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Fas and Fas Ligand Expressed on Cells of the Immune System, not on the Target Tissue, Control Induction of Experimental Autoimmune Uveitis

Jennifer L. Wahlsten,* Heather L. Gitchell,* Chi-Chao Chan,* Barbara Wiggert, † and Rachel R. Caspi†**

The Fas-Fas ligand (FasL) interaction is important for maintaining lymphocyte homeostasis by signaling for activation-induced cell death. Mice homozygous for the lpr or gld mutations do not express functional Fas or FasL, respectively, and spontaneously develop progressive autoimmune symptoms. Recent studies implicated expression of FasL on immunologically privileged tissues in protection from immune-mediated damage. Conversely, tissue expression of Fas may facilitate damage. We evaluated the susceptibility of lpr and gld mice to induction of experimental autoimmune uveitis (EAU), a T cell-mediated autoimmune disease induced with retinal Ags, which targets the neural retina. gld as well as lpr mice immunized with a retinal Ag developed disease of lower incidence and severity than wild-type controls. Delayed hypersensitivity responses were not significantly different among immunized gld, lpr, or wild-type mice, although in vitro Ag-specific lymphocyte responses of the mutant mice were lower. To evaluate whether the diminished ability of gld and lpr mice to develop EAU was due to a defect at the level of the tissue or the immune system, radiation bone marrow chimeras constructed between wild-type and mutant mice were immunized to induce EAU. Mutant recipients of wild-type bone marrow, but not wild-type recipients of mutant bone marrow, developed normal disease scores. These results indicate that normal expression of Fas and of FasL on cells of the immune system is important for EAU expression. Unexpectedly, neither lack of Fas nor lack of FasL on the ocular tissues affected expression of EAU. The Journal of Immunology, 2000, 165: 5480–5486.

E xperimental autoimmune uveitis (uveoretinitis) (EAU) is an organ-specific, T cell-mediated autoimmune disease that can be induced in rodents by active immunization with retinal Ags or their fragments, or by adoptive transfer of retinal-specific, syngeneic CD4+ T cells. EAU manifests itself as a destructive inflammation of the neural retina and related tissues (1–4). The pathophysiology of EAU in the mouse model closely resembles human uveitic diseases of putative autoimmune origin and serves as a model for these blinding ocular inflammations (4). In addition, because of shared basic immunopathogenic mechanisms, elucidation of the mechanisms affecting EAU can also shed light on the mechanisms involved in other tissue-specific autoimmune disease models mediated by T cells.

Fas (CD95) and its ligand, FasL (CD95L), are transmembrane proteins belonging to the TNF/nerve growth factor receptor and TNF protein families, respectively (5). Fas and FasL interaction is important for maintaining normal peripheral lymphocyte homeostasis during an immune response (5), in which cellular signaling through Fas elicits activation-induced cell death (6). Fas and FasL are expressed on various tissues as well as on cells of the immune system, including T cells (5). In mice and in humans, Fas is expressed on ocular tissues, and is thought to contribute to the immunologically privileged status of the eye by causing apoptosis of invading Fas-positive leukocytes (7, 8). Interestingly, both in mice and in humans, ocular tissues express Fas as well, and its expression is increased in ocular inflammatory conditions (7–9 and Chan and Tarrant, unpublished). Expression of Fas in the eye raises the possibility that it may have a role in tissue damage by promoting apoptotic death of ocular cells.

Mice homozygous for the mutant genes lpr (lymphoproliferation) or gld (generalized lymphoproliferation disease) do not express functional Fas or FasL (10, 11), respectively, and develop progressive autoimmune symptoms (12). Thus, lack of these molecules precipitates a spontaneous autoimmune process. However, previous studies evaluating the susceptibility of gld and lpr mice to induction of experimental autoimmune encephalomyelitis (EAE), which shares essential cellular mechanisms with EAU, demonstrated a marked resistance of the gld and lpr mice to the development of clinical EAE compared with wild-type (WT) B6 mice and pointed out the need for FasL on the infiltrating cells and of Fas on cells of the CNS (13–15).

