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IL-4 Suppression of In Vivo T Cell Activation and Antibody Production

Suzanne C. Morris, William C. Gause, † and Fred D. Finkelman *

Injection of mice with a foreign anti-IgD Ab stimulates B and T cell activation that results in large cytokine and Ab responses. Because most anti-IgD-activated B cells die before they can be stimulated by activated T cells, and because IL-4 prolongs the survival of B cells cultured with anti-Ig, we hypothesized that treatment with IL-4 at the time of anti-IgD Ab injection would decrease B cell death and enhance anti-IgD-induced Ab responses. Instead, IL-4 treatment before or along with anti-IgD Ab suppressed IgE and IgG1 responses, whereas IL-4 injected after anti-IgD enhanced IgE responses. The suppressive effect of early IL-4 treatment on the Ab response to anti-IgD was associated with a rapid, short-lived increase in IFN-γ gene expression but decreased CD4 T cell activation and decreased or delayed T cell production of other cytokines. We examined the possibilities that IL-4 stimulation of IFN-γ a effect of IL-4 was not reversed by IL-1, IL-2, or anti-TNF-α (CD25) and anti-II-2Rβ (CD122) mAbs. Early IL-4 treatment failed to inhibit anti-IgD-induced Ab production in Fas-defective lpr mice; however, the poor responsiveness of lpr mice to anti-IgD made this result difficult to interpret. These observations indicate that exposure to IL-4, while T cells are first being activated by Ag presentation, can inhibit T cells activation or promote deletion of responding CD4 T cells. The Journal of Immunology, 2000, 164: 1734 –1740.

Lymphocyte populations become activated in a specific order during a T cell-dependent immune response. In mice injected with a foreign Ab to mouse IgD, the activation of B cells by the cross-linking of their membrane Ig (mIg) 1 IgD precedes the activation of CD4 T cells (1). B cell activation contributes to the subsequent activation of CD4 T cells by enhancing processing of the anti-IgD Ab and presentation of the processed Ab to CD4 T cells specific for Ab-derived determinants (2, 3). These T cells synthesize DNA, secrete cytokines, and express membrane molecules that further activate B cells (4–6). As a result, CD4 T cell activation in this system is followed by a burst of B cell proliferation and Ab secretion (7). Cytokine production in these anti-IgD Ab-immunized mice also follows a specific sequence: IL-2, IL-3, and IL-9 production peak within 3 days of immunization whereas IL-4 and IL-6 production follow by an additional 24 h or more (8). The IL-4 produced by T cells in this response has particularly important effects on B cell responses: it increases the magnitude of the Ab response (9) and promotes production of allergy-associated Ig isotypes (IgE and IgG1) while suppressing production of complement-fixing isotypes (IgG2a and IgG3) (10).

The experiments described in this paper were performed to determine whether altering the timing of lymphocyte stimulation by IL-4 during the course of a response to anti-IgD Ab would modify that response. In particular, we were influenced by cell transfer studies that suggest that the lag between mlgD cross-linking-induced B cell activation and the activation of helper T cells in this system results in the death of most activated B cells before they can be “rescued” by T cell help (11). Because costimulation with IL-4 can increase the proliferative response and prolong the survival of B cells that have had their mlgD cross-linked (12), we hypothesized that IL-4 treatment, starting simultaneously with injection of anti-IgD Ab, would considerably enhance the Ab response to anti-IgD Ab. We have found instead that such treatment suppresses T cell activation and cytokine production as well as Ab responses in this system.

Materials and Methods

Animals

Female BALB/c mice were purchased from the Small Animals Division of the National Cancer Institute (Frederick, MD). Male C57BL/6J and C57BL/6.lpr mice were purchased from The Jackson Laboratory (Bar Harbor, ME). Mice were used at 7–12 wk of age.

Cytokines

Murine rIL-4 was a gift of Dr. Robert Coffman (DNAX Research Institute, Palo Alto, CA). Human rIL-2 and human rIL-1β (IL-1) were gifts of Dr. Richard Chizzonite (Hoffmann-LaRoche, Nutley, NJ).

