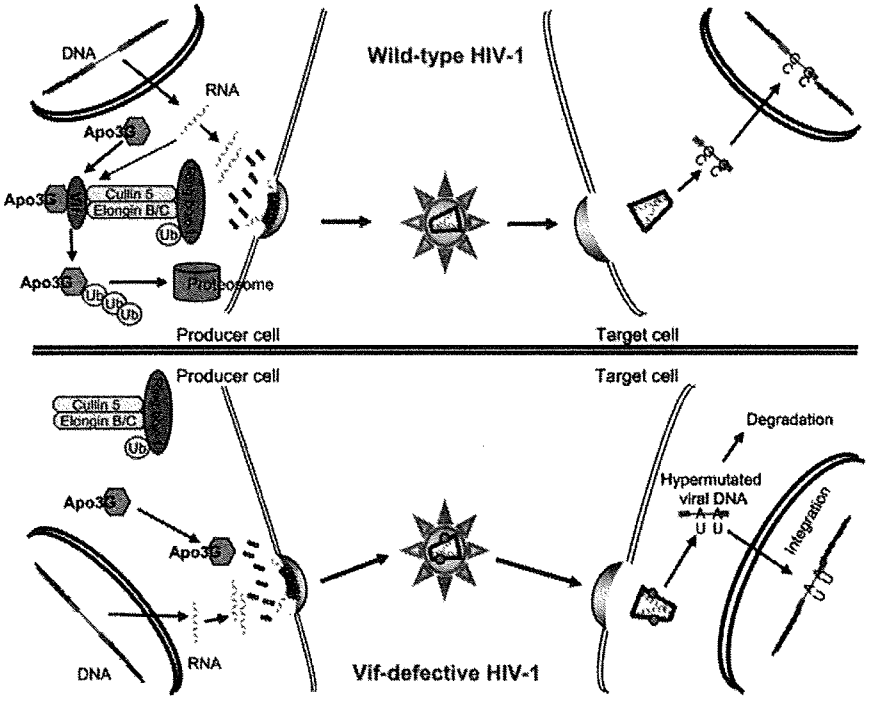

Fig. 2. A putative model for APOBEC3G-mediated restriction of HIV-1 replication and Vif-mediated recovery from the restriction. In the wild-type HIV-1 replication (upper panel), Vif connects hApo3G to an E3 ubiquitin ligase complex including Elongin B/C, Cullin5, and Ring-box-1 to induce polyubiquitylation and proteosomal degradation of hApo3G, resulting in exclusion of hApo3G from the virion with viral genome remaining intact even after viral entry. In contrast, in *vif*-deleted HIV-1 replication (lower panel), hApo3G is incorporated into the virion and its replication ability is abrogated after viral entry into the cells. Thereafter, these C-to-U mutations in the viral minus-strand DNA result in G-to-A mutations in the complementary plus-strand DNA during reverse transcription.

revealed Apo3G, a member of the APOBEC family of cytidine deaminases, to be the restriction factor responsible for inhibition of *vif*-deleted HIV-1 replication in human non-permissive cells (46). Unlike TRIM5α and Fv-1, the target of Apo3G-mediated restriction is not viral CA, but viral single-stranded cDNA synthesized during reverse transcription. It is packaged into virus particles produced from Apo3G-expressing cells and inhibits viral replication after viral entry into the cells (Fig. 2). HIV-1 Vif can inhibit the uptake of Apo3G into the virion by inducing polyubiquitylation and proteosomal degradation of cellular Apo3G, resulting in abrogation of Apo3G-mediated restriction (47) (Fig. 2).

Several mechanisms for Apo3G-mediated restriction against HIV-1 infection have been reported. First, it has been reported that the cytidine deaminase activity of Apo3G can induce hypermutation (a large number of G-to-A substitutions) in proviral DNA during reverse transcription, resulting in failure of infectious HIV-1 production (48–53) (Fig. 2). Second, the possibility of Apo3G-mediated inhibition of tRNA annealing or processing during reverse transcription has been shown (54–56). Additional mechanisms, including inhibition at the step of viral plus-strand cDNA transfer, have also been suggested (56–58).

Restriction of retroviral infection by Apo3G derived from non-human species has also been reported (51, 59–62), and the Vif-Apo3G interaction is considered to be species-specific (51, 63). Indeed, it has been indicated that hApo3G is insensitive to SIVagm Vif while agmApo3G is insensitive to HIV-1 Vif, and that the determinant for this specificity is at the 128th residue in Apo3G (51, 64–67). However, a recent report has shown that SIVagm Vif can support SIVagm replication in an hApo3G-positive human T cell line (A3.01): *vif*-deleted SIVagm replication was severely restricted with accumulation of G-to-A mutations in the viral genome, suggesting ambiguity of species specificity (68).

Restriction of HIV-1 and SIV replication by other members of the APOBEC family has been reported, although it might not be as efficient as Apo3G. Thus, APOBEC proteins are now considered to be a new class of host restriction factors against retroviral replication (61, 69). For instance, human APOBEC3F can inhibit HIV-1 replication in the absence of Vif (59, 60, 70, 71) whereas human APOBEC3B does so even in the presence of

Vif (59, 72, 73). Association of deaminase activity with Apo3G-mediated restriction of HIV-1 replication has been strongly suspected, but the possibility of involvement of deaminase activity-independent mechanisms in this restriction has also been suggested (57, 58). Indeed, several groups have reported Apo3G and APOBEC3F variants lacking in deaminase activity without loss of restriction activity, as well as variants lacking in restriction activity without loss of deaminase activity (74–77). Additionally, a recent report has suggested a deaminase-independent inhibitory effect of Apo3G on viral DNA synthesis following reverse transcription (78). However, this possibility is controversial (79, 80), and the precise mechanism for Apo3G-mediated restriction of HIV-1 infection remains unclear.

CYCLOPHILIN A: A HOST FACTOR INVOLVED IN RETROVIRAL REPLICATION

CypA, a ubiquitous protein, was first identified as the target of CsA, an immunosuppressive reagent (81). CypA has proline-isomerase activity that catalyzes *cis-trans* isomerization of the Pro residue (82, 83). CsA binding to CypA inhibits this isomerase activity (83). CypA binding to HIV-1 Gag CA has been shown by analysis using the yeast two-hybrid system (84). The Ala-Gly-Pro-Ile residues from the 88th to the 91st in CA are the key portion for its binding to the active site of CypA (85–87). Interestingly, the peptidyl-prolyl bond between the 89th Gly (Gly89) and the 90th Pro (Pro90) exhibits the *trans* conformation, (in contrast to the *cis* conformation usually observed in other known CypA targets) (87, 88), and this Pro90 residue but not other Pro is considered to be critical for the binding of CA to CypA. Thus, it has been suggested that CypA acts as a molecular chaperone without exerting *cis-trans* isomerase activity on HIV-1 CA (87). However, this is still controversial and the possibility of CypA-mediated *cis-trans* isomerization of the Gly89-Pro90 peptidyl-prolyl bond has also been suggested (88).

It has been well established that CypA promotes HIV-1 replication after viral entry in the early phase in human cells (85, 89–95) (Fig. 3). CypA is efficiently incorporated into the virion produced from HIV-1-infected cells through interaction with CA in the context of Gag polyprotein (Fig. 3). Disruption of CypA incorporation

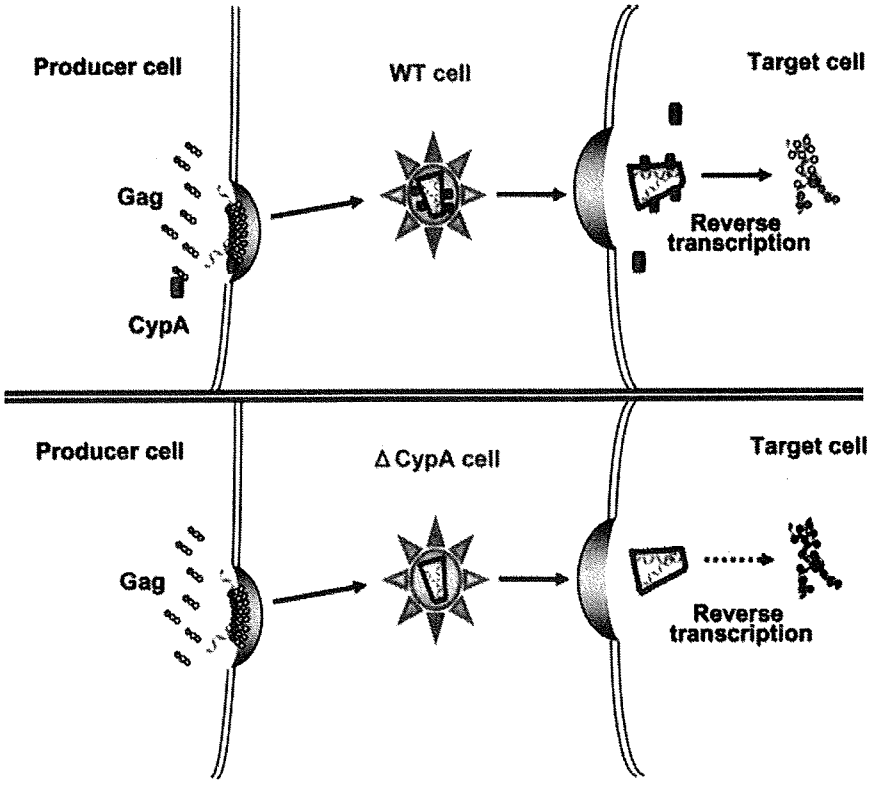

Fig. 3. A putative mechanism for CypA-mediated enhancement of HIV-1 replication. CypA is required for efficient reverse transcription (upper panel), and HIV-1 infection in CypA-deficient human cells shows inefficient reverse transcription (lower panel).

into the virion by CsA administration or by Gag mutations resulted in reduction in infectivity of the produced viruses (85, 89, 91, 95–98). Several reports have shown that both CA dimerization and CypA multimerization are required for the efficient CA-CypA binding which is critical for HIV-1 infectivity (99, 100). Recently, promotion of HIV-1 replication by post-entry interaction of CA with CypA in target cells has been shown, suggesting the importance of CypA for efficient HIV-1 replication (94, 101, 102).

Only retroviruses with CA capable of binding to CypA exhibit CypA-dependent viral replication (84, 85, 90, 92, 95). This suggests involvement of CA-CypA interaction in the determination of retroviral tropism (14, 16, 17, 34, 98, 101–111). The effect of CypA on SIV replication in human cells has not been clearly determined but, for the first time, a recent study has shown that human CypA exerts an inhibitory effect on *vif*-deleted SIV replication, which may be recovered by SIV Vif excluding the CypA from the virion (112). This Vif function can be distinguished from the anti-hApo3G function of Vif described above.

PERSPECTIVES: HOST FACTORS INVOLVED IN THE POST-ENTRY STEP OF THE EARLY PHASE OF RETROVIRAL REPLICATION

Restriction of HIV-1 replication in non-human primate cells after viral entry occurs at the step prior to reverse transcription, and TRIM5α plays a crucial role in this restriction (13–15, 101, 106, 113–115). Interestingly, CypA-dependency is considered to occur at the same step in the retroviral replication cycle (116).