In the present study, we sought to evaluate whether lack of Fas or FasL alters the susceptibility of gld and lpr mice on the C57BL/6 (B6) background to EAU induced by immunization with the interphotoreceptor retinoid-binding protein (IRBP). Our results showed that IRBP-immunized B6.gld as well as B6.lpr mice have a diminished capacity to develop EAU. Experiments using bone marrow (BM) chimeras, in which WT, gld, or lpr mice served alternatively as BM donor or as recipient, led to the conclusion that normal expression of Fas and FasL on cells of the immune system is required for induction of EAU, but presence of Fas or FasL on ocular tissue does not affect EAU induction. Furthermore, lpr and...


Materials and Methods

Animals

C57BL/6 WT mice (B6), C57BL/6 mice congeneric for CD45.1 (CD45.1), and C57BL/6 mice homozygous for gld or lpr defects (gld or lpr, respectively) were either purchased from The Jackson Laboratory (Bar Harbor, ME) or were bred on site from breeding pairs kindly supplied by Tom Ferguson (Washington University, St. Louis, MO). All animals were housed under specific pathogen-free conditions, were given water and chow ad libitum, and were used at 2–6 mo of age. Mutant mice with obvious splenomegaly or in poor physical condition were excluded from the study. Ages of the mice used in the different experiments are specified in the corresponding figure legends. WT mice between 2 and 6 mo of age show no discernible changes in susceptibility to disease or in immunological responses. Use of the animals conformed to institutional and National Institutes of Health guidelines.

Reagents

IRBP was isolated from bovine retinas by Con A-Sepharose affinity chromatography and fast performance liquid chromatography, as described previously (16). BSA, α-methyl-d-mannopyranoside (α-MMP), Con A, pertussis toxin (PTX), CFA, and conalbumin were purchased from Sigma (St. Louis, MO). NeutroAvidin (HRP conjugated) was purchased from Pierce (Rockford, IL). Mycobacterium tuberculosis strain H37RA was purchased from Difco (Detroit, MI). ELISA kits and minikits for cytokine measurement were purchased from Endogen (Woburn, MA). All Abs for flow cytometry were purchased from Becton Dickinson-PharMingen (La Jolla, CA).

Induction and scoring of EAU

By immunization. WT C57BL/6 mice were immunized s.c. in the thighs and base of tail with 125 μg IRBP in 0.2 ml emulsion 1:1 v/v with CFA containing 2.5 mg/ml M. tuberculosis, and were simultaneously injected i.p. with 1 μg PTX in 0.1 ml as an additional adjuvant. gld or lpr mice were immunized with either the same dose or with 200 μg IRBP and 2 μg PTX in the same volume of CFA.

By adoptive transfer. Donors immunized as above with 125 μg IRBP were sacrificed 14 days after immunization, and their pooled lymph node and spleen cells were restimulated for 72 h in culture with 30 μg/ml IRBP before injecting 40 × 10^6 cells i.p. into recipients. Eyes were collected 21 days after immunization, or 10 days after adoptive transfer, within 5 min of euthanasia. The eyes were prefixed for 1 h in 4% phosphate-buffered glutaraldehyde and then were transferred into 10% phosphate-buffered formaldehyde until processing. Fixed and dehydrated tissue was embedded in methacrylate, and 4–6-μm sections were cut through the pupillary-optic nerve plane. Sections were stained by hematoxylin and eosin. An ocular pathologist evaluated the presence and grade of disease in a masked fashion after examining six sections cut at different levels for each eye. Severity of EAU for each eye was scored on a scale of 0 (no disease) to 4 (maximum disease) in half-point increments, according to a described semiquantitative system (17). Briefly, the minimal criterion to score an eye as positive by histopathology was inflammatory cell infiltration of the anterior chamber, ciliary body, choroid, vitreous, or retina (EAU grade 0.5). Progressively higher grades were assigned for presence of discrete lesions in the tissue, such as vasculitis, granuloma formation, retinal folding, photoreceptor detachment, photoreceptor damage, etc. The grading system takes into account lesion type, size, and number.

Delayed-type hypersensitivity (DTH)

Two days before the termination of an experiment, mice received 10 μg of IRBP in 10 μl intradermally into the pinna of one ear. The other ear was injected similarly, but with PBS. Ear swelling was measured at the termination of the experiment 48 h later with a spring-loaded micrometer. DTH results are expressed as Ag-specific swelling, calculated as the difference in microns between thickness of the IRBP-injected ear and the PBS-injected ears.

