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Allogeneic Orthotopic Liver Transplantation in Mice: A Preliminary Study of Rejection Across Well-Defined MHC Barriers

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A mouse model of orthotopic liver transplantation (OLT) has recently been established in our center.¹ In this study, OLT was performed between allogeneic mouse strains where the major and minor MHC antigenic barriers are well defined. Survival and the histopathologic patterns of rejection were correlated with the identity of MHC barrier.

MATERIALS AND METHODS

Ten to twelve-week-old male inbred mice were obtained from the Jackson Laboratory, Bar Harbor, Me. Orthotopic liver transplantation was performed as described by Qian and coworkers.¹ Briefly, following cholecystectomy and cuff preparations, the liver grafts were placed orthotopically after the native liver had been removed. The suprahepatic vena cava anastomosis was completed with a 10-0 running suture. The cuff technique was used for anastomosis of both the infrahepatic vena cava and portal vein. No attempt was made to reconstruct the graft arterial supply. The donor bile duct was connected to that of the recipient by inserting a polyethylene tube in both. Blood loss was replaced with Ringer's Lactate solution. No immunosuppressive therapy was used in this study. Animals living less than 1 week postoperatively were considered as surgical deaths, and were excluded from analysis. An autopsy was performed on all animals surviving more than 1 week, and tissue from the liver graft was submitted for histologic analysis. In addition, wedged resection biopsies were performed in some long-term survivors to assess the structural integrity of the graft and to check for rejection.

RESULTS

Isografts

All BALB/c liver isograft recipients survived for more than 100 days (see Table 1). Microscopically, random sampling of several healthy isograft recipients showed mild portal tract expansion, because of mild ductular proliferation in a few animals. However, no cholestasis was noted.

Allografts

The survival of allograft recipients is shown in Table 1. Liver grafts transplanted across both class I and II major

and minor MHC barriers (C3H → C57 BL/10; BALB/c → C3H; and B10BR → B10D2) survived for only short periods (median, 15 to 16 days; range, 8 to 41 days). On the other hand, liver allograft recipients (ATH → ATL) of only class II disparate grafts and that of ASW → ATH and B10D2 → B10HTG combinations, transplanted across H-2D locus differences, survived longer than 100 days.

Histopathologic studies showed that when class I and II major and minor histocompatibility barriers were breached, a brisk form of cellular rejection was found. It was characterized by a portal mononuclear inflammatory infiltrate with portal vein infiltration, and damage and extension into the lobules associated with infarcts. However, a more indolent form of liver rejection was seen when the H-2A and H-2E or H-2D loci were crossed. It was characterized by mild portal inflammation, which was often arranged in aggregates around bile ducts. Bile duct epithelial cell pyknosis and focal duct loss was seen in ATH → ATL combination.

DISCUSSION

This is the first attempt at defining the role of the MHC antigens in mouse liver allograft rejection; it has been previously done for skin and heart allografts.²⁻³ The results of this preliminary study showed that the severity of liver graft rejection appeared to be related to the degree of disparity at the histocompatibility complex. A histologically similar form of acute cellular rejection was seen when both class I or II in combination with minor histocompat-

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TABLE 1. Survival of Liver Grafts

| Donor | Recipient | Disparity | Actual Survival (d) | Median Survival (d) |
|--------|-----------|------------------------------------------------------------------|-------------------------------|---------------------|
| BALB/c | BALB/c | — | >100, >100, >100, >100, >100, | >100 |
| C3H | C57BL/10 | K ^b A ^b E ^b D ^b + mH | 8, 15, 41 | 15 |
| BALB/c | C3H | K ^d A ^d E ^d D ^d + mH | 8, 13, 15, 15, 16 | 15 |
| B10BR | B10 D2 | K ^b A ^b E ^b D ^b | 9, 10, 16, 18, 18 | 16 |
| ATH | ATL | A ^b E ^b | 38, >100, >100, >100, >100 | >100 |
| ASW | ATH | D ^b | 16, >100, >100, >100, >100 | >100 |
| B10 D2 | B10HTG | D ^d | 14, >100, >100, >100 | >100 |

ibility antigens were violated. Crossing class II loci or a single class I locus resulted in survival of longer than 100 days. However, several of these long-term survivors have developed a pattern of rejection which is histologically similar to "chronic" rejection as seen in human liver allograft recipients.⁴ Further studies are currently underway to more precisely define the role of the MHC antigens in liver allograft rejection and to determine whether an

acceptable animal model of chronic rejection can be developed.

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