Antibodies

The following Abs were produced and tested for specificity as previously described: affinity-purified goat Ab specific for mouse IgD (GaM6) (13), affinity-purified rabbit anti-mouse IgE (14), affinity-purified goat anti-rabbit IgG that was absorbed with mouse IgG (a gift of Dr. Ellen Vitetta, University of Texas Health Science Center, Dallas, TX) (15), goat IgG, rat IgG2b anti-mouse FcγRII Ab (24G2) (16), rat IgG2a anti-mouse IgE mAb (EM95) (17), mouse IgG1 anti-FITC mAb (CG5) (produced in our laboratory by Dr. Diana Goroff), rat IgG2b anti-IL-4 mAb (BVD4-1D11.2)
(18), rat IgG1 anti-IL-4 mAb (BVD6-24G2.3) (19), rat IgG1 anti-IFN-γ mAb (XMG-6) (20, 21), mouse IgM anti-CD25 mAb (7D4) (22, 23), rat IgG1 anti-CD25 mAb (PC-61) (24), rat IgG2b anti-CD4 mAb (GK1.5) (25), rat IgG1 anti-CD122 mAb (TMB1) (26), mouse IgG2a anti-IgD mAb (FF1-4D5) (27), mouse IgG2b anti-IgD mAb (H9/7/1) (28), rat IgG1 anti-TNF-α mAb (MP6-XT22) (18), and two isotype control mAbs, rat IgG2b anti-NP (J1.2) and rat IgG1 anti-β galactosidase mAb (GL113) (gifts of John Abrams, DNAX, Palo Alto, CA). Purified mouse IgG anti-human IL-2 mAb (5B1) was a gift of Dr. Richard Chizzonite (Hoffmann-LaRoche). Rabbit anti-mouse IgG1 Abs were produced and affinity purified (7). Some Abs were conjugated with alkaline phosphatase, FITC, or biotin as previously described (4, 15, 29).

Ab assays
GoM6-treated mice were bled at times that peak serum IgE and IgG1 levels are normally found (7, 30, 31). Serum IgG1 was quantitated by radial immunodiffusion with RmMyl antisera (The Binding Site, San Diego, CA) (11). Purified mAb CG5 was used as a standard for mouse IgG1. Serum IgE concentration was determined by ELISA (30). Serum IgG1 anti-goat IgG tiers were determined by ELISA (32).

Enzyme-linked immunospot (ELISPOT) assay
The frequency of IL-4–producing cells was determined by an ELISPOT assay performed as previously described (33), with the exceptions that wells were coated with the anti-IL-4 mAb, BVD4-1D11.2, (10 μg/ml) in PBS, bound IL-4 was detected with biotin-labeled BVD6-24G2.3 (4 μg/ml), and murine rIL-4 was used as a positive control.

Preparation of cytokine-anti-cytokine Ab complexes
IL-2 or IL-4, at a concentration of 200–1000 μg/ml, was mixed at a 2:1 molar ratio with neutralizing anti-IL-2 or anti-IL-4 mAb, respectively, which were at an initial concentration of 10 to 40 mg/ml, to prepare complexes. These complexes greatly extend the in vivo half-life of the cytokines (34). After 2 min at room temperature, complexes were diluted with normal saline to the concentration at which they would be injected into mice. Complexes were always freshly prepared before use.

Immunofluorescence staining
Spleen cell preparations were prepared and depleted of erythrocytes. Two million cells in 100 μl of HBSS supplemented with 10% newborn bovine serum and 0.2% Na3citrate (HNA) were stained on ice for 30 min with no Ab (control) or with 1 μg of fluorescein- or biotin-labeled Abs in the presence of 1 μg of 24G2, to inhibit binding of reagents to FcγRII, then washed 2 times with HNA. Biotin-labeled cells were incubated with ImmunoSelect streptavidin-R-PE (Life Technologies, Gaithersburg, MD) by the same procedure. After staining, cells were washed once with HNA and once with HBSS plus 0.2% Na3citrate, then fixed in 2% paraformaldehyde in PBS. One hundred thousand cells were analyzed for fluorescein- or PE-associated fluorescence, or both, with a Becton Dickinson FACSscan (Becton Dickinson, Mountain View, CA), using linear or log amplifiers and scatter gates chosen to select small to medium-sized lymphocytes. Percentages of specifically stained cells and median fluorescence intensity (MFI) of the cells was calculated with the Cellquest program (Becton Dickinson, Mountain View, CA).

Isolation and purification of RNA
Cytokine gene expression was evaluated 1, 2, 3, 4, 5, 7, and 10 days after GoM6 injection. Spleens were homogenized in RNAzol (Tel-Test, Friendswood, TX) with a Polytron PT3000 (Brinkmann Instruments, Westbury, NY). Total RNA was isolated and quantitated as described previously (8). Purified RNA (10 μg) was electrophoresed on a 1% agarose gel containing ethidium bromide to check RNA concentration and verify that the RNA was not degraded.

