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Original Article

Differential cell surface expression of rhesus macaque's major histocompatibility complex class I alleles *Mamu-B**1703 and *Mamu-B**0101

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The major histocompatibility complex class I allele *Mamu-B17 of rhesus macaques is an elite controller of simian immunodeficiency virus (SIV) infection whereas *Mamu-B**01 has no inhibitory effect on SIV replication. The mechanism is still elusive. In this study, the so-called 'missing G' in the leading peptide sequence of *Mamu-B**1703 allele was artificially inserted back through PCR amplification, and the new sequence was renamed as *Mamu-B**1703(+G). The plasmids harboring *Mamu-B**1703, *Mamu-B**1703(+G) and *Mamu-B**0101 cDNA sequence fused to *EGFP* gene were transfected into K562 and Cos-7 cells, respectively. Our data showed that these plasmids had similar transfection efficiencies and expression potentials in K562 cells, but the surface density of Mamu-B*1703 complexes, which was slightly influenced by the artificial change of the leading peptide length, was much higher than that of Mamu-B*0101 molecules. These results might partially account for the differential effects of *Mamu-B**17 and *Mamu-B**01 alleles on SIV replication in rhesus macaques.**

Keywords major histocompatibility complex class I; rhesus macaque; *Mamu-B**17; *Mamu-B**01

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Introduction

The rhesus macaques infected with simian immunodeficiency virus (SIV) have become an excellent model for studying acquired immunodeficiency syndrome pathology and its vaccines [1]. Their classical major histocompatibility complex (MHC) class I alleles are titled with *Mamu-A* and *Mamu-B*, which are corresponding to human *HLA-A* and *HLA-B* alleles, respectively [2]. The MHC class I molecules of both species play an important role in cellular immune responses against intracellular pathogens such as viruses. A large number of studies have shown that some human MHC class I alleles, such as *HLA-B**57 and *HLA-B**27, can control the viral load and disease progress in human immunodeficiency virus (HIV)-infected humans [3–5]. And genetic mutations in *HLA-B**5703-restricted epitopes can abrogate its viral and disease control capacity [6]. Similarly, the SIV replication is reported to be markedly suppressed in the rhesus macaques with *Mamu-B**17 (MHC class I) allele [7] whereas another allele, *Mamu-B**01, is believed to have no inhibitory effect on the virus replication [8]. The mechanism is still elusive although a number of SIV epitopes have been identified to be restricted by *Mamu-B**17 rather than by *Mamu-B**01 alleles.

As their human counterparts, the open reading frames of *Mamu-A* and *Mamu-B* are also composed of six domains (sequentially named as leading peptide, α1, α2, α3, transmembrane, and cytoplasmic domains). Although the leading peptide is post-translationally removed, it is important for MHC class I assembly and transmitting to cell surfaces. Most of the Mamu-A and Mamu-B precursors have a 24-aa long leading peptide, but a few of *Mamu-B* alleles, such as *Mamu-B**1703 (EU682520) and *Mamu-B**360102 (EU682518), have a 21-aa leading peptide [9] because there is an evolutional deletion mutation (the deleted guanine nucleotide is named as 'missing G') between the first two ATG codons in the leading peptide-encoding sequence of these alleles.

It is unclear whether the deletion mutation in the leading peptide region of *Mamu-B**17 alleles is able to affect the surface expression level of Mamu-B*17 complexes. *Mamu-B**17 alleles seem to be functional because they are reported to be dominantly present in over 10% of the captive-bred Indian-origin rhesus macaque population [10,11]. And these alleles exhibit elite control effect on SIV_{mac239} infection in Indian macaques [7]. At least 16 *Mamu-B**17-restricted epitopes derived from SIV proteins have been identified to date [10,12]. Due to the importance of *Mamu-B**17 alleles in the elite control models, it is

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attractive to determine whether the deletion mutation would enhance the localization of Mamu-B*17 molecules on cell membrane and thus improve the antigen presentation ability of these MHC class I complexes in the immune response to the virus infection.

