

EFFECT OF CLASS II ANTIGEN MATCHING ON RENAL ALLOGRAFT SURVIVAL IN MINIATURE SWINE

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Although results from multicenter trials have been mixed (1, 2), most single-center studies have shown that HLA-DR matching leads to significant improvement in human renal allograft survival (3, 4). The true effect of matching may have been clouded by pharmacologic immunosuppression and, more recently, by the addition of aggressive pretransplant blood transfusions (2, 4). Studies of the role of class II antigen matching in rodents in the absence of other immunosuppression have yielded conflicting results, with one group reporting prolonged survival with matching (5) and another group finding no effect (6). Even if the effect of matching was consistently found in rodents, the recent reports of Hart and Fabre (7, 8), showing differential anatomical distribution between rodents and man of class II antigens on vascular endothelium, a potential site of recipient/donor immune interaction, suggest that conclusions may not be directly transferable to man. The use of large-animal models in which the effect of class II matching have been studied have been difficult. In general, they have depended on rare recombinants among siblings or have used mixed lymphocyte nonreactivity and serologic class II antigen typing to identify class II identical animals (9). These methods have been limited by the inability to repeat results with the same matched combinations, coupled with the uncertainty of genotypic class II identity because of limited typing reagents.

Studies of transplantation biology in this laboratory have made use of our partially inbred miniature swine (10). Because they are defined only at the major histocompatibility complex (MHC),¹ they provide a closer model for human transplantation studies than do inbred rodent species. The recent identification of a recombinant haplotype (11) has now enabled us to test the effect of isolated class I and II antigen matching in this large-animal model. This recombinant haplotype, SLA^g, has been demonstrated by serology, protein chemistry, and restriction digest mapping of DNA (D. Singer and D. H. Sachs, unpublished results) to contain the class I antigens of the *c* haplotype and the class II antigens of the *d* haplotype. We have also recently demonstrated in our herd that the

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¹ *Abbreviations used in this paper:* BUN, blood urea nitrogen; CTL, cytotoxic T lymphocyte; df, degrees of freedom; MHC, major histocompatibility complex; MLR, mixed lymphocyte reaction; PBS, phosphate-buffered saline; SLA, swine leukocyte antigen.

expression of class II MHC antigens on vascular endothelium is identical to that of man (12). Renal allograft survival in nonrecombinant miniature swine has previously been shown to be correlated with MHC matching (13). In addition, a non-MHC-linked immune response gene has been shown to further regulate survival of completely matched grafts, such that recipients lacking a rejector gene were tolerant of the MHC-matched graft despite multiple mismatched minor histocompatibility antigens (14). In preliminary studies of transplants using the recombinant animals, a beneficial role of class II matching alone in two animals was found (15). We have therefore extended these studies and now report that overall survival of class II only-matched kidneys is clearly prolonged over completely mismatched or class I only-matched kidneys. In addition, we show that this prolongation is dependent on MHC gene dose differences, is subject to the effects of both MHC-linked and MHC-unlinked genes, and is associated with specific systemic tolerance.

Materials and Methods

Animals. Three herds of miniature swine, selectively inbred for the porcine MHC, swine leukocyte antigen (SLA), with haplotypes designated *a*, *c*, and *d*, have previously been described (10), as has a recently derived recombinant haplotype designated *g* (11). All animals were bred and maintained at the NIH Animal Center, Poolesville, MD.

Kidney Transplants. Animals used for transplantation were 3–6 mo old and weighed 20–40 kg. The technique of renal allografting has been described (13). Briefly, two animals were subjected to bilateral nephrectomy and reciprocal exchange of one kidney. In certain instances, one animal served as a donor for two recipients. Transplants were placed orthotopically using a Carrel patch arterial anastomosis and end-to-end venous and ureteral anastomoses. Serial serum creatinine and blood urea nitrogen (BUN) levels were obtained to assess renal function after transplant. These values paralleled each other with rejection, so only BUN values are shown in the results. Occasional animals whose BUN increased between days 2 and 3 were surgically explored for a possible ureteral leak, which was repaired if detected. Rejection was defined as death of the animal with an associated decrease in renal function and confirmatory gross and pathologic findings. No exogenous immunosuppression was administered, nor were animals given blood transfusions.

Skin Grafts. Split-thickness skin grafts were placed on renal allograft recipients that had survived beyond 3 mo, or on normal matched controls. The skin was either fresh (if the renal donor was alive) or frozen (taken at the time of renal transplant). The graft bed was prepared with a single pass of a disposable electric Davol Dermatome (Davol, Inc., Cranston, RI). An occlusive compression dressing was removed on day 3 after skin grafting. The day of rejection was defined as the point at which the skin was totally necrotic.

