The "Privileged" Liver and Hepatic Tolerogenicity


Abstract

The mechanism underlying the immunological advantage of hepatic allografts relative to other organs is incompletely understood. We used molecular probes for the repetitive units on the Y chromosome, to identify an increasing number of male liver venous endothelial cells in needle biopsy samples of men who received female donor liver grafts. We have also shown repopulation of liver endothelium by bone marrow derived cells in a male to female mouse bone marrow transplant model. We conclude that the liver has unique venous endothelium characterized by turnover and replacement by bone marrow derived cells.

Comments

Gao et al have proposed that liver allografts acquire a survival advantage by the gradual replacement of their portal and central venous endothelial cells by recipient cells of bone marrow origin. The clinically based hypothesis, supported by studies of the rapid turnover and replacement of these cells in mouse radiation chimeras, is reminiscent of Woodruff’s explanation more than 4 decades ago of allograft acceptance by “... replacement of certain elements of graft, for example connective tissue stroma and vascular endothelium.”

Several years later (in 1965), after the field of kidney transplantation had been launched with very little warning, Medawar was perplexed by the unexpected successes and wrote that “...foreign kidneys do sometimes become acceptable to their hosts for a reason other than acquired tolerance in a technical sense...” One possible explanation is the progressive and perhaps very extensive replacement of the vascular endothelium of the graft by endothelium of host origin, a process that might occur insidiously and imperceptibly during a homograft reaction weakened by immunosuppressive drugs.

In 1971, the senior author of the current Lancet report (G.M. Williams) published the first of a series of studies of allograft vasculature, beginning with a simple model of reendothelialization of free aortic allografts with or without recipient immunosuppression with 6-mercaptopurine (6-MP). The endothelial replacement occurred more rapidly and completely in the non-treated animals in which rejection promptly destroyed the donor endothelium, but the same repopulation by recipient cells occurred more slowly in immunosuppression-protected allografts and in radiation chimeras analogous to those in the mouse experiments of 2001. Although the technology of 30 years ago did not provide unequivocal evidence that the replacement cells were of bone marrow origin, this possibility was considered by the investigators.

It is clear from the human and mouse studies of Gao et al that endothelium is, in fact, replaced in the venous system of the liver allograft. Studies of comparable arterial changes were not described in their human liver graft specimens and were not seen in the arterioles of the native parenchymal organs of mouse radiation chimeras. However, partial arterial endothelial replacement has been documented in a small number of kidney allografts after relatively short follow-ups and in 7 related donor kidneys studied by Randhawa et al that had functioned for 26 to 29 years. The patchy areas of recipient vascular endothelium in these kidneys, and in the coronary arteries of cardiac allografts described by others, were thought by Randhawa et al to have followed injury or rejection of the original donor cells with replacement by recipient mononuclear or endothelial progenitor cells of bone marrow origin. However, the potentially adverse implications of reendothelialization initiated by rejection or mechanical endothelial damage (eg, ischemia) do not apply with the natural turnover of endothelial cells in the liver venous system.

The changes in both the venous and arterial system of allografts are of considerable interest. As the authors imply, however, the possible graft survival advantage should not be equated with the “hepatic tolerogenicity” that was first recognized in 1962 with the observation that nonhepatic abdominal visceral allografts in untreated dogs have a reduced severity of rejection if they are accompanied by the donor liver. By 1965, it was established that most canine liver recipients who survived for 4 months under azathioprine immunosuppression were tolerant (ie, no longer needed treatment to sustain graft survival). After noting that, "...the frequency and rapidity with which dogs could be withdrawn from immunosuppression is remarkable...", it was added that, "...The consistency with which this state of host versus graft nonreactivity... seemed to develop exceeds that reported after canine renal homotransplantations... It also is important to note that cessation of therapy was not followed by a graft versus host reaction." The liver allograft was subsequently shown to self-induce permanent tolerance without immunosuppression in at least 3 species: unpredictably in a significant minority of randomly paired outbred pigs, invari...
ably with a small number of strain combinations of inbred rats, and in at least 50% of experiments in about 85% of all tested mouse strain pairings. The self-induced tolerance is antigen-specific; i.e., extends to other donor tissues and organs. Although the induction of spontaneous tolerance has been widely construed to be a specific capability of the liver, donor-specific tolerance can be induced in mice by heart and kidney allografts, but only with a small number of strain combinations.

With the discovery in 1992 that 30 of 30 long-surviving human recipients of livers and kidneys had low-level donor leukocyte microchimerism, it was realized that organ engraftment was the product of a double immune reaction: i.e., the responses of co-existing donor and recipient cells, each to the other, causing reciprocal clonal exhaustion, followed by peripheral clonal deletion. Although clonal exhaustion-deletion had been postulated in 1969 as the seminal basis of organ tolerogenicity but dismissed as an unsubstantiated theory, the existence and importance of clonal exhaustion-deletion has been established since 1990. It was concluded that the alternative explanations of organ allograft acceptance (recently summarized by Bishop and McCaughan) had, "...defied attempts at verification, probably because the proposed elements of each theory are simply epiphenomena of the key event: leukocyte migration and repopulation [i.e., localization]."

It was evident that the liver is the most tolerogenic organ because of its huge content of leukocytes. Reciprocal modulation of the migratory immune competent donor leukocytes and the host immunocytes explained why graft-versus-host disease was so uncommon after clinical organ transplantation compared with the high risk of this complication in cytoablated recipients of bone marrow cells or leukocyte-rich organs. How the small number of donor leukocytes that persist after the acute posttransplant cell migration maintain the clonal exhaustion-deletion achieved at the outset has been described elsewhere in detail. The chimerism-dependent deletional tolerance and its chimerism-dependent maintenance are the crucial mechanisms for prolonged survival of any organ allograft including the liver. However, changes in the graft, such as the replacement of vascular endothelium, may be significant adjunct mechanisms.

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References
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