Several groups have reported modest restriction of HIV-1 replication by human TRIM5α, a restriction which is not altered by disruption of the CA-CypA interaction or by elimination of endogenous CypA (117–119). In contrast, restriction of HIV-1 replication by the TRIM5α derived from OWM (such as rhesus macaques) is abrogated by CsA-mediated or small interfering RNA-mediated inhibition of OWM-derived CypA function, indicating involvement of CypA in TRIM5α-mediated restriction of HIV-1 replication in OWM cells (117, 118, 120). In the owl monkey (a new world monkey), a CypA-TRIM5α-fusion protein has been found and involvement of CypA in the restriction has been suggested (17). Thus, CypA may exert restriction activity against HIV-1 replication in association with TRIM5α in non-human primates but not in humans. Elucidation of the key factors involved in this difference in CypA function between non-human primates and humans may contribute to understanding of the species-specific restriction mechanism against retroviral replication.

REFERENCES

1. Suzuki S. (1975) FV-4: a new gene affecting the splenomegaly induction by Friend leukemia virus. *Jpn J Exp Med* **45:** 473–478.
2. Gardner M.B., Rasheed S., Pal B.K., Estes J.D., O'Brien S.J. (1980) Akvr-1, a dominant murine leukemia virus restriction gene, is polymorphic in leukemia-prone wild mice. *Proc Natl Acad Sci USA* **77:** 531–535.
3. Rasheed S., Gardner M.B. (1983) Resistance to fibroblasts and hematopoietic cells to ecotropic murine leukemia virus infection; an Akvr-1R gene effect. *Int J Cancer* **31:** 491–496.
4. Hartley J.W., Rowe W.P., Huebner R.J. (1970) Host-range restrictions of murine leukemia viruses in mouse embryo cell cultures. *J Virol* **5:** 221–225.
5. Pincus T., Hartley J.W., Rowe W.P. (1971) A major genetic locus affecting resistance to infection with murine leukemia viruses. I. Tissue culture studies of naturally occurring viruses. *J Exp Med* **133:** 1219–1233.
6. Ikeda H., Odaka T. (1983) Cellular expression of murine leukemia virus gp70-related antigen on thymocytes of uninfected mice correlates with Fv-4 gene-controlled resistance to Friend leukemia virus infection. *Virology* **128:** 127–139.
7. Takeda A., Matano T. (2007) Inhibition of infectious murine leukemia virus production by Fv-4 env gene products exerting dominant negative effect on viral envelope glycoprotein. *Microbes Infect.* **9:**1590–6.
8. Goff S.P. (2004) Genetic control of retrovirus susceptibility in mammalian cells. *Annu Rev Genet* **38:** 61–85.
9. Rein A., Kashmiri S.V., Bassin R.H., Gerwin B.L., Duran-Troise G. (1976) Phenotypic mixing between N- and B-tropic murine leukemia viruses: infectious particles with dual sensitivity to Fv-1 restriction. *Cell* **7:** 373–379.
10. Gautsch J.W., Elder J.H., Schindler J., Jensen F.C., Lerner R.A. (1978) Structural markers on core protein p30 of murine leukemia virus: functional correlation with Fv-1 tropism. *Proc Natl Acad Sci USA* **75:** 4170–4174.
11. Kozak C.A., Chakraborti A. (1996) Single amino acid changes in the murine leukemia virus capsid protein gene define the target of Fv1 resistance. *Virology* **225:** 300–305.
12. Towers G., Bock M., Martin S., Takeuchi Y., Stoye J.P., Danos O. (2000) A conserved mechanism of retrovirus restriction in mammals. *Proc Natl Acad Sci USA* **97:** 12 295–12 299.
13. Besnier C., Takeuchi Y., Towers G. (2002) Restriction of lentivirus in monkeys. *Proc Natl Acad Sci USA* **99:** 11 920–11 925.
14. Cowan S., Hatziioannou T., Cunningham T., Muesing M.A., Gottlinger H.G., Bieniasz P.D. (2002) Cellular inhibitors with Fv1-like activity restrict human and simian immunodeficiency virus tropism. *Proc Natl Acad Sci USA* **99:** 11 914–11 919.
15. Munk C., Brandt S.M., Lucero G., Landau N.R. (2002) A dominant block to HIV-1 replication at reverse transcription in simian cells. *Proc Natl Acad Sci USA* **99:** 13 843–13 848.
16. Stremlau M., Owens C.M., Perron M.J., Kiessling M., Autissier P., Sodroski J. (2004) The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* **427:** 848–853.
17. Sayah D.M., Sokolskaja E., Berthoux L., Luban J. (2004) Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV-1. *Nature* **430:** 569–573.
18. Keckesova Z., Ylinen L.M., Towers G.J. (2004) The human and African green monkey TRIM5alpha genes encode Ref1 and Lv1 retroviral restriction factor activities. *Proc Natl Acad Sci USA* **101:** 10 780–10 785.
19. Perron M.J., Stremlau M., Song B., Ulm W., Mulligan R.C., Sodroski J. (2004) TRIM5alpha mediates the postentry block to

N-tropic murine leukemia viruses in human cells. *Proc Natl Acad Sci USA* **101:** 11 827–11 832.
20. Si Z., Vandegraaff N., O'Huigin C., Song B., Yuan W., Xu C., Perron M., Li X., Marasco W.A., Engelman A., *et al.* (2006) Evolution of a cytoplasmic tripartite motif (TRIM) protein in cows that restricts retroviral infection. *Proc Natl Acad Sci USA* **103:** 7454–7459.
21. Song B., Javanbakht H., Perron M., Park D.H., Stremlau M., Sodroski J. (2005) Retrovirus restriction by TRIM5alpha variants from Old World and New World primates. *J Virol* **79:** 3930–3937.
22. Yap M.W., Nisole S., Lynch C., Stoye J.P. (2004) Trim5alpha protein restricts both HIV-1 and murine leukemia virus. *Proc Natl Acad Sci USA* **101:** 10 786–10 791.
23. Ylinen L.M., Keckesova Z., Wilson S.J., Ranasinghe S., Towers G.J. (2005) Differential restriction of human immunodeficiency virus type 2 and simian immunodeficiency virus SIVmac by TRIM5alpha alleles. *J Virol* **79:** 11 580–11 587.
24. Hatziioannou T., Perez-Caballero D., Yang A., Cowan S., Bieniasz P.D. (2004) Retrovirus resistance factors Ref1 and Lv1 are species-specific variants of TRIM5alpha. *Proc Natl Acad Sci USA* **101:** 10 774–10 779.
25. Mische C.C., Javanbakht H., Song B., Diaz-Griffero F., Stremlau M., Strack B., Si Z., Sodroski J. (2005) Retroviral restriction factor TRIM5alpha is a trimer. *J Virol* **79:** 14 446–14 450.
26. Javanbakht H., Yuan W., Yeung D.F., Song B., Diaz-Griffero F., Li Y., Li X., Stremlau M., Sodroski J. (2006) Characterization of TRIM5alpha trimerization and its contribution to human immunodeficiency virus capsid binding. *Virology* **353:** 234–246.
27. Nisole S., Stoye J.P., Saib A. (2005) TRIM family proteins: retroviral restriction and antiviral defence. *Nat Rev Microbiol* **3:** 799–808.
28. Reymond A., Meroni G., Fantozzi A., Merla G., Cairo S., Luzi L., Riganelli D., Zanaria E., Messali S., Cainarca S., *et al.* (2001) The tripartite motif family identifies cell compartments. *Embo J* **20:** 2140–2151.
29. Stremlau M., Perron M., Lee M., Li Y., Song B., Javanbakht H., Diaz-Griffero F., Anderson D.J., Sundquist W.I., Sodroski J. (2006) Specific recognition and accelerated uncoating of retroviral capsids by the TRIM5alpha restriction factor. *Proc Natl Acad Sci USA* **103:** 5514–5519.
30. Perez-Caballero D., Hatziioannou T., Yang A., Cowan S., Bieniasz P.D. (2005) Human tripartite motif 5alpha domains responsible for retrovirus restriction activity and specificity. *J Virol* **79:** 8969–8978.
31. Javanbakht H., Diaz-Griffero F., Stremlau M., Si Z., Sodroski J. (2005) The contribution of RING and B-box 2 domains to retroviral restriction mediated by monkey TRIM5alpha. *J Biol Chem* **280:** 26 933–26 940.
32. Perez-Caballero D., Hatziioannou T., Zhang F., Cowan S., Bieniasz P.D. (2005) Restriction of human immunodeficiency virus type 1 by TRIM-CypA occurs with rapid kinetics and independently of cytoplasmic bodies, ubiquitin, and proteasome activity. *J Virol* **79:** 15 567–15 572.
33. Schwartz O., Marechal V., Friguet B., Arenzana-Seisdedos F., Heard J.M. (1998) Antiviral activity of the proteasome on incoming human immunodeficiency virus type 1. *J Virol* **72:** 3845–3850.
34. Berthoux L., Sebastian S., Sokolskaja E., Luban J. (2004) Lv1 inhibition of human immunodeficiency virus type 1 is counteracted by factors that stimulate synthesis or nuclear translocation of viral cDNA. *J Virol* **78:** 11 739–11 750.
35. Wu X., Anderson J.L., Campbell E.M., Joseph A.M., Hope T.J. (2006) Proteasome inhibitors uncouple rhesus TRIM5alpha restriction of HIV-1 reverse transcription and infection. *Proc Natl Acad Sci USA* **103:** 7465–7470.
36. Sakuma R., Noser J.A., Ohmine S., Ikeda Y. (2007) Rhesus monkey TRIM5alpha restricts HIV-1 production through rapid degradation of viral Gag polyproteins. *Nat Med* **13:** 631–635.
37. Fisher A.G., Ensoli B., Ivanoff L., Chamberlain M., Petteway S., Ratner L., Gallo R.C., Wong-Staal F. (1987) The sor gene of HIV-1 is required for efficient virus transmission in vitro. *Science* **237:** 888–893.
38. Strebel K., Daugherty D., Clouse K., Cohen D., Folks T., Martin M.A. (1987) The HIV 'A' (sor) gene product is essential for virus infectivity. *Nature* **328:** 728–730.
39. Akari H., Sakuragi J., Takebe Y., Tomonaga K., Kawamura M., Fukasawa M., Miura T., Shinjo T., Hayami M. (1992) Biological characterization of human immunodeficiency virus type 1 and type 2 mutants in human peripheral blood mononuclear cells. *Arch Virol* **123:** 157–167.
40. Blanc D., Patience C., Schulz T.F., Weiss R., Spire B. (1993) Transcomplementation of VIF- HIV-1 mutants in CEM cells suggests that VIF affects late steps of the viral life cycle. *Virology* **193:** 186–192.
41. Borman A.M., Quillent C., Charneau P., Dauguet C., Clavel F. (1995) Human immunodeficiency virus type 1 Vif- mutant particles from restrictive cells: role of Vif in correct particle assembly and infectivity. *J Virol* **69:** 2058–2067.
42. Fan L., Peden K. (1992) Cell-free transmission of Vif mutants of HIV-1. *Virology* **190:** 19–29.
43. Gabuzda D.H., Lawrence K., Langhoff E., Terwilliger E., Dorfman T., Haseltine W.A., Sodroski J. (1992) Role of vif in replication of human immunodeficiency virus type 1 in CD4+ T lymphocytes. *J Virol* **66:** 6489–6495.
44. Sakai H., Shibata R., Sakuragi J., Sakuragi S., Kawamura M., Adachi A. (1993) Cell-dependent requirement of human immunodeficiency virus type 1 Vif protein for maturation of virus particles. *J Virol* **67:** 1663–1666.
45. von Schwedler U., Song J., Aiken C., Trono D. (1993) Vif is crucial for human immunodeficiency virus type 1 proviral DNA synthesis in infected cells. *J Virol* **67:** 4945–4955.
46. Sheehy A.M., Gaddis N.C., Choi J.D., Malim M.H. (2002) Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* **418:** 646–650.
47. Yu X., Yu Y., Liu B., Luo K., Kong W., Mao P., Yu X.F. (2003) Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex. *Science* **302:** 1056–1060.
48. Harris R.S., Bishop K.N., Sheehy A.M., Craig H.M., Petersen-Mahrt S.K., Watt I.N., Neuberger M.S., Malim M.H. (2003) DNA deamination mediates innate immunity to retroviral infection. *Cell* **113:** 803–809.
49. Lecossier D., Bouchonnet F., Clavel F., Hance A.J. (2003) Hypermutation of HIV-1 DNA in the absence of the Vif protein. *Science* **300:** 1112.
50. Mangeat B., Turelli P., Caron G., Friedli M., Perrin L., Trono D. (2003) Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. *Nature* **424:** 99–103.
51. Mariani R., Chen D., Schrofelbauer B., Navarro F., Konig R., Bollman B., Munk C., Nymark-McMahon H., Landau N.R. (2003) Species-specific exclusion of APOBEC3G from HIV-1 virions by Vif. *Cell* **114:** 21–31.
52. Yu Q., Konig R., Pillai S., Chiles K., Kearney M., Palmer S., Richman D., Coffin J.M., Landau N.R. (2004) Single-strand specificity of APOBEC3G accounts for minus-strand deamination of the HIV genome. *Nat Struct Mol Biol* **11:** 435–442.

