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SIV-infected Chinese-origin rhesus macaques express specific MHC class I alleles in either elite controllers or normal progressors

Daniel Wambua¹, Ryan Henderson^{1,2}, Christopher Solomon^{1,2}, Meredith Hunter³, Preston Marx³, Alessandro Sette², and Bianca R. Mothé^{1,2,*}

¹ Department of Biology, California State University - San Marcos, San Marcos, CA 92096

² Department of Vaccine Discovery, La Jolla Institute for Allergy and Immunology, La Jolla, CA 92037

³ Department of Tropical Medicine, School of Public Health, and Tulane National Primate Research Center, Tulane University, Covington, LA , USA 70433

Abstract

We characterized twelve SIV-infected Chinese-origin rhesus macaques for their entire MHC class I allele composition. Several MHC class I alleles were present in animals with varying outcomes of infections, either elite control or normal progression to AIDS disease. These MHC class I alleles may prove interesting targets for additional characterization.

Rhesus macaques have been extensively used in infectious diseases research. This model provides key insights into disease pathogenesis and allows for the evaluation of novel vaccine concepts. Two populations of rhesus macaques, consisting of Indian-origin rhesus macaques and Chinese-origin rhesus macaques, have been utilized extensively in AIDS research and for other models of infectious diseases [7, 8]. In the context of Simian Immunodeficiency Virus (SIV) research, the vast majority of studies performed with Indian rhesus macaques have shown progression to AIDS in a relatively short time period [23, 32]. For this reason, researchers have investigated other non-human primate animal models to mimic more closely HIV infections in humans. Chinese-origin rhesus macaques have been an interesting choice because SIV infection in these animals yields a prolonged progression, more similar to HIV infection in humans [10, 15].

While physiologically these two set of animals appear to be identical, genetic factors affecting immune responses appear to be quite varied. Several independent observations have implicated cellular immunity, specifically cytotoxic T-lymphocyte (CTL) responses, in the control of AIDS viral replication [3, 11, 14]. MHC class I and II molecules determine the repertoire of T-cell responses that an individual can develop against SIV and/or any other foreign pathogen [30]. The Indian rhesus macaques have been more extensively characterized in terms of their MHC allele composition, resulting in instrumental findings in the setting of SIV infection, including the identification of viral evasion from CTL responses [1, 6], the identification of specific MHC alleles which influence disease progression [17, 24, 26, 36] and that several MHC class I molecules are expressed in high frequencies (over 10% of captive populations), including Mamu-A*01 [2], -B*17 [25] and B*01 [19], amongst others [20, 31]. The fact that Indian rhesus macaques used in biomedical research in the United States have been interbreeding since 1978 when India banned the exportation

* Corresponding author: bmothe@csusm.edu .

of these animals [12] is probably a major contributing factor to the high frequency of expression of these MHC class I molecules. Due to these higher frequencies and the extensive characterization of several of these alleles, Indian rhesus macaques are the most widely utilized model in AIDS research studies [7, 8, 12]. However, as previously mentioned, the rapid progression to disease displayed after SIV infection of Indian rhesus and more recently, the increased demand of these animals resulting in delayed studies has led to the desire in developing alternative animal models.

Chinese-origin rhesus macaques are relatively accessible for research but are not well characterized at their MHC loci. Specifically, little information is known about the MHC allele make-up of Chinese origin rhesus macaques, although studies have been performed in recent years to address this shortcoming [13, 21, 27-29, 33-35]. Recently, several MHC class I alleles have been characterized for their peptide binding motifs, including Mamu-A1*2601, Mamu-B*08301 and Mamu-A1*2201 [33]. Interestingly, these macaque MHC class I molecules share peptide binding repertoires with common HLA molecules, increasing the interest of the Chinese-origin rhesus macaque as a model for immunogenicity for human diseases. Yet, specific MHC class I alleles have not been investigated for their role in the outcome of AIDS infection in this model.

In this study, we characterized a set of Chinese-origin rhesus macaques that were infected with SIV yielding different outcomes of infection. Specifically, we sequenced this cohort of 12 for their expressed MHC class I alleles. We were interested in determining whether there was a correlation with disease outcome and specific allele(s). Five of the twelve animals became elite controllers (slow disease progression) and seven animals progressed to AIDS, but more slowly than typical for Indian-origin rhesus macaques. We extracted RNA and sequenced the entire complement of MHC class I alleles as previously described [33].

