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Association of MHC-I genotypes with disease progression in HIV/SIV infections

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Virus-specific cytotoxic T lymphocytes (CTLs) are major effectors in acquired immune responses against viral infection. Virus-specific CTLs recognize specific viral peptides presented by major histocompatibility complex class-I (MHC-I) on the surface of virus-infected target cells via their T cell receptor (TCR) and eliminate target cells by both direct and indirect mechanisms. In human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infections, host immune responses fail to contain the virus and allow persistent viral replication, leading to AIDS progression. CTL responses exert strong suppressive pressure on HIV/SIV replication and cumulative studies have indicated association of HLA/MHC-I genotypes with rapid or slow AIDS progression.

Keywords: CTL, HIV, HLA, Mamu, MHC-I, MHC-I haplotype, SIV

INTRODUCTION

Innate and acquired immune responses play an important role in the control of infectious pathogens. Pathogenic microbes are able to escape from the host innate immune responses and replicate in the hosts. After the acute growth phase, pathogen-specific neutralizing antibody and cytotoxic T lymphocyte (CTL) responses are induced and prevent the onset of pathogenic manifestations in most of acute infectious diseases. In HIV and simian immunodeficiency virus (SIV) infections, these acquired immune responses are induced but fail to contain the virus and allow persistent viral replication, leading to AIDS progression, while persistent SIVsm infection of natural hosts, sooty mangabeys, does not result in disease onset (Silvestri et al., 2003). Effective neutralizing antibody responses are not efficiently induced in the acute phase (Burton et al., 2004). In contrast, virus-specific CTL responses play a main role in the reduction of viral loads from the peak to the set-point levels (Borrow et al., 1994; Koup et al., 1994; Matano et al., 1998; Jin et al., 1999; Schmitz et al., 1999). Previous studies suggest that, among various viral antigen-specific CTL responses, those directed against the viral structural protein Gag contribute to the control of viral replication (Edwards et al., 2002; Zuniga et al., 2006; Borghans et al., 2007; Kiepiela et al., 2007).

In virus-infected cells, antigenic peptides that are processed from viral proteins via the proteasome pathway and bound to MHC-I (HLA class I) molecules are presented on the cell surface. CTLs recognize antigenic peptide (epitope)-MHC-I complexes on the cell surface by their TCRs and eliminate the virus-infected cells by inducing apoptosis or lysis. Because presentation of antigenic peptides is restricted by MHC-I molecules, CTL efficacy is affected by MHC-I (HLA class I) genotypes.

ASSOCIATION OF HLA ALLELES WITH HIV PROGRESSION

HIV-infected individuals without anti-retroviral therapy (ART) mostly develop AIDS in 5–10 years after HIV exposure (Lui et al., 1988; Farewell et al., 1992). Humans have a single polymorphic HLA-A, HLA-B, and HLA-C locus per chromosome. A number of studies on HIV-infected individuals reported the association of HLA genotypes with disease progression (Tang et al., 2002; Kiepiela et al., 2004; Wang et al., 2009; Leslie et al., 2010). Indeed, association of *HLA-B*57* (Migueles et al., 2000; Altfeld et al., 2003; Miura et al., 2009) and *HLA-B*27* (Goulder et al., 1997; Feeney et al., 2004; Altfeld et al., 2006; Schneidewind et al., 2007) with lower viral loads in the chronic phase and slow disease progression has been indicated. HLA-B*57-restricted $Gag_{240-249}$ TW10 (TSTLQEQIGW) and HLA-B*27-restricted $Gag_{263-272}$ KK10 (KRWIILGLNK) epitope-specific CTL responses exert strong suppressive pressure on HIV replication and often select for viral genome mutations resulting in viral escape from these CTL recognition with viral fitness costs (Goulder et al., 1997; Feeney et al., 2004). Some HIV-infected individuals possessing those HLA alleles associating with slower disease progression control viral replication for long periods, while the frequency of such elite controllers is under 1% (Lambotte et al., 2005; Grabar et al., 2009). In contrast, HLA genotypes such as *HLA-B*35* associating with rapid disease progression have also been reported (Carrington et al., 1999; Gao et al., 2001). *HLA-B*35* subtypes are divided into *HLA-B*35-Px* and *HLA-B*35-Py* based on the specificity of binding ability to epitope peptides in the P9 pocket. The former group, *HLA-B*35-Px* alleles including *HLA-B*3502*, *B*3503*, and *B*3504* associate with rapid disease progression, whereas the latter *HLA-B*35-Py* alleles including *HLA-B*3501* and *HLA-B*3508* associate with relatively slower progression (Gao et al., 2001). Such differences in disease progression among *HLA-B* subtypes are also known in *HLA-B*58* (Leslie et al., 2010).

