Brief Definitive Report

A Tumor-suppressor Function for Fas (CD95) Revealed in T Cell–deficient Mice

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Summary

Fas (CD95) and its ligand are central regulatory molecules in hematopoietic cells. Previous studies have suggested a role for Fas in the regulation of tumor progression, but Fas has not yet been conclusively identified as a tumor suppressor. Fas-deficient individuals lack malignant tumors, perhaps because of regulation by T cells. To investigate such a possibility, mice deficient in both T cells and Fas were generated, and they were found to develop severe B cell dysregulation characterized by malignant, lethal B cell lymphoma. Lymphoma arose from a monoclonal $B220^+CD19^-CD5^-CD23^-$ B cell secreting immunoglobulin M, κ rheumatoid factor. In contrast, animals containing αβ T cells, γδ T cells, and/or functional Fas suppressed the development of lymphoma. These data indicate that Fas functions as a tumor suppressor, and identifies roles for both αβ T cells and γδ T cells in Fas-independent tumor regulation.

Central regulators of immune responses include Fas (CD95) and its ligand. Activated lymphocytes upregulate Fas, rendering themselves susceptible to apoptosis upon interaction with cells expressing Fas ligand (1). The central importance of these molecules is illustrated by Fas-deficient mice and humans, who have defective peripheral lymphocyte tolerance because of an inability to complete activation-induced cell death (2–5). These regulatory interactions may involve both T and B cells (6, 7).

Such findings suggest that Fas deficiency promotes lymphoid tumor development. Indeed, a regulatory role for Fas in tumor progression has been suggested by its altered expression on some human cancers (8), and the allelic loss of chromosome 10q23, to which Fas maps (9), in prostate (10), brain (11), skin (12), endometrial (13), and lymphoid (14) malignancies. Defects in Fas alone, however, do not induce malignancy, causing instead a nonmalignant lymphoproliferation of $CD3^+CD4^-CD8^-$ T cells in both mice and humans (3, 15, 16). While B cell "tumors" have been described in Fas-deficient *lpr* mice on the SJL background, which itself develops B cell hyperplasias, these polyclonal populations resemble mature B cells and are not malignant (17). Instead, the absence of functional Fas promotes pathological B cell hyperactivity resulting in T cell–dependent autoantibody production and systemic autoimmune disease (18). Thus, while Fas deficiency clearly causes lymphocyte dysregulation, it alone does not result in malignant transformation.

As one explanation of these findings, Fas-deficient tumors in situ may be regulated by T cells, which have previously been shown to reject experimental tumors (19). To test this hypothesis, T cell–deficient *lpr* mice were developed and observed. Such mice spontaneously developed intraabdominal B cell lymphoma with significant associated mortality. In contrast, animals possessing αβ T cells, γδ T cells, and/or functional Fas suppressed lymphoma development. Thus, Fas functions as a tumor suppressor, and both αβ and γδ T cells regulate lymphoma progression.

Materials and Methods

Mice. T cell–deficient *lpr* animals were obtained by intercrossing the F1 offspring of TCR $\beta^{-/-}$ TCR $\delta^{-/-}$ C57BL/6 and MRL/*lpr* mice (both from the Jackson Laboratory, Bar Harbor, ME). Mice were screened for the TCR-β genotype by PCR on tail DNA using primers TCRJB12F (5′-CTCATGTCTGGGACTACATTCTAATGAGGC), TCRJB13R (5′-ACCTACAACAATGAGCCGGCTTCCTTCTCC), and NEO1471FR (5′-ACGGTATCGCCGCTCCCGATTCGCAGC). The TCRJB12F-TCRJB13R combination yielded a 241-bp fragment corresponding to the wild-type locus, while the TCRJB12F-NEO1471FR combination yielded a 550-bp fragment corresponding to the targeted β locus. TCR-δ genotype was screened by Southern analysis of EcoRV-digested tail DNA, using a 700-bp probe isolated from the TCR-δ locus between Cδ1 and Vδ5 (Hayday, A.C., unpublished data), which detected both wild-type

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(7.0 kb) and targeted (3.1 kb) alleles. Fas genotype was determined by PCR as described previously (20). All mice, homozygotic at all three loci, were raised under specific pathogen–free conditions at the Yale University School of Medicine.

