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*J Immunol* 1999; 163:644-649; ;
http://www.jimmunol.org/content/163/2/644
CD4-Mediated Signals Induce T Cell Dysfunction In Vivo

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Triggering of CD4 coreceptors on both human and murine T cells can suppress TCR/CD3-induced secretion of IL-2. We show here that pretreatment of murine CD4+ T cells with the CD4-specific mAb YTS177 inhibits the CD3-mediated activation of the IL-2 promoter factors NF-AT and AP-1. Ligation of CD4 molecules on T cells leads to a transient stimulation of extracellular signal-regulated kinase (Erk) 2, but not c-Jun N-terminal kinase (JNK) activity. Pretreatment with anti-CD4 mAb impaired anti-CD3-induced Erk2 activation. Costimulation with anti-CD28 overcame the inhibitory effect of anti-CD4 Abs, by induction of JNK activity. The in vivo relevance of these studies was demonstrated by the observation that CD4+ T cells from BALB/c mice injected with nondepleting anti-CD4 mAb were inhibited in their ability to respond to OVA Ag-induced proliferation and IL-2 secretion. Interestingly, in vivo stimulation with anti-CD28 mAb restored IL-2 secretion. Furthermore, animals pretreated with anti-CD4 elicited enhanced IL-4 secretion induced by OVA and CD28. These observations suggest that CD4-specific Abs can inhibit T cell activation by interfering with signal 1 transduced through the TCR, but potentiate those delivered through the costimulatory molecule CD28. These studies have relevance to understanding the mechanism of tolerance induced by nondepleting anti-CD4 mAb used in animal models for allograft studies, autoimmune pathologies, and for immunosuppressive therapies in humans.


Received for publication February 25, 1999. Accepted for publication April 28, 1999.

1 Abbreviations used in this paper: PTK, protein tyrosine kinase; Erk, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PI-3, phosphatidylinositol-3; MAPK, mitogen-activated protein kinase; L, ligand; CAT, chloramphenicol acetyltransferase; TPA, 12-O-tetradecanoylphorbol-12 acetate.

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* This work is supported in part by the Wilhelm Sander-Stiftung and the SFB 465 of the Deutsche Forschungsgemeinschaft (to E.S.) and National Institutes of Health Grants AI28281 (to S.P.) and AI35514 (to N.C.). N.C. was supported by a Deutscher Akademischer Austausch Dienst grant.

11) or PMA + ionomycin- (12) mediated T cell activation to induce a functional unresponsiveness of T cells. The molecular mechanisms of the inhibitory effects of anti-CD4 Abs involve inhibition of TCR-induced ZAP-70 phosphorylation, ras activation, mitogen-activated protein kinases (MAPK), and, finally, inhibition of IL-2 gene transcription (13). In vivo studies in mice and humans have implicated that anti-CD4 mAb preferentially inhibit the Th1 pathway and spare Th2 responses (14, 15). The molecular nature of this response, however, is unclear.

In the two-signal model for T cell activation (16–19), ligation of the TCR/CD3 complex delivers signal 1, which up-regulates activation molecules on T cells, e.g., CD40 ligand (L). Interaction of CD40L with CD40 leads to expression of B7 family proteins on APC, which, in turn, bind to the costimulatory molecule CD28 on T cells (20, 21). Signals transduced through CD28 comprise the signal 2 (17). Abrogation of the sequential cascade leading to signal 2, using mAbs to CD40L, B7-1/B7-2, or CTLA4Ig, has been demonstrated to lead to T cell unresponsiveness (22, 23). The biochemical nature of CD28-mediated signals has been shown to involve the activation of c-Jun N-terminal kinase (JNK), a critical event in the complete activation of T effector cell function (24).