Posttransplantation Antibody Response. Pretransplant and weekly posttransplant serial serum samples were tested for alloantibody responses using a two-stage, complement-dependent cytotoxicity assay (10) on Ficoll/Hypaque-purified peripheral blood lymphocytes. Either trypan blue exclusion or ⁵¹Cr release was used to assess percent lysis. Maximum release for the ⁵¹Cr assay was determined by the lysis caused by 1 N HCl and the background was complement alone. Hyperimmune allo sera (10) were included in all assays as positive controls.

2-Mercaptoethanol Treatment of Serum. To distinguish between IgM vs. IgG alloantibodies, posttransplant sera were diluted 1:1 with phosphate-buffered saline (PBS). 2-Mercaptoethanol (Bio-Rad Laboratories, Richmond, CA) was then added to a final concentration of 0.1 M. The samples were incubated for 30 min at 37°C and then dialyzed against PBS. Control samples were treated identically, but no 2-mercaptoethanol was

added. The treated samples were then tested for cytotoxic activity in a two-stage, complement-dependent assay.

Statistical Analysis. Survival times are reported as mean \pm SD. Statistical significance was calculated on a Wang 2200 computer using either a Student's two-tailed *t* test with degrees of freedom (df) calculated assuming unequal standard deviation, or a 2×2 contingency table for Chi square analysis.

Results

Experimental Protocol. The discovery and propagation of the recombinant *g* haplotype (11) allowed selective transplantation across either class I or class II differences (Fig. 1). Because these animals were not fully inbred, multiple minor antigen differences were also present (13). Thus, transplants between animals of the *d* and *g* haplotypes resulted in class II-matched, class I-mismatched grafts. Alternatively, transplants between animals of the *g* and *c* haplotype resulted in class I-matched, class II-mismatched grafts. Finally, transplants between animals of the *c* and *d* haplotype resulted in both class I- and class II-mismatched grafts. Also shown in Fig. 1 is the *a* haplotype used in heterozygous recipients. By selecting homozygous or heterozygous recipient pairs, the effect of MHC gene dose could also be studied. No immunosuppressive therapy was used, to avoid confounding the effect of MHC matching.

Graft Survival as Controlled by MHC Antigen Mismatch. Fig. 2 shows the overall results obtained with the four types of MHC matching: none, complete, class I, or class II. Deaths from all causes beyond the first week are included. In confirmation of early work in this model, completely mismatched grafts were rapidly and uniformly rejected with a mean survival time of 12 ± 1.9 d. MHC-matched grafts showed prolonged survival over complete mismatches. Also as demonstrated previously (13), a percentage of these matched grafts enjoyed permanent acceptance with normal renal function, despite multiple mismatches

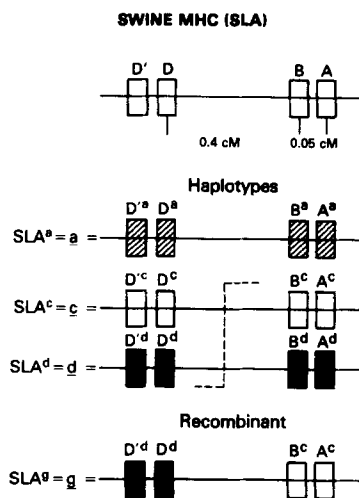


FIGURE 1. Schematic diagram of the porcine MHC complex demonstrating the two identified class I antigens, A and B, and the two class II antigens, D and D'. The three original miniature swine haplotypes *a*, *c*, and *d* are next indicated. Finally the recombinant haplotype, *g*, is shown, and the contributions from the *c* and *d* haplotypes demonstrated.