Pathology. Lethal lymphoma was diagnosed by the development of malignant ascites and associated death, along with histopathological evidence for lymphoma at autopsy (Figs. 1 and 2). Formalin-fixed tissue was embedded in paraffin, sectioned, and stained with hematoxylin and eosin via standard protocol by the Department of Pathology, Yale University School of Medicine. For immunofluorescent studies, tissues were frozen in OCT embedding medium (Miles Inc., Elkhart, IN) at −80°C. 4-μM sections were dried in room air for 30 min, washed three times in PBS for 5 min, fixed in ethyl ether/ethanol (50% vol/vol) for 10 min, washed in 95% ethanol for 20 min, and washed three times in PBS for 5 min. Fluorescein-conjugated antibodies were applied at a concentration of 25 μg/ml in PBS for 45 min in a humidified chamber. Sections were then washed twice with PBS, mounted with Permount (Fisher Scientific, Springfield, NJ), and visualized by an Axioskop fluorescent microscopy (Carl Zeiss, Inc., Thornwood, NY). Antibodies included FITC-conjugated 145-2C11 (anti-CD3), H129.19 (anti-CD4), 53-7.3 (anti-CD5), 53-6.7 (anti-CD8α), 1D3 (anti-CD19), B3B4 (anti-CD23), 1M7 (anti-CD44), 16A (anti-CD45RB), RA3-6B2 (anti-B220), 36-7-5 (anti–H-2K^k), AF6-88.5 (anti–H-2K^b), MEL-14 (anti-CD62L), A1 (anti-Ly49A), 5E6 (anti-Ly49C), PK136 (anti-NK1.1), H57-597 (anti–TCR-Cβ; all from Pharmingen, San Diego, CA), polyclonal goat anti–mouse IgM and polyclonal goat anti–mouse IgG (Sigma Chemical Co., St. Louis, MO), and polyclonal goat anti–mouse IgD (Southern Biotechnology Associates, Birmingham, AL).

V(D)J Sequencing. Genomic DNA was isolated from whole tissue by proteinase K/phenol extraction. PCR was performed with AmpliTaq® in a GeneAmp 9600 (Perkin-Elmer Corp., Norwalk, CT) at 94°C, 30 s; 60°C, 1 min; 72°C, 1 min for 35 cycles. Forward primers included VH7183F (5′-GAAGTGAAGCTGGTGGAGTCTGGGGGAG) and VHJ558F (5′-GAGGTCCAGCTGCAGCAGTCTGGACCTG); reverse primers included JH4R (5′-CTGAGGAGACGGTGACTGAGGTTCCTTG) or JH4INR (5′-CAGGCTCCACCAGACCTCTCTAGA) (21). Control primers for the wild-type TCR-α locus have been described elsewhere (20). PCR products were cloned by the TA Cloning® Kit (Invitrogen, San Diego, CA) and sequenced by Sequenase™ Version 2.0 (U.S. Biochemical Corp., Cleveland, OH).

Antibody Assays. Serum IgM was determined by an ELISA Ig isotyping kit (Pierce Chemical Co., Rockford, IL); for inhibition, the serum equivalent of 100 μg IgM was preincubated with 1 mg total mouse IgG (Southern) at 37°C for 1 h. Data reflect either lymphoma-free or lymphoma-afflicted T cell–deficient *lpr* animals. Serum κ rheumatoid factor was determined as described (22). Statistical significance was evaluated by unpaired Student's *t* test.