53. Zhang H., Yang B., Pomerantz R.J., Zhang C., Arunachalam S.C., Gao L. (2003) The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA. *Nature* **424:** 94–98.
54. Guo F., Cen S., Niu M., Saadatmand J., Kleiman L. (2006) Inhibition of formula-primed reverse transcription by human APOBEC3G during human immunodeficiency virus type 1 replication. *J Virol* **80:** 11 710–11 722.
55. Guo F., Cen S., Niu M., Yang Y., Gorelick R.J., Kleiman L. (2007) The interaction of APOBEC3G with human immunodeficiency virus type 1 nucleocapsid inhibits tRNA3Lys annealing to viral RNA. *J Virol* **81:** 11 322–11 331.
56. Mbisa J.L., Barr R., Thomas J.A., Vandegraaff N., Dorweiler I.J., Svarovskaia E.S., Brown W.L., Mansky L.M., Gorelick R.J., Harris R.S., *et al.* (2007) Human immunodeficiency virus type 1 cDNAs produced in the presence of APOBEC3G exhibit defects in plus-strand DNA transfer and integration. *J Virol* **81:** 7099–7110.
57. Li X.Y., Guo F., Zhang L., Kleiman L., Cen S. (2007) APOBEC3G inhibits DNA strand transfer during HIV-1 reverse transcription. *J Biol Chem* **282:** 32 065–32 074.
58. Luo K., Wang T., Liu B., Tian C., Xiao Z., Kappes J., Yu X.F. (2007) Cytidine deaminases APOBEC3G and APOBEC3F interact with human immunodeficiency virus type 1 integrase and inhibit proviral DNA formation. *J Virol* **81:** 7238–7248.
59. Bishop K.N., Holmes R.K., Sheehy A.M., Davidson N.O., Cho S.J., Malim M.H. (2004) Cytidine deamination of retroviral DNA by diverse APOBEC proteins. *Curr Biol* **14:** 1392–1396.
60. Wiegand H.L., Doehle B.P., Bogerd H.P., Cullen B.R. (2004) A second human antiretroviral factor, APOBEC3F, is suppressed by the HIV-1 and HIV-2 Vif proteins. *Embo J* **23:** 2451–2458.
61. Cullen B.R. (2006) Role and mechanism of action of the APOBEC3 family of antiretroviral resistance factors. *J Virol* **80:** 1067–1076.
62. Bishop K.N., Holmes R.K., Sheehy A.M., Malim M.H. (2004) APOBEC-mediated editing of viral RNA. *Science* **305:** 645.
63. Simon J.H., Miller D.L., Fouchier R.A., Soares M.A., Peden K.W., Malim M.H. (1998) The regulation of primate immunodeficiency virus infectivity by Vif is cell species restricted: a role for Vif in determining virus host range and cross-species transmission. *Embo J* **17:** 1259–1267.
64. Bogerd H.P., Doehle B.P., Wiegand H.L., Cullen B.R. (2004) A single amino acid difference in the host APOBEC3G protein controls the primate species specificity of HIV type 1 virion infectivity factor. *Proc Natl Acad Sci USA* **101:** 3770–3774.
65. Mangeat B., Turelli P., Liao S., Trono D. (2004) A single amino acid determinant governs the species-specific sensitivity of APOBEC3G to Vif action. *J Biol Chem* **279:** 14 481–14 483.
66. Schrofelbauer B., Chen D., Landau N.R. (2004) A single amino acid of APOBEC3G controls its species-specific interaction with virion infectivity factor (Vif). *Proc Natl Acad Sci USA* **101:** 3927–3932.
67. Xu H., Svarovskaia E.S., Barr R., Zhang Y., Khan M.A., Strebel K., Pathak V.K. (2004) A single amino acid substitution in human APOBEC3G antiretroviral enzyme confers resistance to HIV-1 virion infectivity factor-induced depletion. *Proc Natl Acad Sci USA* **101:** 5652–5657.
68. Takeuchi H., Kao S., Miyagi E., Khan M.A., Buckler-White A., Plishka R., Strebel K. (2005) Production of infectious SIVagm from human cells requires functional inactivation but not viral exclusion of human APOBEC3G. *J Biol Chem* **280:** 375–382.
69. Harris R.S., Liddament M.T. (2004) Retroviral restriction by APOBEC proteins. *Nat Rev Immunol* **4:** 868–877.
70. Liddament M.T., Brown W.L., Schumacher A.J., Harris R.S. (2004) APOBEC3F properties and hypermutation preferences indicate activity against HIV-1 in vivo. *Curr Biol* **14:** 1385–1391.
71. Zheng Y.H., Irwin D., Kurosu T., Tokunaga K., Sata T., Peterlin B.M. (2004) Human APOBEC3F is another host factor that blocks human immunodeficiency virus type 1 replication. *J Virol* **78:** 6073–6076.
72. Doehle B.P., Schafer A., Cullen B.R. (2005) Human APOBEC3B is a potent inhibitor of HIV-1 infectivity and is resistant to HIV-1 Vif. *Virology* **339:** 281–288.
73. Rose K.M., Marin M., Kozak S.L., Kabat D. (2005) Regulated production and anti-HIV type 1 activities of cytidine deaminases APOBEC3B, 3F, and 3G. *AIDS Res Hum Retroviruses* **21:** 611–619.
74. Bishop K.N., Holmes R.K., Malim M.H. (2006) Antiviral potency of APOBEC proteins does not correlate with cytidine deamination. *J Virol* **80:** 8450–8458.
75. Holmes R.K., Koning F.A., Bishop K.N., Malim M.H. (2007) APOBEC3F can inhibit the accumulation of HIV-1 reverse transcription products in the absence of hypermutation. Comparisons with APOBEC3G. *J Biol Chem* **282:** 2587–2595.
76. Newman E.N., Holmes R.K., Craig H.M., Klein K.C., Lingappa J.R., Malim M.H., Sheehy A.M. (2005) Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity. *Curr Biol* **15:** 166–170.
77. Shindo K., Takaori-Kondo A., Kobayashi M., Abudu A., Fukunaga K., Uchiyama T. (2003) The enzymatic activity of CEM15/Apobec-3G is essential for the regulation of the infectivity of HIV-1 virion but not a sole determinant of its antiviral activity. *J Biol Chem* **278:** 44 412–44 416.
78. Iwatani Y., Chan D.S., Wang F., Maynard K.S., Sugiura W., Gronenborn A.M., Rouzina I., Williams M.C., Musier-Forsyth K., Levin J.G. (2007) Deaminase-independent inhibition of HIV-1 reverse transcription by APOBEC3G. *Nucleic Acids Res.* 35(21):7096-108
79. Opi S., Takeuchi H., Kao S., Khan M.A., Miyagi E., Goila-Gaur R., Iwatani Y., Levin J.G., Strebel K. (2006) Monomeric APOBEC3G is catalytically active and has antiviral activity. *J Virol* **80:** 4673–4682.
80. Miyagi E., Opi S., Takeuchi H., Khan M., Goila-Gaur R., Kao S., Strebel K. (2007) Enzymatically active APOBEC3G is required for efficient inhibition of human immunodeficiency virus type 1. *J Virol* **81:** 13 346–13 353.
81. Handschumacher R.E., Harding M.W., Rice J., Drugge R.J., Speicher D.W. (1984) Cyclophilin: a specific cytosolic binding protein for cyclosporin A. *Science* **226:** 544–547.
82. Fischer G., Wittmann-Liebold B., Lang K., Kiefhaber T., Schmid F.X. (1989) Cyclophilin and peptidyl-prolyl cis-trans isomerase are probably identical proteins. *Nature* **337:** 476–478.
83. Takahashi N., Hayano T., Suzuki M. (1989) Peptidyl-prolyl cis-trans isomerase is the cyclosporin A-binding protein cyclophilin. *Nature* **337:** 473–475.
84. Luban J., Bossolt K.L., Franke E.K., Kalpana G.V., Goff S.P. (1993) Human immunodeficiency virus type 1 Gag protein binds to cyclophilins A and B. *Cell* **73:** 1067–1078.
85. Franke E.K., Yuan H.E., Luban J. (1994) Specific incorporation of cyclophilin A into HIV-1 virions. *Nature* **372:** 359–362.
86. Gamble T.R., Vajdos F.F., Yoo S., Worthylake D.K., Houseweart M., Sundquist W.I., Hill C.P. (1996) Crystal structure of human cyclophilin A bound to the amino-terminal domain of HIV-1 capsid. *Cell* **87:** 1285–1294.
87. Zhao Y., Chen Y., Schutkowski M., Fischer G., Ke H. (1997) Cyclophilin A complexed with a fragment of HIV-1 gag protein: insights into HIV-1 infectious activity. *Structure* **5:** 139–146.
88. Bosco D.A., Eisenmesser E.Z., Pochapsky S., Sundquist W.I., Kern D. (2002) Catalysis of cis/trans isomerization in native HIV-1 capsid by human cyclophilin A. *Proc Natl Acad Sci USA* **99:** 5247–5252.