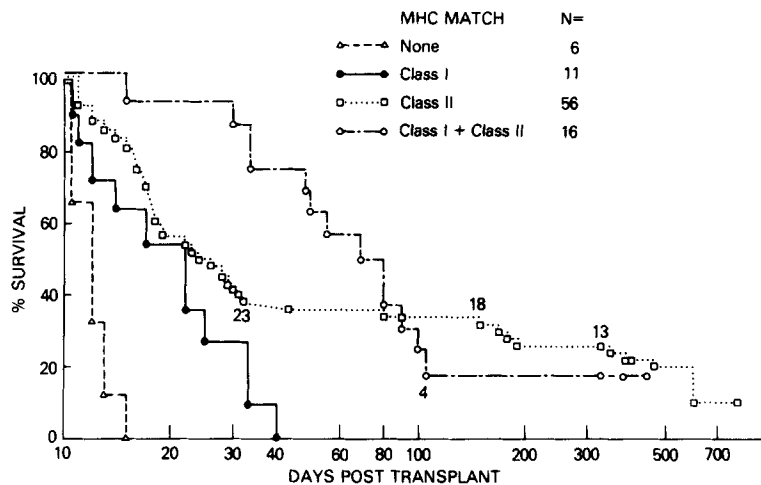


FIGURE 2. Life table survival of renal allografts in miniature swine. Survival curves are shown for each type of antigen mismatch. Deaths from all causes after a technically successful transplant are included. The number of animals in each group are indicated in the legend, as well as the number of animals alive at various points for class II-matched and class I plus class II-matched grafts.

at non-MHC loci. In fact, with few exceptions, all deaths beyond 100 d were from causes other than rejection. As mentioned in the introduction, this survival was previously found to be regulated by a non-MHC-linked immune response gene(s) (14).

After reconfirming the effect of matching for the whole MHC, the effect of partial MHC matching was studied. Class I-matched, class II-mismatched grafts, (all *ag/ac* combinations) although prolonged over completely mismatched grafts, were all rejected with a survival time of 21.8 ± 10.4 d ($P = 0.086$, 11 df). The most striking results were seen in the group that received class II-matched, class I-mismatched grafts. While the percentage of early deaths in this group was nearly the same for that of class I-matched grafts, by day 30 posttransplant, these two survival curves separated, and the class II-matched graft survival paralleled and eventually equalled that of the fully matched grafts. Therefore, class II-matched grafts showed a bimodal distribution in survival with the long-term survival equaling that of complete MHC-matched grafts.

Prolonged Survival of Class II-matched Grafts Analyzed by Specific Donor/Recipient Pairs. The bimodal survival seen in Fig. 2 suggested that certain animals had a greater tendency to reject class II-matched, class I-mismatched renal allografts than did others. To examine this possibility, class II-matched grafts were divided into groups by recipient/donor combinations (Fig. 3). This analysis demonstrated that prolonged survival of the allograft was associated nonrandomly with certain combinations. Additionally, it suggested that at least three genetic factors regulated length of allograft survival, namely donor MHC gene dose, a recipient MHC-linked effect, and a recipient non-MHC-linked effect (possibly an immune response gene). The effect of MHC gene dose can be seen in several groups: All *dd* animals rejected their class II-matched renal grafts, but recipients of haplo-identical (*dg*) grafts showed longer survival (26.8 ± 7.4 d) than those recipients

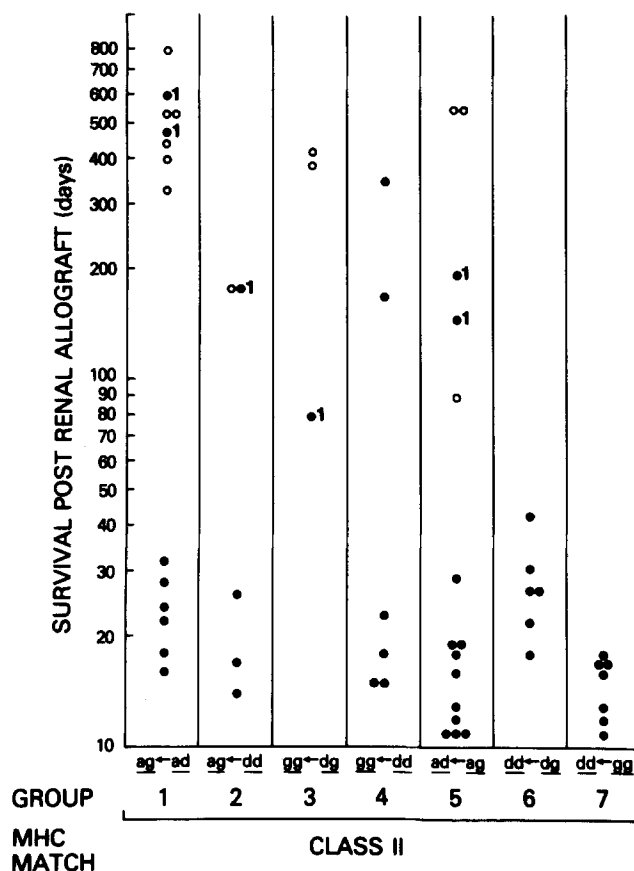


FIGURE 3. Class II-matched renal allograft survival analyzed by donor/recipient combination. Each combination of recipient MHC genotype (left pair of letters) and donor genotype (right pair of letters) are plotted, with survival of each animal in each group given in days. (○) Animals still alive. (●) Animals that died from rejection. A superscript 1 indicates animals that died from nonrenal causes. Each circle indicates one animal.