Results and Discussion

T cell–deficient, Fas-deficient animals developed intraabdominal lymphoid malignancy with associated mortality at a penetrance of at least 70% (Figs. 1 and 2). Affected mice possessed severe hepatosplenomegaly and malignant, exudative ascites (Fig. 1 and data not shown). Such animals

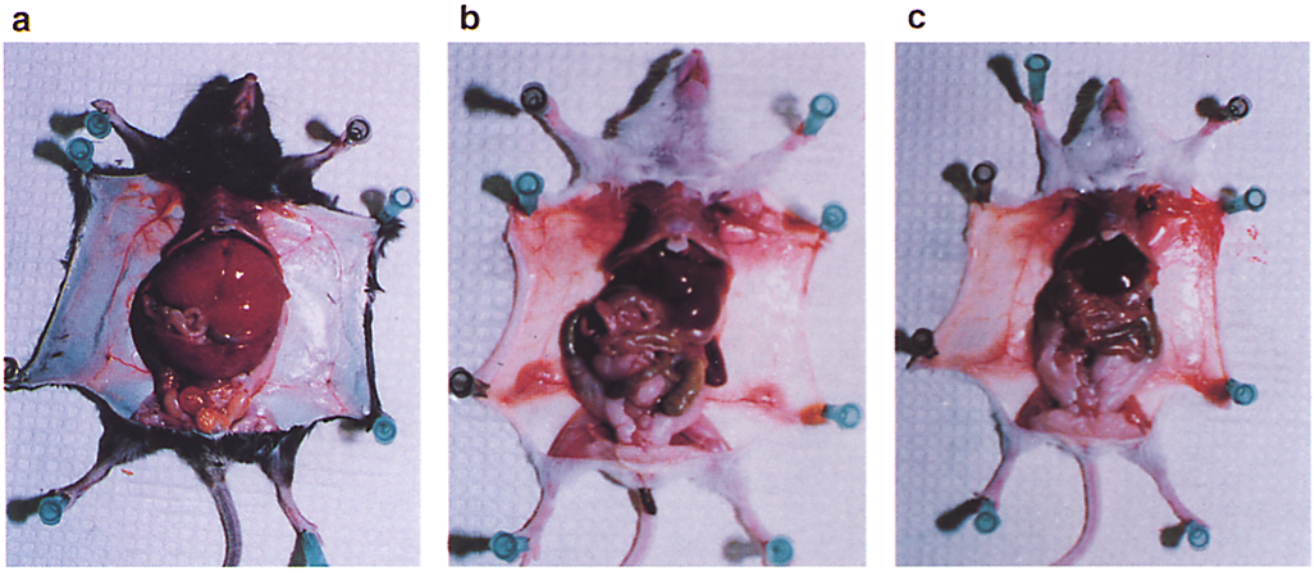

Figure 1. Representative autopsies of T cell–deficient *lpr* mice. (*A*) An αβ, γδ T cell–deficient *lpr* mouse with exudative hepatosplenomegaly caused by lymphoid malignancy. This animal contained a massively enlarged liver and spleen, the latter extending across the midline below the right hepatic lobe. Autopsies were similar in lymphoma-afflicted αβ, γδ T cell–deficient, Fas-intact mice, but hepatosplenomegaly and ascites were less prominent (not shown). Here, a moribund, 12 wk-old αβ, γδ T cell–deficient *lpr* mouse was killed and dissected, along with age-matched counterparts. The anterior peritoneum was removed to allow visualization of the peritoneal cavity. (*B*) Normal liver appearance, but splenomegaly and peripheral lymphadenopathy in a T cell–intact *lpr* mouse. Despite increased size, T cell–intact *lpr* spleens (*left side of animal*) had an appearance distinct from lymphoma-bearing αβ, γδ T cell–deficient *lpr* spleens, which were of greater size and weight, and contained grossly visible exudates and/or fibrosis. Abdominal contents were similar in γδ T cell–deficient *lpr* animals (not shown). (*C*) Normal abdominal contents and lymph nodes in a T cell–intact, Fas-intact animal. Autopsy findings were similar in αβ T cell–deficient *lpr* and γδ T cell–deficient, Fas-intact mice (not shown). αβ T cell–deficient Fas-intact and lymphoma-free αβ, γδ T cell–deficient animals possessed similar abdominal contents, but less prominent peripheral lymph nodes (not shown; 22).