RT-PCR
A coupled RT-PCR was used to quantitate tissue mRNA levels (8). RNA samples were reverse-transcribed with Superscript reverse transcriptase (Life Technologies, Grand Island, NY) and cytokine-specific primers (8, 33) were used to amplify selected cytokines. For each cDNA product, the optimum number of cycles for PCR amplification was determined experimentally. Relative concentrations of IFN-γ, IL-2, IL-3, IL-9, IL-4, and IL-10 mRNA were determined. Primers for the “housekeeping gene,” hypoxanthine phosphoribosyltransferase (HPRT), were used in each experiment to verify that equal amounts of RNA were added in each PCR. All cytokine values were normalized individually to the corresponding hypoxanthine phosphoribosyltransferase values. Amplified PCR product was detected by Southern blot analysis (8), and the resulting signal was quantitated with a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

Results
GoM6-induced serum IgG1 and IgE responses are inhibited by simultaneous injection of IL-4
To determine whether early stimulation with IL-4 would affect GoM6-induced Ab responses, BALB/c mice were left untreated or were injected with GoM6 or GoM6 and a complex of IL-4 and anti-IL-4 mAb (IL-4C) that has long-acting IL-4 activity. Mice were bled 6, 8, and 10 days after the initial injection. IL-4C treatment inhibited the day 8 IgG1 response by 66% and the IgE response by 87% (Fig. 1). Injection of mice with the low dose of anti-IL-4 mAb used in the IL-4C was insufficient to suppress IgG1 or IgE responses by itself (Fig. 2). Injection of free IL-4, which has a short in vivo half-life, at the same dose used in the IL-4C, also had little effect on serum levels of IgG1 and IgE. Inhibition of IgG1 and IgE by a single dose of IL-4C was comparable to that caused by administration of IL-4C on days 0, 2, 4, and 6 (data not shown).

IL-4C that contained 1 μg of IL-4 and 6 μg of anti-IL-4 mAb inhibited GoM6-induced IgG1 and IgE responses to the same extent.
IL-4C inhibits GaMδ-induced T cell activation

Because IL-4 enhances anti-Ig Ab-induced B cell activation, we suspected that the suppressive effect of IL-4 on GaMδ-induced Ab responses might result from inhibition of the CD4+ T cell response to GaMδ. To examine this possibility, we determined the effects of IL-4C treatment on T cell IL-2Rα (CD25) and cytokine expression in GaMδ-treated BALB/c mice. Mice sacrificed 4 days after GaMδ injection show a considerable increase in the percentage of splenic CD4+ T cells that express CD25 in the extent of CD25 expression by these cells. These effects of GaMδ were suppressed by 55–65% by IL-4 (Fig. 5). IL-4 treatment also modulated GaMδ cytokine gene expression. GaMδ caused considerable increases in IL-2, IL-3, and IL-9 gene expression by 3 days after injection, and IL-4 and IL-10 gene expression by 4 days after injection. CD4+ T cells have previously been shown to be the source of mRNA for these cytokines (8). Treatment with IL-4C inhibited GaMδ-induced IL-2, IL-9, and IL-10 responses, and delayed GaMδ-induced IL-3 and IL-4 responses (Fig. 6). In contrast, IL-4C treatment caused a large increase in IFN-γ gene expression that peaked within 1 day of IL-4C injection and returned over the next 2 days to the levels observed in mice that had not received IL-4C (Fig. 6).

An ELISPOT assay was used to determine whether the day 4 decrease in IL-4 gene expression is associated with a decrease in IL-4 secretion. Numbers of spleen cells that secrete detectable amounts of IL-4, without any in vitro restimulation, increased considerably following GaMδ injection; this increase was nearly suppressed to background levels by IL-4C treatment (Fig. 7). Taken together with previous evidence that most of the cytokine responses to GaMδ are CD4+ T cell derived (6, 8), these observations demonstrate that IL-4C treatment at the time of GaMδ injection has a marked suppressive effect on CD4+ T cell activation.
IL-4 suppression of the immune response to GaMδ injection is not mediated by IFN-γ

