IN: CLINICAL TRANSPLANTS 1993
TERASAKI, P.I. and CECKA, M. eds.
UCLA TISSUE TYPING LABORATORY
LOS ANGELES, CA.

1640

The Blind-Folding of HLA Matching

Thomas E. Starzl, M.D., Ph.D.,[a] Massimo Trucco, M.D.,[b] Abdul Rao, M.D.,[a] and Anthony Demetris, M.D.[c]

Transplant Institute and Departments of [a] Surgery, [b] Pediatrics, and [c] Pathology
University of Pittsburgh Health Science Center
Pittsburgh, Pennsylvania

It has been 29 years since the first prospective trials of HLA matching in kidney transplantation began (1) with the logical assumption that results could be thereby improved. Except for the identification of histocompatible siblings as "special" donors, a matching effect was not evident (2). This conclusion breathed life into the still struggling fields of liver and heart transplantation in which patients could not be supported by artificial organs while waiting for a well-matched donor. Since then, transplant surgeons have continued to claim that HLA matching does not accurately predict the outcome of cadaver kidney transplantation (3-5) or of transplantation of extra-renal organs including the liver (6,7). The fact that thousands of conflicting reports have not brought this controversy to a close, beyond a consensus that there has been a small improvement in outcome with the uncommon perfect HLA match (8), means that other factors must be sought.

In the meanwhile, it was immediately obvious that a perfect or near perfect match is a supreme determinant of success for bone marrow transplantation (9,10). A plausible explanation for this dichotomy has been provided by the recent discovery that leukocytes migrate perioperatively from transplanted whole organs to widely distributed recipient tissues where they can be identified many years later (11-13). The leukocytes leaving the graft are replaced by recipient cells moving in the opposite direction. The events under immunosuppression, leading eventually to the chimerism in the graft as well as ubiquitously in the recipient, imply that there is a mutual engagement, activation, and ultimately inactivation of the immunocytes of both parties. The cell mixture can be seen as an *in vivo* two-way mixed lymphocyte reaction (MLR) (Fig. 1). Such a cell interaction cannot transpire after bone marrow transplantation because the conditioning cytoablation of the recipient with irradiation or myelotoxic drugs eliminates host hematopoietic cells. Thus, the conditions in the bone marrow patient who can stimulate but not respond immunologically resemble a one-way MLR.

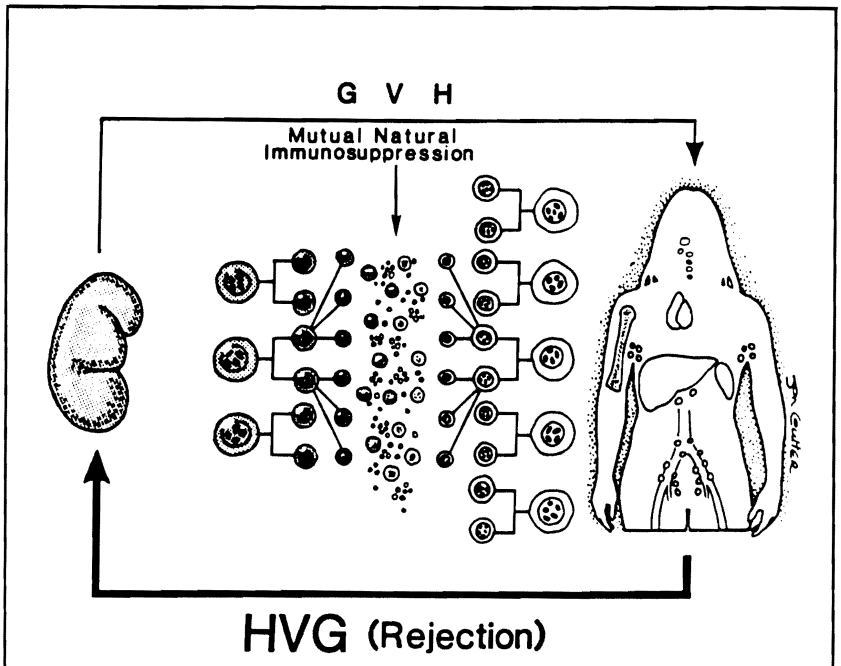

Figure 1. The mutual engagement of migratory tissue leukocytes from the graft with those of the recipient. Although the potential exists for graft versus host (GVH) disease reactions, this rarely is evident with leukocyte-poor organs like the kidney. HVG—host versus graft.

