The Blind-Folding of HLA Matching

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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.
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 $3 \times 10^6$/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.

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).

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


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