In this study, *Mamu-B**1703 and *Mamu-B**0101 (EU682524) cDNA sequence fused with the enhanced green fluorescent protein (EGFP) gene were transfected and expressed in K562 and Cos-7 cells, respectively. The 'missing G' in the leading peptide sequence of *Mamu-B**1703 allele was artificially inserted back through PCR amplification and the new sequence, which should express a precursor protein with a leading peptide of 24 aa as other *Mamu-B* alleles, was renamed as *Mamu-B**1703(+G). Our data demonstrated that the heavy chain of Mamu-B*1703, though the precursor of which has lost three amino acids in its leading peptide region, could still be expressed in K562 cells, assembled with β_2m light chain and transferred to the cell surfaces. The surface density of Mamu-B*1703 complexes was much higher than that of Mamu-B*0101 molecules. These data might partially account for the differential effect of *Mamu-B**17 and *Mamu-B**01 alleles on SIV replication in rhesus macaques, although further investigation is warranted to clarify this issue.

Materials and Methods

Cell lines

Human chronic myelogenous leukemia cell line K562 was purchased from China Centre for Type Culture Collection (CCTCC, Wuhan, China) and African green monkey cell line Cos-7 (kidney) was from KeyGEN (Nanjing, China). K562 cells were maintained in RPMI 1640 medium (Invitrogen, Carlsbad, USA) plus 10% fetus bovine serum (FBS; Invitrogen) and Cos-7 cells maintained in Dulbecco's modified Eagle's medium (DMEM; Invitrogen) plus 10% FBS in a humidified 5% CO_2 incubator at 37°C. The cells were sub-cultured every 2–3 days.

Vectors and reagents

Eukaryotic expression vector pEGFP-N1 was bought from ClonTech (Palo Alto, USA) and pET-3d was from Novagen (Madison, USA). The transfection reagent Trans-EZ was a product of Shanghai Sunbio Medical Biotechnology Co. (Shanghai, China) and DMRIE-C reagent was purchased from Invitrogen.

Antibodies

Mamu-B*1703-IW9 monomer was constructed by refolding Mamu-B*1703-BSP fusion protein, human β_2m and IW9 peptide as reported previously by our laboratory [13]. The anti-Mamu-B*1703 antiserum was raised in C57BL/6 mice (provided by Southern Medical University Animal Center, Guangzhou, China) by immunization with purified Mamu-B*1703-IW9 monomers. The antiserum titer was 1:200,000 as determined by enzyme-linked immunosorbent assay in a 96-well plate pre-coated with either Mamu-B*1703-IW9 monomers or human HLA-A*0201/NLV monomers [14]. PE-conjugated goat-anti-mouse IgG was purchased from Dako (Glostrup, Denmark) and mouse-anti-human HLA-A, -B, -C (clone W6/32) was bought from BioLegend (San Diego, USA).

Transfection and expression

*Mamu-B**1703 and *Mamu-B**0101 sequences were amplified using a PCR procedure as reported previously [13] except for using the following primers: Forw-1703 (5′-atagaagcttgccaccatggcgcccggaaccctcct-3′) and Back-1703 (5′-gggatcccgagccgtgagagacacatcagagc-3′) for amplifying *Mamu-B**1703; Forw-0101 (5′-atagaagcttgccaccatgcagttcatggcgccccgaac-3′) and Back-1703 for amplifying *Mamu-B**0101. Using the same PCR procedure and another pair of primers, Forw-1703(+G) (5′-atagaagcttgccaccatgcgggtcatggcgcccggaaccctcct-3′) and Back-1703, three codons (encoding Met-Arg-Val) were added before the leading peptide region of wild-type *Mamu-B**1703 [renamed as *Mamu-B**1703(+G)]. PCR products were then digested by *Bam*HI plus *Hin*dIII and then were inserted into pEGFP-N1. After being identified by direct sequencing (Invitrogen), the plasmids encoding the heavy chains of Mamu-B*1703, Mamu-B*1703(+G), Mamu-B*0101 and HLA-A*0201 [14] complexes, respectively, were transfected into the cell lines mediated by Trans-EZ (for Cos-7) or DMRIE-C (for K562) according to the manufacturers' protocols in a 24-well plate. The cells were further cultured for 48 h in a humidified 5% CO_2 incubator at 37°C. The expression of transfected genes was revealed by EGFP fluorescence under an inverted confocal microscope LSM510 Meta (Zeiss, Oberkochen, Germany). Each experiment was done twice in triplicate and the cells were pooled together when they were observed to have approximately equal EGFP$^+$ cells. After staining with mouse anti-Mamu-B*1703 antiserum and PE-conjugated goat-anti-mouse IgG or staining with mouse-anti-human HLA-A, -B, -C mAb (clone W6/32), and the same second antibody, cells were further analyzed by CantoII flow cytometry (Becton Dickinson, Mountain View, USA) and the mean fluorescence intensity (MFI) of PE of EGFP$^+$ cells was calculated using FACSDiva software (Becton Dickinson). The subcellular distribution of the expressed fusion proteins after PE fluorescent staining was revealed by the inverted confocal microscope LSM510 Meta and analyzed by LSM Image Browser Ver. 4.0 (Zeiss).