89. Braaten D., Aberham C., Franke E.K., Yin L., Phares W., Luban J. (1996) Cyclosporine A-resistant human immunodeficiency virus type 1 mutants demonstrate that Gag encodes the functional target of cyclophilin A. *J Virol* **70:** 5170–5176.
90. Braaten D., Franke E.K., Luban J. (1996) Cyclophilin A is required for the replication of group M human immunodeficiency virus type 1 (HIV-1) and simian immunodeficiency virus SIV(CPZ)GAB but not group O HIV-1 or other primate immunodeficiency viruses. *J Virol* **70:** 4220–4227.
91. Braaten D., Luban J. (2001) Cyclophilin A regulates HIV-1 infectivity, as demonstrated by gene targeting in human T cells. *Embo J* **20:** 1300–1309.
92. Franke E.K., Luban J. (1996) Inhibition of HIV-1 replication by cyclosporine A or related compounds correlates with the ability to disrupt the Gag-cyclophilin A interaction. *Virology* **222:** 279–282.
93. Hatziioannou T., Perez-Caballero D., Cowan S., Bieniasz P.D. (2005) Cyclophilin interactions with incoming human immunodeficiency virus type 1 capsids with opposing effects on infectivity in human cells. *J Virol* **79:** 176–183.
94. Sokolskaja E., Sayah D.M., Luban J. (2004) Target cell cyclophilin A modulates human immunodeficiency virus type 1 infectivity. *J Virol* **78:** 12 800–12 808.
95. Thali M., Bukovsky A., Kondo E., Rosenwirth B., Walsh C.T., Sodroski J., Gottlinger H.G. (1994) Functional association of cyclophilin A with HIV-1 virions. *Nature* **372:** 363–365.
96. Ott D.E., Coren L.V., Johnson D.G., Sowder R.C., 2nd, Arthur L.O., Henderson L.E. (1995) Analysis and localization of cyclophilin A found in the virions of human immunodeficiency virus type 1 MN strain. *AIDS Res Hum Retroviruses* **11:** 1003–1006.
97. Ackerson B., Rey O., Canon J., Krogstad P. (1998) Cells with high cyclophilin A content support replication of human immunodeficiency virus type 1 Gag mutants with decreased ability to incorporate cyclophilin A. *J Virol* **72:** 303–308.
98. Bukovsky A.A., Weimann A., Accola M.A., Gottlinger H.G. (1997) Transfer of the HIV-1 cyclophilin-binding site to simian immunodeficiency virus from Macaca mulatta can confer both cyclosporin sensitivity and cyclosporin dependence. *Proc Natl Acad Sci USA* **94:** 10 943–10 948.
99. Colgan J., Yuan H.E., Franke E.K., Luban J. (1996) Binding of the human immunodeficiency virus type 1 Gag polyprotein to cyclophilin A is mediated by the central region of capsid and requires Gag dimerization. *J Virol* **70:** 4299–4310.
100. Javanbakht H., Diaz-Griffero F., Yuan W., Yeung D.F., Li X., Song B., Sodroski J. (2007) The ability of multimerized cyclophilin A to restrict retrovirus infection. *Virology* **367:** 19–29.
101. Towers G.J., Hatziioannou T., Cowan S., Goff S.P., Luban J., Bieniasz P.D. (2003) Cyclophilin A modulates the sensitivity of H.I.V-1 to host restriction factors. *Nat Med* **9:** 1138–1143.
102. Kootstra N.A., Munk C., Tonnu N., Landau N.R., Verma I.M. (2003) Abrogation of postentry restriction of HIV-1-based lentiviral vector transduction in simian cells. *Proc Natl Acad Sci USA* **100:** 1298–1303.
103. Kamada K., Igarashi T., Martin M.A., Khamsri B., Hatcho K., Yamashita T., Fujita M., Uchiyama T., Adachi A. (2006) Generation of HIV-1 derivatives that productively infect macaque monkey lymphoid cells. *Proc Natl Acad Sci USA* **103:** 16 959–16 964.
104. Hatziioannou T., Princiotta M., Piatak M., Jr., Yuan F., Zhang F., Lifson J.D., Bieniasz P.D. (2006) Generation of simian-tropic HIV-1 by restriction factor evasion. *Science* **314:** 95.
105. Shibata R., Kawamura M., Sakai H., Hayami M., Ishimoto A., Adachi A. (1991) Generation of a chimeric human and simian immunodeficiency virus infectious to monkey peripheral blood mononuclear cells. *J Virol* **65:** 3514–3520.
106. Shibata R., Sakai H., Kawamura M., Tokunaga K., Adachi A. (1995) Early replication block of human immunodeficiency virus type 1 in monkey cells. *J Gen Virol* 76(Pt 11): 2723–2730.
107. Dorfman T., Gottlinger H.G. (1996) The human immunodeficiency virus type 1 capsid p2 domain confers sensitivity to the cyclophilin-binding drug SDZ NIM 811. *J Virol* **70:** 5751–5757.
108. Owens C.M., Yang P.C., Gottlinger H., Sodroski J. (2003) Human and simian immunodeficiency virus capsid proteins are major viral determinants of early, postentry replication blocks in simian cells. *J Virol* **77:** 726–731.
109. Hatziioannou T., Cowan S., Von Schwedler U.K., Sundquist W.I., Bieniasz P.D. (2004) Species-specific tropism determinants in the human immunodeficiency virus type 1 capsid. *J Virol* **78:** 6005–6012.
110. Owens C.M., Song B., Perron M.J., Yang P.C., Stremlau M., Sodroski J. (2004) Binding and susceptibility to postentry restriction factors in monkey cells are specified by distinct regions of the human immunodeficiency virus type 1 capsid. *J Virol* **78:** 5423–5437.
111. Ikeda Y., Ylinen L.M., Kahar-Bador M., Towers G.J. (2004) Influence of gag on human immunodeficiency virus type 1 species-specific tropism. *J Virol* **78:** 11 816–11 822.
112. Takeuchi H., Buckler-White A., Goila-Gaur R., Miyagi E., Khan M.A., Opi S., Kao S., Sokolskaja E., Pertel T., Luban J., *et al.* (2007) Vif counteracts a cyclophilin A-imposed inhibition of simian immunodeficiency viruses in human cells. *J Virol* **81:** 8080–8090.
113. Himathongkham S., Luciw P.A. (1996) Restriction of HIV-1 (subtype B) replication at the entry step in rhesus macaque cells. *Virology* **219:** 485–488.
114. Hofmann W., Schubert D., LaBonte J., Munson L., Gibson S., Scammell J., Ferrigno P., Sodroski J. (1999) Species-specific, postentry barriers to primate immunodeficiency virus infection. *J Virol* **73:** 10 020–10 028.
115. Hatziioannou T., Cowan S., Goff S.P., Bieniasz P.D., Towers G.J. (2003) Restriction of multiple divergent retroviruses by Lv1 and Ref1. *Embo J* **22:** 385–394.
116. Braaten D., Franke E.K., Luban J. (1996) Cyclophilin A is required for an early step in the life cycle of human immunodeficiency virus type 1 before the initiation of reverse transcription. *J Virol* **70:** 3551–3560.
117. Keckesova Z., Ylinen L.M., Towers G.J. (2006) Cyclophilin A renders human immunodeficiency virus type 1 sensitive to Old World monkey but not human TRIM5 alpha antiviral activity. *J Virol* **80:** 4683–4690.
118. Stremlau M., Song B., Javanbakht H., Perron M., Sodroski J. (2006) Cyclophilin A: an auxiliary but not necessary cofactor for TRIM5alpha restriction of HIV-1. *Virology* **351:** 112–120.
119. Sokolskaja E., Berthoux L., Luban J. (2006) Cyclophilin A and TRIM5alpha independently regulate human immunodeficiency virus type 1 infectivity in human cells. *J Virol* **80:** 2855–2862.
120. Berthoux L., Sebastian S., Sokolskaja E., Luban J. (2005) Cyclophilin A is required for TRIM5{alpha}-mediated resistance to HIV-1 in Old World monkey cells. *Proc Natl Acad Sci USA* **102:** 14 849–14 853.

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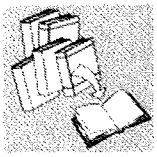
REVIEW



Anti-HIV adaptive immunity: determinants for viral persistence

Hiroyuki Yamamoto and Tetsuro Matano*

International Research Center for Infectious Diseases, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

SUMMARY

The immense difficulty in primary control of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection by adaptive immune responses has been a topic of exceptional importance. $CD8^+$ cytotoxic T lymphocytes (CTLs) do play a central role in primary resolution of viremia, but their potency in viral control is generally constrained in the natural courses of HIV/SIV infections. The overall repertoire of CTLs is dependent on both the host and the virus genetic polymorphisms, and the potency of each individual CTL is affected by immunological and virological determinants. HIV/SIV infections lack early appearance of neutralising antibodies (NAbs), and our recent finding has suggested a possibility of their absence contributing to diminished virus-specific $CD4^+$ T-cell responses leading to failure in primary viral control. Extrapolations from studies in macaque models of SIV infection and analyses of the cohorts of HIV control in humans have to date delineated the numerous requirements for attainment of viral control. Understanding of the individual components of adaptive immune responses and their optimal concert required for HIV/SIV control would contribute to development of an effective AIDS vaccine. Here, we discuss current insights into CTLs and NAbs, and speculate their possible protective mechanism against establishment of persistent HIV/SIV infection. Copyright © 2008 John Wiley & Sons, Ltd.

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ACUTE MEMORY $CD4^+$ T-CELL DEPLETION BY HIV INFECTION

The kinetics of human immunodeficiency virus (HIV) infection, especially in the acute phase, has been a long-pursued question. The first turning point came with identification of chemokine receptors including CCR5 as the coreceptor for viral entry into the cells [1–4], contributing to determination of the primary viral target cell population. CCR5-tropic viruses were shown to play a central role in viral transmission [5–7], and studies using macaques infected with CCR5-tropic simian immunodeficiency virus (SIV) revealed predominant viral infection of activated $CD4^+$ T lymphocytes in the gut in the early phase [8,9]. Subsequent key studies showed acute depletion of memory $CD4^+$ T lymphocytes that were enriched with CCR5 expression [10,11], starting at the gut lamina propria around week 1 and then systemically around week 2 post-infection [12–14]. This CCR5-tropic depletion can be an obstacle to *de novo* induction of potent virus-specific immune responses, which may contribute to failure in primary viral control [15].

In agreement with these findings, trials of prophylactic AIDS vaccines eliciting $CD8^+$ cytotoxic T lymphocyte (CTL) responses in macaques against chimeric CXCR4-tropic simian-human immunodeficiency viruses (SHIVs) and CCR5-tropic SIVs have revealed an immense difference in attainability of viral control between the two. In the former model of CXCR4-tropic SHIV infection that shows aggressive natural infection courses with massive acute depletion of naïve

*Corresponding author: T. Matano, International Research Center for Infectious Diseases, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan. E-mail: matano@m.u-tokyo.ac.jp

Abbreviations used

HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus; SHIV, simian-human immunodeficiency virus; CTL, cytotoxic T lymphocyte; HLA, human leukocyte antigen; MHC, major histocompatibility complex; MHC-I, MHC class I; NAb, neutralising antibody; hu-PBL-SCID mice, human peripheral blood leukocyte-reconstituted severe combined immunodeficiency mice; DC, dendritic cell.