of homozygous (*gg*) grafts (15.4 ± 3.3 d) (groups 6 and 7; $P = 0.0068$, 7 df). Also, all *gg* recipients of *dd* grafts died of rejection, whereas no recipients of *dg* grafts died of rejection (groups 3 and 4; $P < 0.005$, 1 df, Chi square). The MHC-linked effect was seen by comparing results in the *dd* animals with results in *gg* animals. All *dd* recipients rejected their class II-matched, *dg* grafts (group 6). Similar *dg* kidneys, however, were not rejected by *gg* recipients (group 3; $P < 0.005$, 1 df, Chi square). Since the only clear difference between the *g* and *d* haplotypes involves the class I MHC antigens, this phenomenon is apparently class I dependent. Possible mechanisms for this effect are addressed further in the Discussion. The *a* haplotype appeared to function in a permissive role, since a percentage of *ad* animals tolerated *ag* (group 5) or *gg* kidneys (data not shown), whereas none of the homozygous *dd* animals permanently accepted class I-mismatched grafts. Finally, a non-MHC-linked immune response gene was suggested by the bimodal distribution in survival observed in groups 1, 2, 4, and

5. Approximately half of the animals died of rejection at times equal to the class I-matched, class II-mismatched grafts (Fig. 2). The remainder of the animals, with the exception of group 4, showed permanent allograft survival. This immune response gene effect is similar to that previously reported for MHC-matched grafts (14). MHC gene dose had an opposite effect, since two animals in group 4, although surviving for prolonged periods, did eventually succumb to chronic rejection.

Evidence for an Anti-allograft Immune Response in Long-term Survivors. Howard and Butcher (16) have suggested that long-term survival of class I, MHC-mismatched skin grafts in certain rat strains results from the lack of an immune response to these MHC antigens, as determined by antibody production and cellular reactivity. It seems unlikely, however, that this was the basis of prolonged survival in our pigs, since a definite anti-allograft response, indicated by decreasing renal function and anti-donor MHC antibodies, was found beginning ~10 d posttransplant. In those animals that succumbed, the BUN increased until death (Fig. 4A), while in the pigs that survived, renal function improved and eventually returned to pretransplant levels. In certain instances, the damage induced during the limited rejection crisis was more severe and apparently repaired more slowly (compare Fig. 4, B and C). After the recovery period, with the exception of group 4 (Fig. 3), there was never a secondary rise in BUN due to rejection. In this group, the two long-term survivors had a slight initial improvement in renal function before continuing with a slow chronic decrease in function until death from uremia. Additional evidence for an anti-allograft immune response was found in the few animals that died from nonrenal causes during the recovery phase. In these animals, cellular infiltrates consistent with rejection were found.

All animals that rejected their allografts, and 6 out of 15 nonrejecting animals that were tested, had detectable levels of antibody against the renal donor MHC haplotype. Table I shows six animals, half of which were acceptors, that demonstrated antibodies specifically reactive against cells of the mismatched donor class I MHC haplotype, *d*, but not the self class I MHC haplotype, *c*. Positive controls, animals immunized by skin grafts (10), lysed >80% of cells with titers of 256 or greater (data not shown). As seen in Table I, acceptor animal sera were lower titered and killed a lower percentage of cells than rejector animal sera or positive control sera. In one animal (916 *ag*), lysis directed toward a minor antigen was found, in addition to that directed toward the MHC antigens. This reactivity was also present in the pretransplant sera. The peak of the antibody response in the acceptors was at 2 wk, with disappearance by 4 wk, except in one animal (916) (Fig. 4, B and C), while antibodies persisted for >6 wk in animals that rejected skin grafts or in nonnephrectomized animals that rejected a transplanted kidney (data not shown). With the exception mentioned above, pretransplant sera had no cytotoxic activity. These data, therefore, demonstrated that kidney allografts induce an immune response in the long-term survivors of class II-matched, class I-mismatched allografts, but that some other host mechanism(s) lead to curtailment of this immune response.

