Acquired Tolerance, Allograft “Acceptance,” and Immune Suppression

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The adaptive response of the immune system, leading on one hand to immunity, or alternatively to nonreactivity, and frequently to gradations in between these extremes, is determined primarily by antigen migration and localization, in contradistinction to antigen per se. This conclusion has been reached through separate lines of evidence. The first began in 1992 with the previously overlooked finding of donor leukocyte chimerism in organ transplant recipients. The second came from observations following experimental infections, with emphasis on the importance of the transport and localization of live microbial antigen (viral, bacterial, and protozoan).

In both circumstances, there are two potential mechanisms of nonresponsiveness: clonal exhaustion/deletion and immune indifference. The kinetics of the migratory antigen, leading on average to acute immune reactivity, or to immune indifference at one extreme and exhaustion/deletion at the other are influenced by dose, timing, route, and localization of the migratory antigen. Although the relation between infectious and transplantation immunity is complicated by the presence of a double immune reaction after transplantation (host vs graft and graft vs host) and the additional factor of immunosuppression, the two mechanisms of acquired tolerance and the rules by which they operate are fundamentally the same.

This concept exposes the meaning of acquired immunologic tolerance as first produced in a transplant setting 44 years ago by Billingham et al. and relates such tolerance to the “allograft acceptance” that we see daily in practice. The enigmatic pattern of immunologic confrontation and resolution seen in organ recipients was explained by responses of coexisting donor and recipient immune cells, each to the other, causing reciprocal clonal expansion, followed by peripheral clonal deletion. An additional role of immune indifference was suggested by the replacement of donor by recipient leukocytes in the transplanted organ (rendering the graft less antigenic) and by ubiquitous distribution of the migratory donor leukocytes in the skin, host parenchymal organs, and other nonlymphoid areas where they may be sequestered from CTL and neutralizing antibodies.

Increasingly potent baseline immune suppressants have allowed these changes in the host/graft relationship to be engineered more efficiently and safely. This has been reflected in a stepwise improvement of patient and graft survival—from zero to feasible but unsatisfactory with azathioprine, striking improvement with the advent of cyclosporine (CyA), and another dramatic one with FK506. These spurts, made possible with better drugs, have been seen with all whole organs and also with bone marrow transplantation. Because FK506 can efficiently rescue the majority of CyA failures, the availability of FK506 has systematically upgraded program performance even when it has not been used from the outset as the baseline immunosuppressant.

REFERENCES


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