In this study, we have investigated signals initiated by CD4-specific mAbs that are able to interfere with the CD3-mediated activation of CD4+ T cells. We show that triggering of CD4 molecules on T cells induces extracellular signal-related kinase (Erk) 2, but not JNK, activation. Pretreatment of T cells with anti-CD4 mAbs suppressed the CD3-mediated induction of Erk2 activity, as well as that of the IL-2 promoter factors NF-AT and AP-1. This suppression could be overcome by costimulation of T cells with...
agonistic anti-CD28 Abs, suggesting that CD4-mediated signals inhibit signal 1 transduced through the TCR/CD3 complex, but do not affect signal 2, mediated through CD28 molecules. The in vivo role of anti-CD4 mAbs was confirmed when mice treated with anti-CD4 mAb had markedly inhibited IL-2 secretion and proliferation in response to Ag-specific stimuli. These results indicate that a “partial activation” of T cells through CD4 coreceptors can lead to a functional unresponsiveness, similar but not identical to T cell anergy.

**Materials and Methods**

**Abs**

The following Abs were used: mAb to murine CD4 (YTS177, rat IgG2b; purified from a hybridoma provided by Drs. H. Waldmann and S. Cobbold (University of Oxford, Oxford, U.K.) (43); murine anti-CD3ε mAb (clone 37.51; PharMingen, San Diego, CA); murine anti-CD28 mAb (clone 2C11; PharMingen), anti-active MAPK (Erk2) (Promega, Madison, WI; catalog no. V6671); anti-active JNK (Promega; catalog no. V7931).

**Cells and cell culture**

BALB/c mouse splenocytes purified by Ficoll-Hypaque density gradient centrifugation were used for the studies on cytokine secretion and proliferation. Purified CD4+ T cells were obtained by removal of adherent cells and subsequent depletion of B220+ and CD8+ cells on magnetic beads (Miltenyi Biotec, Auburn, CA). The purity of the CD4 T cells was 95–97%, as determined by flow cytometry. EL4 T cells were cultured in RPMI 1640 media supplemented with 10% FCS. To trigger the T cells through CD4 receptors, cells were treated with YTS177 mAb for murine T cells (1 μg/ml) for 2 h and washed once with PBS. Cells were resuspended in PBS with 2% FCS and goat anti-rat (GAR) IgG (10 μg/ml) for the time intervals indicated. For proliferation and cytokine secretion assays, cells were stimulated with plate-bound anti-CD3ε mAb (clone 2C11, 1 μg/ml) in the absence or presence of soluble anti-CD28 mAb (clone 37.51; agonistic Ab; 1 μg/ml) or with a combination of 12-Tetradecanoylphorbol-12-acetate (TPA; 10 ng/ml) and ionomycin (1 μM).

**DNAs and DNA transfections**

Chloramphenicol acetyltransferase (CAT) reporter gene constructs bearing multiples of the Pu-1 (NF-AT, IL-4) (25), Pu-2 (NF-AT, IL-2) (26), TREcoll (AP-1) (27), and a κB site from the MHC class II invariant chain promoter (NF-κB) (28) were used for transient transfections into EL4 cells using a conventional DEAE dextran sulfate transfection protocol, as described previously (26). Then, 20 h after transfection, the cells were divided and either left untreated or stimulated with YTS177 for 2 h, washed with PBS, followed by stimulation with plate-bound anti-CD3 mAb in the absence or presence of soluble anti-CD28 mAb (clone 37.51; agonistic Ab; 1 μg/ml) or with a combination of TPA and ionomycin. The cells were incubated for another 20 h, harvested, sonicated, and used for CAT assays. For the CAT assay, 100 μg of cell extracts were incubated with 1.0–1.5 μCi [3H]chloramphenicol and acetyl CoA. Acetylated CoA was extracted in ethyl acetate and separated by TLC. Percent acetylation was calculated by PhosphoImaging (Molecular Dynamics, Sunnyvale, CA). Transient transfection experiments were done only in EL4 T cells, due to the poor transfection efficiency of primary murine T cells.