Isotype Class of the Antibody Response. Several possible explanations were suggested for the short duration of the antibody response. The appearance of inhibitory material (e.g., antiidiotypic antibodies or anticomplementarity) was an

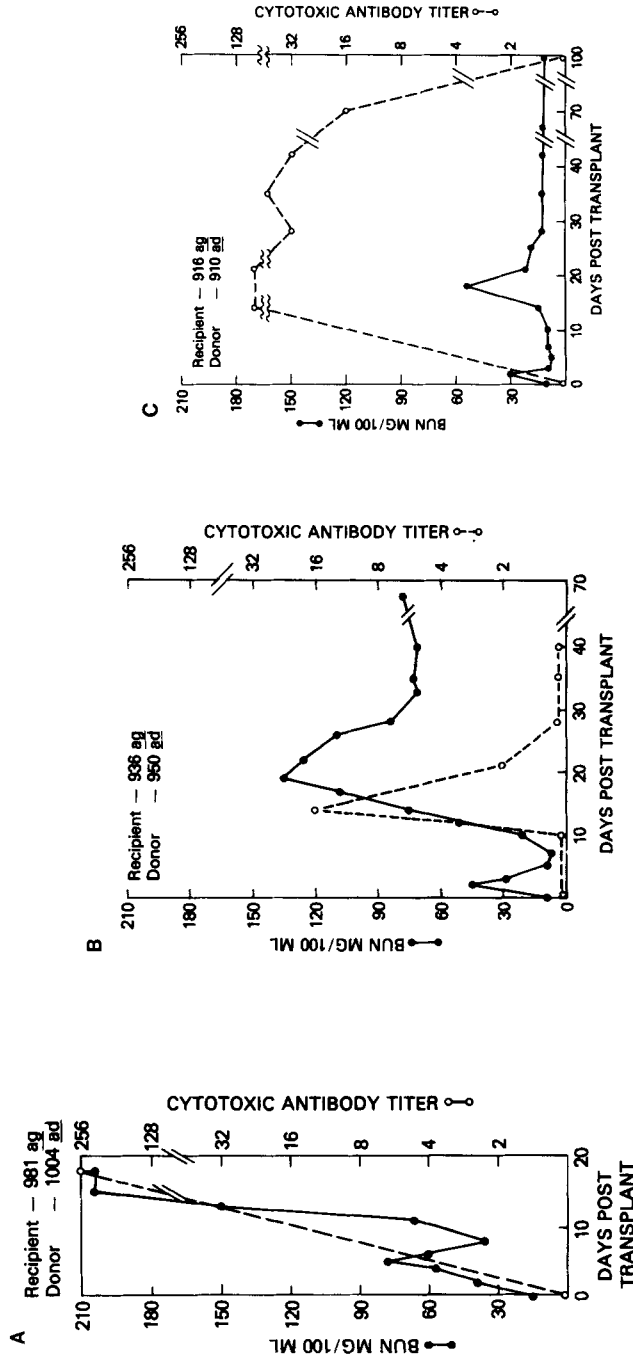


FIGURE 4. Posttransplant renal function and anti-donor MHC antibody response in recipients of class II-matched grafts. Representative examples of the three posttransplant courses are demonstrated. (A) Animal 981 ag rejected its graft at day 18 and developed high-titered IgG antibodies. (B) Animal 936 ag mounted a less vigorous rejection and eventually became tolerant of its response in recipients of class II-matched grafts. The associated antibody response was of limited duration and was of the IgM isotype. (C) 916 ag had a mild rejection episode with rapid return to normal renal function. The anti-HMC antibody response was persistent, but did not interfere with renal function.

TABLE I

Postrenal Transplant Antibody Response: Evidence for MHC Linkage of Target Antigens

Recipient No./haplo-type	Donor No./haplotype	Target cells (animal No./haplotype)						
		158 <i>dd</i>	882 <i>dd</i>	1100 <i>dd</i>	457 <i>cc</i>	869 <i>cc</i>	909 <i>cc</i>	441 <i>cc</i>
920 <i>ag</i> *	885 <i>dd</i>	1:512 (90) [‡]	ND	>256 (100)	0	0	0	0
933 <i>ag</i>	949 <i>ad</i>	1:128 (90)	ND	1:256 (100)	0	0	0	0
981 <i>ag</i>	1,004 <i>ad</i>	>256 (100)	1:128 (100)	>256 (100)	0	0	0	0
983 <i>gg</i>	979 <i>dg</i>	1:64 (49)	1:32 (88)	1:64 (75)	0	0	0	0
936 <i>ag</i>	950 <i>ad</i>	1:32 (35)	1:32 (55)	1:64 (31)	0	0	0	0
982 <i>ag</i>	1,002 <i>ad</i>	1:64 (38)	1:128 (77)	1:128 (54)	0	0	0	0
916 <i>ag</i>	910 <i>ad</i>	1:128 (86)	1:64 (54)	1:256 (27)	0	1:128 (46) [‡]	1:128 (45)	0

* All sera are 2 wk posttransplant. Animals 920, 933, and 981 died from rejection at 2 wk.

