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## Inhibition of *Plasmodium vinckei*-malaria in mice by recombinant murine interferon- $\gamma$

### Short communication

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The activation of effector cells is an important aspect of immunity to malaria. Macrophages and natural killer cells are stimulated by interferon- $\gamma$  (IFN- $\gamma$ ) to generate and release reactive superoxide ( $O_2$ ) and its oxygen intermediates (Allison and Eugui, 1983). Rodent malaria infection was found to increase interferon production (Clark and Cowden, 1985) and oxidative killing of parasitized red blood cells (Ockenhouse and Shear, 1983, 1984; Ockenhouse et al., 1984). The release of tumor necrosis factor (TNF) by activated macrophages during malaria infection has also been described, but its role remains obscure (Grau et al., 1987). In this communication we report the effect of recently developed recombinant murine IFN- $\gamma$  and TNF in mice infected with *Plasmodium vinckei*. Ten-week-old inbred male BALB/c-mice were infected with the rodent malaria parasite *P. vinckei* (kindly provided by Dr. Büngener, Tropeninstitut Hamburg). Blood was drawn from the tail of parasitized mice into 20  $\mu$ l heparinized capillary tubes, diluted with phosphate buffered saline (PBS) to final concentration of  $10^3$ – $10^5$  parasitized erythrocytes and then injected intraperitoneally (i.p.) Control animals received the same volume of PBS.

Recombinant murine interferon- $\gamma$  (r-IFN- $\gamma$ ), derived from *E. coli* (Genentech, USA), was supplied and tested for activity by Boehringer Ingelheim, FRG (Gray and Coeddel, 1983). The specific activity was  $1$ – $2 \times 10^7$  U/mg protein. r-IFN- $\gamma$  was stored at 4°C and dissolved immediately before application in PBS containing 2% mouse albumin. 100  $\mu$ l were injected i.p. opposite to the injection site of the malaria parasites. Control animals received the same volume and concentration of PBS buffered mouse albumin. Recombinant murine TNF (supplied by Boehringer Ingelheim, FRG) was injected i.p. in concentrations of 0.01, 0.1, 1 and 10  $\mu$ g/100  $\mu$ l PBS containing 2% mouse albumin.

Survival time, haematological and parasitological parameters were recorded in 3 series of experiments to 1. standardize the *P. vinckei*-inoculum, the r-IFN- $\gamma$  concentration and the TNF concentration, 2. determine the effect of r-IFN- $\gamma$  application before and after parasite inoculation, and 3. determine the effect of the combined r-IFN- $\gamma$  and TNF application. Test groups were always matched with control groups of untreated mice. The analysis was performed by non-parametric statistics (Wilcoxon-test). Haematological and parasitological findings will be published elsewhere.

After establishing a suitable course of *P. vinckei*-infection and the optimal concentration of r-IFN- $\gamma$ , the survival times of 4 groups of mice were compared: one untreated control group, two other groups which received r-IFN- $\gamma$  either before or after infection, and a fourth group in which prophylactic and therapeutic applications of r-IFN- $\gamma$  were combined (Table 1). The results demonstrated that r-IFN- $\gamma$  given after infection only slightly, but significantly, prolonged the median survival time. In mice receiving r-IFN- $\gamma$  before malaria infection, the median survival time was significantly longer. If the prophylactic and therapeutic regimens were combined, the effect on the survival period was even more pronounced (Table 1).

In another set of experiments a therapeutic effect of TNF in infected mice could not be demonstrated, but TNF treated mice showed an increase in the mononuclear blood cell count compared to untreated controls. Moreover there was no difference in the course of the malaria

Table 1. Three of four groups of mice infected with  $10^4$  parasitized erythrocytes received r-IFN- $\gamma$  in a) a prophylactic regimen:  $3 \times 10^4$  U/100  $\mu$ l PBS, 2% mouse albumin at 26 h, 16 h and 6 h before infection; b) a therapeutic regimen:  $10^4$  U/100  $\mu$ l PBS, 2% mouse albumin daily for 7 days after infection; c) a combination of a and b

| r-IFN- $\gamma$<br>(U/100 $\mu$ l)                                     | Number of mice<br>(n) | Median survival<br>time (days) | Wilcoxon-test<br>(p) |
|--|-----------------------|--------------------------------|----------------------|
| Control group . . . . .  | 5                     | 10.25                          | —                    |
| a) $3 \times 10^4$ prophylactic . . . . .                              | 10                    | 11.00                          | <0.01                |
| b) $1 \times 10^4$ 7 days post infection . . . . .                     | 10                    | 10.75                          | <0.05 >0.01          |
| c) $3 \times 10^4$ prophylactic and 7 days<br>post infection . . . . . | 10                    | 12.25                          | <0.01                |

infection between groups receiving only a prophylactic regimen of r-IFN- $\gamma$  and receiving a prophylactic regimen of r-IFN- $\gamma$  plus a therapeutic regimen of TNF.

In rodent malaria, lymphokine activation of macrophages leads to enhanced phagocytosis of parasitized erythrocytes and to the production of intra- and extracellular oxygen intermediates (Dockrell and Playfair, 1983). In addition, IFN- $\gamma$  stimulates the secretion of a factor, possibly TNF, which was thought, to inhibit parasite multiplication (Haidaris and Haynes, 1983).

Based on these reports, *P. vinckei*-infected BALB/c-mice were treated with r-IFN- $\gamma$  and TNF. The rapidly fatal course of murine *P. vinckei*-malaria, which precludes interference of disease development by B-cell mediated immunity was regarded as an advantage of this animal model, allowing the study of lymphokine activity during malaria infection.

r-IFN- $\gamma$  was presented in three different ways: a prophylactic and a therapeutic regimen, and a combination of both. Increasing doses of the prophylactic regimen effectively slowed the progress of the disease. The therapeutic regimen was less efficient, r-IFN- $\gamma$  being effective too late to appreciably inhibit parasite multiplication. The combination of prophylactic and therapeutic applications acted in a cumulative way. The macrophage system, already activated before infection, was subjected to prolonged stimulation by daily r-IFN- $\gamma$  doses. However, therapeutic applications of TNF did not further increase the effect of r-IFN- $\gamma$ . Our results showed, that TNF did not influence the course of murine malaria infection in any way.

The animals died from malaria in all the experiments regardless of the time and amount of r-IFN- $\gamma$  given. However, the findings raise the possibility that r-IFN- $\gamma$  may play a role as a supportive therapeutic agent in the treatment of animal and human malaria, especially in the case of life threatening *P. falciparum*-infection, or against parasite strains which are partially or totally resistant against chemotherapeutic drugs.

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