Because IL-4C treatment of GaMδ-injected mice induces a large, short-lived increase in IFN-γ gene expression and IFN-γ can suppress IgG1 and IgE responses to GaMδ (20), it seemed possible that IL-4 suppression of the GaMδ-induced immune response was IFN-γ mediated. To test this possibility, we examined whether an anti-IFN-γ mAb, at a dose that blocks in vivo effects of endogenously produced IFN-γ (20), would block IL-4C inhibition of GaMδ-induced IgG1 and IgE responses. As previously reported (20), GaMδ-induced IgG1 and IgE responses were slightly or substantially enhanced, respectively, by injecting mice with anti-IFN-γ mAb (Fig. 8). This mAb, however, only partially blocked IL-4C inhibition of the GaMδ-induced IgG1 response and had no effect on IL-4C inhibition of the GaMδ-induced IgE response (Fig. 8). Thus, IL-4C induction of IFN-γ production does not account for the inhibitory effects of IL-4 on the response to GaMδ Ab.

IL-4C suppression of the immune response to GaMδ injection is not mediated by inhibition of IL-2 production or receptor expression or inhibition of IL-1 production

IL-4C treatment suppresses IL-2 gene expression (Fig. 6), and IL-4 has been reported to suppress IL-2Rα (CD25) and IL-2Rβ (CD122) expression (35). Because IL-2 is an autocrine growth factor for T cells (36), it seemed possible that suppression of IL-2 production or IL-2 signal transduction might be responsible for IL-4 inhibition of GaMδ-induced IgG1 and IgE responses. To examine these possibilities, we determined whether treatment of BALB/c mice with mAbs that block the IL-2Rα (anti-CD25 and CD122 mAbs) would mimic the effect of IL-4 on the Ab response to GaMδ, and whether treatment with IL-2 (in the form of IL-2C) would block the ability of IL-4 to inhibit GaMδ-induced Ab production. Injection of anti-CD25 and CD122 mAbs failed to inhibit IgG1 and IgE responses to GaMδ (Fig. 9). Injection of IL-2C 2 days after mice received GaMδ (the time when IL-2 responses are normally first detected in GaMδ-injected mice; Ref. 8) enhanced the GaMδ-induced IgG1 and IgE responses but did not suppress the ability of IL-4 to inhibit these responses (Fig. 10). Therefore, IL-4 inhibition of IL-2R expression or IL-2 production does not account for IL-4C inhibition of GaMδ-induced IgG1 or IgE responses. Additional studies demonstrated that suppression of IL-2 production or signaling does not account for IL-4C inhibition of GaMδ-induced splenic cytokine gene expression (data not shown).

Because IL-4 is known to inhibit macrophage production of IL-1 (37), which can contribute to T cell activation (38), we examined whether injection of BALB/c mice with 1 μg of IL-1 could reverse IL-4 suppression of anti-IgD-induced Ab responses. IL-4C inhibition of the anti-IgD-induced IgG1 and IgE response was not reversed by IL-1 (Fig. 11). An additional experiment demonstrated that the suppressive effect of IL-4 was not reversed when mice were treated with both IL-1 and IL-2C (data not shown). Thus, it appears unlikely that IL-4 suppression of endogenous IL-1 production is responsible for the inhibitory effect of IL-4 on anti-IgD-induced Ab production.
IL-4 inhibition of GaMδ-induced Ab responses is not TNF-α dependent

Activation of memory T cells by anti-CD3 mAb, in the presence of either IL-2 or IL-4, can stimulate T cell death (39). Signaling through both the TNFR and Fas have been reported to contribute to this process (40). To investigate whether IL-4 suppression of GaMδ-induced Ab production might be mediated by this process, we examined whether anti-TNF-α mAb could block IL-4-induced suppression and whether IL-4 can suppress GaMδ-induced Ab responses in lpr mice, which have a defect in Fas expression (41). Anti-TNF-α mAb had little effect on IL-4 suppression of GaMδ-induced IgG1 and IgE responses (Fig. 12). Attempts to study the role of Fas in IL-4 suppression of GaMδ-induced Ab responses, however, provided equivocal results. Fas-deficient mice, even Fas-deficient mice that had not yet developed detectable lymphadenopathy or serum autoantibodies, made much smaller IgG1 and IgG1 anti-goat IgG responses to GaMδ than did wild-type mice, and GaMδ injection failed to increase serum IgE levels above the high basal levels in these mice (data not shown). Although IL-4C treatment, which convincingly inhibited GaMδ-induced IgG1, IgG1 anti-goat IgG, and IgE responses in wild-type mice, had no effect, or a slight stimulatory effect, on these responses in Fas-deficient mice, the failure of GaMδ to induce substantial IgG1 and

FIGURE 10. Inhibition of IL-2 production does not account for IL-4C inhibition of GaMδ-induced IgG1 and IgE responses. BALB/c mice (five/group) were left untreated or were injected i.v. with 800 μg of GaMδ and either 2 μg each of anti-CD22 (TMB1) and anti-CD25 (PC61) mAbs or 2 μg each of isotype-matched control mAbs (J1.2 and GL.113). Mice were bled 8 and 10 days after injection. Serum IgG1 and IgE levels were determined. Geometric means and SE are shown for day 8.