**Western blot analyses**

To detect activated Erk2 and JNK in cell extracts, EL4 cells were stimulated with anti-CD3, anti-CD4, and anti-CD28 mAbs under various conditions, as described above. A total of 50 μg of proteins were electrophoresed on a 10% SDS-PAGE and transferred to nitrocellulose membrane (Hybond-ECL; Amersham, Arlington Heights, IL). Blots were blocked in 5% milk solution for 2 h. The presence of active Erk2 and JNK was detected by probing membranes with Abs to active MAPK and JNK. The reactivity of the Abs was measured by incubating with peroxidase-conjugated anti-rabbit IgG Ab. The reaction was detected by the enhanced chemiluminescence kit (Amerham) and quantitated by densitometry (BioRad, Hercules, CA). The density of each band was calculated over background density of the autoradiogram (5 arbitrary units).

**Animal experiments**

BALB/c mice (6–8 wk old) were purchased from The Jackson Laboratory (Bar Harbor, ME). For Ab treatment, animals were injected i.p. with a 100 μg/dose/mouse of YTS177 mAb or control rat IgG2b on days −1 and 1. Mice were immunized s.c. with 100 μg of OVA emulsified in CFA on day 1. Anti-CD28 Ab (clone 35.1) was administered i.p. on days 1 and 3 at concentrations of 100, 10, and 1 μg/dose/mouse. Three mice were used in each group. Splenocytes were harvested on day 7 and analyzed for OVA-induced proliferative responses, as well as IL-2 and IL-4 secretion.

**T cell assays**

Proliferative responses of murine T cells were measured by standard [3H]thymidine incorporation following by liquid scintillation. Briefly, 2 × 105 purified CD4 T cells were cultured in the presence of various stimuli. For OVA-stimulated cultures, adherent cells from naive C57BL/6 mice were treated with OVA, irradiated, and used as APC. Cell cultures were harvested on day 3 for IL-2, IL-4, and TNF-α measurements. In some cases, cells were cultured with a combination of TPA + ionomycin. Lymphoproliferation was assessed by addition of 1 μCi [3H]thymidine 16 h before harvesting and radioactivity determined as cpm on a liquid scintillation counter (Wallach, Gaithersburg, MD). Ionomycin was measured in culture supernatants of murine T cells stimulated under various conditions for 48 h. IL-2, IL-4, and TNF-α were measured using commercial ELISA kits (BioSource International, Camarillo, CA) using the manufacturers’ protocol. Optical densities were read at 405 nm on a MRX Dynatech (Chantilly, VA) microplate reader.
**Results**

*In vitro anti-CD4 mAb treatment inhibits TCR/CD3-mediated signals, leading to a decreased IL-2 gene transcription and secretion*

To determine the influence of CD4 coreceptors on T cell proliferation and secretion of IL-2 and TNF-α, splenic CD4+ T cells were pretreated with the CD4-specific mAb YTS177. Fig. 1 shows that YTS177 treatment of purified CD4+ splenic T cells induced the secretion of TNF-α, but did not stimulate IL-2 secretion and T cell proliferation. Pretreatment of the same cells with YTS177 inhibited the CD3-mediated secretion of IL-2 and T cell proliferation, while it did not affect the CD3-induced TNF-α secretion. Pretreatment of T cells with control mouse IgG2b Ab had no effect on anti-CD3-induced proliferation and cytokine secretion (data not shown).

T cell activation through the costimulatory molecule CD28 augmented the CD3-mediated cytokine secretion and T cell proliferation. In addition, anti-CD28 Ab could overcome the inhibitory effect of YTS177 on these T cell functions (Fig. 1). These results suggest that CD4 activation could interfere with the TCR/CD3, but not CD28-mediated signals.