$CD4^+$ T lymphocyte subsets enriched with CXCR4 expression [11,16], vaccine-based viral control has in fact been achieved consistently [17–22]. In contrast, in the latter model of CCR5-tropic SIV infection, vaccine-based successful viremia control has not consistently been attained [23–28] but observed under the conditions with specific host genetic backgrounds affecting CTL efficacies [29].

ANTI-HIV CTL POTENCY

Virus-specific CTLs play an indispensable role in control of immunodeficiency virus infection [30–35]. Enrolment of $CD8^+$ CTLs in primary control of HIV/SIV replication is directly visible as the initial decline of viral loads from the peak to the set point. Yet infection persists, and eventually the host progresses to AIDS (Figure 1). Hence the question remains as to what determines the persistence of viremia even under vigorous CTL pressure. To this important question, several explanations have been posed to date; some have suggested possible contribution of the aberrance of virus-specific $CD4^+$ T cell responses to failure in viral control [36,37]. Other reports have indicated that ongoing immune activation itself may fuel infection persistence, in part in a hen-and-egg fashion of CTL dysfunction or exhaustion [38–40]. Analyses on the various aspects of difficulty in HIV/SIV control by CTLs have newly highlighted several important issues related to its functionality, including competitive equilibrium between CTL potency and viral escape, influence of viral and host major histocompatibility complex (MHC) polymorphisms, and kinetics of infected cell killing. These may provide important clues for development of effective CTL-based AIDS vaccines.

HIV infections mostly exhibit chronic disease progression, but occasionally show rapid AIDS progression or, in reverse, delayed disease courses with viral control. Genetic analyses attributed some of the latter cases of inefficient viral replication to viral polymorphisms such as *nef* deletion [41] or host polymorphisms such as CCR5Δ32 variants [42,43]. These were followed by a finding of worse prognoses in HIV-infected human leukocyte antigen (HLA) homozygotes compared to heterozygotes [44] and a wave of cumulative analyses indicating association of HLA/MHC genotypes with rapid or delayed AIDS progression [45–49]. For instance, most of the HIV-1-infected individuals possessing *HLA-B*57* have been indicated to show a better prognosis with lower viral loads, and involvement of HLA-B*57-restricted epitope-specific CTL responses in this viral control has been suggested [50]. This notion is back to back with the existence of HLA alleles associated with rapid disease progression such as *HLA-B*35* [44]. Similarly, association between MHC class I (MHC-I) genotypes and viral loads has been intensively investigated in macaque models of SIV infection. In Indian rhesus macaques, association of *Mamu-A*01*, *Mamu-A*02*, *Mamu-B*08* and

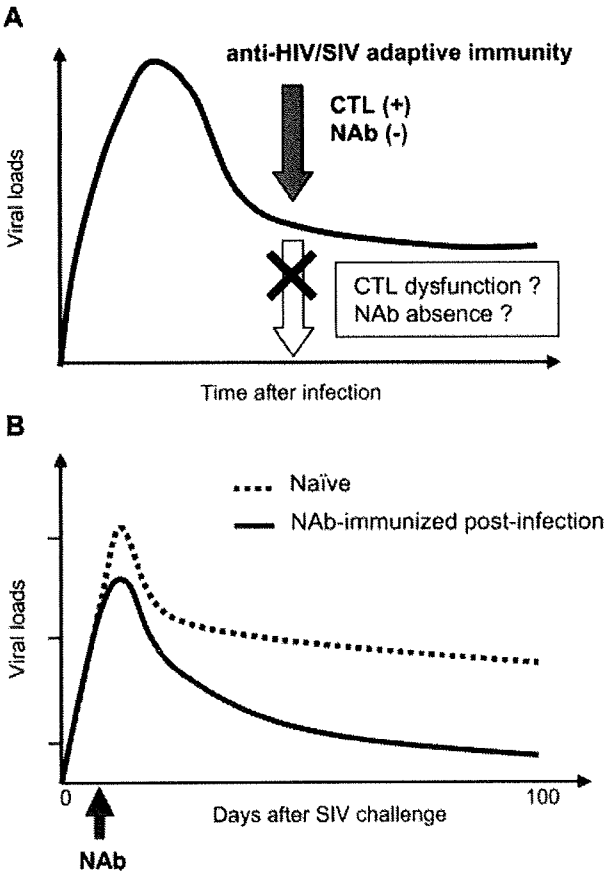

Figure 1. Schema for indicating changes in viral loads in HIV/SIV infections. (A) Persistent HIV/SIV natural infection. Virus-specific CTL responses play a central role in the resolution from viremia peak to the set point (indicated by a black arrow), whereas NAb induction is inefficient in this early phase. Yet viral replication persists and its mechanism has been unclear; speculations include CTL dysfunction, lack of memory $CD4^+$ T-cell help and absence of NAb responses. (B) Effect of post-infection passive immunisation with polyclonal NAbs on primary SIVmac239 replication in rhesus macaques [94]. NAb-immunised macaques showed lower or undetectable viral loads compared to naive controls

*Mamu-B*17* with enhanced SIV control has been indicated [35,51–54], while *Mamu-B*01* and *Mamu-A*08* have been observed as alleles associated with rapid disease progression [35]. It is reasonable to surmise that the overall spectrum of MHC-I-restricted epitope-specific CTL responses is the major determinant for the association, and this inherent, MHC-I-dependent difference in host resistance to viral infection might modify vaccine efficacy. Indeed, we have recently shown consistent vaccine-based SIV control in a group of Burmese rhesus macaques sharing an MHC-I haplotype, suggesting a possibility of MHC-dependent attainment of vaccine-based HIV/SIV control with effective CTL induction [29].

Thus the potency of CTLs largely depends on the host genetic backgrounds, while viral genome polymorphisms can also affect CTL efficacy. Selection of viral mutations resulting in escape from CTL recognition is frequently observed in HIV infections, and potent CTLs often select for escape mutations even at the cost of viral fitness [29,55–59], suggesting that CTLs specific for viral epitopes derived from structurally conserved regions may exert stronger suppressive effect on viral replication. Viral replication *in vivo* may likely be affected by a single CTL escape mutation [50,60–62], while a clear association of viremia recrudescence with accumulation of multiple CTL escape mutations has been observed in HIV/SIV infections, indicating possible involvement of multiple epitope-specific CTLs in viral control [59].

Broad, multiple epitope-specific CTL induction seems preferable for viral control, but it may not always result in advantageous induction of effective CTL responses due to the inherent hierarchy of CTLs [63]. For instance, there may be a possibility of disturbance in subdominant effective CTL responses by dominant ineffective CTL induction. Furthermore, whether oligoclonal immunodominant CTL responses or polyclonal subdominant responses are superior in viral control remains unclear. Analysis of SIVmac239-infected Indian rhesus macaques exhibiting low viral loads (elite controllers) has shown dominant Gag-specific CTL responses during primary viral control followed by induction of subdominant CTL responses responsible for the control in the chronic phase [64]. Accordingly, our long-term follow up of Burmese rhesus macaques exhibiting vaccine-based control of SIVmac239 replication has shown disappearance of Gag-specific CTL responses dominant during primary viral control and subsequent appearance of non-Gag-specific CTL responses responsible for sustained control in the chronic phase [65].

Turning to the potency of individual CTLs *in vivo*, numbers of attempts have been made for its evaluation. In addition to the analyses of CTL frequency, its pattern of cytokine secretion, its direct cytolytic activity, and avidity of its T cell receptor (TCR) with the epitope-MHC complex, the importance of examining its suppressive effect on viral replication *in vitro* has been suggested, although the levels of *in vitro* anti-viral efficacy resulting in viral control *in vivo* have not been determined [66,67]. Our recently established assay for measurement of *in vitro* anti-viral efficacy of bulk $CD8^+$ cells derived from peripheral blood may be helpful for evaluation of *in vivo* anti-viral efficacy of overall CTL responses [68]. Interestingly, a report has recently indicated that Gag-specific CTLs can respond to SIV infection more rapidly *in vitro* compared with Tat- and Env-specific CTLs, presumably by recognising virion-derived Gag epitopes presented in the early phase post-viral entry, suggesting a possibility of modification of CTL anti-viral efficacy by its recognition/killing kinetics during the viral replication cycle [69]. In support of this result, an inverse correlation between the breadth of Gag-specific CTL responses and viral loads has been indicated in a large-scale African cohort and SIV-infected rhesus macaques [69,70].

ANTI-HIV NAB POTENCY

Another major issue to be addressed in natural HIV/SIV infections is the characteristic lack of potent neutralising antibody (NAb) responses in the acute phase (Figure 1) [71]. To date, disoriented and delayed virus-specific antibody responses have been observed in the subacute phase, which permit consequent viral escape from neutralisation [72–74]. Monoclonal anti-CD20 antibody-mediated B-cell depletion experiments in macaques during the acute phase of SIV infection have suggested a possibility of modest contribution of such inefficient humoral immune responses to partial resolution from primary infection [75–77], but the effect of the absence of efficient post-infection NAb responses on

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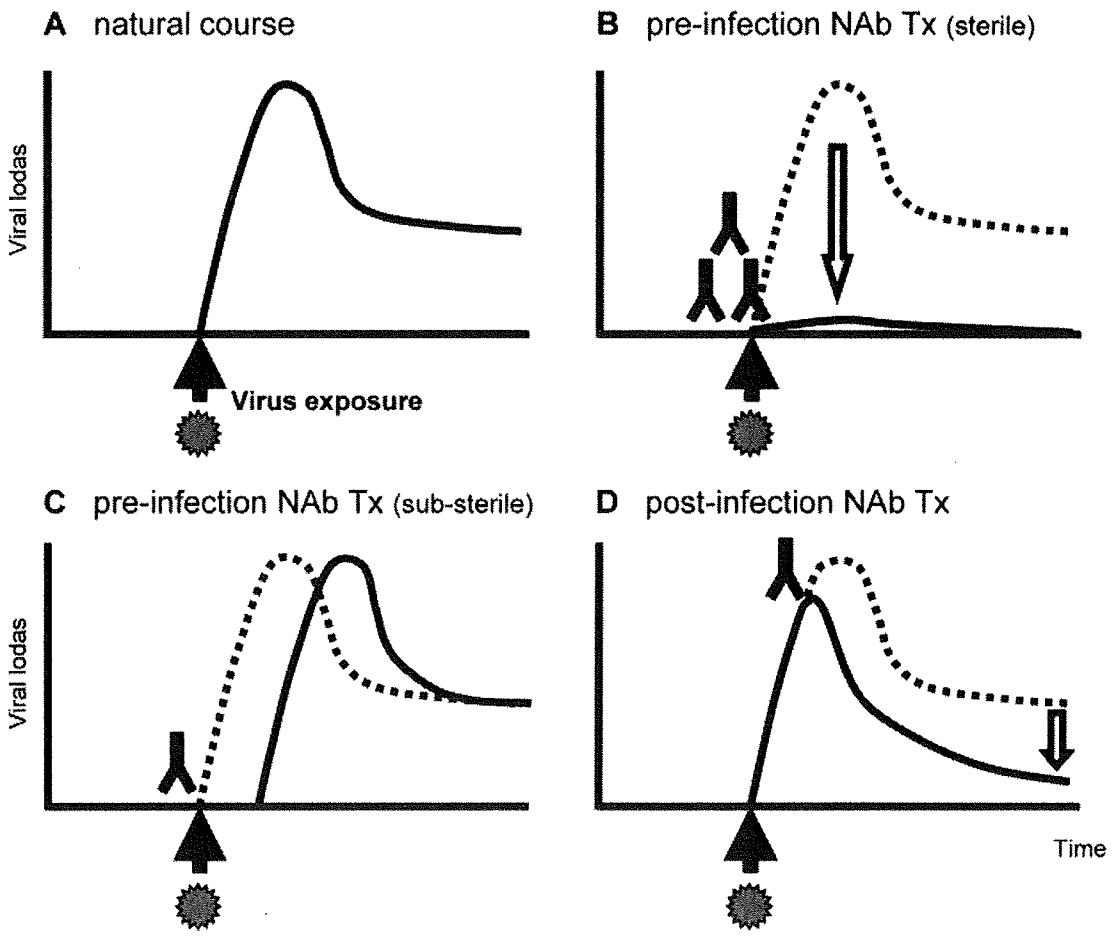