Statistics analysis

Data were collected from three independent experiments performed in triplicates. Values were analyzed by Prism software

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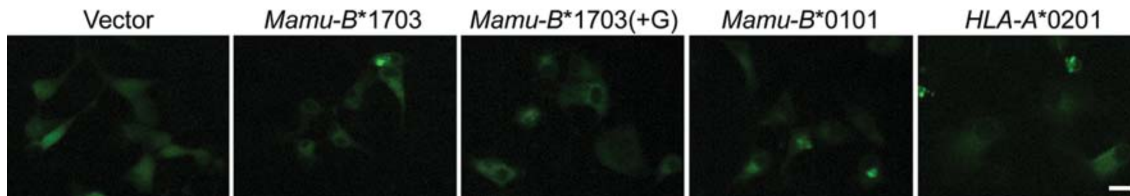

Figure 1 Expression of *Mamu-B1703, *Mamu-B**1703(+G), *Mamu-B**0101, and *HLA-A**0201 cDNA fused with the *EGFP* gene in Cos-7 cell line** The transfection was mediated by Trans-EZ reagent. The expression of the transfectants was revealed by EGFP fluorescence. Bar = 10 μm.

4.0 (GraphPad, San Diego, USA). One-way ANOVA followed by Newman–Keuls *post hoc* test was used to compare between treatment groups. Data were presented as mean ± SD and $P < 0.05$ was considered significant.

Results

Expression of rhesus macaque MHC class I alleles in Cos-7 cells

The rhesus macaques MHC class I alleles were initially transfected and expressed in Cos-7 cells. As *Mamu-B**1703 cDNA sequence encodes a 21-aa leading peptide, which has 'lost' the three beginning amino acid residues (Met-Arg-Val) as compared with most other *Mamu-B* alleles, we artificially inserted a guanine nucleotide (G) between the fourth and fifth nucleotide of the cDNA sequence to restore the 'lost' amino acid residues [*Mamu-B**1703(+G)]. Both *Mamu-B**1703 and *Mamu-B**1703(+G) plasmids were transfected into Cos-7 cells, respectively. *HLA-A**0201 and *Mamu-B**0101 in the same vector were also transfected as controls. As shown in **Fig. 1**, all of the transfected plasmids, including pEGFP-N1 vector, could be expressed in this cell line. Different from the cellular distribution manner of EGFP alone, the MHC class I molecules of humans and rhesus macaques did not diffuse into nucleoplasm (as revealed by their fused EGFP fluorescence). These results suggested that all these MHC class I molecules could be expressed and transmitted to the appropriate subcellular compartments.

Surface localization of rhesus macaque MHC class I molecules on K562 cells

To further examine whether the heavy chains of Mamu-B*1703, Mamu-B*1703(+G) and Mamu-B*0101 could be assembled into complexes correctly and transported onto the cell surfaces, we transfected the plasmids into K562 cells that do not display MHC class I antigens on cell membrane *per se* [**Figs. 2** and **3(A)**, mock and