ANIMAL AIDS MODELS

Robust non-human primate AIDS models showing high pathogenic homology to human HIV infections are essential for

AIDS research. While it is difficult to analyze the early phase in human HIV infection, animal models have considerable advantages in immunological analysis in the acute phase. Furthermore, comparisons among the hosts infected with the same virus strain are possible in animal AIDS models, although highly diversified HIVs are prevalent in humans. An important characteristic of HIV infection is selective loss of memory $CCR5^+$ $CD4^+$ T lymphocytes in the acute phase leading to persistent virus replication (Connor et al., 1997; Zhang et al., 1999; Brenchley et al., 2004). HIV tropism for $CCR5^+$ $CD4^+$ memory cells is considered as one central mechanism for persistent infection. R5-tropic SIVmac251/SIVmac239 or SIVsmE660/SIVsmE543-3 infection of rhesus macaques inducing the acute, selective loss of memory $CD4^+$ T lymphocytes is currently considered the best AIDS model for analysis of AIDS pathogenesis and evaluation of vaccine efficacy (Veazey et al., 1998; Nishimura et al., 2004; Bontrop and Watkins, 2005; Mattapallil et al., 2005; Morgan et al., 2008). Recent studies indicated an association of restriction factor TRIM5α genotypes with disease progression in macaques infected with pathogenic SIVs such as SIVsmE660/SIVsmE543-3 but not in SIVmac239 infection (Kirmaier et al., 2010; Lim et al., 2010; de Groot et al., 2011; Fenizia et al., 2011; Letvin et al., 2011; Reynolds et al., 2011; Yeh et al., 2011). Macaque AIDS models of chimeric simian-human immunodeficiency virus (SHIV) infection are also known. Infection with X4-tropic SHIVs such as SHIV89.6P results in acute $CD4^+$ T cell depletion, while R5-tropic SHIVs such as SHIV162P3 induce persistent infection leading to chronic disease progression (Tsai et al., 2007; Nishimura et al., 2010; Zhuang et al., 2011). These SHIVs are useful especially for the analysis of Env-specific antibody responses (Ng et al., 2010; Watkins et al., 2011).

GENETIC FEATURES OF MHC-I IN MACAQUES

Human classical MHC-I alleles are composed of a single polymorphic HLA-A, HLA-B, and HLA-C locus per chromosome. MHC-I haplotypes in rhesus macaques, however, have variable numbers of Mamu-A and Mamu-B loci (Boyson et al., 1996; Adams and Parham, 2001; Daza-Vamenta et al., 2004; Kulski et al., 2004; Otting et al., 2005; **Figure 1**). A number of studies described SIV infections in macaques sharing one or two MHC-I alleles, while few studies have examined SIV infection in macaques sharing an MHC-I haplotype.

