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Immunodeficient Mouse Models of Lymphoid Tumors

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Abstract

Severe combined immunodeficient (SCID) mice lack functional T- and B-cells and readily accept human xenografts, including hematopoietic malignancies. Accordingly, SCID mice have been used to study the growth and behavior of lymphoid tumors in vivo. The SCID mouse models of disease mimic human diseases and have provided valuable information. However, this mouse strain has some residual immunity that somewhat limits posttransplantation growth of human xenografts. Recently, the SCID mutation was backcrossed onto the nonobese diabetic (NOD) strain background. The result was an animal with additional immunological defects beyond those seen in SCID mice. The NOD/SCID strain appears to be more promising as a tool for xenotransplantation of lymphoid tumors. Moreover, these SCID and NOD/SCID mouse models have been used to develop novel therapeutic strategies. Results from such studies may also help to elucidate the pathogenesis of lymphoid tumors. *Int J Hematol.* 2003;77:336-341.

Key words: Animal model; SCID mouse; NOD/SCID mouse; Lymphoma; ATL

1. Introduction

A variety of cell lines from patients with lymphoid tumors have been established and used for experimental studies. Such studies have contributed to advances in understanding of the pathogenesis of the diseases. However, accumulating evidence has shown that these cell lines are of limited relevance to the primary disease state. Therefore, appropriate animal models that mimic human diseases have long been desired.

Since the 1960s, athymic nude mice have been used for establishing in vivo models of human malignant diseases. However, it has been shown that transplantation of hematological tumors into nude mice is difficult in general. An attractive alternative to the nude mouse model became available when severe combined immunodeficient (SCID) mice were developed in the 1980s. The SCID mouse was first described by Bosma et al [1]. Because this mouse strain lacks functional T- and B-cells, successful engraftment of human hematological malignant tumors can occur [2,3]. However, this mouse strain retains normal natural killer (NK) cell activity and myeloid cell differentiation. Such residual immunity may interfere with transplantability. Recently, the SCID mutation was backcrossed onto the nonobese diabetic (NOD) strain background. The result was an animal with additional immunological defects beyond those seen in SCID mice [4,5]. The NOD/SCID strain appears to be more promising as a tool for xenotransplantation of lymphoid tumors.

In this review, I discuss the usefulness of immunodeficient mouse models in the study of the growth and behavior of lymphoid tumors in vivo. In addition, specific applications of the mouse models for evaluating therapeutic strategies are presented.

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2. SCID Mouse Models

2.1. Adult T-Cell Leukemia

Adult T-cell leukemia (ATL), which shows characteristic clinical features, develops after a long latent period in a very minor population of persons infected with a human retrovirus termed human T-cell leukemia virus type I (HTLV-I) [6,7]. Functional analyses of HTLV-I viral products, such as Tax and Rex, gave us better understanding of the mecha-

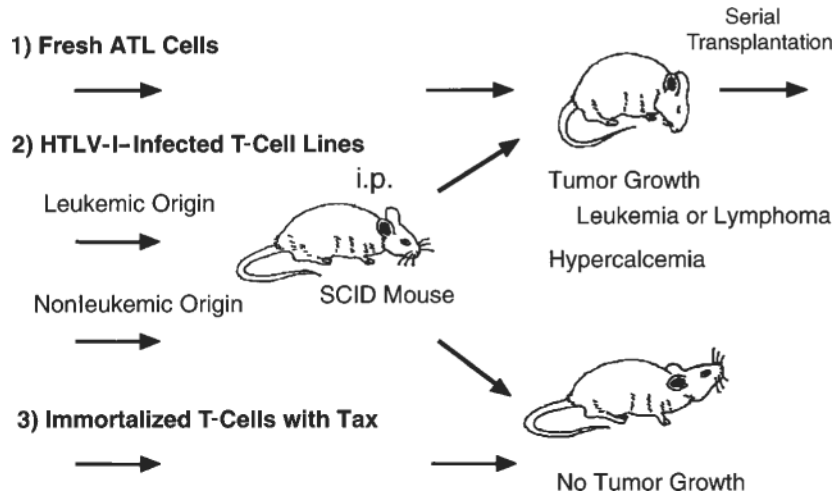

Figure 1. In vivo proliferation models of adult T-cell leukemia (ATL) cells developed with severe combined immunodeficient (SCID) mice. HTLV-I indicates human T-cell leukemia virus type I; i.p., intraperitoneal injection.