Lymphocyte proliferation

Draining lymph nodes (inguinals and iliacs) were collected at the termination of an experiment and pooled within each group. Triplicate cultures of 5 × 10^6 cells/0.2 ml/well were stimulated with 30 μg/ml IRBP in 96-well flat-bottom plates in RPMI 1640 containing 1% naive mouse serum and 20 mg/ml α-MMP (to neutralize possible traces of Con A, which is used during the purification of IRBP). The cultures were incubated for 48 h and were pulsed with [3H]thymidine (1 μCi/10 μl/well) for the last 18 h. The data are presented as the average difference in cpm between triplicate cultures of IRBP-stimulated and unstimulated lymph node or splenocyte cells ± SD from a representative experiment.

Determination of lymphokine content in culture supernatants by ELISA

Spleens were removed at the termination of an experiment and pooled within each group. The cells were cultured in 24-well flat-bottom plates (5 × 10^5 cells/ml/well) with 30 μg/ml of IRBP in RPMI 1640 medium containing 1% fresh-frozen syngeneic mouse serum and 20 ng/ml α-MMP. Supernatants were collected for cytokine production analysis after 48 h. IFN-γ, IL-4, and IL-5 were measured by ELISA using paired Ab minikits from Endogen. IL-10 was measured using an ELISA kit from Endogen.

BM chimeras

Recipient mice were exposed to two doses of 550 rads, given 8 h apart, in a GammaCell irradiator utilizing a 137Cs source 24 h before BM transplantation. Syngeneic BM cells were obtained by flushing freshly dissected femurs of donor mice and titias with RPMI 1640 through a 23-gauge needle. The cells were teased into a single-cell suspension, and 75 × 10^6 viable cells in 0.2 ml of RPMI 1640 supplemented with 1% normal mouse serum were injected i.v. into irradiated recipients. Extent of chimerism in recipient mice 2 mo after reconstitution was determined by flow cytometry when using CD45.1 congenic mice on a C57BL/6 background as donors or as recipients, and ranged between 88 and 98%. Between 1 and 2 × 10^8 splenocytes were stained for two-color analyses with 1 μg of FITC-conjugated anti-CD4 (clone RM4-4) and 1 μg of either PE-conjugated anti-CD45.1 (clone A20) or PE anti-CD45.2 (clone 104) in the presence of 2 μg of anti-CD16 (Fc block). A total of 3 × 10^7 total events was collected and analyzed using a Becton Dickinson FACscalibur and CellQuest analysis software (San Jose, CA).

Reproducibility and statistical analysis

Experiments were repeated at least twice. Statistical analysis of EAU scores was done according to the test of Snedecor and Cochran (18) for linear trend in proportions (nonparametric, frequency based). Each mouse (average of both eyes) was treated as one statistical event. Delayed hypersensitivity scores were analyzed using an independent t test. Probability values of p < 0.05 were considered to be significant.

Results

gld and lpr mice are less susceptible to induction of EAU by immunization

To determine whether functional Fas or FasL expression is necessary for active EAU induction, we immunized B6 mice with 100 μg IRBP and gld or lpr mice with 100 μg or 200 μg IRBP as described in Materials and Methods. In six separate experiments comparing gld or lpr mice with WT controls (three each combined for gld and lpr), gld and lpr mice developed EAU with a greatly reduced incidence and severity (Fig. 1A). Resistance to EAU induction in the mutants was maintained even when the IRBP and PTX doses were doubled. These data show that functional expression of Fas and FasL is required for full induction of EAU.

Immunological responses of IRBP-immunized gld and lpr mice

At the termination of each experiment, 48-h DTH responses were measured. Lymph nodes and spleens were processed for proliferation assays and for determination of cytokine production to IRBP. In contrast to the striking inhibition of disease scores, DTH responses of gld or lpr mice immunized with either 125 or 200 μg IRBP were not different from the responses of WT mice (Fig. 1B), indicating that adequate priming had taken place. Because EAU is driven by a cell-mediated pathology, DTH responses of the gld and lpr mutants are an important measure of their immunocompetence.
to mount a cell-mediated in vivo response. Proliferative responses in culture to IRBP in lpr and gld mice were detectably lower than in B6 WT, with lpr appearing to be more affected than gld (Fig. 1C). In three repeat experiments, the response of gld mice was on average 73% of WT, and of lpr mice 42% of WT, when immunized with an equivalent amount of IRBP. Furthermore, both gld and lpr showed markedly decreased production of IFN-γ (Fig. 2).