Figure 2. A schematic comparison of viral loads in NAb passive immunisation experiments. (A) In HIV/SIV natural infections, absence of NAb induction accompanies failure in primary viral control. (B) In pre-infection passive NAb immunisation, NAb titers overwhelming the challenged virus inoculum in theory provide an ultimate reduction in the peak viral load. (C) Pre-infection passive immunisation with insufficient doses of NAbs for sterile protection may cause transient delay or reduction in viral replication but permit persistent viral replication. (D) Post-infection passive NAb immunisation results in reduction of set-point viral loads beyond the period of detection of the administered NAb responses

primary HIV/SIV replication has not been formally scrutinised.

In vivo anti-viral activity of several monoclonal anti-HIV-1 NAbs such as b12, 2F5, 4E10 and 2G12 has been intensively assessed by pre-challenge passive NAb immunisation experiments against CXCR4-tropic SHIV infection in macaques [78–81]. These studies indicated a possibility of dose-dependent sterile protection (Figure 2), but the neutralising titers required for the protection were relatively high, suggesting difficulty in attainment and maintenance of those titers by prophylactic vaccination [82]. Sterile protection against CCR5-tropic SIV has not consistently been achieved by pre-challenge administration of antiserum or polyclonal antibodies [83,84] while protection against CCR5-tropic SHIV by pre-challenge monoclonal NAb administration has been indicated [85–87].

Compared with the appreciable sterile protective activity of pre-existing NAbs against viral challenge, post-infection NAb efficacy against established immunodeficiency virus infection has been a field of ambiguity. In one study, NAb administration at 6 h after CXCR4-tropic $SHIV_{DH12}$ challenge provided sterile protection while passive immunisation at 24 h post-challenge did not, suggesting a moment between 6 and 24 h

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post-infection as the threshold of post-exposure prophylaxis efficacy [88]. In another, NAb passive immunisation of rhesus macaques at day 1 and day 14 after CCR5-tropic SIVsmE660 challenge exhibited divergent patterns of infection and suggested a possibility of its suppressive effect on viral replication in some of them [89,90]. Suppressive activities of passively infused anti-SIV antibodies on viral replication in SIVmac251-infected rapid progressors were not observed *in vivo* past the set point [91]. In human peripheral blood leukocyte-reconstituted SCID mice (hu-PBL-SCID mice), monoclonal anti-HIV-1 NAbs administered 3 days after HIV-1 challenge were overwhelmed by established viral replication whereas several hours post-challenge as well as pre-challenge NAb infusion provided sterile protection [92,93].

Our recent results have, however, clearly shown the potency of post-infection NAbs against immunodeficiency virus replication *in vivo*. We performed passive NAb immunisation post-infection in SIVmac239-challenged rhesus macaques by using polyclonal antibodies purified from chronically infected macaques with NAb induction. The passive immunisation at day 7 post-challenge, preceding peak replication, resulted in significant suppression of viral replication past the limited duration of detectable NAb responses (Figures 1 and 2D) [94]. *De novo* SIVmac239-NAb responses were not involved in this viral control. Analysis revealed immediate accumulation of viral RNA to peripheral lymph node dendritic cells (DCs) after NAb passive immunisation, and pulsing of DCs with antibody-neutralised SIV activated virus-specific $CD4^+$ T lymphocytes *in vitro* in an antibody Fc-dependent manner, suggesting antibody-mediated virion uptake to DCs and a possibility of enhanced T cell priming. This study provided evidence indicating that potent NAb induction post-infection can in fact result in primary immunodeficiency virus control, and points out a possibility of non-sterile HIV control by prophylactic vaccine-induced, sub-sterile titers of NAbs post-infection, lending support for current efforts on vaccine induction of NAbs. Reversely, it suggested direct and indirect contribution of primary NAb absence to viral persistence.

The current mainstream of vaccine strategy for NAb induction is a rational design of immunogens mimicking broadly reactive neutralisation epitopes based on structural approaches on the HIV/SIV envelope protein and NAbs [71,95–99]. Broadly reactive monoclonal NAbs such as b12, 447-52D, 2G12, 2F5 and 4E10 have been characterised [100–103], and some have recently been confirmed to be potent to suppress rebound viremia when administered to HIV-infected humans undergoing structured treatment interruption (STI) [104]. Yet viral escape from autologous NAb responses in HIV-infected humans has been reported to occur in a manner of rapid and repetitive chase accompanying conformational masking, which may continuously limit the total neutralisation spectrum [72–74,105]. It is of our great interest if or how vaccine-induced primary and secondary NAb responses can overcome this propensity of escape and provide viral control.

A POSSIBILITY OF NON-STERILE HIV CONTROL

While given the difficulty in sterile HIV control, our passive immunisation study has indicated a possibility of non-sterile viral control by transient NAb responses post-infection [94], which may reflect another essence of immune dysfunction at the initial stage of HIV infection. Inefficient primary NAb induction can be seen as the lack of one effector out of the two wings of adaptive immune responses, humoral and cellular, but in addition may also affect the remaining cellular immune responses and contribute to their dysfunction due to abrogated antigen presentation.

Activities of specific antibody-mediated pathogen internalisation conventionally categorised in the genre of opsonisation are well known to occur in responses against bacterial and parasitic infections [106], but their involvement in antigen presentation have been clarified only recently [107]. Possible involvement of antibody-mediated antigen presentation in modification of cellular immunity [108,109] has not been discussed directly in the context of antiviral adaptive immunity [110,111], and this synergistic mechanism has not drawn primary attention in self-remitting acute viral infections, where the appearance of anti-viral NAbs mostly results in viral control. NAbs may facilitate induction of virus-specific $CD4^+$ T lymphocytes via efficient virion uptake into DCs, in turn functionally supporting virus-specific cellular immunity behind the scenes and providing consistent, fail-safe control of viral replication in combination with augmented CTLs. Reversely,

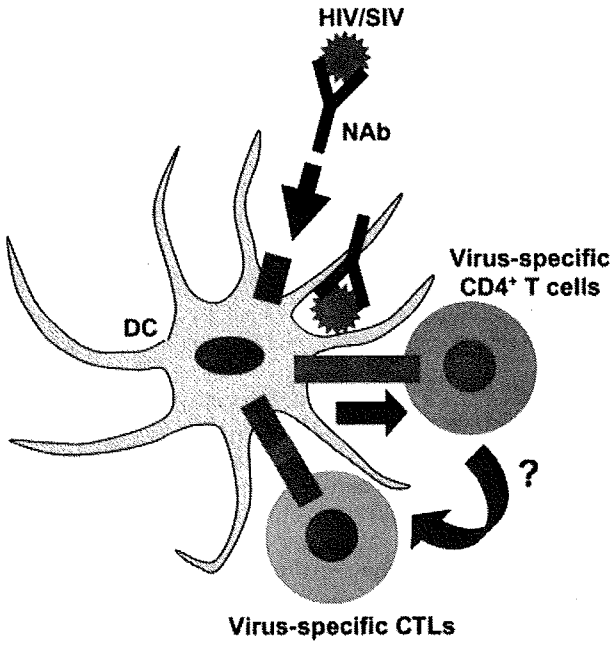

Figure 3. A putative model of NAbs synergising with virus-specific cellular immunity for HIV/SIV control. In the acute phase of viral infection, non-neutralising virus-specific antibodies may enhance antibody-mediated virion uptake into DCs leading to efficient antigen presentation to virus-specific $CD4^+$ T lymphocytes but fail to protect these cells from viral infection. In contrast, virus-specific NAbs, if induced, can not only induce but also protect virus-specific $CD4^+$ T cells, resulting in elicitation of virus-specific $CD4^+$ T-cell responses. Whether the protection of virus-specific $CD4^+$ T cells results in modification of virus-specific CTL function is an open question

abrogation of this process in infections of neutralisation-resistant viruses such as HIV and SIV may result in establishment of persistent viral infection in the absence of potent cellular immune responses [112].

Elicitation of virus-specific $CD4^+$ T lymphocytes could result in expansion of the targets of HIV infection [113]. In the antibody-mediated enhancement of antigen presentation leading to cellular immune induction described above, virus neutralisation activity would be required at least during the acute phase for protection of the induced virus-specific $CD4^+$ T lymphocytes from HIV/SIV infection via transmission from virus-exposed DCs [114,115]. Thus, our passive NAb immunisation study highlighted the active and protective role of NAbs in induction of functional virus-specific $CD4^+$ T-cell responses (Figure 3).

PERSPECTIVES

Elucidation of the determinants for HIV persistence would contribute to clarification of the requisites for viral control. Full commitment of potent CTLs under MHC restriction in concert with MHC-independent NAb responses would result in inhibition of persistent HIV infection. Further analyses determining the requisites for viral control may reveal novel endpoints for well-concerted elicitation of anti-HIV immunity by prophylactic vaccination.