nisms of the development of ATL and neoplastic cell growth. It has been shown that Tax transactivates many cellular genes, including those of growth factors and their receptors [8]. Abnormal expression of such genes is thought to play important roles in immortalizing primary T-cells. However, the precise mechanisms of neoplastic cell growth and the development of ATL after HTLV-I infection remain unclear. To address these questions, we and others using SCID mice for the first time established a model of in vivo cell proliferation of fresh ATL cells [9,10]. Thereafter we developed a model using HTLV-I–infected cell lines and a serial transplantation model. Our model systems are detailed in Figure 1.

First we injected peripheral blood mononuclear cells (PBMC) or lymph node cells depleted of B-cells and monocytes, from 8 ATL patients, into SCID mice. Daily injection of human interleukin 2 (IL-2) followed [10]. SCID mice were treated with antimurine IL-2Rβ antibody for abrogation of NK cell function prior to inoculation. ATL cells from 6 of 8 ATL patients were found to grow in SCID mice. Serum levels of soluble IL-2Rα were markedly elevated in xenografted mice. Integration of HTLV-I and the TCRβ gene rearrangement were identical between the original ATL cells and those proliferating in the mice. Tumor cells infiltrated into various organs in SCID mice as is observed in ATL patients. These data indicated that this model closely resembles the human disease. Second, we examined the tumorigenicity of HTLV-I–infected cell lines in SCID mice [11]. Eleven HTLV-I–infected cell lines were injected into untreated SCID mice, and 4 of them were found to give rise to tumors in SCID mice. Most leukemic cell lines grew in SCID mice, but no nonleukemic cell lines were transplantable. Detailed study of this model suggested that (1) HTLV-I–infected cell lines of nonleukemic cell origin do not have enough leukemogenic changes to acquire tumorigenic potential in SCID mice; (2) the IL-2 autocrine mechanism is not directly involved in tumor cell growth; (3) viral gene expression is not needed for maintenance of neoplastic cell growth; and (4) tax gene expression is not sufficient for neoplastic cell growth in vivo. Third, we succeeded in serial transplantation of ATL cells into SCID mice [12]. In this model, it was found that only a leukemic cell clone from an ATL patient could be successively transplanted into SCID mice, although it is known to be difficult to maintain leukemic cells in vitro. This finding suggests that the microenvironment provided by SCID mice is suitable for ATL cell growth. Of interest was that this serial transplantation model was found to develop humoral hypercalcemia associated with marked elevations in serum C-terminal parathyroid hormone–related protein (C-PTHrP) levels [13]. Bone histomorphometric analysis showed that bone formation indices were very low in SCID mice engrafted with ATL cells. Hypercalcemia is frequently associated with ATL and contributes significantly to mortality in this disease [14]. Therefore this model will be valuable for developing novel therapeutic strategies to treat hypercalcemia.

2.2. Epstein-Barr Virus–Associated B-Cell Lymphoproliferative Disease

After primary infection Epstein-Barr virus (EBV) establishes lifelong persistent infection in B-cells. This latent infection is kept under control by virus-specific cytotoxic T-lymphocytes (CTL). Immunosuppressive states, including organ transplantation and acquired immunodeficiency syndrome, are major risk factors for development of B-cell lymphoproliferative disease (BLPD) [15]. Mosier et al [16] were the first to report that SCID mice developed EBV-positive human B-cell lymphoma after inoculation with PBMC from EBV-seropositive donors. This finding has been confirmed by many groups. In contrast, PBMC from EBV-seronegative donors do not give rise to tumors in SCID mice. Such B-cell tumors are distinct from Burkitt lymphoma and instead closely resemble BLPD in immunosuppressive patients. The surface phenotype is similar to that seen in lymphoblastoid cell lines (LCLs) generated by

EBV infection of normal B-cells in vitro as well as BLPD with expression of B-cell activation antigens and adhesion molecules. In vitro–transformed LCLs also grow when injected into SCID mice [17,18]. Tumor cells are monoclonal or oligoclonal and contain EBV DNA. They usually have a normal karyotype. A marked difference has been found in the ability of PBMC from EBV-seropositive donors to give rise to tumors in SCID mice. The variable patterns of tumorigenesis are at least partly explained by qualitative differences in EBV infection [19].