We believe that the migration from organ allografts of donor leukocytes and their ubiquitous persistence in recipient tissues is the seminal explanation for allograft acceptance and the first stage in the development of donor-specific nonreactivity (tolerance) (11-13). In a direct extension of this concept (14), we augmented the naturally occurring leukocyte migration in 16 unconditioned and randomly matched recipients by infusing them with $3x10^6$/kg donor bone marrow cells on the day of cadaveric renal (n=9), liver (n=6), and heart (n=1) transplantation. Using standard FK506-prednisone immunosuppression, all 16 have good whole-organ function 3 to 13 months later, and all have easily demonstrable chimerism of blood mononuclear leukocytes in the 0.5-5% range. Although rejection was diagnosed in 9 (56%) of the 16 cases, this was easily treated. Trivial skin graft- versus-host-disease (GVHD) in 2 (12.5%) patients regressed without therapy. Sustained donor-specific hyperactivity as early as 40 days postoperatively was demonstrable with *in vitro* tests in the majority of recipients, and, in all but one, antidonor reactivity assessed with MLR was less than third party.

The ultimate donor-specific nonreactivity which may or may not require continued immunosuppression in the circumstances of whole organ transplantation (12,13,15) with or without leukocyte augmentation is not only of the recipient immunocytes to the donor antigens but also the other way round. This is exemplified by the rarity of GVHD in chimeric recipients of intestinal (16) and liver grafts (12) that contain a dense migratory leukocyte component. With each further day under the protective umbrella of effective immunosuppression, a corollary expectation is that the responsible donor-versus-recipient interactions, also governed initially by rules of histocompatibility, are influenced by a kind of "mutual natural immunosuppression." Here, each increased level of incompatibility provokes countervailing increases in the variably cancelling donor-versus-recipient and recipient-versus-donor cell reactivity (Fig. 2). If the initial storm can be weathered, as has been increasingly possible with modern immunosuppression, the anticipated typing effect will dwindle.

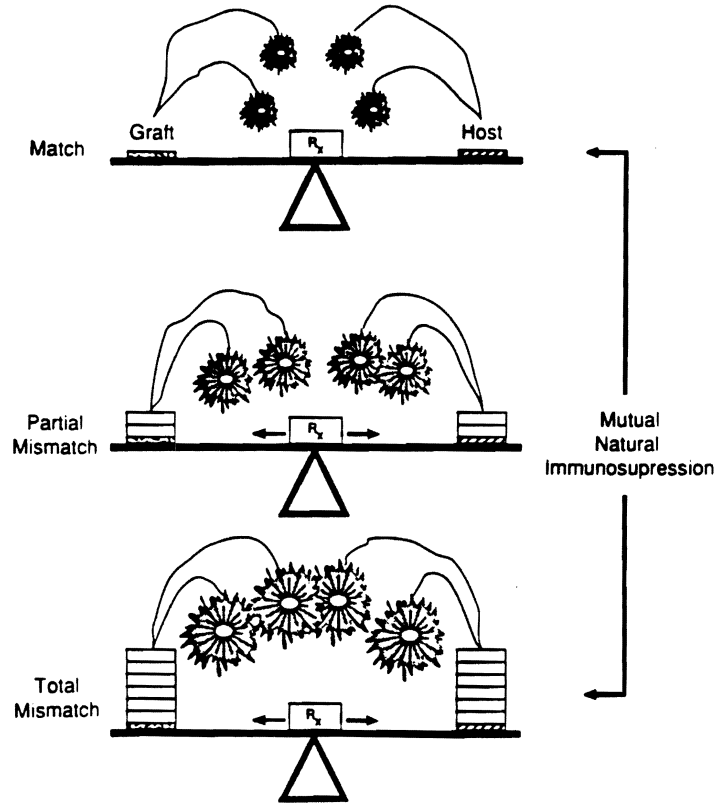

Figure 2. Variable cancelling of histocompatibility matching effect after whole-organ transplantation by the donor/recipient leukocyte interaction shown in Figure 1. RX—iatrogenic immunosuppression.