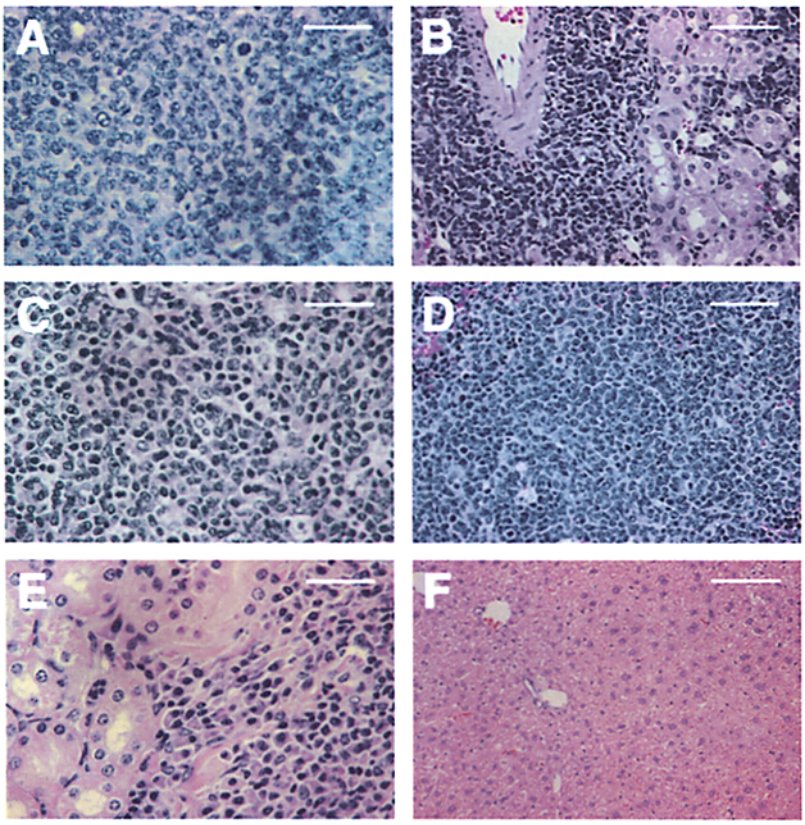

Figure 2. Histopathology of *lpr*-induced lymphoma. (*A*) High grade lymphoma infiltrating the liver of an αβ, γδ T cell–deficient *lpr* mouse (bar = 67 μm), which was also present in the kidney (*B*; bar, 100 μm), periaortic lymph nodes (*C*; bar, 67 μm), and spleen (*D*; bar, 100 μm). (*E*) Mixed lymphocytic infiltrate in the kidney of a T cell–intact *lpr* mouse (bar, 100 μm), similar in morphology and constituency to the infiltrates in the liver of the same animal (not shown). Similar lesions were also found in αβ T cell–deficient *lpr*, γδ T cell–deficient *lpr*, and some lymphoma-free *αβ*, γδ T cell–deficient animals (not shown). (*F*) Infiltrate-free normal liver histology in a T cell–intact, Fas-intact mouse (bar, 200 μm). Similarly normal histology was noted in αβ T cell–deficient *lpr*, γδ T cell–deficient *lpr*, and most lymphoma-free αβ, γδ T cell–deficient animals (not shown).

generally possessed increased abdominal girth (25–30 cm at the umbilical line, vs. 15–20 cm for normal mice) because of malignant ascites accumulation (sometimes >10 ml) and abdominal organ enlargement. Notably, these mice lacked *lpr*-induced peripheral (e.g., inguinal, axillary) lymphadenopathy because of the absence of *lpr* T cells (Fig. 1). Mice in this study varied in color because of their mixed genetic background, which included both MRL (white) and C57BL/6