At the transcriptional level, the expression of the IL-2 gene is controlled by several inducible transcription factors (29). In transient transfection assays using CAT reporter gene constructs controlled by multiple copies of the distal NF-AT site from the murine IL-2 promoter (NF-AT; 4× Pu-bd), the most proximal NF-AT site from the murine IL-4 promoter (NF-AT; 3× Pu-bd), the AP-1 site from the human collagenase promoter (AP-1; 5× TREcoll), and the NF-κB site from the murine MHC class II-associated invariant chain promoter (NF-κB; 4× NF-κBMCIV) were transfected into EL4 cells. Cells were pretreated for 2 h with medium alone (open bars), YTS177 mAb (filled bars), followed by medium alone (medium), anti-CD3 (CD3), anti-CD3 + CD28 mAb (CD3 + CD28) or TPA + ionomycin (TPA + Io) treatment for 20 h as indicated. Cells were harvested, sonicated, and CAT assays were performed as described in Materials and Methods. Shown are the representatives of two separate experiments.

**FIGURE 2.** Pretreatment of EL4 T cells with YTS177 interferes with anti-CD3-induced activation of NF-AT and AP-1, but not NF-κB transcription factors. CAT reporter gene constructs controlled by multiple copies of the distal NF-AT site from the murine IL-2 promoter (NF-AT; 4× Pu-bd), the most proximal NF-AT site from the murine IL-4 promoter (NF-AT; 3× Pu-bd), the AP-1 site from the human collagenase promoter (AP-1; 5× TREcoll), and the NF-κB site from the murine MHC class II-associated invariant chain promoter (NF-κB; 4× NF-κBMCIV) were transfected into EL4 cells. Cells were pretreated for 2 h with medium alone (open bars), YTS177 mAb (filled bars), followed by medium alone (medium), anti-CD3 (CD3), anti-CD3 + CD28 mAb (CD3 + CD28) or TPA + ionomycin (TPA + Io) treatment for 20 h as indicated. Cells were harvested, sonicated, and CAT assays were performed as described in Materials and Methods. Shown are the representatives of two separate experiments.

**FIGURE 3.** The anti-CD4 Ab YTS177 induces Erk2, but not JNK activation. CD4+ EL4 cells were treated with 1 μg/ml YTS177 mAb followed by cross-linking with goat anti-rat IgG (lanes 1–5) or TPA/ionomycin (T/I; lane 6), as indicated. The Erk2 activity was determined by Western blots, using anti-active MAPK (Erk2) or JNK. The numbers below represent the induction (mean of two experiments) of Erk2 and JNK activation as calculated by densitometry. The density of the bands was calculated over background density of the autoradiogram (2 arbitrary units).

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with anti-CD3 + CD28 Abs overcame the inhibitory effect of anti-CD4 mAbs on NF-AT and AP-1 factors (Fig. 2). The inhibitory effects of CD4 signals are proximal to the cell surface, since anti-CD4 mAb did not inhibit TPA + ionomycin-induced NF-AT and AP-1 activation, which bypass the requirement of receptor-associated kinases.

**CD4 signals modulate MAPK activation**

To delineate the signals transduced through CD4 molecules to downstream targets, we investigated the activation of MAPK by YTS177. Fig. 3 shows that stimulation of CD4+ T cells with YTS177 gave rise to a transient activation of Erk2. Maximal activity of Erk2 was observed after stimulation for 30 min, declining to the basal level within 2 h. In striking contrast, no JNK activation was detected under identical induction conditions, whereas TPA + ionomycin treatment induced both Erk2 and JNK activities.