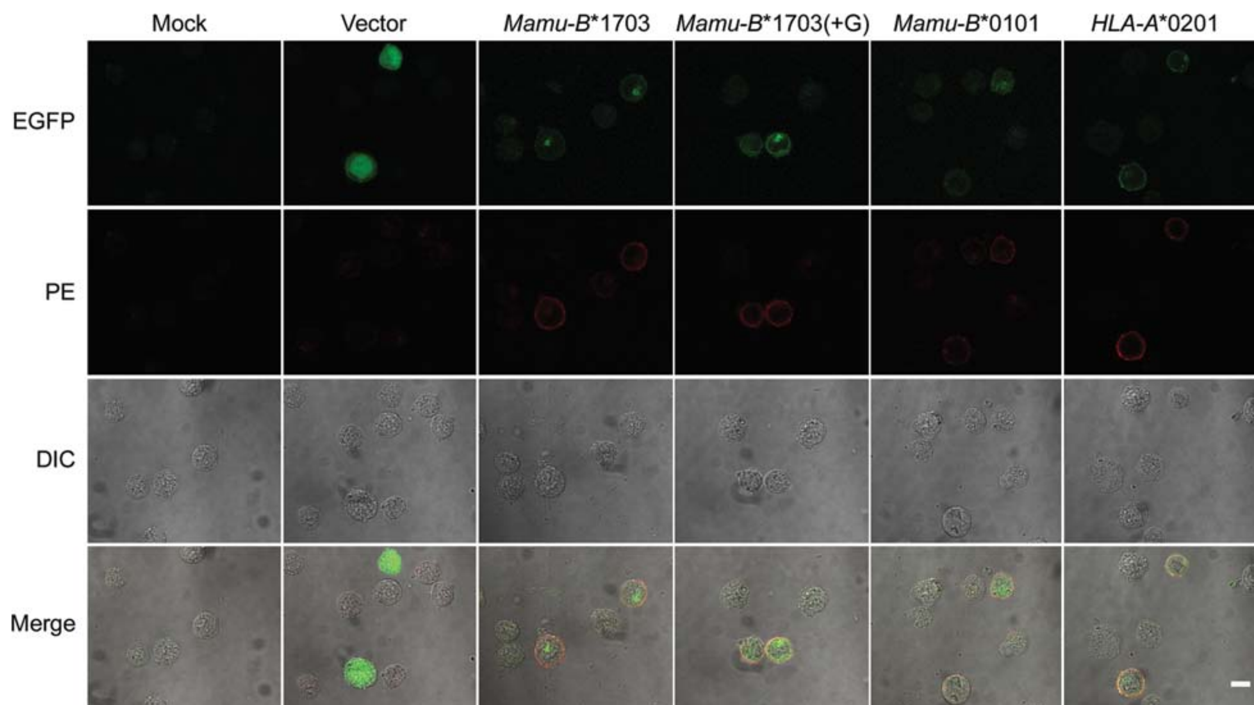

Figure 2 Subcellular localization of the expressed proteins of *Mamu-B1703, *Mamu-B**1703(+G), *Mamu-B**0101, and *HLA-A**0201 cDNA fused with the *EGFP* gene in K562 cells** The plasmids were transfected into K562 cells by DMRIE-C reagent, respectively. After 48 h culture, the cells were collected and stained with anti-Mamu-B*1703 antiserum and PE-conjugated anti-mouse IgG. EGFP (green) and PE (red) fluorescence as well as differential interference contrast (DIC) images were obtained by confocal microscopy. Merged images (merge) were also shown. Bar = 10 μm.