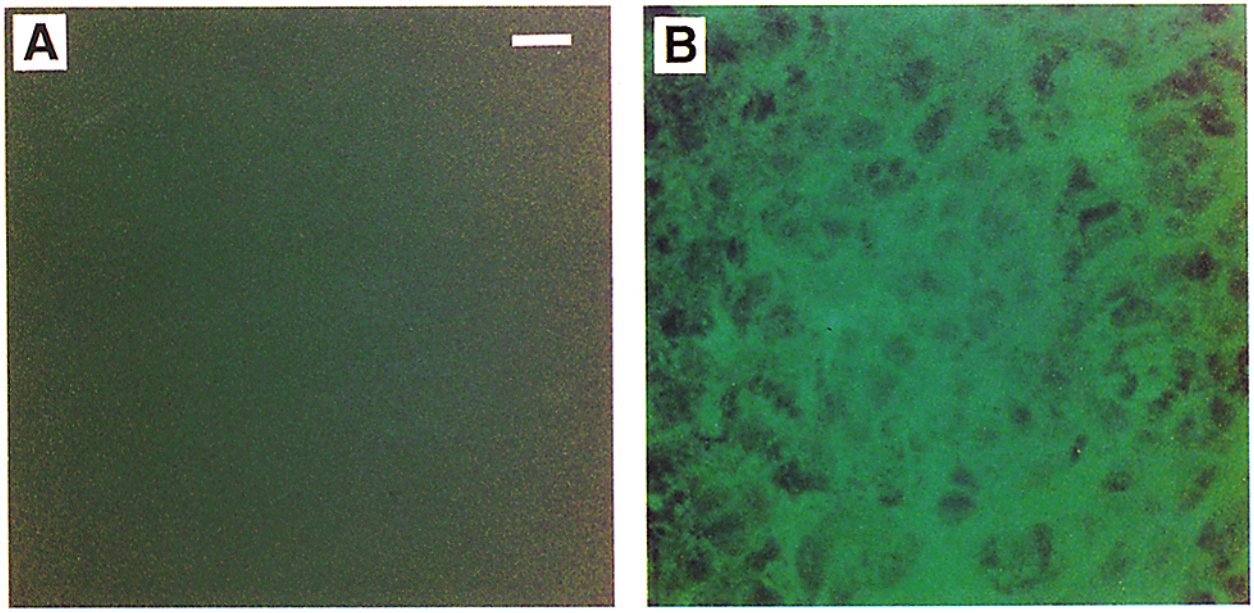

Figure 3. Immunofluorescent characterization of *lpr*-induced B cell lymphoma. (*A*) Negative staining for CD3. Similarly negative were CD19, CD5, CD23, TCR β, CD4, CD8, CD62L, IgG, IgD, MHC class I, NK1.1, Ly-49A, and Ly-49C (not shown). (*B*) Positive staining of all infiltrating cells for IgM. Similarly positive were CD44, CD45RB, and B220 (not shown). Bar, 10 μm.

