Special Article

Immunodeficient Mice Xenografted with Human Lymphoid Cells: New Models for in Vivo Studies of Human Immunobiology and Infectious Diseases

DONALD E. MOSIER

Accepted: February 20, 1990

This review article deals with the transfer of human lymphoid or hematopoietic tissues to severely immunodeficient mice to create new small animal models for the study of human biology and disease. The degree of functional reconstitution in the three current models is discussed. SCID mice with human grafts have been infected with human immunodeficiency virus (HIV) to generate a small animal model for AIDS research. Epstein-Barr virus (EBV)-related lymphoproliferative disorders can also be modeled by the transfer of adult peripheral blood mononuclear cells to SCID mice.

KEY WORDS: Severe combined immune deficient (SCID) mice; human xenografts; human immunodeficiency virus (HIV) infection; Epstein-Barr virus (EBV) lymphomagenesis.

INTRODUCTION

Our capacity to understand lymphocyte biology in humans is limited by the relative difficulty of direct human experimentation and the technical constraints of human lymphocyte culture. The ability to transfer adoptively human lymphoid cells (or other tissues) to a permissive animal host would open a new area of experimentation which might allow the study of many human pathogens in surrogate human model systems. While it has been possible to transfer malignant human cells to nude mice for many years (1), it is only in the past 2 years that the xenografting of normal human cell populations to mice has been accomplished. Three recent studies (2–4) have reported transfer of human lymphoid or myeloid cells to severely immune deficient strains of laboratory mice. Two laboratories have reported infection of these xenotransplanted mice with human immunodeficiency virus (HIV) (5, 6), indicating their utility in the study of human infectious diseases. One report (7) shows the transfer of a human autoimmune disorder to mice with severe combined immune deficiency (SCID), and several other such reports will soon appear. This paper presents a brief summary of current models for the xenotransplantation of human cells to immune deficient mice. I review mainly studies from our laboratory (2, 6) on the transfer of adult human peripheral blood leukocytes to mice with severe combined immune deficiency (8) to create what are now termed hu-PBL-SCID mice, as well as briefly comment upon studies by others (3, 5) on SCID mice engrafted with human fetal tissue (SCID-hu mice) and nu.xid.bg mice transplanted with human bone marrow (4).

SEVERE IMMUNE-DEFICIENT MOUSE STRAINS

In order to transplant human cells to mice successfully, two fundamental tenets of transplantation immunology must be fulfilled. First, the mouse recipient must be immune deficient, so that xenogeneic graft rejection does not take place. Second, it is essential that immunocompetent human cells

1Division of Immunology, Medical Biology Institute, 11077 North Torrey Pines Road, La Jolla, California 92037.
do not cause graft-versus-host disease in the mouse. This potential problem has turned out to be much less severe than anyone might have predicted (see below).

The immune-deficient mouse strains that serve as existing or potential recipients for human xenografts are listed in Table 1.

Mice with the nude mutation lack functional T cells and can accept xenografts (1), but there is no indication that they will be useful for engrafting normal human lymphoid cells. SCID mice have an autosomal recessive mutation that interferes with the rearrangement of immunoglobulin and T-cell receptor genes in lymphoid progenitors (9), with the result that they lack functional T and B lymphocytes and are severely immunodeficient. As such, they should be incapable of rejecting human tissue xenografts by conventional cellular or humoral mechanisms. SCID mice do possess natural killer (NK) cells (10); however, the role of NK cells in xenograft rejection is unknown. While SCID mice cannot reject human cells, it might be expected that the injection of adult peripheral blood mononuclear cells (PBL) into SCID mice would lead to lethal graft-versus-host disease (GVHD) mediated by xenoreactive human T cells. This is clearly not the case since SCID mice survive following the intravenous or intraperitoneal injection of as many as $10^6$ PBL with no clinical or histological evidence of GVHD (1), although the existence of mild GVHD has been postulated in a second report (7).

The triple mutant strain nude.xid.beige (11) lacks both T and B cells and has reduced activity of natural killer (NK) cells and lymphokine-activated killer (LAK) cells. Work by Kamel-Reid and Dick (3) has shown that *nu.xid.bg* mice allow proliferation of human myeloid precursors found in bone marrow grafts, while SCID mice do not. In preliminary trials, both our laboratory and that of John Dick (12; personal communication) have found that *nu.xid.bg* mice are more difficult to engraft with mature PBL than are SCID mice. Irradiation of the triple mutant mice with 400 cGy was essential for human marrow engraftment (3), whereas irradiation of SCID mice may improve engraftment of PBL but is certainly not essential for such engraftment.

Other immune-deficient mouse strains are under development, and their availability may further aid the establishment of xenografts of normal human tissue. One goal of these efforts is to reduce further NK cells in potential recipients. It should be emphasized as a practical detail that the rearing and maintenance of severely immune-deficient mouse strains are not a trivial commitment, and it is essential that these animals be maintained either in a germ-free environment or as a specific pathogen-free colony. It is clear from observations in our laboratory, for example, that opportunistic infections of SCID mice lead to an elevation of NK levels and increased resistance to the engraftment of human lymphocytes.

**SUMMARY OF CURRENT HUMAN-TO-IMMUNODEFICIENT MICE XENOTRANSPLANT MODELS**

**The hu-PBL-SCID Model**

In work originally designed to assess the severity of human-versus-mouse GVHD, we found (2) that transfer of adult human peripheral blood mononuclear cells by intraperitoneal injection, but not intravenous injection, led to persistent engraftment of human lymphoid and myeloid cells. This is clearly not the case since SCID mice survive following the intravenous or intraperitoneal injection of as many as $10^6$ PBL with no clinical or histological evidence of GVHD (1), although the existence of mild GVHD has been postulated in a second report (7).