IL-10 and IL-5 were also affected, although to a lesser degree, and IL-4 production was diminished only in the lpr. Thus, across the board, responses of lpr mice were affected more than those of gld mice. In addition, the Th1 response, as represented by Ag-specific IFN-γ production, appeared to be compromised to a greater degree than the Th2 response, as represented by Ag-specific IL-4, IL-5, and IL-10. Thus, the gld and lpr mutants appeared to be developing a Th1-low cellular response to IRBP.

Whether the altered cytokine profile indicates an altered interaction with APC in these mice, or another type of relative immune deficit, is unclear. It is well known that gld and lpr mice with time accumulate nonfunctional double-negative lymphocytes that are not responsive to Ag. Although most mice used in this study were under 3 mo of age, at the finite cell numbers of cells present in the culture dish such double-negative cells could dilute the Ag-reactive cells, explaining at least in part the reduced immunological responses in vitro. More important, however, the ability of both lpr and gld mice to develop good DTH responses after active immunization with IRBP indicates that at the level of the organism they were able to prime and recruit adequate numbers of effector cells.

**FIGURE 1.** Disease and immunological responses of gld, lpr, and WT mice immunized with IRBP 21 days after immunization with the indicated dose of IRBP. Data are compiled from six experiments, four of which were done with mice 2–2.5 mo old, and two with mice 2–6 mo old (most <4 mo). A, EAU scores by histopathology. Disease is graded on a scale of 0–4 by a masked observer. Each point represents one mouse (average of both eyes), and the horizontal lines show the average score of the group. B, DTH responses in micrometers of the same mice. DTH was measured by ear swelling 48 h after challenge and is presented as the difference between the thickness of the IRBP-injected ear and the PBS-injected ear. Each point is one mouse, with the horizontal line showing the average of the group. The EAU scores of gld vs their WT controls, and lpr vs their WT controls are significantly different (p < 0.05). The DTH scores do not differ. Naive mice uniformly had an EAU score of 0. Average DTH to IRBP in naive mice was 1.2, 0.3, and 1.3 μm for WT, gld, and lpr (n = 13, 6, and 6), respectively. C, Proliferation of draining lymph node cells to IRBP (30 μg/ml). Shown is the average difference in cpm between IRBP-stimulated and unstimulated lymph node cells ± SD of triplicate cultures (representative experiment of three). Background counts in unstimulated control cultures ranged between 500 and 3000 cpm for the different groups. Counts in IRBP-stimulated lymph node cell cultures from naive WT, lpr, and gld mice were the same as counts in unstimulated cultures from the same mice and well within the background range (1600–1800 cpm).

**FIGURE 2.** IRBP-specific cytokine production by splenocytes of gld, lpr, and WT mice. Spleens harvested 21 days after immunization were pooled within groups, and cultures of 5 × 10⁸ cells/ml were stimulated with IRBP. Shown is cytokine content as assayed by ELISA in supernatants collected after 48 h. Cytokine production by IRBP-stimulated cells from naive WT, lpr, and gld mice was uniformly at or below the level of detection, which was 0.137, 0.111, 0.008, and 0.008 ng/ml for IFN-γ, IL-10, IL-4, and IL-5, respectively.
Ocular histopathology of normal and uveitic gld and lpr mice

Because Fas and FasL are normally expressed in retinal tissues, it was important to examine whether the lpr and gld mutations result in an alteration of the normal retinal architecture, which could affect disease development. Representative histopathologic sections of retina from normal and diseased gld, lpr, and WT mice are shown in Fig. 3. The histopathology images shown correspond to disease scores of 0, 0.5, and 2. Importantly, no changes in ocular architecture or nonspecific accumulations of lymphocytes were observed in the retinas of unimmunized gld or lpr mice. EAU histology in gld or lpr mice resembled typical changes seen in WT mice at the equivalent disease grade, with a combination of cellular infiltrate and typical retinal folding and/or destruction of the photoreceptor cell layer. It should be kept in mind that EAU scores of 2 for gld and lpr mice are not typical for those genotypes and are shown only for comparison. Original magnification, ×200.