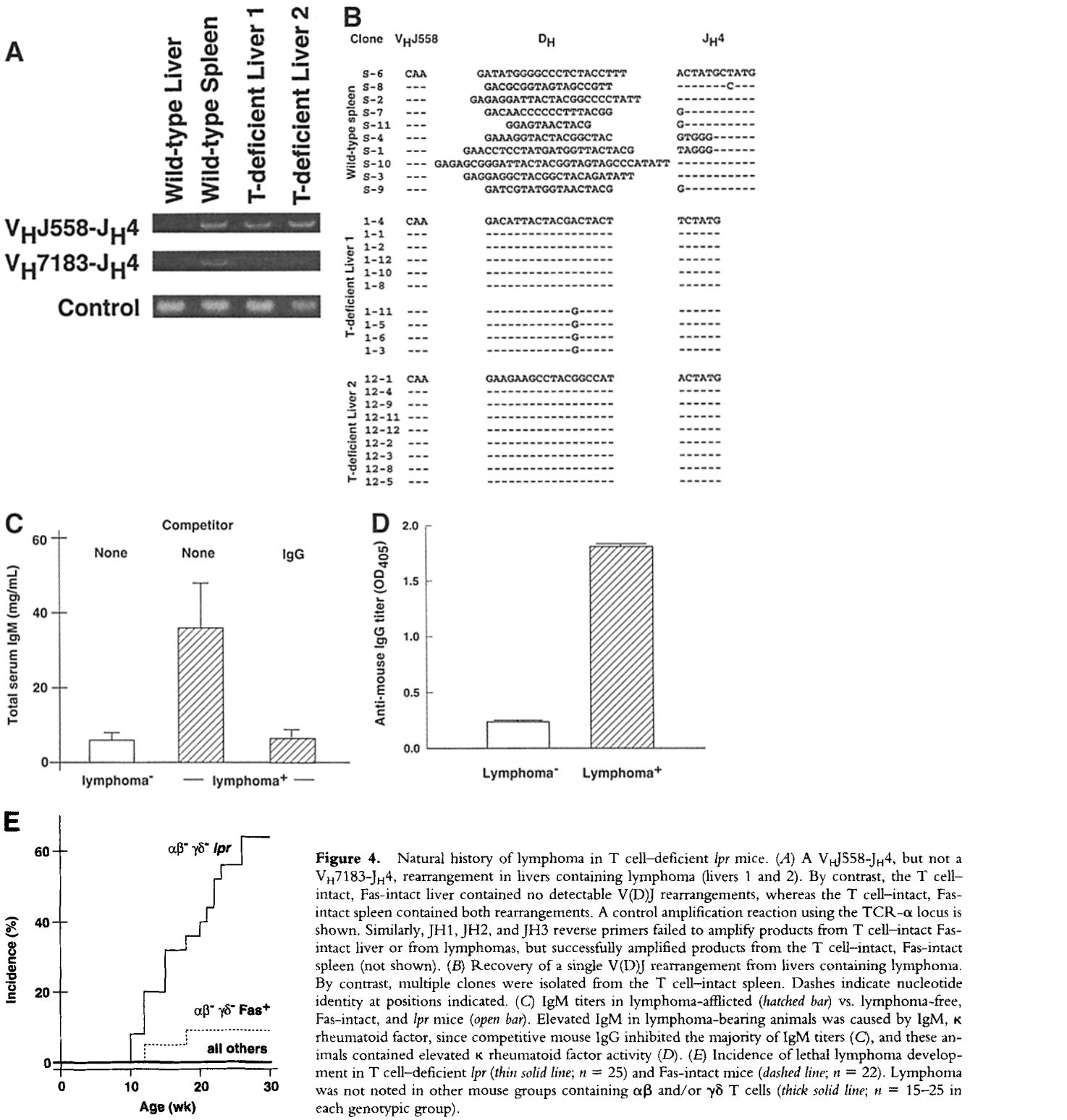

Figure 4. Natural history of lymphoma in T cell–deficient *lpr* mice. (*A*) A V_HJ558-J_H4, but not a V_H7183-J_H4, rearrangement in livers containing lymphoma (livers 1 and 2). By contrast, the T cell–intact, Fas-intact liver contained no detectable V(D)J rearrangements, whereas the T cell–intact, Fas-intact spleen contained both rearrangements. A control amplification reaction using the TCR-α locus is shown. Similarly, JH1, JH2, and JH3 reverse primers failed to amplify products from T cell–intact Fas-intact liver or from lymphomas, but successfully amplified products from the T cell–intact, Fas-intact spleen (not shown). (*B*) Recovery of a single V(D)J rearrangement from livers containing lymphoma. By contrast, multiple clones were isolated from the T cell–intact spleen. Dashes indicate nucleotide identity at positions indicated. (*C*) IgM titers in lymphoma-afflicted (*hatched bar*) vs. lymphoma-free, Fas-intact, and *lpr* mice (*open bar*). Elevated IgM in lymphoma-bearing animals was caused by IgM, κ rheumatoid factor, since competitive mouse IgG inhibited the majority of IgM titers (*C*), and these animals contained elevated κ rheumatoid factor activity (*D*). (*E*) Incidence of lethal lymphoma development in T cell–deficient *lpr* (*thin solid line*; $n = 25$) and Fas-intact mice (*dashed line*; $n = 22$). Lymphoma was not noted in other mouse groups containing αβ and/or γδ T cells (*thick solid line*; $n = 15$–25 in each genotypic group).

(black) coat color genes; lymphoma (as well as lack of lymphoma) was found among mice bearing either coat color.