FIGURE 11. IL-4C inhibition of the GaMδ-induced IgG1 response is not reversed by treatment with IL-1. BALB/c mice (five/group) were left untreated or were injected i.v. with 100 μg each of two different anti-IgD mAbs (FF1-4D5 and Hδa/1). Anti-IgD mAb-injected mice received no additional treatment or also received 1 μg of IL-1, IL-4C (5 μg of IL-4 + 30 μg of anti-IL-4 mAb), or both IL-1 + IL-4C. Mice were bled 8 and 10 days after injection. Serum IgG1 and IgE levels were determined. Geometric means and SE are shown.
IgE responses in lpr mice made the lack of effect of IL-4C difficult
to interpret. Our attempts to obtain a sufficient quantity of a blocking
anti-Fas ligand mAb (42, 43) to determine whether acute
inhibition of Fas-Fas ligand interactions would block the inhibitory ef-
fects of IL-4C have, to date, been unsuccessful. Thus, the possibility
that IL-4 inhibits the GoMδ-induced Ab response by inducing Fas-
mediated cell death has neither been established nor eliminated.

Discussion

The study described here was undertaken to determine whether early exposure of lymphocytes to IL-4 following immunization
would enhance the Ab response to an immunogen by increasing B
cell resistance to mIg cross-linking-induced deletion. Instead, we
found that administration of a long-acting preparation of IL-4
along with a potent immunogen, anti-IgD Ab, strongly suppressed
anti-IgD-induced IgG1 and IgE responses, even though IL-4 is
produced during responses to anti-IgD Ab (6, 8) and enhances isotype switching to IgG1 and IgE (44). The suppressive effect
of IL-4 requires the presence of IL-4 when mIg cross-linking is
initiated. It is lost if IL-4 administration is delayed for one day, and
a two day delay actually increases the anti-IgD Ab-induced IgG1
response. We have been unable to determine whether IL-4 admin-
istration has the same inhibitory effects on primary IgG1 or IgE
responses to immunization with conventional Ags, such as OVA,
as opposed to anti-IgD Ab, because conventional Ags fail to in-
duce the large primary IgG1 and IgE responses observed with
anti-IgD Ab administration (data not shown).

The inhibitory effect of accelerated exposure to IL-4 during the
immune response to anti-IgD Ab likely results from an effect of
IL-4 on CD4+ T cell activation. IL-4C treatment suppresses CD4+
T cell activation, as demonstrated by inhibition of CD25 expres-
sion, cytokine gene expression, and IL-4 secretion. It is unlikely,
however, that IL-4 inhibits CD4+ T cell activation by suppressing
IL-2R expression or IL-2 production. Anti-CD25 and anti-CD122
mAbs had no effect on anti-IgD-induced Ab responses, and treat-
ment with IL-2 did not reverse IL-4 inhibition of the Ab response
to anti-IgD. It is also unlikely that IL-4 inhibits GoMδ-induced
CD4+ T cell activation, or deviates the GoMδ-induced type 2
cytokine response, by stimulating IFN-γ production. Although
IL-4C treatment does stimulate substantial IFN-γ gene expression
(possibly by activating CD8+ T cells to produce this cytokine, as
was observed in mice infected with Schistosoma mansoni; Ref. 45),
neutralization of IFN-γ does not block the ability of IL-4 to in-
hbit GoMδ-induced IgE production. IL-4 suppression of inflam-
matory responses that might potentially costimulate T cell activa-
tion is another potential mechanism of IL-4 suppression of anti-
IgD-induced Ab production that has been ruled out by our studies:
treatment with IL-1, at a dose known to enhance T cell-dependent
Ab responses (46) did not reverse the inhibitory effects of IL-4.

