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Liver Graft Induced Donor Specific Unresponsiveness Without Class I and/or Class II Antigen Differences

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LIVER allografting induces specific systemic unresponsiveness to subsequent other donor tissues in pigs,¹ rats,² and mice.³ Although the mechanism remains unclear, soluble donor class I major histocompatibility complex (MHC) antigens and/or anti-donor class II alloantibodies have been proposed as critical components of the induced unresponsiveness.^{2,4,5} If those explanations are correct, a liver graft should not be able to protect extrahepatic tissues if one or both of these potential mechanisms are inoperative. In the present study, the induction of unresponsiveness by liver allografts was observed in mouse strain combinations where there was class I MHC mismatching only (B10AKM→B10BR, absence of anti-donor class II antibodies), class II MHC mismatching only (ATH→ATL, absence of class I alloantigens), and only minor histocompatibility complex (mHC) mismatching (B10BR → C3H, absence of both class I and class II alloantigens). The results offered a perspective about the role of factors other than soluble class I antigens and class II antibodies in explaining the mechanisms of liver allograft-induced tolerance.

MATERIALS AND METHODS

Animals

All mice used in this study were purchased from Jackson Laboratory (Bar Harbor, Me) and then kept at the University of Pittsburgh Animal Facility until use. Ten to 12-week-old male mice were used as donors and recipients in liver, heart, and skin transplantation.

Liver, Heart, and Skin Transplantations

Orthotopic liver transplantation was performed by Qian's technique as previously described.⁶ Heterotopic heart transplantation was performed in the abdomen using the method of Corry⁷ immediately after liver grafting. Heart graft function was assessed daily by palpation. Rejection was defined as the total cessation of

palpable pulsation, confirmed by autopsy and histologic examination.

Skin grafting was completed by placing full thickness tail skin grafts (8 mm × 8 mm) on the dorsal flank of the recipient. Grafts were held in place by a gauze dressing and a tape for at least 7 days. The grafts were assessed daily thereafter. Rejection was defined as complete graft destruction. Donor skins were transplanted on to the liver recipients more than 100 days following acceptance of the hepatic grafts. No immunosuppressive therapy was used in this study.

RESULTS

Almost all donor skin and heart grafts in liver grafted recipients survived more than 100 days (Table 1), even when no class I MHC alloantigen mismatching (ATH to ATL) and no class II MHC alloantigen mismatching (B10AKM to B10BR) were present, or both class I and class II alloantigens were mismatched (B10BR to C3H). The heart grafts in B10AKM to B10BR combinations were spontaneously accepted long term even without prior liver grafting (data not shown).

The results in this study suggest that the donor-specific systemic unresponsiveness induced by liver allografting may not be due to soluble MHC class I antigens and/or MHC class II antibodies, which have long been proposed as the components responsible for liver graft-induced unresponsiveness.

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Table 1. Survival of Donor Grafts in Liver Grafted Recipient

Liver Donor	Recipient	Disparity	Donor Graft Survival (d)	
			Skin	Heart
None	C3H	I, II, mHC	15, 18, 19	7, 7, 7, 7, 7
C57BL/10	C3H		39, >100, >100, >100	>100, >100
None	B10BR	I	13, 13, 23, 23, 23	
B10AKM	B10BR		>100, >100, >100, >100, >100	
None	ATL	II	14, 16, 19, 19, 19	9, 11, 19, 22, 23
ATH	ATL		56,* >100, >100	>100, >100
None	C3H	mHC	20, 22, 22, 23	13, 13, 13, 13
B10BR	C3H		>100, >100, >100, 100	>100, >100, >100

Abbreviations: I, major histocompatibility complex class I; II, major histocompatibility complex class II.

*Animal died with living skin graft.

DISCUSSION

The immunosuppressive properties of liver grafting have been intriguing for decades. When the liver is transplanted with other organs, the additional donor original grafts are rejected less vigorously than expected.^{8,9} The mechanisms remain obscure, although they have been actively investigated. Soluble donor class I antigens released by liver graft¹⁰ have been considered as main components contributing to tolerance induction.

As recently reported in a rat model,⁴ continuous infusion of donor soluble class I antigen induced a marginal prolongation of heart graft survival (from 8.1 ± 0.7 to 10.0 ± 1.5 days), which was amplified by adding the monoclonal anti-class I antibody (15.6 ± 3.0 days). However, the results of the present study in the mouse model show that liver transplantation is able to induce systemic tolerance, in the combinations where the donor and recipient share the same MHC class I antigens. Therefore, it is unlikely that allogeneic MHC class I antigen or antibodies exist, since the donor and recipient are syngeneic for these molecules.

Anti-donor class II antibodies have been proposed as another mechanism of the immunosuppressive effects of liver grafting. In the rat model, anti-allo-class II MHC antibody titers reached their high levels and were maintained for several months after liver grafting.⁵ However, marginal enhancement was achieved by transferring liver grafted recipient rat serum IgG from which antibodies to class I antigens had been absorbed. Therefore the class II antibodies present in liver grafted rat serum were considered to be the factor responsible for enhancement.^{11,12}

However, in our mouse model, liver graft-induced unresponsiveness existed in a system where there was no class II disparity, and therefore alloantibodies to class II are unlikely to be present. In B10BR to C3H combination donor and recipient shared the same MHC. Despite that there were no allogeneic class I antigens and anti-class II antibodies in recipient serum, the liver grafts were still able to protect both skin and heart grafts. The results of this *in vivo* study suggest that it is inappropriate to overemphasize the role of class I alloantigens and/or class II MC alloantibodies in explanation of liver graft-induced specific unresponsiveness.

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