Histopathology revealed invasion and infiltration by mitotically active atypical B lymphocytes (Fig. 2), which stained $IgM^+IgD^-IgG^-B220^+CD19^-CD5^-CD23^-CD3^-$ by immunofluorescence (Fig. 3). Lymphoma cells possessed atypical but homogeneous morphology, numerous mitotic figures, and large nuclei indicative of an aggressive, malignant process. Lymphoid organs, including the liver, were generally 80–90% involved (not shown). In contrast, typi-

cal *lpr*-induced infiltrates in the liver and kidney were pleomorphic (Fig. 2 *E*) and involved only 5–10% of involved organs, in contrast to the widespread infiltration seen in lymphoma-bearing animals.

PCR analysis of genomic DNA revealed that the lymphomas were restricted to the expression of a V_HJ558-J_H4 heavy chain rearrangement: other common V(D)J rearrangements were not detected, including V_H7183-J_H1, J_H2, J_H3, or J_H4, as well as V_HJ558-J_H1, J_H2, or J_H3 (Fig. 4 *A* and data not shown). Monoclonality was verified by sequence analysis of PCR products, which demonstrated identical V(D)J rearrangements among several PCR clones from the lymphoma, but variable rearrangements among PCR clones from the wild-type spleen (Fig. 4 *B*). The presence of an A→G mutation among the clones in one lymphoma may reflect oligoclonality, but the presence of identical V-D and D-J joins of the same V, D, and J regions strongly suggests that these sequences represent mutations within a single clone caused by AmpliTaq error or perhaps somatic mutation (23). These lymphomas secreted an IgM, κ rheumatoid factor, as evidenced by severe elevations in serum IgM that could be inhibited by competitive mouse IgG (Fig. 4 *C*; $P < 0.001$), as well as elevated serum κ rheumatoid factor (Fig. 4 *D* and data not shown; $P < 0.001$).

Lethal lymphoma was observed in the majority of αβ, γδ T cell–deficient *lpr* mice (~60–70% by 7 mo of age), but was partially penetrant in T cell–deficient, Fas-intact animals (~10% by 7 mo of age; Figs. 1 and 4 *E*; $P < 0.01$). Tumors were not observed in mice containing either T cell subtype, regardless of Fas phenotype ($P < 0.001$). These findings were clearly demonstrated in αβ T cell–deficient animals, which possessed a mean survival of more than 10 mo without lymphoma development (Figs. 2 and 4 *E* and data not shown). T cell–intact *lpr* and γδ T cell–deficient *lpr* animals demonstrated increased mortality compared to Fas-intact counterparts which resulted from profound systemic autoimmunity (unpublished data), but histological examination of the liver, spleen, lymph nodes, and kidneys from these mice failed to reveal subclinical lymphoma in 30–36-wk-old animals (Figs. 2 and 4 and data not shown). Thus, mice containing either αβ or γδ T cells were capable of preventing the development of lymphoma.

Accordingly, these findings demonstrate a tumor suppressor function for Fas and a regulatory role for αβ and for γδ T cells in tumorigenesis. Since lymphoma was suppressed in *lpr* animals containing either T cell but lacking functional Fas, these results strongly suggest that both types of T cells may regulate B cell lymphoma via a Fas-independent mechanism. This may involve perforin or other Fas-independent cytotoxic mechanisms (19) that are activated by MHC/peptide complexes (24) or nonpeptide ligands (25). Alternatively, T cells may circumvent the need for Fas-dependent regulation by inducing terminal differentiation, as seen in the reduction of *myc*-induced lymphomas by the induction of B cell differentiation (26). Still, Fas is directly implicated in the regulation of this lymphoma since T cell–intact, Fas-intact animals developed malignancy at a significantly decreased penetrance compared to T cell–deficient *lpr* counterparts. Fas may affect tumorigenesis by interacting directly with other tumor suppressor genes like p53 (27), or protooncogenes like bcl-2 (28). These studies seem germane to the development of B cell lymphoma in acquired immune deficiency syndrome, where chronic antigen stimulation may substitute for Fas deficiency in promoting a pool of premalignant B cells that progress to malignancy in the absence of T cell regulation (29).

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