This bidirectional censoring of histocompatibility effect has been studied in rats (17) and particularly in mice (18), within which species permanent survival of liver allografts and their disseminated nonparenchymal (chimeric) cells is the rule without immunosuppression across a full range of MHC disparities. We have suggested that, in this process of censoring, the multiple immunobiologic changes that occur after organ transplantation (eg, altered cytokine profiles, suppressor and veto cells, enhancing antibodies) are epiphenomena of sustained two-way interactions between the coexisting donor and recipient immunocyte populations (11,19).

The debate whether HLA matching increases kidney allograft survival a little versus not at all, has sustained a flood of disputatious articles since 1966. It has seldom been emphasized that these differences, even when they are thought to be significant, are trivial compared to the large number of badly matched kidneys that do well. The two-way paradigm of mixed chimerism presented here provides an explanation.

REFERENCES

1. Terasaki PI, Vredevoe DL, Mickey MR, et al. Serotyping for homotransplantation. VII. Selection of kidney donors for thirty-two recipients. Ann NY Acad Sci 1966; 129:500.

2. Starzl TE, Porter KA, Andres G, et al. Long-term survival after renal transplantation in humans: With special reference to histocompatibility matching, thymectomy, homograft glomerulonephritis, heterologous ALG, and recipient malignancy. Ann Surg 1970; 172:437.

3. Matas AJ, Sutherland DER, Najarian JS. The impact of HLA matching on graft survival. Transplantation 1992 54:568.

4. Ferguson R for the Transplant Information Share Group (TISG): A multicenter experience with sequential ALG/ cyclosporine therapy in renal transplantation. Clinl Transplant 1988; 2:285.

5. Salvatierra O. Optimal use of organs for transplantation. N Engl J Med 1988; 318:1329

.6. Donaldson PT, O'Grady J, Portmann B, et al. Evidence for an immune response to HLA class I antigens in the vanishing bile duct syndrome after liver transplantation. Lancet 1987; 1:945.

7. Markus BH, Duquesnoy RJ, Gordon RD, et al. Histocompatibility and liver transplant outcome. Does HLA exert a dualistic effect? Transplantation 1988; 46:372.

8. Takemoto S, Terasaki PI, Cecka JM, et al. Survival of nationally shared HLA-matched kidney transplants from cadaveric donors. N Engl J Med 1992; 327:834.

9. Gatti RA, Meuwissen HJ, Allen HD, et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968; II: 1366.

10. Bach FH, Albertini RJ, Joo P, et al. Bone marrow transplantation in a patient with the Wiskott-Aldrich syndrome. Lancet 1968; II:1364.

11. Starzl TE, Demetris AJ, Murase N, et al. Cell migration, chimerism, and graft acceptance. Lancet 1992; 339:1579.

12. Starzl TE, Demetris AJ, Trucco M, et al. Cell migration and chimerism after whole organ transplantation: The basis of graft acceptance. Hepatology 1993; 17:1127.

13. Starzl TE, Demetris AJ, Trucco M, et al. Chimerism and donor specific nonreactivity 27 to 29 years after kidney allotransplantation. Transplantation 1993; 55:1272.

14. Fontes P, Rao A, Demetris A, et al. Augmentation with bone marrow of donor leukocyte migration for kidney, liver, heart, and pancreas islet transplantation. Lancet (in press).

15. Strober S, Dhillon M, Schubert M, et al. Acquired immune tolerance to cadaveric renal allografts: A study of three patients treated with total lymphoid irradiation. N Engl J Med 1989; 321:28.

16. Todo S, Tzakis AG, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. Ann Surg 1992; 216:223.

17. Demetris AJ, Murase N, Fujisaki S, et al. Hematolymphoid cell trafficking, microchimerism, and GVHD reactions after liver, bone marrow, and heart transplantation. Transplant Proc 1993; 25:3337.

18. Qian S, Demetris AJ, Murase N, et al. Murine liver allograft transplantation: Tolerance and donor cell chimerism. Hepatology (in press).

19. Starzl TE, Demetris AJ, Murase N, et al. Cell chimerism permitted by immunosuppressive drugs is the basis of organ transplant acceptance and tolerance. Immunol Today 1993; 14:326.

ACKNOWLEDGMENTS

Aided by Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.