1907

ELSEVIER

Chimerism, Graft-Vs-Host Disease, Rejection, and Their Association With Reciprocal Donor-Host Immune Reactions After Cell, Organ, and Composite Tissue Transplantation

R. Llull, N. Murase, Q. Ye, A.J. Demetris, and T.E. Starzl

WE HAVE postulated that a small number of donor-derived leukocytes and the recipient immune system mutually interact and reciprocally attenuate both host-vs-graft (HVG) and graft-vs-host (GVH) reactions.[1] Multiple cell and organ transplant models confirm the coexistence of donor cell traffiking and graft acceptance.[2] However, the outcome of GVH and HVG reactions after drug discontinuation remains unpredictable. In this study, we hypothesize that both the graft's antigenicity and migratory cell load play a determinant role in the development of chimerism, graft-vs-host disease (GVHD), and rejection during the final drug-free stage.

MATERIALS AND METHODS

BN recipients underwent different cell, organ, or composite tissue allografts from LEW donors. Immunosuppression involved short (28 days) or prolonged (100 days) treatment with tacrolimus (1 mg/kg/d IM for 14 days, then weekly). Cell inoculi (spleen, bone marrow) and organ allografts (liver, heart, small bowel) were studied and compared to composite tissue allografts (CTA; rat hind limb) which conversely offer both a strong antigenic barrier as well as a continuous source of viable migratory donor leukocytes (ie, vascularized bone marrow).[3]

RESULTS AND DISCUSSION

Following short-term immunosuppression, tolerogenic allografts (bone marrow, liver) reached long-term survival and tissue-detectable microchimerism (Table 1). Only heart allografts, with high antigenicity and low migratory cell load, underwent moderate to severe chronic rejection and disappearance of mixed tissue microchimerism by flow cytometric techniques. Those allografts with a heavy migratory cell load such as the bone marrow, spleen, and small bowel presented significant expansion of tissue and peripheral chimerism and concomitantly, the greatest incidence of GVHD. Bone marrow inoculi displayed low GVHD susceptibility. CTAs, which are highly antigenic and contain the greatest viable migratory cell load, underwent delayed rejection after short-term immunosuppressive coverage. However, when exposed to prolonged immunosuppression, the chimeric expansion was allowed to stabilize throughout tacrolimus coverage. After its discontinuation, transient, nonlethal GVH reaction ensued in 9 of 13 animals. Their recovery was then consistently followed by slow reduction of cytometrically detectable chimeric leukocytes from peripheral blood, repopulation of the donor bone marrow with recipient elements, and allograft chronic rejection. Of notice, allografted hind limbs remained free of either GVH or rejection signs. These results emphasize the role of viable graft-contained migratory cells for the introduction of mechanisms of peripheral immunomodulation and GVHD induction. The relative antigenicity of the grafted tissue also seems to impact the survival of the peripheralized chimeric immunocytes since abolition of the chimeric component is

From the Thomas E. Starzl Transplantation Institute, Departments of Surgery and Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

Address reprint requests to R. Llull, the Thomas E. Starzl Transplantation Institute, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15261.

Table 1. Rejection, GVHD, and Chimerism After Short and Prolonged Immunosuppression

	Graft Survival Following			Drug-free Tissue-Blood Chimerism		Outcome	
Graft	No Treatment	Short Treatment	Prolonged Treatment	At 30 D	At >100 D	GVHD	Rejection
Bone marrow	>100	>100	>100	++	+	No	No
Liver	28.5	>100	>100	++	+	No	No
Heart	8.0	>100	>100	+	−	No	Chronic
Spleen	>100	60.0	75.5	+++	NT	Lethal	—
Intestine	12.0	43.0	45.5	3%	NT	Lethal	—
CTA	7.5	38.5	176.0	3–7%	1–3%	Transient	Chronic

0041-1345/97/$17.00
PII S0041-1345(96)00550-7

associated with the graft's chronic rejection. The fact that a bone marrow containing allograft recipient undergoes a continuum of mild, self-limited GVH, graft prolongation, and eventual chronic rejection suggests that the establishment of tolerance within a chimeric system is dynamic rather than deletional and responds to mutually interacting donor and host-derived elements.

REFERENCES

1. Starzl TE, Demetris AJ, Murase N, et al: Lancet 339:1579, 1992

2. Murase N, Starzl TE, Tanabe M, et al: Transplantation 60:158, 1995

3. Llull R, Murase N, Demetris AJ, et al: Transplant Proc 27:2363, 1995