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Transplantation Unresponsiveness Induced by Liver Allografts in Mouse Strains With Various Histocompatibility Disparities

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LONG-TERM survival of fully allogeneic liver grafts without immunosuppression and induction of donor-specific systemic unresponsiveness to subsequent extrahepatic grafts have been documented in pigs[1] and rats.[2] However, the mechanisms of unresponsiveness are still poorly understood.[3] Since a mouse model of orthotopic liver transplantation (OLT) has been established,[4] it has become possible to more thoroughly investigate the genetic and immunologic basis for this unresponsiveness. In the present study, three strain combinations crossing various histocompatibility barriers (all with long-term liver graft acceptance) were chosen to determine the ability of liver grafting to induce donor-specific unresponsiveness to subsequent skin grafts.

MATERIALS AND METHODS

Animals

Inbred strains of 10- to 12-week-old male mice, C57BL/10, C3H, B10AKM, B10BR, and B10D2 were purchased from the Jackson Laboratory (Bar Harbor, Me) for use in these experiments. The *H-2* haplotypes of strains used are shown in Table 1.

Surgical Procedures

OLT was performed in combinations of C57BL/10 to C3H, B10AKM to B10BR, and B10BR to C3H using previously published techniques.[4] Full-thickness tail skin grafts were placed on the dorsum of the mice who had accepted liver grafts for more than 100 days, according to Billingham and Medawar.[5] Band tapes were used to keep the grafts in place for 7 days and then removed. No immunosuppression was used in this study. The skin grafts were examined once a day for the first 2 weeks and 2 to 3 times a week thereafter. Skin grafts that failed from obvious technical complications were excluded from further analysis. Skin grafts that survived more than 100 days were biopsied for histological studies.

RESULTS

Despite transplantation across various histocompatibility barriers in the three groups studied, long-term (>100 days) liver allograft survival was achieved in all animals, except for one in each group (41, 80, and 68 days, respectively).

Table 1. *H-2* Haplotypes of Strains Used

Strains	*H-2* Haplotype	Alleles at *H-2* Loci					
		K	A_b	A	E_b	E	D
C3H	k	k	k	k	k	k	k
C57BL/10	b	b	b	b	b	b	b
B10BR	k	k	k	k	k	k	k
B10AKM	m	k	k	k	k	k	q
B10D2	d	d	d	d	d	d	d

The survival of skin grafts is shown in Table 2. Without prior liver transplantation, all allogeneic skin grafts were acutely rejected. Histologically verified donor specific unresponsiveness to allogeneic grafts was observed in all liver tolerant mice, regardless of the strain combination. Third-party skin grafts were uniformly rejected.

DISCUSSION

The unique properties of liver allografts have been studied for decades. As early in 1965, Garnier and colleagues discovered that allogeneic orthotopic liver grafts were able to escape irreversible rejection in the pig.[7] Calne et al then demonstrated that liver grafts induced donor-specific hyporesponsiveness to subsequent skin or kidney grafts from the same donor. One explanation for this observation involved the release of soluble MHC antigens by the grafted liver.[1] Ten years later, Zimmerman observed the same results in the inbred rat.[2] Since then, inbred rats have been the major source of information on liver graft tolerogenesis.[8]

This is the first attempt at investigating tolerogenic and immunosuppressive properties of liver grafts in inbred mice. The advantages of using mice are obvious. Numerous genetically well-defined mouse strains and a plethora of immunologic reagents are available to study the genetics and immunology associated with the unresponsive state. Using this model, results identical to those observed in inbred strains of rats were achieved. Namely, liver grafts were able to induce donor-specific unresponsiveness to subsequent skin grafts in mouse strains with various histoincompatibilities.

Interestingly, in the B10BR to C3H combination, which crossed only minor histocompatibility barriers, the liver grafts were able to induce unresponsiveness to subsequent skin grafts. Therefore, the induction of unresponsiveness by liver grafting is not restricted solely to the MHC system, but likely involves the minor histocompatibility complex as well.

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Table 2. Skin Graft Survivals

Liver Donor	Recipient	Disparity	Skin Donor	Skin Survival (d)
None	C3H	$K^bA^bE^bD^b$ + MHC*	C57BL/10	15, 18, 19
C57BL/10	C3H		C57BL/10	>100, >100
C57BL/10	C3H		B10D2†	13, 13, 13
None	B10BR	D^q	B10AKM	13, 13, 23, 23, 23
B10AKM	B10BR		B10AKM	23, >100, >100, >100
B10AKM	B10BR		B10D2	13, 13, 13, 13
None	C3H	MHC*	B10BR	22, 23
B10BR	C3H		B10BR	>100, >100
B10BR	C3H		B10D2†	13, 13

*Minor histocompatibility.
†$B10D_2$ as third party.

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