To further identify the mechanism of CD4-mediated inhibitory effects, we investigated whether YTS177 pretreatment affected the activation of MAPK by anti-CD3 or anti-CD3 + CD28 Abs. Stimulation of EL4 T cells with anti-CD3 mAb alone induced the activation of Erk2, which was completely inhibited by YTS177 pretreatment (Fig. 4). Anti-CD3 alone did not induce JNK activation (Fig. 4, lanes 2–5). Costimulation with anti-CD3 + CD28 Abs could not overcome the inhibitory effect of YTS177 mAb on Erk2 activation completely (Fig. 4, lanes 7–10). Fig. 4 shows that pretreatment of CD4+ EL4 cells with YTS177 for 2 h resulted in an inhibition of anti-CD3 + CD28 Abs-induced Erk2 activation in a dose-dependent manner (Fig. 4, lanes 2–5). In contrast, the CD3 + CD28 Abs-mediated activation of JNK remained resistant to the anti-CD4 mAb pretreatment (Fig. 4, lanes 7–10). These findings show that anti-CD4 mAbs inhibit TCR/CD3-mediated Erk2 activation, but do not affect CD3 + CD28-induced JNK activation. Similar results were observed using human anti-CD4 Ab and human Jurkat CD4+ T cells (data not shown).

**In vivo treatment of mice with anti-CD4 mAb inhibits Ag-induced T cell responses**

To confirm these observations in vivo, BALB/c H-2d mice were injected i.p. with either control rat IgG2b or a nondepleting anti-CD4 mAb, YTS177, followed by s.c. immunization with OVA in CFA, with or without anti-CD28 mAb (see Materials and Methods). CD4 T cells isolated 7 days later were analyzed for OVA-induced proliferative responses, IL-2, and IL-4 secretion. Fig. 5 shows that CD4 T cells from animals treated with YTS177 mAb were inhibited in their ability to proliferate and secrete IL-2 in response to OVA stimulation, compared with those treated with control IgG2b. In vivo administration with anti-CD28 mAb overcame the inhibition of T cell functional responses (Ag-specific proliferation and IL-2 secretion).

Animals injected with OVA alone (with or without anti-CD4 mAb) did not induce an IL-4 response. In vivo administration with an agonistic anti-CD28 mAb induced a strong IL-4 response in a dose-dependent manner. Surprisingly, anti-CD4-treated animals did not inhibit the response; on the contrary, they elicited augmented IL-4 secretion.

Taken together, these findings demonstrate that signals transduced through the CD4 molecule (e.g., Erk2 and NF-κB) inhibit TCR-mediated IL-2 secretion, but not those induced through the costimulatory molecule CD28. Furthermore, ligation of CD4 molecules with anti-CD4 mAb potentiates Ag + CD28-induced IL-4 secretion.

**Discussion**

In this study, we have described molecular mechanisms that appear to be involved in the anti-CD4 Ab-mediated inhibition of IL-2 gene transcription in T cells in vitro and in vivo. We have shown that signals transduced through the CD4 molecule result in a partial inhibition of the TCR/CD3-mediated induction of T cells, i.e., in the suppression of Erk2 as well as NF-AT and AP-1, but not JNK and NF-κB induction. In our view, this observation might be of relevance for the induction of a transient unresponsiveness of peripheral T cells and, possibly, thymocytes in vivo. Costimulation through the CD28 Ab overcame this inhibitory effect of anti-CD4, by inducing JNK activity. Moreover, the anti-CD28 Ab-mediated switch of immune responses to a Th2 phenotype in vivo was substantially potentiated by anti-CD4 treatment.

Naïve T cells require two signals for complete activation, resulting in maximal IL-2 secretion and effector cell functions (18, 23). Signal 1 is delivered by recognition of Ag peptide-MHC class II on APC by TCR/CD3 on T cells. This signal initiates a cascade of intermolecular interactions involving CD40L (on T cells), CD40 (on APC) followed by B7 (on APC), and CD28 (on T cells). Signal 2 comprises of biochemical events triggered through CD28. The ability of anti-CD4 mAb to inhibit TCR/CD3-induced signal 1
leads to disruption of intermolecular signal cascades required for complete T cell activation. Thus, lack of provision of signal 2 in vivo results in Ag-specific T cell unresponsiveness. In this study, we have demonstrated that anti-CD4 mAb inhibited TCR-mediated signal 1. Restoring the cascade by providing exogenous anti-CD28 mAb overcame the inhibitory effect of anti-CD4 mAb in vitro and in vivo.