In Table I, we illustrate the alleles detected in this cohort as well as the disease outcome for each animal, resulting in either elite control or normal progression to AIDS. One set of alleles, Mamu-B*1001 and -B*8701 appeared in two of the five elite controllers and not in normal progressors ($p=.20$; binomial distribution). Another set of alleles, Mamu-B*04 and -A2*0102 also appeared in two of the five elite controllers but was also detected in one of the animals that progressed normally to AIDS. Mamu-B*03 appeared in two elite controllers and two normal progressors.

Conversely, there were several alleles that only appeared in animals that progressed to AIDS. Specifically, Mamu-B*39 appeared in three out of the seven normal progressors ($p=.38$). Mamu-A1*49 and Mamu-B*8301 also appeared in two of the seven normal progressors ($p=.33$). Another set of alleles appeared equally in elite controllers and normal progressors. These alleles include Mamu-A1*1701 (1 elite controller and 1 normal) and -A1*2601 (1 elite controller and 1 normal).

This study is the first to explore the role of the presence of the specific alleles on the outcome of AIDS infection using the Chinese rhesus macaque model. While we did not identify specific allele(s) that were present in either all of the elite controllers or normal progressors, we did identify alleles that were expressed exclusively in one set of animals or the other. In our study, Mamu-B*1001 and -B*8701 appeared only in elite controllers. The presence of specific alleles was not statistically significant, probably due to the small sample size. Previous studies have identified MHC class I alleles which correspond with slower progression to AIDS in SIV-infected rhesus macaques and HIV-infected humans [4, 5, 9, 16, 18, 22, 26]. The mechanism of how these alleles and others correlated with elite control specifically influence progression, including how their restricted CD8+ T-cells control viral replication remains elusive to the field and a target for additional characterization.

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Table I

The disease outcome and MHC class I identification in a set of 12 SIV-infected Chinese-origin rhesus macaques

Animal	Pathology	Locus	Allele	Genbank AID
T01	Elite controller	A	Mamu-A1*02601	EF580136.1
			Mamu-A7*0103	EF580144.1
		B	Mamu-B*1001	EU682525.1
			Mamu-B*8701	EF580170.1
			Mamu-B*03602	EU682527.1
T02	Elite controller	A	n3-Mamu-I*010801	FJ009194.1
		B	Mamu-B*1001	EU682525.1
			Mamu-B*8701	EF580170.1
			Mamu-B*8501	EF580165.1
T06	Elite controller	A	n1-Mamu-A1*3201	EF580142.1
		B	Mamu-B*04	U41826.1
			Mamu-B*03	EU682521.1
T09	Elite controller	A	Mamu-A2*0102	EF580155.1
		B	Mamu-B*04	U41826.1
			Mamu-B*0030101	EU682521.1
T11	Elite controller	A	Mamu-A2*0103	EF580155.1
			Mamu-A1*00704	EU682510.1
		B	Mamu-B*05601	FJ380946.1
T03	Normal Progressor	A	Mamu-A2*0102	EF580155.1
		B	Mafa-B*470101	AY958145.2
			Mamu-B*0030102	EU682521.1
T04	Normal Progressor	A	Mamu-A*250202	EU109712.1
		B	Mamu-B*3901	EF580146.1
			Mamu-B*09003	EF580173.1
T05	Normal Progressor	B	Mamu-B*00501	U41827.1
			Mamu-B*04	U41826.1
			Mamu-B*03	EU682521.1
T07	Normal Progressor	A	Mamu-A1*01803	EF580152.1
			Mamu-A1*04901	EU682509.1
		B	Mamu-B*4704	AM902561.1
			Mamu-B*8301	EF580161.1
T08	Normal Progressor	A	Mamu-A1*00901	EU334728.1
			Mamu-A1*1804	EF580152.1
		B	Mamu-B*03901	EF580146.1
			Mamu-B*00103	EU682524.1
T10	Normal Progressor	A	Mamu-A1*49	EU682509.1

Animal	Pathology	Locus	Allele	Genbank AID
			Mamu-A1*02601	EF580136.1
		B	Mamu-B*3901	EF580146.1
			Mamu-B*08301	EF580161.1
			Mamu-B*0703	EF580149.1
T12	Normal Progressor	A	Mamu-A1*1701	EU682510.1
		B	Mamu-B*04506	EF580167.1
			Mamu-B*6901	EF580148.1
			Mamu-B*03702	EU682526.1
			Mamu-B*03602	EU682527.1