Effect of Staggered Cyclophosphamide-Immunosuppression on Resistance to Experimental Junin Virus Infection

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Summary

Otherwise resistant adult mice were rendered susceptible to intracerebral Junin virus (JV) infection only when a staggered cyclophosphamide (CY) schedule was used.

Forty-five-day old Balb/c mice, intracerebrally JV-infected and immunosuppressed with four 50 mg/kg body weight CY doses at days −1, +1, +4, +6 (day 0: viral infection) developed a lethal disease (86.6 per cent mortality) with high CNS viral titers and brain lesions. Neutralizing antibodies were absent throughout, while immunofluorescent antibody levels were considerably diminished.

The transfer of hyperimmune serum conferred partial though significant protection on CY-treated animals but no correlation was found between CNS viral titers and mortality since in both infected CY-treated and untreated mice similar brain viral content was found.

This was also confirmed by immune spleen cell transfer at day 0 where the clearance achieved was unable to modify the time course of the disease.

Feasible mechanisms explaining recovery from JV infection by means of the protective effect of antibodies and the cell-mediated clearance are discussed.

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Introduction

It is known that Lymphocytic Choriomeningitis virus (LCM), the prototype of Arenavirus group, is considered a standard model for viral immunopathology. However, another member of this group, Junin virus (JV), provides an alternative model with certain distinguishing features.

Thus, 1-to-10 day-old mice intracerebrally (i.c.) infected with JV show 90--100 per cent mortality, high brain viral titers but neither immunofluorescent (IF) nor neutralizing (NT) antibodies are observed up to the time of death, 14—17 days postinfection (p.i.) (4).

Lethal JV infection may been attributed to cellular immune response, as suggested by a variety of experiments (13, 17, 18).

A totally different set of conditions exists in adult i.c. JV infected mice. Mortality seldom surpasses 10 per cent and virus cannot be recovered from brain by conventional techniques (1). However, virus rescue has been achieved through a much more sensitive procedure: coculture of dissociated tissue with a permissive cell line (3). On the other hand, NT, Complement Fixing and IF antibodies are invariably present (1).

Nevertheless, adult mouse infection coupled with a suitable cyclophosphamide (CY) immunosuppression schedule results in a lethal disease, similar in mortality to that observed in the neonatally infected mouse (7).

In this research we undertook to determine the effect of CY treatment on mortality, on viral multiplication, on humoral immune response as measured by specific NT antibodies, on histopathologic changes and on viral antigen presence in infected brains. Besides, we endeavoured to ascertain, by means of transfer studies, the relationship between cellular and humoral immunity in the recovery of CY-treated mice from i.c. JV infection.

Materials and Methods

Animals

Forty-five-day-old inbred Balb/c mice from the National Atomic Energy Commission (Argentina) breeding colony were used in all experiments.

Virus

Stocks of XJ Junin virus strain (XJJV) were prepared as clarified 10 per cent homogenates of suckling mouse brain. The animals were inoculated with $10^3 \text{LD}_{50}$ (newborn) by i.c. route.

Cyclophosphamide (CY) (Endoxan-Asta)

It was obtained from Inca Laboratories (Argentina), and rehydrated with saline to provide the desired dilution immediately before use.

Treated mice: The effect of CY immunosuppression was evaluated by giving various drug doses one day before infection. In one batch, this single-dose schedule was either 100, 200 or 300 mg/kg body weight. In another batch, a staggered schedule previously shown to modify the time course of infected adult mice was employed (7).