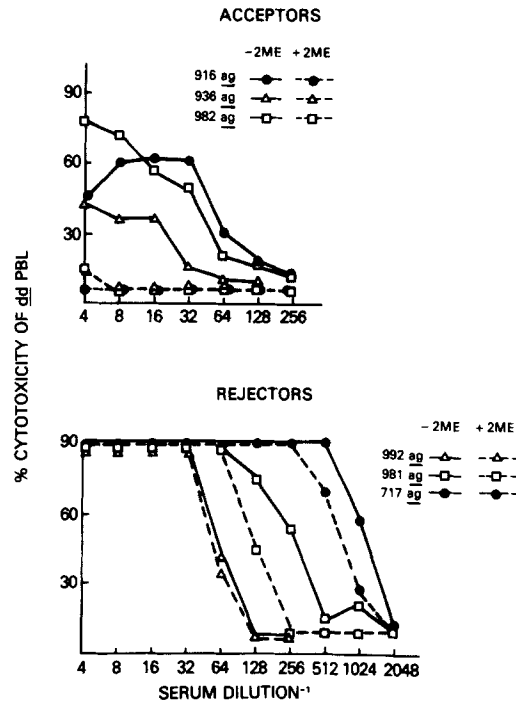
[‡] Titer (percent release Cr⁵¹) in a two-stage complement-dependent cytotoxicity assay on peripheral blood lymphocytes.[‡] Cytotoxicity against these *cc* targets by No. 916 was seen in pretransplant sera. All other pretransplant sera were negative.

FIGURE 5. IgM vs. IgG antibody response in posttransplant animals. 2 wk sera from animals that A, subsequently survived their renal allografts (916, 936, and 982) or B, from animals that rejected their kidney (981), skin (992), or hyperimmune sera (717), were treated with 2-mercaptoethanol, 0.1 M, for 1 h at 37°C. Titer and percent cytotoxicity as determined by complement-dependent lysis on Na⁵¹CrO₄-labeled *dd* peripheral blood lymphocytes are shown. Control samples (solid lines) received identical treatment, but were not exposed to 2-mercaptoethanol.

unlikely explanation, since the mixing of late noncytotoxic serum samples with earlier cytotoxic samples only resulted in a decrease in cytotoxic activity, explainable by dilution (data not shown). Since the cytotoxic activity was only seen early, it was reasoned that the antibodies might be of the IgM class. Consistent with this hypothesis, the cytotoxic activity was sensitive to 2-mercaptoethanol (Fig. 5),

which is known to disrupt IgM antibodies (17). When 2-wk sera from animals that were rejecting similarly matched kidney or skin grafts were subjected to the same 2-mercaptoethanol treatment, at most a 50% reduction in activity was seen. This implies that at 2 wk, an IgG response was possible, but that in those animals that survived the kidney transplant, a detectable switch from IgM to IgG production did not occur.

Evidence for Systemic Tolerance in Long-term Survivors. Animals that had survived class I-mismatched, class II-matched renal allografts were grafted with skin from the same renal donor or third-party, class II-mismatched animals. Skin grafts from the renal donor to renal recipient showed prolonged survival (31.7 ± 20.4 d) over similar class I-mismatched skin grafts placed on control animals (11.67 ± 2.6 d, $P = 0.043$, 5 df) and over third-party skin grafts on renal graft recipients (Fig. 6). Although prolonged, all skin grafts were eventually rejected. At the time of rejection there was no decrease in renal function, as determined by measurement of serum BUN or creatinine, nor did anti-donor cytotoxic serum antibodies appear. These results implied that tolerance to MHC antigens and perhaps to kidney-specific antigens was present. They also suggested that skin-specific antigens may have been responsible for eventual rejection.