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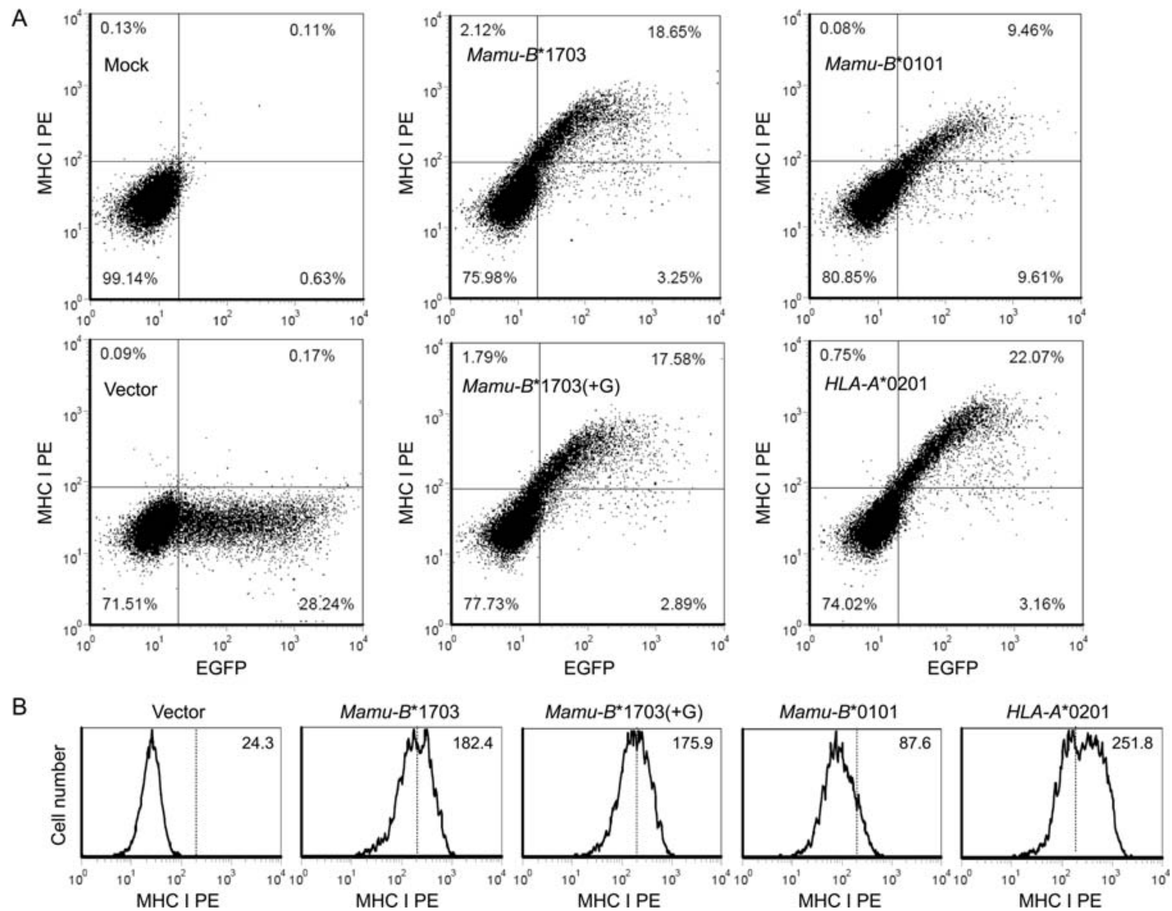

Figure 3 Flow cytometry analysis of K562 cells transfected with the recombinant plasmids harboring *Mamu-B1703, *Mamu-B**1703(+G), *Mamu-B**0101, and *HLA-A**0201 cDNA fused with the *EGFP* gene** The cells were treated as described in **Fig. 2** and analyzed by a CantoII flow cytometer. (A) Dotplots collected from the total cell population of each sample and the percentages of each quadrant were shown. (B) Histograms of PE fluorescence gated on $EGFP^+$ cells. MFI values of PE fluorescence were shown at upright of each plot. The figure is a representative of three independent experiments.

vector], thus facilitating surface staining with anti-MHC class I antibodies. As shown in **Fig. 2**, all of the transfected plasmids could be transcribed in this human chronic myelogenous leukemia cell line. And similar to the expression manner in Cos-7 cells, the MHC class I molecules expressed in K562 cells were largely localized in the cytoplasm and cell membrane but did not enter the nuclei. It is worth noting that a ring-like distribution pattern of these MHC class I molecules (green) was observed in most of the transfected cells by confocal microscopy (**Fig. 2**). These molecules were obviously distributed on the cell surfaces because they were accessible to the surface-staining antibodies (red) (**Fig. 2**), suggesting that all these Mamu-B complexes could be assembled correctly with human β_2m and specific peptides, and be transported onto the cell surfaces for presenting antigens.

