**NOTE** Virology

**Plasma Levels of the Chemokine RANTES in Macaque Monkeys Infected with Pathogenic and Non-Pathogenic SIV/HIV-1 Chimeric Viruses at an Early Stage of Infection**

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**ABSTRACT.** Plasma levels of the chemokine RANTES were examined in monkeys infected with either a pathogenic simian and human immunodeficiency chimeric virus (SHIV) or a non-pathogenic SHIV to determine whether RANTES levels were related to the pathogenicity of the virus, the plasma viral load, or the kinetics of CD4+ T-cells. In the results no significant correlation was found between the RANTES kinetics and changes in the CD4+ T-cell numbers nor the plasma viral loads in any of the monkeys, although a transient decrease of the RANTES level was observed in the pathogenic virus-infected monkeys. At least, the plasma RANTES level can not be used as an index of the pathogenicity of the virus at the early stage of infection.

KEY WORDS: AIDS, RANTES, SHIV.

The RANTES (regulated upon activation, normal T cell expressed and secreted) is an inducible pro-inflammatory cytokine belonging to the c-c or β-chemokine subfamily [6]. Proteins in this subfamily are also involved in a variety of immune and inflammatory responses, acting primarily as chemoattractants and activators for monocytes and T lymphocytes [9]. It has been demonstrated that RANTES, together with two other β-chemokines, macrophage inflammatory protein (MIP)-1α and MIP-1β, induce a dose-dependent inhibition of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) replication *in vitro*. Of the three chemokines, RANTES was reported to be the most effective [4]. Thus, a high serum level of RANTES has been found to be associated with resistance to HIV infection [1]. However, this observation has been challenged by other authors who have either found the opposite result [11] or no correlation at all [3]. To our knowledge, there have been no reports yet on RANTES kinetics in monkeys infected with chimeric simian and human immunodeficiency virus (SHIV). SHIVs have been shown to exhibit different levels of pathogenicities providing useful animal models for Acquired Immunodeficiency Syndrome (AIDS) [5, 7, 8].

Therefore, we sought to compare the RANTES level in the plasmas of macaques that had been infected with non-pathogenic and pathogenic SHIVs and this is the first report of its kind. For the non-pathogenic virus, we used NM-3rN, a chimeric virus from SIVmac and HIV-1 NL432 which carries the *env*, *tat*, *rev*, *vpr* and *vpu* from HIV-1 and the other regions from SIVmac [7]. For the pathogenic virus, we used another SHIV, 89.6P, which is highly pathogenic, and kindly provided by Drs. K. A. Reimann and N. L. Letvin [8]. The aim of this study was therefore, to determine the kinetics of RANTES from these HIV-infected monkeys and see how they were related to the pathogenicities of the viruses.

Eight monkeys were used. Four monkeys were infected with NM-3rN (10 TCID50) and the other 4 monkeys were infected with 89.6P (10 TCID50). Acid citrate dextrose (ACD) anti-coagulated blood was taken at 3-day intervals throughout the study and platelet-poor plasma was separated immediately. CD4+ and CD8+ T-cells were measured as described [2]. Plasma viral load was measured using an ABI PRISM 7700 machine (PE Applied Biosystems) as described [10]. The RANTES level was measured by using a human-specific commercial enzyme-linked immunosorbent assay (R&D Human RANTES ELISA kit) which is known to cross-react with rhesus RANTES.

There was an increase of plasma viral load in the 89.6P-infected monkeys which peaked at two weeks post infection and this was inversely correlated with the kinetics of the CD4+ T cells, which had become almost depleted in the same period (Fig. 1 A&B). On the other hand, there was only a slight difference in the CD4+ T cell kinetics in the NM-3rN-infected monkeys, though there was a transient increase in the plasma viral load two weeks after infection (Fig. 1 A&B). Soon after infection, the level of RANTES, which was constitutively expressed in all monkeys, decreased transiently in the 89.6P-infected monkeys but it soon rebounded to the pre-infection levels where it remained stable throughout the study period although there were some small fluctuations. On the other hand, no significant change was observed in the NM-3rN-infected monkeys (Fig. 1 C).

The decreasing and rebounding plasma RANTES levels observed in the 89.6P-infected monkeys were not as dramatic as the changes in the CD4+ T cell kinetics or the plasma viral load. Plasma RANTES levels of each two of the four monkeys were followed up for two more weeks but there was no change in the results (results not shown). Therefore, it was...
concluded that the RANTES kinetics in the NM-3rN- and 89.6P-infected monkeys were not significantly different. That is, the RANTES kinetics in the plasma of these SHIV-infected monkeys could not be used as a means of distinguishing between the pathogenic and nonpathogenic viruses at the early stage of infection.

REFERENCES


Fig. 1. Kinetics of plasma viral load (A), CD4+ T-cell count (B) and Plasma RANTES levels (C) in monkeys infected with NM-3rN and 89.6P chimeric SHIVs. The kinetics shown above is the average (± SD) of the four monkeys in each (NM-3rN- or 89.6P-infected) group while each value at day zero is also the average (± SD) of three points measured before infection.