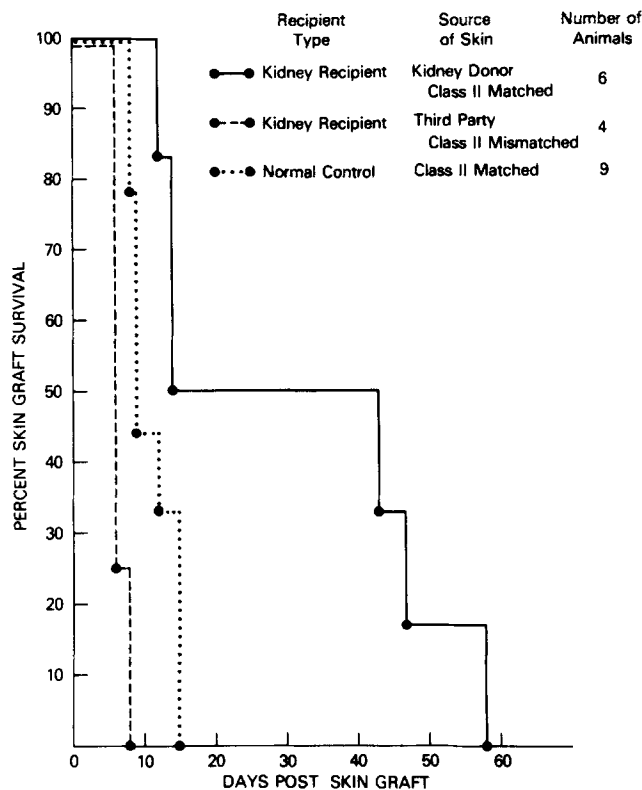


FIGURE 6. Skin graft survival in recipients tolerant of class II-matched renal allografts. Animals tolerant of renal allografts for >90 d underwent split-thickness skin grafts from the renal donor (●—●) or from third-party, class II-mismatched animals (●- -●). Normal controls were animals of similar MHC type but without a renal allograft (●· · · ●).

Discussion

The effect of DR matching on renal allografts in inbred miniature swine has been studied. These transplants are analogous to human, living, related donor transplants with identifiable MHC differences and limited unidentifiable minor histocompatibility differences. The existence of a recently derived, well-characterized recombinant haplotype (10) offers an advantage to this system over others such as monkeys or dogs, since use of this recombinant haplotype permits complete genotypic matching for the class II antigens. In rhesus as in humans, the ability to identify DR matches is limited by the availability of typing reagents (18). In fact, in monkeys, serologic DR matching is associated with a 20–30% cellular D region mismatch, implying additional undetected, class II antigen mismatching or a class I-specific mixed leukocyte reaction (MLR). In our miniature swine, genetic and serologic DR matching only occasionally resulted in a limited MLR response (19), which could be blocked by class I-specific sera (M. Pescovitz, unpublished observations). Using these animals, without exogenous immunosuppression and despite known class I MHC antigen mismatches, a clear benefit for class II antigen matching was seen. In fact, long-term survival after class II-only matched grafts equaled that of MHC-matched grafts.

The survival pattern of class II-matched grafts suggested a bimodal distribution, with some animals rejecting their allografts at times only slightly prolonged over mismatched grafts. A similar bimodal distribution has been reported in Rhesus monkeys (20) and has been suggested in humans when time to first rejection episodes was examined (21). By performing transplants in multiple different donor/recipient combinations, a pattern of survival resulted which suggested three important factors for survival, each of which will be discussed separately.

First, the data suggest an effect of mismatched MHC gene dose. Improved survival of haploidentical grafts has been reported in other experimental renal allograft systems (22, 23). The actual mechanism is uncertain both in these reports and in the pig. Whether it results from an effect on the afferent or efferent arm of the immune response is not clear. MLR and cell-mediated lympholysis reactions are generally less vigorous between haploidentical porcine cells than between homozygous animals, although there is wide variation (M. Pescovitz, unpublished observation). However, homozygous and heterozygous target cells are lysed equally well by a single cytotoxic T lymphocyte (CTL) effector population, providing no obvious correlation between *in vitro* and *in vivo* MHC gene dose effects.

Second, there appears to be an MHC-linked effect on survival. Since the only MHC differences between the *dd* recipients that reject *dg* grafts and the *gg* recipients that accept *dg* grafts are the class I MHC antigens, this apparently maps this effect to the class I antigens. This could imply a class I immune response gene, although the fact that heterozygous *ad* animals sometimes accept grafts would mitigate against this possibility, since it would make the gene recessive. Evidence for MHC-linked higher rejection rates exists in several other species, including rodent and man. The MHC-linked immune response gene for MHC antigens reported for rats was also seen for a class I antigen mismatch (16). In these experiments, along with the failure to reject skin, the rats also failed to