Concerning the pathogenesis of BLPD, several groups have found that tumor incidence is reduced when T-cells are depleted from PBMC prior to inoculation. This finding indicates an essential role of T-cells in tumorigenesis [20-22]. Johannessen et al [22] showed that tumor incidence fell from 81% to 11% when mice were inoculated with only B-cells. Tumor incidence also was dramatically reduced when PBMC were depleted of $CD4^+$ T-cells. On the basis of these results, Johannessen et al proposed a multistep model for tumorigenesis in PBMC-inoculated SCID mice as follows: (1) Autologous T-cells support outgrowth of EBV-positive tumorigenic B-cells; (2) tumor cells sustain themselves in a cytokine-mediated autocrine manner; and (3) tumor formation becomes independent of T-cell assistance. The same group also found that 4 of 5 BLPD biopsy specimens obtained from organ graft patients gave rise to tumors in the SCID mouse model [23]. These tumors represented the original tumor cell clones and expressed human IL-2, IL-6, IL-10, and interferon γ similar to that observed in PBMC-derived SCID tumors. These findings together indicate BLPD in graft recipient and PBMC-derived SCID tumors appear to develop by similar mechanisms. Thus the SCID mouse model will provide opportunity for further studies in BLPD pathogenesis. BLPD biopsy material can be expanded in SCID mice, thus giving rise to homogeneous tumors sufficient for research.

2.3. Other Non-Hodgkin's Lymphoma

Both T-cell and B-cell non-Hodgkin's lymphoma (NHL) cell lines have been successfully transplanted into SCID mice. Primary NHL cells also have been shown to grow in SCID mice. Ghetie et al [24] found that a Burkitt lymphoma cell line, Daudi, grew in SCID mice. A palpable tumor grew only at the site of injection when Daudi cells were subcutaneously injected. In contrast, disseminated tumors developed after intravenous or intraperitoneal injection. Waller et al [25] reported that primary T-cell NHL cells were successfully transplanted into SCID mice. Itoh et al [26] inoculated 50 NHL specimens into SCID mice and found that 23 of 50 specimens gave rise to tumors. High-grade rather than low-grade malignancy groups were more tumorigenic. However, 13 tumors had newly developed B-cell clones. These tumors were shown to have EBV, a finding that suggested that the tumors originated from EBV-infected B-cells present in the specimens. Only 10 cases were maintained at the first passage without contamination of EBV-positive B-cell clones. Taken together, these results indicate that the usefulness of SCID mouse models of NHL other than those related to EBV is limited.

2.4. Hodgkin's Disease

It has been shown that both Hodgkin cell lines and primary Hodgkin cells are able to grow in SCID mice. Kapp et al [27] showed that SCID mice developed disseminated tumors resembling the human disease after intravenous injection of Hodgkin's disease (HD)-derived cell lines L540 and L540cy. Bargou et al [28] reported that inoculation of Hodgkin cell line HD-MyZ into SCID mice led to development of disseminated tumors with infiltrative and destructive growth. Tumor cells proliferating in vivo had the same features as HD-MyZ cells. An HD-derived cell line of Hodgkin and Reed-Sternberg (H-RS) cell origin (L1236) also was found to be tumorigenic in SCID mice [29]. L1236 cells had immunoglobulin gene rearrangement sequences identical to those of H-RS cells obtained from the same patients. This cell line contained no EBV DNA. After subcutaneous injection of L1236 cells into SCID mice, disseminated intralymphatic growth was observed after necrotic regression of initially growing tumors at the injection site. Regarding xenotransplantation of primary Hodgkin cells, Kapp et al [30] transplanted tumor biopsy samples from 13 HD patients beneath the renal capsule or into the liver of SCID mice. HD-derived tissues from 3 patients were found to give rise to tumors in SCID mice. All tumors had an abnormal karyotype. EBV-encoded transcripts were found in the majority of the tumor cells. It was suggested that the tumor cells might be derived from EBV superinfected H-RS cells or from EBV-infected bystander cells.

