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Original article

Neutralization breadth and potency of serum derived from recently human immunodeficiency virus type 1-infected Thai individuals

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Abstract

Neutralizing antibody responses play important roles in controlling several viral infections including human immunodeficiency virus type 1 (HIV-1). Potent and broad neutralizing antibody responses have been reported in some HIV-1-infected individuals; therefore, elucidating the mechanisms underlying neutralizing antibody responses will provide important information for the development of anti-HIV-1 vaccines. We herein performed a comparative study on the neutralization breadth and potency of serum samples collected from Thai individuals recently and chronically infected with HIV-1. Neutralization tests using a series of envelope glycoproteins (Env)-recombinant viruses revealed that although several serum samples derived from recently infected individuals did not show any HIV-1-specific neutralizing activity, the remaining serum samples exhibited neutralizing activity not only for recombinant viruses with CRF01_AE Env, but also for viruses with subtypes B and C Env. Furthermore, some serum samples derived from recently infected individuals showed the neutralization potency. Our results may provide a deeper insight into the characteristics of neutralizing antibody responses that develop during the course of HIV-1 infection among individuals in Thailand.
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Keywords: Recent HIV-1 infection; Neutralization; CRF01_AE; Thailand

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is a major causative agent of acquired immune deficiency syndrome (AIDS). After the sexual transmission of HIV-1, dendritic cells interact with the virus at the mucosa and transmit HIV-1 to $CD4^+$ T lymphocytes [1]. T lymphocytes are then productively infected with HIV-1 in systemic lymphoid tissues, leading to the peak viral load [2]. Anti-HIV-1 host immune responses are elicited in parallel with viral productive infection [3], and the viral load rapidly declines to a stable level [4], known as the viral set point [3]. The viral load at the set point has been shown to affect HIV-1 disease progression and the prognosis of infected individuals [5–7]. A vaccine strategy that reduces the set point viral load has potential as a candidate HIV-1 vaccine [8]. Host immune responses against HIV-1 may be a major determinant of the set point viral load; therefore, it is important to examine immune responses in the acute phase of HIV-1 infection in order to accumulate the information required for vaccine development.

HIV-1 has been characterized by extensive genetic heterogeneity [9] and divided into four groups, M (major), O (outlying), N (new or non-M, non-O) and P (pending). Viruses

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in group M have been further classified into many subtypes and circulating recombinant forms (CRFs). Of these, subtypes A, B, C, D and G, as well as CRF01_AE and CRF02_AG, are the major subtypes and CRFs responsible for the worldwide HIV-1 pandemic [10]. While subtype B of HIV-1 is the predominant subtype in the Americas, Europe and Australia, the epidemic of non-B subtypes and CRFs is growing in Africa and Asia. CRF01_AE is prevalent throughout Southeast Asia [10] and is responsible for more than 80% of infected cases in Thailand [11]. Previous studies reported that serum samples derived from CRF01_AE-infected Thai individuals exhibited subtype-specific neutralizing activity [12,13]. These studies were conducted using serum samples derived from chronically infected individuals. However, the immunological characteristics of serum samples from recently HIV-1-infected Thai individuals have not yet been elucidated in detail.

The captured BED-enzyme-linked immunosorbent assay (ELISA) has been used as a simple method to estimate the incidence of HIV [14]. It was developed as an assay to detect recent HIV-1 seroconversion. It measures the proportion of HIV-1-specific IgG with respect to total IgG in blood samples. The target viral antigen is a branched peptide containing immunodominant sequences from the envelope glycoprotein, gp41 of subtypes B, E (CRF01_AE) and D. Recent seroconverters have a lower proportion of HIV-specific IgG in their sera than those with long-term infection [14]; therefore, study participants are classified as recent seroconverters if their blood samples have a normalized optical density (ODn) below a threshold cut-off based on a calibrator specimen in the assay.

In the present study, we performed a comparative study on the neutralization breadth and potency of serum samples derived from recently and chronically HIV-1-infected Thai individuals using a panel of recombinant viruses containing *env* genes derived from chronically CRF01_AE-infected, recently CRF01_AE-infected, recently subtype B-infected and recently subtype C-infected individuals.