Normal expression of Fas and FasL on cells of the immune system is required for full induction of EAU

To elucidate whether the diminished induction of EAU in gld or lpr mice results from a defect at the level of the tissue or the immune system, we initially performed adoptive transfers of primed T cells that had been Ag stimulated in culture, from WT into gld or lpr mice, and vice versa. Due to the limited number of mutant mice available, and because the most disease-permissive situation is transfer into B6, the additional controls of homologous gld→gld and lpr→lpr transfers was omitted. The results of these adoptive transfer experiments were reminiscent of the results after active immunization, i.e., gld and lpr mice developed markedly less disease than the WT (Fig. 4). Interestingly, gld recipients of WT cells had reduced EAU scores, despite having DTH responses equivalent to WT. lpr recipients of WT cells did not appear to develop either EAU or DTH responses. Transfer of mutant cells into either WT or the reciprocal mutant recipients induced diminished DTH responses and diminished EAU scores.

Because EAU expression is heavily dependent on recruited nonspecific inflammatory leukocytes, such adoptively transferred EAU is caused by a mixed population of effectors. The Ag-specific T cells come from the donor, and the nonspecific recruited leukocytes come from the host. The data with respect to the role of Fas and FasL on immunocytes vs tissue are therefore difficult to interpret. To create a situation in which both the Ag-specific and the recruited cells come from the donor, we produced lethally irradiated BM chimeras, as described in Materials and Methods, in which WT, gld, or lpr mice served as either hosts or donors. WT, gld, and lpr hosts receiving WT lymphocytes all developed EAU with an average grade and range of scores that were not significantly different from one another (Fig. 5A). In contrast, WT hosts receiving gld or lpr lymphocytes did not develop significant EAU. Interestingly, although WT as well as lpr recipients of gld BM did develop appreciable DTH, there was no EAU whatsoever in these recipients, suggesting that FasL on cells of the immune system was needed for effecting the tissue damage typical of EAU, but not for effecting DTH. Gld recipients of lpr lymphocytes exhibited progressive morbidity after immunization for EAU induction, and had to be sacrificed on day 15 rather than day 21, which made interpretation of these data difficult. Nevertheless, since EAU onset in B6 mice is between days 12 and 14 after immunization, they had...
at least in theory enough time to develop EAU, had they been able to do so. In the aggregate, these data support the hypothesis that normal expression of Fas and of FasL on cells of the immune system is required for full induction of EAU, but their expression at the level of the tissue is not required for EAU pathogenesis.

Cellular responses in BM chimeras immunized for EAU induction

Cellular responses to IRBP were measured in the various BM chimeras 21 days after immunization. As shown in Fig. 5B, 48-h DTH responses in WT, gld, or lpr mice receiving WT lymphocytes were not significantly different, corresponding to the disease scores shown in Fig. 5A. Fig. 5C shows a representative proliferation experiment comparing IRBP-specific splenocyte proliferation of the different BM chimera groups. Interestingly, proliferative responses of splenocytes from recipients of WT lymphocytes (Fig. 5C) did not correspond to EAU disease scores (Fig. 5A), with splenocyte proliferation of gld or lpr recipients of WT lymphocytes considerably less than WT recipients of WT lymphocytes, although their EAU scores were the same. This suggests that in vitro proliferative responses do not necessarily correspond to pathogenicity. Although neither WT nor lpr recipients of gld lymphocytes developed EAU (Fig. 5A), these mice had measurable DTH responses (Fig. 5B) and splenocyte proliferation (Fig. 5C). Recipients of lpr BM did not develop either EAU or immunological responses (responses were measured only in wild type; proliferation and DTH of gld recipients, which experienced morbidity and had to be sacrificed early, were not measured). Control BM chimeras of lpr donor cells in lpr recipients did not develop morbidity. Thus, lpr-derived BM appeared to be unable to reconstitute either WT or gld recipients, and therefore the results from this donor-recipient combination must be interpreted with caution.

Discussion

In the present study, we have shown that mice homozygous for the gld or lpr defect on the C57BL/6 background had a reduced susceptibility to induction of EAU by immunization. They also had a
reduced capacity to develop disease in response to adoptive transfer of primed WT lymph node cells. However, radiation chimeras transplanted with WT BM developed normal disease scores following immunization. Conversely, lpr and gld lymphoid cells invariably were unable to support EAU induction in WT hosts, and in some combinations were unable to elicit DTH, irrespective of whether they were transferred as Ag-primed, or as a reconstituting BM inoculum.