PROTECTIVE MHC-I ALLELES IN INDIAN RHESUS MACAQUES AGAINST SIV INFECTION

Simian immunodeficiency virus infections of Indian rhesus macaques are widely used as an AIDS model. *Mamu-A*01*, *Mamu-B*08*, and *Mamu-B*17* are known as protective alleles and macaques possessing these alleles tend to show slow disease progression after SIVmac251/SIVmac239 challenge (Muhl et al., 2002; Mothe et al., 2003; Yant et al., 2006; Loffredo et al., 2007b). Fourteen Mamu-A*01-restricted SIVmac239 CTL epitopes have been reported (Allen et al., 2001; Mothe et al., 2002b). Mamu-A*01-restricted Tat_{28-35} SL8 (STPESANL)-specific and $Gag_{181-189}$ CM9 (CTPYDINQM)-specific CTL responses are induced dominantly in SIVmac239 infection. Both epitope-specific CTLs show strong suppressive capacity against SIVmac239 replication *in vitro* (Loffredo et al., 2005), while the latter but not the former play a major role in suppression of viral replication *in vivo* (O'Connor et al., 2002; Loffredo et al., 2007c). In SHIV89.6P infection, Mamu-A*01-positive macaques elicit CM9-specific CTL responses and show slower disease progression than Mamu-A*01-negative animals (Zhang et al., 2002). Eight Mamu-B*08-restricted SIVmac239 CTL epitopes have been reported; previous studies indicated that $Vif_{123-131}$ RL9 (RRAIRGEQL), $Vif_{172-179}$ RL8 (RRDNRRGL), and $Nef_{137-146}$ RL10 (RRHRILDIYL) epitope-specific CTL responses contribute to viral control (Loffredo et al., 2007a; Loffredo et al., 2008; Valentine et al., 2009; Mudd et al., 2012). SIVmac239 Vif_{66-73} HW8 (HLEVQGYW), $Nef_{165-173}$ IW9 (IRYPKTFGW), and $Nef_{195-203}$ MW9 (MHPAQTSQW) have been reported as Mamu-B*17-restricted CTL epitopes (Mothe et al., 2002a). In addition, cRW9 (RHLAFKCLW) in an alternate reading frame is known as a cryptic epitope (Maness et al., 2007). The cRW9-coding region [nucleotides 6889–6915 in SIVmac239 (accession number M33262)] is located in the same open reading frame that encodes exon 1 of the Rev protein but is downstream of the splice donor site. So, it is not predicted to be translated under normal biological circumstances. However, SIVmac239-infected Mamu-B*17-positive macaques efficiently induce cRW9-specific CTL responses.

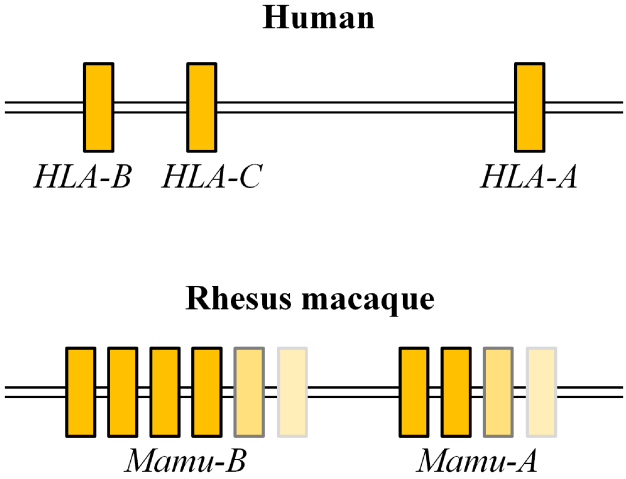

FIGURE 1 | Comparison of genome structures of MHC-I sub-regions in humans and rhesus macaques. Humans have a single polymorphic HLA-A, HLA-B, and HLA-C locus per chromosome, while rhesus macaques have variable numbers of Mamu-A and Mamu-B loci per chromosome.

ASSOCIATION OF MHC-I HAPLOTYPES WITH DISEASE PROGRESSION AFTER SIVmac239 CHALLENGE IN BURMESE RHESUS MACAQUES

We accumulated groups of Burmese rhesus macaques sharing individual MHC-I haplotypes (Tanaka-Takahashi et al., 2007; Naruse et al., 2010). SIVmac239 challenge of Burmese rhesus macaques mostly results in persistent viremia (geometric means of setpoint plasma viral loads: about 10^5 copies/ml) leading to AIDS (mean survival periods: about 2 years; Nomura et al., 2012). Further analysis revealed the association of MHC-I haplotypes with disease progression after SIVmac239 challenge.

Table 1 | Association of MHC-I haplotypes with disease progression in SIV infection (Nomura et al., 2012).