make antibodies or in vivo CTL to the mismatched antigens and the effect was shown to be dominant. The swine reported here differ in that skin grafts were rejected across differences in which kidneys were accepted, an anti-MHC antibody response developed, and rejection was recessive. In man, the DR 6 class II antigen has been found to be associated with significantly higher levels of renal allograft rejection than other DR types (24). This may be more analogous to class II immune response genes described in mice for soluble antigens. Another possible explanation for this difference in survival would be the existence of an unknown background gene(s). As the *dd* and *gg* herds have been separated for several generations, it is possible that a background rejector gene(s) has been fixed in the *dd* herd. This would have to be different from the previously demonstrated gene(s), which results in rejection across minor antigen-only differences, since the *dd* animals used in these transplants did not have this gene (14). Therefore, there would be at least two non-MHC-linked immune response genes, one of which is only apparent when a strong, class I MHC difference is provided. A final explanation for the difference is suggested by a recent report by Isakov (25), who found a direct correlation between cytotoxic cell precursor frequency and the ability to reject thyroid allografts in murine D region disparate grafts. Because the *gg* and *dd* recipients differ at the class I antigen, they also see different class I antigens as foreign. In swine, then, CTL precursors reactive against the class I antigens of *d* (AB^d) (*gg* anti-*dg*) would be of lower frequency than CTL precursors reactive against the class I antigen of *g* (AB^c) (*dd* anti-*dg*). The fact that heterozygous *ad* animals sometimes accept kidneys could then be explained by genetic tolerance to a greater number of class I specificities. Although formal precursor frequency analysis has not been done in these pigs, in vitro CTL activity is generally greater in AB^d anti- AB^c combinations than in AB^c anti- AB^d combinations (19).

Third, as mentioned in the introduction, a non-MHC-linked immune response gene has been shown to regulate survival across minor histocompatibility antigens in swine (14). The bimodal distribution of survival seen in some class II-matched groups was similar to that seen for transplants across these minor antigen differences. Since the rejector phenotype for minor antigens segregated in the *c* herd (and probably the *a* herd) to which the original *g* haplotype animal was mated, it would be expected that a fraction of *g* haplotype animals should reject MHC-matched grafts and, even more likely, should reject MHC-mismatched grafts. If this bimodal distribution truly resulted from an inheritable recipient genotype, then the progeny of tolerant parents should all be acceptors. Breedings are currently underway to test this hypothesis. Since the *dd* recipients were all of the acceptor phenotype (14), this gene should not have been relevant in this limited group.

The tolerance developed to the kidney appears to be systemic. First, there was prolongation of donor-specific skin but not of third-party skin. The rejection that finally did ensue was possibly related to skin-specific antigens, since there was no associated evidence of renal dysfunction. In addition, no antibody was detectable nor did in vitro cellular activity develop after skin graft rejection. Experiments are currently underway to determine whether continued presence of the kidney is necessary to maintain this tolerance.

The mechanism of tolerance maintenance is likewise presently under study. Suppressor cells active in an *in vitro* MLR response have been identified in the long-term survivors (reference 26 and unpublished data) and the phenotype of the cells involved is now being addressed, using monoclonal antibodies to porcine helper and CTL subsets (27). Whether these cells function *in vivo* in addition to *in vitro* is uncertain. The failure to detect a switch in the anti-MHC IgM response to IgG in the long-term survivors could indicate another phase in the immune response in which to study suppression *in vitro*. The ultimate test of suppressor cell regulation—passive cellular transfer—may not be possible in these swine, since they are not fully syngeneic.

These experiments may be of clinical relevance. The results suggest that matching for class II MHC antigens has a major role in vascular graft acceptance. They also suggest that other risk factors could be identified that lead to rejection. If these factors could be identified pretransplant, better-matched grafts or adjustment of immunosuppressive regimens could be adopted.

Summary

The benefit of class II major histocompatibility complex (MHC) antigen matching to renal allograft survival, in the absence of immunosuppression, has been studied in partially inbred miniature swine. Permanent (>6 mo) renal allograft survival was found in 30% of recipients of either class II only or fully matched grafts. Analysis of the survival of the class II-only matched grafts by specific recipient/donor haplotype combinations indicated that survival was regulated by at least three genetic factors, including antigen gene dose, a class I MHC allele-dependent effect, and non-MHC-linked immune response phenomenon.

Animals accepting class II-matched kidneys developed spontaneous tolerance to the graft, despite mounting an initial immune response marked by renal damage and the development of serum cytotoxic antibodies directed at the donor MHC antigens. The antibodies were only of the IgM class, suggesting that conversion of the humoral response to IgG was blocked. After acceptance of the kidney, three out of five animals showed specific prolongation of donor skin grafts. At the time of rejection of these skin grafts, no decrease in renal function nor reappearance of anti-donor antibodies was observed.

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