Effect of Sensitized T Cell Transfer on Mouse Hepatitis Virus Type 4 Infection in Athymic Nude Mice

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After intraperitoneal inoculation with neurotropic mouse hepatitis virus, JHM strain (MHV-4), acute fatal hepatitis can be produced in athymic nude (nu/nu) mice but not in euthymic (nu/) counterparts, suggesting that T cell-mediated immunity might play a crucial role as already described with MHV-NuU infection [2, 8]. We previously reported differences in delayed-type hypersensitivity (DTH) to MHV-4 among mouse strains, indicating that B10. D2 and DBA/2 mice were high and low responder strains, respectively [3, 4]. However, we could not detect any difference in T cell activity between these strains of mice infected with MHV-4, because T cell transfer from B10. D2 mice to DBA/2 mice, and vice versa, did not affect the magnitude of the DTH response in the recipient mice [5]. In the present study we attempted an immunotherapy against MHV-4 induced hepatitis in T cell deficient nude mice by adoptive effects of T cells from the high and low DTH responder strains of mice. Six- to 8-week-old female B10. D2 and DBA/2 mice were inoculated intraperitoneally with \(1 \times 10^6\) plaque forming units (PFU) of MHV-4 grown on DBT cells [1]. On day 8 postinoculation (p.i.) when infected mice showed a maximum DTH response [3, 5], single cell suspensions were prepared from the spleens from infected or non-infected mice of both strains, and the T cell enrichment was performed as described previously [2]. The recipients, H-2 matched BALB/c-nu/nu mice, which had been inoculated intraperitoneally with \(1 \times 10^6\) PFU of MHV-4 2 days before, received intravenously \(1 \times 10^7\) cells from the donor mice, B10. D2 or DBA/2 mice. On day 4 and 7 p.i., three recipient mice of each group were examined for virus titers in the liver, virus neutralizing (VN) antibody and interferon (IFN) titers in the serum [2, 7].

On day 4 p.i. there were no significant differences in virus titers among the groups. A significant difference in virus titers was observed on day 7 p.i. In mice having received T cells from infected B10. D2 or DBA/2 mice, no virus was detected from the liver, while high virus titers were seen in those having received T cells from non-infected mice of both strains. There were no significant differences in IFN titers of day 4 p.i. In the recipient nude mice having received T cells from infected donors, IFN titers on day 7 p.i. were lower than those with transfer from non-infected donors. No VN antibody was detected in any cases on day 4 nor 7 p.i. (Table 1).

Irrespective of T cell transfer, a number of necrotic foci was observed in the liver of the infected nude mice on day 4 p.i. (Table 2). On day 7 p.i., mice which had received naive B10. D2 or DBA/2 T cells showed severe hepatic necrosis with infiltration of neutrophils and some mononuclear cells (Fig. 1a). On the contrary, in animals having received T cells from infected B10. D2 or DBA/2 mice, the liver had some infiltration of mononuclear cells and some neutrophils but no severe necrotic lesions were seen (Fig. 1b).

Adoptive transfer of the immune T cells cured hepatic lesions and reduced the virus titers in the infected nude mice, inducing cell infiltration mainly composed of mononuclear cells without production of circulating VN antibody. In these responses no significant differences were observed between T cells from B10. D2 mice and those from DBA/2 mice. These findings might support our previous results that the bone marrow-derived cells such as monocytes-macrophages rather than T cells were responsible for the difference of DTH response [5]. However, it was still unclarified: 1) whether the mononuclear cells observed in the liver were effective for the protection or not, 2) whether the mononuclear cell infiltration was a result of DTH response or only a consequence of inflammatory responses. Although the importance of T cell-mediated
immunity in MHV-4 infection was demonstrated in this study, it is not fully elucidated whether or not cells recruited by the DTH-responses could be associated with the protection of virus-induced lesions. Further studies of the mechanism of T cell-mediated elimination of MHV-4 are in progress using the helper as well as cytotoxic T cell clones we have recently established [6, 9].
 ROLE OF T CELL IN VIRAL HEPATITIS

Fig. 1. Severe necrosis with neutrophilic infiltration (1a) and focal mononuclear cell infiltration without necrosis (1b) in the liver of MHV-4 infected nude mice which had received T cell transfer from either non-infected (1a) or infected (1b) B10.D2 mice, respectively. Day 7 p.i. HE stain ×170.

REFERENCES


要 約

感染 T 細胞移入ヌードマウスにおけるウイルス性肝炎の修飾 (短報): 久和 茂・山口健次郎・農田 裕・藤原公策 (東京大学医科学研究所獣医学研究部, 1)日本大学農業医学部獣医第二病理学教室) — ヌードマウスにマウス肝炎ウイルス JHM 株を腹腔内接種後 2 日に、感染 B10.D2 あるいは DBA/2 マウス T 細胞を移入すると、接種後 7 日の肝臓ウイルス値は非感染マウス T 細胞移入マウスのそれと比較して著しく低く、肝壞死病変はより軽微で単核細胞浸潤はより強かった。感染マウス T 細胞移入ヌードマウスでは、中和抗体は検出されず、インターフェロン値は非感染マウス T 細胞移入例より低かった。