REFERENCES

1. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996; **272**: 872–877.
2. Deng H, Liu R, Ellmeier W, *et al.* Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 1996; **381**: 661–666.
3. Dragic T, Litwin V, Allaway GP, *et al.* HIV-1 entry into $CD4^+$ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 1996; **383**: 667–673.
4. Endres MJ, Clapham PR, Marsh M, *et al.* CD4-independent infection by HIV-2 is mediated by fusin/CXCR4. *Cell* 1996; **87**: 745–756.
5. Wolinsky SM, Wike CM, Korber BT, *et al.* Selective transmission of human immunodeficiency virus type-1 variants from mothers to infants. *Science* 1992; **255**: 1134–1136.
6. McNearney T, Hornickova Z, Markham R, *et al.* Relationship of human immunodeficiency virus type 1 sequence heterogenicity to stage of disease. *Proc Natl Acad Sci USA* 1992; **89**: 10247–10251.
7. Zhu T, Mo H, Wang N, *et al.* Genotypic and phenotypic characterization of HIV-1 in patients with primary infection. *Science* 1993; **261**: 1179–1181.
8. Veazey RS, DeMaria M, Chalifoux LV, *et al.* Gastrointestinal tract as the major site of $CD4^+$ T cell depletion and viral replication in SIV infection. *Science* 1998; **280**: 427–431.
9. Veazey RS, Mansfield KG, Tham IC, *et al.* Dynamics of CCR5 expression by $CD4^+$ T cells in lymphoid tissues during simian immunodeficiency virus infection. *J Virol* 2000; **77**: 9710–9715.
10. Pitcher CJ, Hagen SI, Walker JM, *et al.* Development and homeostasis of T cell memory in rhesus macaque. *J Immunol* 2002; **168**: 29–43.
11. Nishimura Y, Igarashi T, Donau OK, *et al.* Highly pathogenic SHIVs and SIVs target different $CD4^+$ T cell subsets in rhesus monkeys, explaining their divergent clinical courses. *Proc Natl Acad Sci USA* 2004; **101**: 12324–12329.

12. Picker LJ, Hagen SI, Lum R, *et al.* Insufficient production and tissue delivery of $CD4^+$ memory T cells in rapidly progressive simian immunodeficiency virus infection. *J Exp Med* 2004; **200**: 1299–1314.
13. Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin MA, Roederer M. Massive infection and loss of memory $CD4^+$ T cells in multiple tissues during acute SIV infection. *Nature* 2005; **434**: 1093–1097.
14. Li Q, Duan L, Estes JD, *et al.* Peak SIV replication in resting memory $CD4^+$ T cells depletes gut lamina propria CD4+ T cells. *Nature* 2005; **434**: 1148–1152.
15. Picker LJ, Watkins DI. HIV pathogenesis: the first cut is the deepest. *Nat Immunol* 2005; **6**: 430–432.
16. Nishimura Y, Brown CR, Mattapallil JJ, *et al.* Resting naïve $CD4^+$ T cells are massively infected and eliminated by X4-tropic simian-human immunodeficiency viruses in macaques. *Proc Natl Acad Sci USA* 2005; **102**: 8000–8005.
17. Barouch DH, Santra S, Schmitz JE, *et al.* Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination. *Science* 2000; **290**: 486–492.
18. Amara RR, Villinger F, Altman JD, *et al.* Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science* 2001; **292**: 69–74.
19. Matano T, Kano M, Nakamura H, *et al.* Rapid appearance of secondary immune responses and protection from acute CD4 depletion after a highly pathogenic immunodeficiency virus challenge in macaques vaccinated with a DNA prime/Sendai virus vector boost regimen. *J Virol* 2001; **75**: 11891–11896.
20. Rose NF, Marx PA, Luckay A, *et al.* An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. *Cell* 2001; **106**: 539–549.
21. Shiver JW, Fu TM, Chen L, *et al.* Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency virus immunity. *Nature* 2002; **415**: 331–335.
22. Willey RL, Byrum R, Piatak M, *et al.* Control of viremia and prevention of simian-human immunodeficiency virus-induced disease in rhesus macaques immunized with recombinant vaccinia viruses plus inactivated simian immunodeficiency virus and human immunodeficiency virus particles. *J Virol* 2003; **77**: 1163–1174.
23. Feinberg MB, Moore JP. AIDS vaccine models: challenging challenge viruses. *Nat Med* 2002; **8**: 207–210.
24. Horton H, Vogel TU, Carter DK, *et al.* Immunization of rhesus macaques with a DNA prime/modified vaccinia virus Ankara boost regimen induces broad simian immunodeficiency virus (SIV)-specific T-cell responses and reduces initial virus replication but does not prevent disease progression following challenge with pathogenic SIVmac239. *J Virol* 2002; **76**: 7187–7202.
25. Casimiro DR, Wang F, Schleif A, *et al.* Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with DNA and recombinant adenoviral vaccine vectors expressing Gag. *J Virol* 2005; **79**: 15547–15555.
26. Mattapallil JJ, Douek DC, Buckler-White A, *et al.* Vaccination preserves CD4 memory T cells during acute simian immunodeficiency virus challenge. *J Exp Med* 2006; **203**: 1533–1541.
27. Letvin NL, Mascola JR, Sun Y, *et al.* Preserved $CD4^+$ central memory T cells and survival in vaccinated SIV-challenged monkeys. *Science* 2006; **312**: 1530–1533.
28. Wilson NA, Reed J, Napoe GS, *et al.* Vaccine-induced cellular immune responses reduce plasma viral concentrations after repeated low-dose challenge with pathogenic simian immunodeficiency virus SIVmac239. *J Virol* 2006; **80**: 5875–5885.
29. Matano T, Kobayashi M, Igarashi H, *et al.* Cytotoxic T lymphocyte-based control of simian immunodeficiency virus replication in a preclinical AIDS vaccine trial. *J Exp Med* 2004; **199**: 1709–1718.
30. Koup RA, Safrit JT, Cao Y, *et al.* Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. *J Virol* 1994; **68**: 4650–4655.
31. Borrow P, Lewicki H, Hahn BH, Shaw GM, Oldstone MB. Virus-specific $CD8^+$ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. *J Virol* 1994; **68**: 6103–6110.
32. Matano T, Shibata R, Siemon C, Connors M, Lane HC, Martin MA. Administration of an anti-CD8 monoclonal antibody interferes with the clearance of chimeric simian/human immunodeficiency virus during primary infections of rhesus macaques. *J Virol* 1998; **72**: 164–169.
33. Schmitz JE, Kuroda MJ, Santra S, *et al.* Control of viremia in simian immunodeficiency virus infection by $CD8^+$ lymphocytes. *Science* 1999; **283**: 857–860.
34. Jin X, Bauer DE, Tittleton SE, *et al.* Dramatic rise in plasma viremia after CD8(+) T cell depletion in simian immunodeficiency virus-infected macaques. *J Exp Med* 1999; **189**: 991–998.
35. Goulder PJ, Watkins DI. HIV and SIV CTL escape: implications for vaccine design. *Nat Rev Immunol* 2004; **4**: 630–640.

Rev. Med. Virol. 2008; **18**: 293–303.
DOI: 10.1002/rmv

36. McNeil AC, Shupert WL, Iyasere CA, *et al.* High-level HIV-1 viremia suppresses antigen-specific CD4(+) T cell proliferation. *Proc Natl Acad Sci USA* 2001; **98**: 13878–13883.
37. Douek DC, Brenchley JM, Betts MR, *et al.* HIV preferentially infects HIV-specific $CD4^+$ T cells. *Nature* 2002; **417**: 95–98.
38. Day CL, Kaufmann DE, Kiepiela P, *et al.* PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* 2006; **443**: 350–354.
39. Petrovas C, Casazza JP, Brenchley JM, *et al.* PD-1 is a regulator of virus-specific $CD8^+$ T cell survival in HIV infection. *J Exp Med* 2006; **203**: 2281–2292.
40. Trautmann L, Janbazian L, Chomont N, *et al.* Upregulation of PD-1 expression on HIV-specific $CD8^+$ T cells leads to reversible immune dysfunction. *Nat Med* 2006; **12**: 1198–1202.
41. Kirchhoff F, Greenough TC, Brettler DB, Sullivan JL, Desrosiers RC. Brief report: absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection. *N Engl J Med* 1995; **332**: 228–232.
42. Samson M, Libert F, Doranz BJ, *et al.* Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 1996; **382**: 668–669.
43. Huang Y, Paxton WA, Wolinsky SM, *et al.* The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med* 1996; **2**: 1240–1243.
44. Carrington M, Nelson GW, Martin MP, *et al.* HLA and HIV-1: heterozygote advantage and B*35-Cw-04 disadvantage. *Science* 1999; **283**: 1748–1752.
45. Kaslow RA, Carrington M, Apple R, *et al.* Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med* 1996; **2**: 405–411.
46. Goulder PJ, Bunce M, Krausa P, *et al.* Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. *AIDS Res Hum Retroviruses* 1996; **12**: 1691–1698.
47. Migueles SA, Sabbaghian MS, Shupert WL, *et al.* HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc Natl Acad Sci USA* 2000; **97**: 2709–2714.
48. Tang J, Tang S, Lobashevsky E, *et al.* Favorable and unfavorable HLA class 1 alleles and haplotypes in Zambians predominantly infected with clade C human immunodeficiency virus type 1 in Zambia. *J Virol* 2002; **76**: 8276–8284.
49. Kiepiela P, Leslie AJ, Honeyborne I, *et al.* Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature* 2004; **432**: 769–775.
50. Bailey JR, Williams TM, Siliciano RF, Blankson JN. Maintenance of viral suppression in HIV-1-infected HLA-B*57 elite suppressors despite CTL escape mutations. *J Exp Med* 2006; **203**: 1357–1369.
51. Muhl T, Krawczak M, Ten Haaft P, Hunsmann G, Sauermann U. MHC class I alleles influence set-point viral load and survival time in simian immunodeficiency virus-infected rhesus monkeys. *J Immunol* 2002; **169**: 3438–3446.
52. Mothe BR, Weinfurter J, Wang C, *et al.* Expression of the major histocompatibility complex class I molecule Mamu-A*01 is associated with control of simian immunodeficiency virus SIVmac239 replication. *J Virol* 2003; **77**: 2736–2740.
53. Yant LJ, Friedrich TC, Johnson RC, *et al.* The high-frequency major histocompatibility complex class I allele Mamu-B*17 is associated with control of simian immunodeficiency virus SIVmac239 replication. *J Virol* 2006; **80**: 5074–5077.
54. Loffredo JT, Maxwell J, Qi Y, *et al.* Mamu-B*08-positive macaques control simian immunodeficiency virus replication. *J Virol* 2007; **81**: 8827–8832.
55. Peyerl FW, Barouch DH, Yeh WW, *et al.* Simian-human immunodeficiency virus escape from cytotoxic T lymphocyte recognition at a structurally constrained epitope. *J Virol* 2003; **77**: 12572–12578.
56. Friedrich TC, Dodds EJ, Yant LJ, *et al.* Reversion of CTL escape-variant immunodeficiency viruses in vivo. *Nat Med* 2004; **10**: 275–281.
57. Leslie AJ, Pfafferott KJ, Chetty P, *et al.* HIV evolution: CTL escape mutation and reversion after transmission. *Nat Med* 2004; **10**: 282–289.
58. Kobayashi M, Igarashi H, Takeda A, Kato M, Matano T. Reversion in vivo after inoculation of a molecular proviral DNA clone of simian immunodeficiency virus with a cytotoxic T-lymphocyte escape mutation. *J Virol* 2005; **79**: 11529–11532.
59. Kawada M, Igarashi H, Takeda A, *et al.* Involvement of multiple epitope-specific cytotoxic T-lymphocyte responses in vaccine-based control of simian immunodeficiency virus replication in rhesus macaques. *J Virol* 2006; **80**: 1949–1958.
60. Goulder PJ, Phillips RE, Colbert RA, *et al.* Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat Med* 1997; **3**: 212–217.
61. Barouch DR, Kunstman J, Kuroda MJ, *et al.* Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature* 2002; **415**: 335–339.
62. Feeney ME, Tang Y, Roosevelt KA, *et al.* Immune escape precedes breakthrough HIV-1 viremia and broadening of the CTL response in a HLA-B-