Surface expression levels of rhesus macaque MHC class I alleles on K562 cells

Although these Mamu-B complexes could be presented on cell surface, it was not known whether they had similar expression levels on the cell surfaces. Flow cytometry was used to analyze the surface expression levels of rhesus macaque MHC class I complexes after the transfected cells were stained with mouse anti-Mamu-B*1703 anti-serum and PE-conjugated rabbit-anti-mouse IgG. Transfection of these plasmids resulted in approximately equal percentages of $EGFP^+$ cells and MFI values of EGFP (namely, with similar transfection efficiencies in K562 cells), but the densities of foreign proteins on the cell surfaces were quite different (as revealed by MFI value of PE on $EGFP^+$ cell surfaces) [**Table 1**, **Fig. 3(B)**]. It was noted that the PE MFI value on *Mamu-B**1703(+G)-transfected cell surfaces (MFI = 169.4 ± 4.6) was only a bit lower than that of *Mamu-B**1703-transfected ones (MFI = 177.4 ± 9.6), whereas they were about the twice value of *Mamu-B**0101-transfected cells (MFI = 91.3 ± 5.2) (**Table 1**). Similar results were obtained when a pan-MHC class I monoclonal antibody (W6/32) was used for surface staining (data not shown). These results demonstrated that the surface density of Mamu-B*1703 complexes was

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Table 1 Comparison of frequencies and MFI values of Mamu-B molecules expressed in K562 cells

Group	$EGFP^+$ (%)	EGFP MFI	PE^+EGFP^+ (%)	PE MFI of $EGFP^+$ cells
Mamu-B*1703	22.3 ± 0.8	64.8 ± 3.8	82.7 ± 3.5**	177.4 ± 9.6**
Mamu-B*1703(+G)	19.5 ± 0.7	60.3 ± 1.8	85.4 ± 1.4**	169.4 ± 4.6**
Mamu-B*0101	18.9 ± 0.8	58.2 ± 2.2	51.2 ± 2.2	91.3 ± 5.2

Data were the mean ± SD from three independent experiments. $^{**}P < 0.01$ versus Mamu-B*0101.

higher than that of Mamu-B*0101, although both of them could be transported to the cell surfaces of K562 cells.

Discussion

*Mamu-B**17 is reported to be associated with effective control of SIV_{mac239} replication in Indian-origin rhesus macaques [7,11]. *Mamu-B**17-positive rhesus macaques have therefore become an important animal model in studying the relationship between SIV replication and the immunogenetic backgrounds of hosts. Although the exact mechanism underlying elite control of SIV_{mac239} infection by *Mamu-B**17 allele remains to be clarified, one possible mechanism has been proposed that there are a number of *Mamu-B**17-restricted epitopes, including Vif/HW8, Env/FW9, Nef/IW9, and Nef/MW9, in SIV_{mac239} proteins, which can induce potent SIV-specific CTL responses [10,15,16]. This viewpoint is strengthened by the fact that macaques with the same elite controller fail to suppress the replication of other SIV strains with mutations in the regions that encode *Mamu-B**17-restricted epitopes [16]. In contrast, another MHC class I allele, *Mamu-B**01, shows no inhibitory effect on SIV_{mac239} replication and perhaps no *Mamu-B**01-restricted epitopes should exist in the virus proteins [8,11].

However, other potential mechanisms may exist and deserve careful studying. Previous study has demonstrated that the marked difference in transit of $H\text{-}2K^k$ and $H\text{-}2D^k$ (two closely related murine MHC class I complexes) to cell surfaces might be a consequence of different processing efficiencies of these molecules in endoplasmic reticulum due to their intrinsic properties [17]. Moreover, some MHC class I complexes such as HLA-B*27, an elite controller to HIV infection in humans, are much more stable than other MHC class I molecules [18,19]. Thus, our hypothesis is that Mamu-B*1703 complexes were more stable and/or transported more efficiently than Mamu-B*0101 molecules to the cell surfaces, and therefore the macaques with a *Mamu-B**1703 allele would present SIV antigenic epitopes more efficiently and induce CTL responses stronger than those with a *Mamu-B**0101 allele, leading to effective control of SIV replication. We provided the first line of evidence in this study that, although *Mamu-B**1703 and *Mamu-B**0101 plasmids had about equal transfection efficiencies [**Fig. 3(A)**], the cells transfected with *Mamu-B**1703 displayed more molecules on their surfaces than those transfected with *Mamu-B**0101, which was revealed by the percentage of antibody-staining positive cells and the MFI values of antibody-conjugated PE fluorescence [**Fig. 3(A,B)**].