2. Materials and methods

2.1. Serum samples

Serum samples were collected from Royal Thai Army (RTA) conscripts (male, 21 years old) who entered the military in 2012 and were tested for anti-HIV-1 antibodies using ELISA, followed by an immunoblot analysis to confirm the diagnosis of HIV-1. Serum samples derived from HIV-1-positive individuals were then subjected to captured BED-ELISA [14] in order to estimate the HIV-1 infection status. A cut-off value of 0.8 was used for the ODn in order to distinguish a recent from chronic infection status. Based on previous findings, we determined the mean period from initial seroconversion to an ODn of 0.8 (the recency period) as 127 days. Serum samples from 17 recently and 19 chronically infected individuals were subjected to experimentation in the present study. This study was conducted with approval from the Institutional Review Broad of the RTA Medical Department.

2.2. Envelope glycoproteins (Env)-recombinant viruses

The pNL4-3 [15]-derived luciferase reporter proviral construct, pNL-envCT [16] and 11 Env-recombinant proviral constructs were previously described [12,17–19]. Briefly, the full-length *env* gene of the laboratory-adapted subtype B reference strain (laboratory-adapted B-Env), pBaL (GenBank accession no. AB253432), 2 CRF01_AE *env* genes (chronic AE-Env), 55PL1 and 107CC2, derived from chronically infected Thai individuals [19] and 4 CRF01_AE *env* genes (early AE-Env), RTA2, RTA9, RTA16 and RTA23, derived from recently infected Thai individuals [18], as well as 2 subtype B *env* genes (early B-Env), pREJO4541.67 and QH0692.42 [20–22], and 2 subtype C *env* genes (early C-Env), ZM249M.PL1 and ZM53M.PB12 [23], derived from recently infected individuals, were cloned into pNL-envCT in order to generate Env-recombinant, luciferase reporter proviral constructs. Four subtypes B and C *env* genes, pREJO4541.67, QH0692.42, ZM249M.PL1 and ZM53M.PB12, were obtained from Drs. Cynthia A. Derdeyn, Feng Gao, Beatrice H. Hahn, Eric Hunter, Ming Li, Yingying Li, David C. Montefiori, and Jesus F. Salazar-Gonzalez through the AIDS Research and Reference Reagent Program (ARRRP), Division of AIDS, NIAID, NIH. According to previous reports [24,25], Env derived from pNL4-3 and pBaL were considered to be Tier 1 Env, while pREJO4541.67, QH0692.42, ZM249M.PL1 and ZM53M.PB12 were considered to be Tier 2 Env. In addition, 6 CRF01_AE Env, 55PL1, 107CC2, RTA2, RTA9, RTA16 and RTA23, showed moderate levels of neutralization susceptibility to broadly neutralizing monoclonal antibodies and patient plasma/serum in our previous reports [18,26]; therefore, these Env were considered to be Tier 2 Env. Viral supernatants were prepared by transfecting 293T cells with a proviral construct using FuGENE HD transfection reagent (Roche, Basel, Switzerland) or PromoKine Transfection reagent (PromoCell, Heidelberg, Germany), as described previously [19]. The viral titer was determined by measuring the concentration of the HIV-1 Gag p24 antigen in viral supernatants using ELISA (HIV-1 p24 Antigen Capture Assay; Advanced Bioscience Laboratory, Rockville, MD, USA). The infectivity of recombinant viruses was evaluated by infecting U87.CD4.CXCR4 and U87.CD4.CCR5 cells [27] with 10 ng of the viruses, as described previously [19]. U87.CD4.CXCR4 cells were used as target cells for the recombinant viruses containing CXCR4-tropic Env, pNL4-3 Env and 107CC2, while U87.CD4.CCR5 cells were used as target cells for recombinant viruses containing CCR5-tropic Env, pBaL Env, 55PL1, RTA2, RTA9, RTA16, RTA23, pREJO4541.67, QH0692.42, ZM249M.PL1 and ZM53M.PB12. Forty-eight hours after infection, luciferase activity in infected cells was measured using the Steady Glo Luciferase assay kit (Promega, Madison, WI, USA) with a VICTOR X4 multilabel plate reader (Perkin Elmer, Waltham, MA, USA), according to the manufacturer's protocol. U87.CD4.CXCR4 and U87.CD4.CCR5 cells were provided by Dr. HongKui Deng and Dr. Dan R. Littman through ARRRP.

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