MHC-I haplotypes	Mean survival periods	Geometric means of setpoint plasma viral loads (copies/ml)	Peripheral $CD4^+$ T cell decline	Predominant CTL responses
90-120-Ia	>40 months	10^4	Slow	Gag/Nef
90-010-Ie	23 months	10^5	Intermediate	Nef
90-120-Ib	24 months	10^5	Intermediate	Nef
90-088-Ij	15 months	10^6	Rapid	-

In our study (Nomura et al., 2012), the group of Burmese rhesus macaques possessing MHC-I haplotype *90-010-Ie* (dominant MHC-I alleles: *A1*066:01* and *B*005:02*) exhibited a typical pattern of disease progression after SIVmac239 challenge (**Table 1**). These animals showed predominant Nef-specific CTL responses, approximately 10^5 copies/ml of setpoint plasma viral loads (geometric means), and 2 years of mean survival periods. Another group of macaques possessing *90-120-Ib* (dominant MHC-I alleles: *A1*018:08* and *B*036:03*) showed similar setpoint viral loads and survival periods. However, the group of Burmese rhesus macaques possessing MHC-I haplotype *90-088-Ij* (dominant MHC-I alleles: *A1*008:01* and *B*007:02*) showed higher setpoint plasma viral loads (geometric means: about 10^6 copies/ml) and shorter survival periods (means: about 15 months; **Table 1**). These animals mostly showed poor CTL responses.

In contrast, the group of Burmese rhesus macaques possessing MHC-I haplotype *90-120-Ia* (dominant MHC-I alleles: *A1*043:01* and *B*061:03*), referred to as A^+ animals, showed lower setpoint plasma viral loads (geometric means: about 10^4 copies/ml) and slower disease progression (means of survival periods: more than 40 months; **Table 1**). These animals predominantly elicited Gag-specific and Nef-specific CTL responses after SIVmac239 challenge. Mamu-A1*043:01-restricted $Gag_{206-216}$ (IINEEAADWDL) and Mamu-A1*065:01-restricted $Gag_{241-249}$ (SSVDEQIQW) were determined as dominant CTL epitopes. SIVmac239-infected A^+ animals selected viral escape mutations from these epitope-specific CTL responses with viral fitness costs in the chronic phase (Kobayashi et al., 2005; Kawada et al., 2006). These mutations are GagL216S, a mutation leading to a leucine (L)-to-serine (S) substitution at the 216th amino acid in SIVmac239 Gag, and GagD244E, aspartic acid (D)-to-glutamic acid (E) at the 244th, or GagI247L, isoleucine [I]-to-L at the 247th. A^+ animals immunized with a prophylactic prime-boost vaccine consisting of a DNA prime followed by a boost with a recombinant Sendai virus vector expressing SIVmac239 Gag controlled an SIVmac239 challenge (Matano et al., 2004). However, vaccinated A^+ animals failed to control a challenge with a mutant SIVmac239 carrying GagL216S and GagD244E, indicating that $Gag_{206-216}$-specific and $Gag_{241-249}$-specific CTL responses are responsible for the control of the wild-type SIVmac239 replication (Kawada et al., 2006, 2008). Interestingly, the Mamu-A1*065:01-restricted SIVmac239 $Gag_{241-249}$ epitope is located in a region corresponding to the HLA-B*57-restricted HIV $Gag_{240-249}$ epitope TW10 and TW10-specific CTL responses have also been indicated to exert strong suppressive pressure on HIV replication. An SIVmac239 $Gag_{241-249}$-specific CTL escape mutation, GagD244E, results in loss of viral fitness similarly with an HIV TW10-specific CTL escape mutation. Both of the Mamu-A1*065:01-restricted SIVmac239 $Gag_{241-249}$ epitope and the HLA-B*57-restricted HIV TW10 epitope are considered to have the same anchor residues, S at position 2 and tryptophan (W) at the carboxyl terminus. Additionally, anchor residues of CTL epitopes presented by Mamu-B*17/Mamu-B*08 were indicated to be similar to those restricted by HLA-B*57/HLA-B*27 (Loffredo et al., 2009; Wu et al., 2011).

CONCLUDING REMARKS

Human HLA genotypes largely affect disease progression in HIV infection, reflecting that CTL responses play a central role in suppression of HIV replication. Animal AIDS models are required for understanding of the interaction between highly diversified viruses and the hosts with polymorphic MHC-I genotypes. SIV infection of Indian rhesus macaques are widely used as an AIDS model, and association of certain MHC-I alleles with slower disease progression has been indicated. We have recently reported SIV infection of Burmese rhesus macaques as a robust AIDS model and indicated association of MHC-I haplotypes with disease progression. Accumulation of those macaque groups sharing MHC-I haplotypes could lead to constitution of a more sophisticated AIDS model facilitating analysis of virus-host immune interaction.

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