Our observations leave open the possibility that exposure to
IL-4 at the time of initial Ag presentation to T cells inhibits T cell
activation or causes the T cells to die by a Fas-mediated process.
Lenardo has demonstrated that exposure of memory T cells to IL-2
or IL-4 when they are activated by TCR cross-linking kills these
cells (39), a process that is termed propriocidal apoptosis (PA). PA
can be mediated by either a Fas/Fas ligand or a TNF/TNFfr
interaction (40). Fas/Fas ligand interactions are thought to be most
important for PA of CD4+ T cells (40), whereas TNF/TNFfr
interactions are thought to be of particular importance to PA of
CD8+ T cells (40). Consistent with this, anti-TNF-α mAb has little
effect on IL-4 inhibition of anti-IgD-induced Ab production, which
depends on CD4+ T cell help and is CD8+ T cell independent
(Ref. 47; and F. D. Finkelman, unpublished data). Unfortunately,
we were unable to determine whether IL-4 inhibits GoMδ-induced
CD4+ T cell activation through a Fas-dependent mechanisms be-
cause Fas-deficient lpr mice fail to develop a substantial IgE or
IgG1 response to GoMδ and we were unable to obtain a neutraliz-
ing anti-Fas ligand mAb.

It is likely that the effects of IL-4 on T cell activation that we
have observed are not restricted to the artificial situation in which
mice are injected with IL-4C, but occur naturally in situations in
which large quantities of IL-4 are endogenously produced. Infec-
tions with some pathogens, such as gastrointestinal nematodes,
cause substantial increases in IL-4 production (48). Systemic IL-4
levels are achieved during these infections that cause large increases
in B cell class II MHC and CD23 expression (49, 50). Dose-response
studies suggest that levels of IL-4 that are sufficient to have these
effects on B cell surface molecule expression should be sufficient
to make B cells resistant to mIg cross-linking-induced death (M. Mori
and F. Finkelman, unpublished data) and prime T cells for PA.

The effects of IL-4 on B cell resistance to mIg cross-linking and
Fas-mediated killing might be expected to increase the risk of au-
toimmune disease by inhibiting the deletion of autoreactive B
cells. Mice that chronically overexpress IL-4 do, in fact, produce
autoantibodies; however, the clinical effect of these autoantibodies
is limited in mice that are not otherwise predisposed to develop
severe systemic autoimmune disease (51). The results of our study
suggest that the risk for autoimmunity that is imposed by the ef-
efts of IL-4 on B cells is counterbalanced by a second, immuno-
suppressive effect of IL-4 that causes deletion or inactivation of T
cells presented with Ag in the presence of high IL-4 levels. Thus,
although newly generated autoreactive B cells are less likely to be
deleted when IL-4 levels are elevated, elevated IL-4 levels should
also make it less likely that these B cells will be induced to dif-
fentiate into autoantibody-secreting cells by autoreactive CD4+
T cells, because elevated IL-4 levels increase the likelihood that
newly generated autoreactive helper T cells will be deleted or
made less responsive by contact with autoantigen.

In contrast to the effects of chronically elevated IL-4 levels, the
production of IL-4 by CD4+ T cells during the course of a specific
immune response should enhance B cell survival without interfer-
ing with T cell activation, because the suppressive effect of IL-4 on
T cells is limited to the initial day of T cell activation. The rela-
ively late production of IL-4 during a T cell-dependent immune
response thus allows IL-4-producing T cells to escape its suppres-
sive effect while limiting the bystander activation of other T cells,
including self-reactive T cells.

Finally, we wish to point out that the immunosuppressive effect
of IL-4 on T cell activation may have therapeutic applications. Experiments in an acute parent into F1 graft-vs-host disease
(GVHD) model, in which graft CD8+ T cells develop into host-
reactive CTLs that destroy the host hemopoietic and immune sys-
tems (52), indicate that treatment with IL-4 at the time of parental
cell transfer eliminates transferred CD8+ T cells and prevents the
development of GVHD (C. Via and F. Finkelman, manuscript in
preparation). As would be predicted from our results in anti-IgD
Ab-injected mice, this effect of IL-4 is seen only when IL-4 is
administered on the day of cell transfer. Later administration of
IL-4 either has no effect on GVHD or converts acute GVHD to
chronic GVHD. Thus, it may be possible to use the T cell suppressive
effect of IL-4 to inhibit development of acute, cytotoxic GVHD dur-
ing bone marrow transplantation or to inhibit the development of
graft-reactive host CTL that are involved in allograft rejection.

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