3. NOD/SCID Mouse Models

The NOD/SCID mouse has additional immunologic defects, including low NK cell function and absence of circulating complement. It was recently shown that this strain supports higher levels of engraftment of human hematological malignant diseases than other strains. Hudson et al [31] compared xenotransplantation of lymphoid malignant tumors in nude, SCID, NOD/SCID, and Rag-1–deficient mice. NOD/SCID mice accepted 100% of the tumors with which they were inoculated and were shown to be the optimal model. Fusetti et al [32] injected 12 human leukemia or lymphoma cell lines into NOD/SCID mice. Ten of 12 cell lines were successfully transplanted. Of interest was that there was a strong correlation between the amount of vascular endothelial growth factor (VEGF) produced in vitro and the efficiency of tumor engraftment. This finding suggested that VEGF expression may play a crucial role in xenotransplantability of human tumors in NOD/SCID mice and SCID mice. Regarding ATL, it has been shown that ATL leukemic cell clones but not HTLV-I in vitro–transformed cell lines have the ability to grow in SCID mice [11]. Phillips et al [33] found that leukemic cells from an ATL patient (MET-1) could grow in NOD/SCID mice. Leukemic cells were shown to infiltrate into a variety of organs, including the lungs, liver, and spleen. In addition, the TCRβ gene rearrangement was identical between the original ATL cells and those serially transplantable in the mice. This finding suggested that the NOD/SCID mouse model resembles our SCID mouse model in many features. More recently, Liu et al [34] showed that several HTLV-I–transformed cell lines were tumorigenic in

NOD/SCID mice. A higher level of engraftment was observed when mice received whole-body irradiation 1 day prior to inoculation of cells. These data suggested that the NOD/SCID mouse as well as the SCID mouse is an invaluable animal model that allows characterization of molecular events in HTLV-I–mediated tumorigenesis.

4. Application of Immunodeficient Mouse Models to Test Novel Therapeutic Strategies

Many papers have been published about the use of immunodeficient mouse models for evaluating novel therapeutic strategies, such as chemotherapy, immunotherapy, and gene therapy. Following are specific examples of how the model has been used to test these therapies.

The toxicity and efficacy of conventional as well as novel chemotherapeutic agents have been evaluated in immunodeficient mouse models. In addition, the model systems allow us to evaluate the pharmacodynamic features of new agents. As novel chemotherapeutic agents, proteasome inhibitors may be effective treatment of lymphoid tumors. Tan and Waldmann [35] showed that the proteasome inhibitor PS-341 yielded prolongation of survival of tumor-bearing mice when combined with anti–IL-2Rα antibody in an NOD/SCID mouse model of ATL. Antiangiogenic agents may be useful in the treatment of NHL. The role of angiogenesis and angiogenic growth factors in NHL has been investigated. Bellamy et al [36] reported that expression of VEGF and related receptors was observed in most B-cell hematopoietic malignant diseases. High circulating levels of VEGF and basic fibroblast growth factor have been shown to correlate with a poor prognosis in patients with NHL [37,38]. Preclinical screening of antiangiogenic agents can be accomplished easily in the immunodeficient mouse model. Endostatin is one of the promising antiangiogenic drugs. Bertolini et al [39] found that sequential administration of endostatin after cyclophosphamide or rituximab effectively induced tumor stabilization in an NOD/SCID mouse model of B-cell lymphoma. Thalidomide has been shown to be effective in the treatment of multiple myeloma [40]. Because inhibition of angiogenesis and angiogenic factors is thought to be one of its antimyeloma effects, thalidomide also may be useful in the treatment of other hematological malignant diseases. Recently, the activity of a new derivative of thalidomide, S-3-amino-phthalimido-glutarimide (S-3APG), was explored [41]. Of interest was that in immunodeficient mouse models S-3APG was able to inhibit proliferation of Burkitt lymphoma cells in addition to myeloma cells without toxicity to normal bone marrow cells.