27-positive long-term non-progressing child. *J Virol* 2004; **78**: 8927–8930.
63. Frahm N, Kiepiela P, Adams S, *et al.* Control of human immunodeficiency virus replication by cytotoxic T lymphocytes targeting subdominant epitopes. *Nat Immunol* 2006; **7**: 173–178.
64. Friedrich TC, Valentine LE, Yant LJ, *et al.* Subdominant $CD8^+$ T-cell responses are involved in durable control of AIDS virus replication. *J Virol* 2007; **81**: 3465–3476.
65. Kawada M, Tsukamoto T, Yamamoto H, *et al.* Long-term control of simian immunodeficiency virus replication with central memory $CD4^+$ T-cell preservation after nonsterile protection by a cytotoxic T-lymphocyte-based vaccine. *J Virol* 2007; **81**: 5202–5211.
66. Yang OO, Kalams SA, Trocha A, *et al.* Suppression of human immunodeficiency virus type 1 replication by $CD8^+$ T cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. *J Virol* 1997; **71**: 3120–3128.
67. Loffredo JT, Rakasz EG, Giraldo JP, *et al.* Tat_{28-35}SL8-specific $CD8^+$ T lymphocytes are more effective than $Gag_{181-189}$CM9-specific $CD8^+$ T lymphocytes at suppressing simian immunodeficiency virus replication in a functional in vitro assay. *J Virol* 2005; **79**: 14986–14991.
68. Tsukamoto T, Yuasa M, Yamamoto H, *et al.* Induction of $CD8^+$ cells able to suppress CCR5-tropic simian immunodeficiency virus replication by controlled infection of CXCR4-tropic simian-human immunodeficiency virus in vaccinated rhesus macaques. *J Virol* 2007; **81**: 11640–11649.
69. Sacha JB, Chung C, Rakasz EG, *et al.* Gag-specific $CD8^+$ T lymphocytes recognize infected cells before AIDS-virus integration and viral protein expression. *J Immunol* 2007; **178**: 2746–2754.
70. Kiepiela P, Ngumbela K, Thobakgale C, *et al.* $CD8^+$ T-cell responses to different HIV proteins have discordant associations with viral load. *Nat Med* 2007; **13**: 46–53.
71. Burton DR, Desrosiers RC, Doms RW, *et al.* HIV vaccine design and the neutralizing antibody problem. *Nat Immunol* 2004; **5**: 233–236.
72. Kwong PD, Doyle ML, Casper DJ, *et al.* HIV-1 evades antibody-mediated neutralization through conformational masking of receptor-binding sites. *Nature* 2002; **420**: 678–682.
73. Wei X, Decker JM, Wang S, *et al.* Antibody neutralization and escape by HIV-1. *Nature* 2003; **422**: 307–312.
74. Richman DD, Wrin T, Little SJ, Petropoulos CJ. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. *Proc Natl Acad Sci USA* 2003; **100**: 4144–4149.
75. Johnson WE, Liffson JD, Lang SM, Johnson RP, Desrosiers RC. Importance of B-cell responses for immunological control of variant strains of simian immunodeficiency virus. *J Virol* 2003; **77**: 375–381.
76. Schmitz JE, Kuroda MJ, Santra S, *et al.* Effect of humoral immune responses on controlling viremia during primary infection of rhesus monkeys with simian immunodeficiency virus. *J Virol* 2003; **77**: 2165–2173.
77. Mao H, Lafont BAP, Igarashi T, *et al.* $CD8^+$ and $CD20^+$ lymphocytes cooperate to control acute simian immunodeficiency virus/human immunodeficiency virus chimeric virus infections in rhesus monkeys: modulation by major histocompatibility complex genotype. *J Virol* 2005; **79**: 14887–14898.
78. Mascola JR, Lewis MG, Stiegler G, *et al.* Protection of macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol* 1999; **73**: 4009–4018.
79. Shibata R, Igarashi T, Haigwood N, *et al.* Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat Med* 1999; **5**: 204–210.
80. Mascola JR, Stiegler G, VanCott TC, *et al.* Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat Med* 2000; **6**: 207–210.
81. Nishimura Y, Igarashi T, Haigwood N, *et al.* Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* 2002; **76**: 2123–2130.
82. Moore JP, Burton, DR. HIV-1 neutralizing antibodies: how full is the bottle? *Nat Med* 1999; **5**: 142–144.
83. Putkonen P, Thorstensson P, Ruden U, *et al.* Prevention of HIV-2 and SIVsm infection by passive immunization in cynomolgus monkeys. *Nature* 1991; **352**: 436–438.
84. Lewis MG, Elkins WR, McCutchan FE, *et al.* Passively transferred antibodies directed against conserved regions of SIV envelope protect macaques from SIV infection. *Vaccine* 1993; **11**: 1347–1355.
85. Parren PW, Marx PA, Hessel AJ, *et al.* Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* 2001; **75**: 8340–8347.
86. Veazey RS, Shattock RJ, Pope M, *et al.* Prevention of virus transmission to macaque monkeys by a

vaginally applied monoclonal antibody to HIV-1 gp120. *Nat Med* 2003; **9**: 343–346.
87. Hessel AJ, Hangartner L, Hunter M, *et al.* Fc receptor but not complement activation is important in antibody protection against HIV. *Nature* 2007; **352**: 436–438.
88. Nishimura Y, Igarashi T, Haigwood NL, *et al.* Transfer of neutralizing IgG to macaques 6 h but not 24 h after SHIV infection confers sterilizing protection: implications for HIV-1 vaccine development. *Proc Natl Acad Sci USA* 2003; **100**: 15131–15136.
89. Haigwood NL, Watson A, Sutton WF, *et al.* Passive immune globulin therapy in the SIV/macaque model: early intervention can alter disease profile. *Immunol Lett* 1996; **51**: 107–114.
90. Haigwood NL, Montefiori DC, Sutton WF, *et al.* Passive immunotherapy in simian immunodeficiency virus-infected macaques accelerates the development of neutralizing antibodies. *J Virol* 2004; **78**: 5983–5995.
91. Binley JM, Clas B, Gettie A, *et al.* Passive infusion of immune serum into simian immunodeficiency virus-infected rhesus macaques undergoing a rapid disease course has minimal effect on plasma viremia. *Virology* 2000; **270**: 237–249.
92. Gauduin MC, Parren PWHI, Weir R, *et al.* Passive immunization with a human monoclonal antibody protects hu-PBL-SCID mice against challenge by primary isolates of HIV-1. *Nat Med* 1997; **3**: 1389–1393.
93. Poignard P, Sabbe R, Picchio GR, *et al.* Neutralizing antibodies have limited effects on the control of established HIV-1 infection in vivo. *Immunity* 1999; **10**: 431–438.
94. Yamamoto H, Kawada M, Takeda A, Igarashi H, Matano T. Post-infection immunodeficiency virus control by neutralizing antibodies. *PLoS ONE* 2007; **2**: e540.
95. Kwong PD, Wyatt R, Robinson J, *et al.* Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature* 1998; **393**: 648–659.
96. Wyatt R, Kwong PD, Desjardins E, *et al.* The antigenic structure of the HIV gp120 envelope glycoprotein. *Nature* 1998; **393**: 705–711.
97. Chen B, Vogan EM, Gong H, *et al.* Structure of an unliganded simian immunodeficiency virus gp120 core. *Nature* 2005; **433**: 834–841.
98. Zanetti G., Briggs JA, Grunewald K, Sattentau QJ, Fuller SD. Cryo-electron tomographic structure of an immunodeficiency virus envelope complex in situ. *PLoS Pathog* 2006; **2**: e83.
99. McMichael AJ. HIV vaccines. *Annu Rev Immunol* 2006; **24**: 227–255.
100. Saphire EO, Parrew PW, Pantophlet R, *et al.* Crystal structure of a neutralizing IgG against HIV-1: a template for vaccine design. *Science* 2001; **293**: 1155–1159.
101. Calarese DA, Scanlan CN, Zwick MB, *et al.* Antibody domain exchange is an immunological solution to carbohydrate cluster recognition. *Science* 2003; **300**: 2065–2071.
102. Zwick MB, Komori HK, Stanfield RL, *et al.* The long third complementarity-determining region of the heavy chain is important in the activity of the broadly neutralizing anti-human immunodeficiency virus type 1 antibody 2F5. *J Virol* 2004; **78**: 3155–3161.
103. Haynes BF, Fleming J, St Clair EW, *et al.* Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* 2005; **308**: 1906–1908.
104. Trkola A, Kuster H, Rusert P, *et al.* Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. *Nat Med* 2005; **11**: 615–622.
105. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. *Proc Natl Acad Sci USA* 2005; **102**: 14943–14948.
106. Nimmerjahn F, Ravetch JV. Fcgamma receptors: old friends and new family members. *Immunity* 2006; **24**: 19–28.
107. Woelbing F, Kostka SL, Moelle K, *et al.* Uptake of *Leishmania major* by dendritic cells is mediated by Fcgamma receptors and facilitates acquisition of protective immunity. *J Exp Med* 2006; **203**: 177–188.
108. Regnault A, Lankar D, Lacabanne V, *et al.* Fcgamma receptor-mediated induction of dendritic cell maturation and major histocompatibility complex class I-restricted antigen presentation after immune complex internalization. *J Exp Med* 1999; **189**: 371–380.
109. Schuurhuis DH, Ioan-Facsinay A, Nagelkerken, *et al.* Antigen-antibody immune complexes empower dendritic cells to efficiently prime specific $CD8^+$ CTL responses in vivo. *J Immunol* 2002; **168**: 2240–2246.
110. Thomas PG, Brown SA, Yue W, So J, Webby RJ, Doherty PC. An unexpected antibody response to an engineered influenza virus modifies CD8+ T cell responses. *Proc Natl Acad Sci USA* 2006; **103**: 2764–2769.
111. Hangartner L, Zinkernagel RM, Hengartner H. Antiviral antibody responses: the two extremes of a wide spectrum. *Nat Rev Immunol* 2006; **6**: 231–243.
112. Castellino F, Germain RN. Cooperation between $CD4^+$ and $CD8^+$ T cells: when, where, and how. *Annu Rev Immunol* 2006; **24**: 519–540.

113. Staprans SI, Barry AP, Silvestri G, *et al.* Enhanced SIV replication and accelerated progression to AIDS in macaques primed to mount a CD4 T cell response to the SIV envelope protein. *Proc Natl Acad Sci USA* 2004; **101**: 13026–13031.
114. Frankel SS, Steinman RM, Michael NL, *et al.* Neutralizing monoclonal antibodies block human immunodeficiency virus type 1 infection of dendritic cells and transmission to T cells. *J Virol* 1998; **72**: 9788–9794.
115. Lore K, Smed-Sorensen A, Vasudevan J, Mascola JR, Koup RA. Myeloid and plasmacytoid dendritic cells transfer HIV-1 preferentially to antigen-specific $CD4^+$ T cells. *J Exp Med* 2005; **201**: 2023–2033.

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