The difference of PE MFI values between *Mamu-B**1703- and *Mamu-B**0101-transfected cells might not be due to the difference of antibody affinities to Mamu-B*1703/β;$_2$m and Mamu-B*0101/β_2m molecules, though the antiserum used as first antibody staining these cells was originally raised for Mamu-B*1703/human β_2m/IW9 monomer [13]. Containing polyclonal antibodies, the antiserum might recognize both Mamu-B*0101/β_2m and Mamu-B*1703/β_2m complexes with equal affinities. In fact, it could not only recognize MHC class I molecules of macaques (Mamu-B*1703/β_2m and Mamu-B*0101/β_2m), but also react efficiently with human HLA-A*0201/β_2m (**Figs. 2** and **3**).

Furthermore, when the transfected cells were stained by anti-human HLA-A, B, C monoclonal antibody (clone W6/32), similar results were observed as that mentioned above (namely, transfection of *Mamu-B**0101 resulted in a lower MFI value of PE when compared with that of *Mamu-B**1703 transfectants). W6/32 monoclonal antibody is a useful tool for studying MHC class I complexes of divergent species in that it recognizes a non-polymorphic epitope shared among HLA-A, -B, and -C/β_2m complexes and it can react with a broad spectrum of other MHC class I molecules, including that of non-human primates, bovine and feline (cat) [20,21]. It can even recognize chimeric MHC class I complexes comprising a heavy chain of human, non-human primates, murine, rat, rabbit, or bovine and a light chain of either human or bovine [20,22]. Yet this monoclonal antibody does not react with molecules of murine β_2m binding with an allogeneic or a heterogenetic MHC class I heavy chain [22,23]. Consistent with these studies, our data also demonstrated that W6/32 antibody recognized the molecules of the MHC class I heavy chains of rhesus macaques and humans binding with human β_2m, but it could not react with complexes comprising the same heavy chains binding with murine β_2m (data not shown). The higher MFI value of PE on *HLA-A**0201-transfected

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cell surfaces suggests that, in the human cell line, the allogeneic complexes of humans are transported more efficiently to the cell surfaces than the heterogenetic molecules consisting of human β_2m light chains and either Mamu-B*1703 or Mamu-B*0101 of rhesus macaque's heavy chains. Therefore, the different PE MFI values of Manu-B*1703 and Mamu-B*0101 molecules, which were derived from either anti-Mamu-B*1703 antiserum or pan-MHC class I antibody W6/32 staining, indicated that these molecules had different densities on the surfaces of transfected cells. This result suggests that the antigenic peptide density presented by Mamu-B*1703 on the cell surfaces is higher than that presented by Mamu-B*0101. As it is believed that higher antigen density can induce stronger immune responses, our data implicate that animals with *Mamu-B**1703 should initiate stronger CTL responses to pathogens than that with *Mamu-B**0101 allele. Thus, it might partially account for the elite control of SIV infection in the hosts containing *Mamu-B**17 alleles, although further investigation is still required to clarify this issue.

By genetic analysis, a deletion mutation should have occurred in the leading peptide region of *Mamu-B**1703 cDNA sequence as compared with other MHC class I alleles [9,24]. Nonetheless, both wild-type *Mamu-B**1703 and its artificial mutant *Mamu-B**1703(+G) should have encoded the same mature protein, the heavy chain of Mamu-B*1703/β_2m complexes. Consistently, such a deletion mutation did not significantly enhance the expression of *Mamu-B**1703 in the transfected cells and the localization of Mamu-B*1703/β_2m complexes on the cell surfaces (**Table 1**, **Figs. 2** and **3**).

In conclusion, both *Mamu-B**1703 and *Mamu-B**0101 plasmids were expressible and had almost the same transfection efficiencies in K562 cells. But Mamu-B*1703/β_2m complexes seemed more easily to dwell themselves on K562 cell surfaces than Mamu-B*0101/β_2m. Although it is impossible at present for us to determine if this is also the case for Mamu-B*1703 and Mamu-B*0101 complexes *in vivo* in rhesus macaque models, our highly artificial model is still of significance considering that *Mamu-B**17, rather than *Mamu-B**01, is an elite controller in SIV-infected rhesus macaque models [7,8]. Additional investigations are required to clarify whether Mamu-B*1703 is expressed at a higher level than other MHC class I alleles *in vivo*, leading to elite control of SIV replication in rhesus macaques.

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