Engagement of the CD4 molecule on T cells with mAb before TCR stimulation has been shown to trigger negative signals leading to T cell unresponsiveness (reviewed in Ref. 13). Several signals, including calcium flux and the activation of p21ras, PI-3, and Raf-1 protein kinases, have been shown to be enhanced following CD4 ligation. We have confirmed previous reports (31) that triggering of CD4+ T cells with anti-CD4 mAb led to partial activation of T cells, including activation of Erk2. However, CD4 ligation failed to induce activation of JNK. In addition, analyses of transcription factors involved in the IL-2 promoter induction showed that YTS177 treatment resulted in consistent activation of NF-κB (7, 9), but not that of NF-AT or AP-1. It is presently unclear how activation leads to the induction of one but not other signaling pathways and transcription factors involved in T cell activation. The published data on the signals transduced through the CD4 molecule are quite controversial (13). While the differences may be due to various culture systems and Abs used for CD4 stimulation, all these studies demonstrated that CD4 ligation leads to delivery of “partial” and transient signals to T cells. However, the physiological role of these signals remains elusive. Recent studies have implicated that CD4 signals may contribute to regulation of T helper cell differentiation (32, 33, 44).

The biochemical mechanism involved in T cell unresponsiveness induced by anti-CD4 mAb resembles induction of anergy by incomplete activation of T cells (34–36). CD4 cross-linking has been shown to induce tyrosine phosphorylation of several substrates through activation of p56lck (reviewed in Ref. 37). Pretreatment of CD4+ T cells with CD4 Abs or expression of truncated CD4, both associated with reduced tyrosine phosphorylation of several substrates, suggests that p56lck plays an important role in membrane-proximal events following CD4 ligation (38–40). In this study, we have examined MAPK downstream of p56lck activation. In the case of anti-CD3, a partial activation of T cells through CD3 or CD4 molecules interfere with MAPK pathways. However, pretreatment of T cells with anti-CD4 mAbs suppressed the following: CD3-induced Erk2 but not JNK kinase activation, whereas pretreatment with anti-CD3 mAbs led to the inhibition of Erk as well as JNK activation by anti-CD3 and anti-CD28 mAbs. Moreover, costimulation of the CD28 pathway overcame the inhibitory effect of anti-CD4 mAbs, whereas CD28 activation is unable to overcome CD3-mediated T cell anergy. These findings indicate that anti-CD4 mediated inhibition differs from the “classical” pathway of T cell anergy.

Previous studies have shown that anti-CD4 mAb treatment induces a shift to Th2 phenotype (14, 15). Although, in our experiments, the inhibitory effects of anti-CD4 mAb on TCR-mediated activation in vitro or in vivo did not lead to such a shift, we observed a modulation of OVA-specific IL-4 secretion induced by anti-CD28 mAb treatment in vivo. Thus, mice treated with anti-CD4 mAb showed an enhanced Th2 type response after activation of CD28 signaling pathway. One interpretation of this effect is the contribution of CD4-mediated stimuli in the modulation of signaling cascades and transcription factors involved in Th2 cell differentiation. The different strengths of anti-CD4 mAb used in earlier studies and our work may explain the need for CD28 costimulation to observe the stimulatory effects of CD4 Ab on IL-4 secretion (32, 33, 41).

In summary, our results have demonstrated the role of CD4-mediated signals in regulation of T cell functions in vivo. Our studies warrant immune suppressive regimens with anti-CD4 mAb to be combined with inhibitors of signal 2 (e.g., CTLA-4Ig (42)). These studies have relevance to understanding the mechanism of tolerance induced by nondepleting anti-CD4 mAb used in animal models for allograft studies, autoimmune pathologies, and for immunosuppressive therapies in humans.

Acknowledgments

We thank Drs. H. Waldmann and S. Cobbold for the YTS117 hybridoma cell line, and Drs. Anneliese Schimpl and Ian Jonhston for critical reading of the manuscript.

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