The combination of donor-host relationships used in this study is complex. In the unmanipulated mouse, the target tissue as well as the entire immune system have the same genetic makeup. In the adoptive transfer recipients, the Ag-specific T cells come from the donor, but the target tissue as well as the recruited nonspecific leukocytes come from the host. In the BM chimera, the target tissue comes from the host, and the entire immune system comes from the donor. Some chimeras, particularly those that received lpr donor cells, showed signs of a graft-vs-host-like wasting syndrome that has been described (19, 20), and have been attributed at least in part to constitutive up-regulation of FasL on lpr donor T cells (21, 22). Although WT recipients of lpr donor cells appeared to show some weakness, most survived until termination of the experiment 21 days after immunization. The wasting syndrome was more pronounced in gld recipients of lpr donor cells, and as a result these mice were euthanized 15 days after immunization. Data from these adoptive transfers should therefore be interpreted with caution. Despite the difficulty in interpreting the data from some of the combinations, the result that all the BM chimeras receiving WT BM, and only they, developed full-blown EAU of essentially equivalent intensity leads to several conclusions: 1) to effectively induce EAU, cells of the immune system must have normal expression of Fas and FasL; 2) expression of Fas and FasL matters not only on the Ag-specific T cells, but also on the recruited nonspecific host leukocytes; 3) the ocular cells do not need to express Fas for tissue damage to occur; and 4) lack of FasL expression in the eye does not result under these conditions in exacerbated expression of disease.

In view of the published literature, these results were unexpected. Constitutive expression of FasL on ocular tissue is considered part of ocular immune privilege and an important protective mechanism against inflammatory responses in the eye by signaling for death of invading Fas-positive inflammatory cells (7, 8). Signaling for cell death of Fas-expressing target tissues by FasL-expressing activated T cells, or even neighboring target tissue cells, has been proposed as a common pathogenic mechanism for tissue destruction in organ-specific autoimmune diseases (23, 24). In line with these paradigms, Sabelko-Downes et al. (15), working in the EAE model, reported that FasL expression on donor effector cells and Fas expression on recipient target tissue are required for clinical development of disease. Applied to uveitis, these paradigms lead to the predictions that retinal cells that cannot deliver the death signal to effector T cells (gld) should be more susceptible to tissue damage, that retinal cells that cannot be given the death signal (lpr) should exhibit less pathology, and finally, that effector cells that cannot be signaled to die (lpr) should cause more severe disease. Unexpectedly, although FasL, as well as Fas are constitutively expressed on murine and human ocular tissue, and are up-regulated during ocular inflammation (C.-C. Chan, unpublished observations; Refs. 7, 9), the present data point to the conclusion that neither lack of Fas nor lack of FasL on ocular tissue alters expression of disease. Nevertheless, our results do not exclude the possibility that apoptosis by mechanisms other than through Fas/FasL interaction, such as the recently described pro-apoptotic effects of aqueous humor on inflammatory cell types (25), may play a role in EAU pathology in this system.

In light of the possibility that Fas and FasL on the tissue may not be involved in pathogenesis of EAU, the question that arises is: why would expression of these molecules be needed on the effector cells to induce disease? The process of apoptosis is an active one, and leukocytes signaled through Fas and FasL activate a variety of genes. It is conceivable that some of these genes might be involved in the effector function of these cells. Recent reports describe the chemoattractant ability of FasL for polymorphonuclear neutrophils (26, 27) and the T cell costimulatory capacity of Fas (28–30). Furthermore, engaging Fas with an anti-Fas Ab has been shown to induce IL-8 secretion, which also is chemotactic for neutrophils (31). Although neutrophils are not the predominant infiltrating population in the eye, they appear to have a role in the photoreceptor cell damage that is typical of EAU (32, 33). However, it should be kept in mind that the studies demonstrating the T cell costimulatory activity of Fas all used anti-Fas Abs, which can elicit different effects than engagement of Fas by its natural ligand (34). Up-regulated levels of FasL on lpr lymphocytes might also affect the interaction of T cells from these mice with Fas-expressing APC, resulting in altered or diminished priming.

In conclusion, the data presented in this work are compatible with the interpretation that in the uveitis model in mice, normal expression of the Fas and FasL molecules is required on cells of the immune system to effect the pathology typical of EAU. In contrast, the ability to express Fas and FasL on the target tissue does not seem to affect disease induction.

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References