Immunodeficient mice engrafted with human lymphoid tumors have been used to evaluate antibody-based therapies. The efficacy of anti–IL-2Rα antibody in ATL has been evaluated in ATL-bearing immunodeficient mice [33]. The scientific basis for the use of this antibody to treat ATL is a striking feature of ATL cells that overexpress IL-2Rα in contrast to normal resting T-cells that lack IL-2Rα expression [7]. Antibodies to IL-2Rα, such as humanized Tac (HAT), murine anti-Tac (MAT), and 7G7/B6, were evaluated for efficacy in the treatment of ATL in NOD/SCID mice engrafted with ATL cells. All antibodies prolonged the survival of the tumor-bearing mice. The 7G7/B6 antibody did not block IL-2 binding to its receptor, and tumor cells from mice were found to produce no IL-2. This finding suggested that the antibodies act by a mechanism other than blockade of IL-2/IL-2Rα interaction. On the other hand, because it is highly expressed on RS cells of HD with a restricted expression profile in normal cells, CD30 is one of the ideal targets for immunotherapy of HD. It has been shown that anti-CD30 antibodies possessing signal properties do not inhibit the growth of HD cells in vitro or in xenografted SCID mice, whereas these antibodies have antitumor activity on anaplastic large-cell lymphoma cells [42,43]. Wahl et al [44] found that a monoclonal antibody against CD30, AC10, and its chimeric form, SGN-30, was effective at inhibiting the growth of HD cells in xenografted SCID mice. This finding became the basis for clinical evaluation of this approach. In a recent study, Nagy et al [45] screened the Human Combinational Antibody Library for antibodies specific to human HLA-DR that kill lymphoma/leukemia cells. The active Fab fragments were engineered to immunoglobulin G_4 antibodies of subnanomolar affinity. These antibodies exhibited excellent tumoricidal activity in vivo in xenografted models of NHL in which SCID mice were treated with anti-asialoGM1 antibody to suppress NK cell activity. The findings suggested that such antibodies offer the potential for a novel therapeutic approach to lymphoid malignant diseases. In addition to naked antibodies, numerous immunotoxins targeting surface antigens have been tested in immunodeficient mice engrafted with lymphoid tumors. For example, Barth et al [46,47] reported that a recombinant anti–IL-2Rα immunotoxin, RFT5(scFv)-ETA′, and a recombinant anti-CD30 immunotoxin, Ki-4(scFv)-ETA′, were highly effective in the treatment of SCID mice bearing HD.

Adoptive transfer studies with SCID mice have yielded data that support the use of EBV-specific CTL against BLPD in organ graft recipients. Boyle et al [48] found that adoptive transfer of EBV-specific CTL into SCID mice engrafted with LCLs significantly delayed tumor development. Lacerda et al [49] also showed that SCID mice inoculated with autologous LCLs had significantly improved survival, relative to that of untreated mice, after adoptive transfer of EBV-specific CTL. Moreover, preferential homing of PKH-26–labeled EBV-specific CTL to autologous tumor in xenografted SCID mice was observed as early as 24 hours after intravenous adoptive transfer.

Oligonucleotide therapy may be effective treatment of lymphoid tumors. The bcl-2 gene was first discovered because of its involvement in the t(14;18) translocation. This translocation is present in the majority of follicular lymphomas and results in overexpression of the Bcl-2 protein, which promotes cell survival. On the basis of these observations, the bcl-2 gene is a logical target for antisense oligonucleotide therapy [50]. Cotter et al [51] found that Bcl-2 antisense oligonucleotides inhibited growth of B-cell lymphoma cell lines bearing the t(14;18) translocation in xenografted SCID mice. Mohammad et al [52] showed that Bcl-2 antisense oligonucleotide therapy was effective against systemic disease in SCID mice bearing follicular lymphoma, whereas it did not prevent disease dissemination into the central nervous system.

5. Conclusions

The immunodeficient mouse models, especially those of SCID mice and NOD/SCID mice, have contributed to advances in understanding of the growth and tumorigenesis of lymphoid malignant tumors. Moreover, they have provided valuable and reliable information concerning novel therapeutic approaches. Such information may also help to elucidate the pathogenesis of lymphoid tumors. Although the potential is great, these models have several limitations. For example, the microenvironments provided by these mice are not identical to those for humans, although they are suitable for lymphoid tumor growth. Contamination of B-cells in samples to be transplanted into mice may induce EBV-positive lymphoma. The pharmacodynamics are somehow different between human and mouse. Taken together, the findings obtained with these models need to be interpreted with due caution. If properly designed and interpreted, studies using the immunodeficient mouse models are still expected to continue to provide further information in the molecular and cellular biology of lymphoid tumors.

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