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Simultaneous Induction of CD4 T Cell Tolerance and CD8 T Cell Immunity by Semimature Dendritic Cells

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Previous studies suggested that depending on their maturation state, dendritic cells (DC) could either induce T cell tolerance (immature and semimature DC) or T cell activation (mature DC). Pretreatment of C57BL/6 mice with encephalitogenic myelin oligodendrocyte glycoprotein (MOG)\textsubscript{35-55} peptide-loaded semimature DC protected from MOG-induced autoimmune encephalomyelitis. This protection was mediated by IL-10-producing CD4 T cells specific for the self Ag. Here we show that semimature DC loaded with the MHC class II-restricted nonself peptide Ag (OVA) induce an identical regulatory T cell cytokine pattern.

However, semimature DC loaded simultaneously with MHC class II- and MHC class I-restricted peptides, could efficiently initiate CD8 T cell responses leading to autoimmune diabetes in a TCR-transgenic adaptive transfer model. Double-peptide-loaded semimature DC also induced simultaneously in the same animal partially activated CD8 T cells with cytolytic function as well as protection from MOG-induced autoimmune encephalomyelitis. Our study suggests that the decision between tolerance and immunity not only depends on the DC, but also on the type and activation requirements of the responding T cell.

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The unique ability of dendritic cells (DC)\textsuperscript{5} to efficiently activate naive T cells correlates with their property to perform different functions at distinct sites. Immature DC in peripheral tissues respond to inflammatory stimuli and microbial products, mature subsequently and home to lymphoid organs. In contrast to immature peripheral DC, mature DC in lymphoid tissues express high levels of MHC class II (MHC II) and costimulatory molecules, allowing efficient priming of naive T cells (1). Many lines of evidence indicate that, in contrast to their mature counterparts, immature DC can tolerate T cells; this was demonstrated by direct DC-targeting of Ag via DEC-205 (2), cross-presentation induced deletion of Ag-specific CD8\textsuperscript{+} T cells (3), as well as inducible DC-specific expression of Ag in vivo (4).

However, analysis of spleen sections showed that the majority of DC of naive mice are of an immature phenotype and can still be driven into further maturation (3, 5, 6). This raised the question about roles of these immature DC in lymphoid organs and fostered the attractive hypothesis of immature DC guaranteeing maintenance of tolerance to peripheral self-Ags (1, 5, 7). Data showing acquisition, processing, and presentation of parietal cell- (8) or pancreatic β-cell-derived self-Ags (9) support this possibility. However, other studies showed that “being immature” was not sufficient for DC to exert tolerogenic functions, because only phenotypically mature DC could induce cross-tolerance of CD8\textsuperscript{+} T cells (10), initiate IL-10-mediated tolerance in a murine model of allergic asthma (11), or induce regulatory T cells, which suppress diabetes in NOD mice (12). Expression of the costimulatory molecules CD80 and/or CD86 on mature DC was also a prerequisite for optimal expansion of suppressive CD4\textsuperscript{+}CD25\textsuperscript{+} T cells (13). Furthermore, injection of semimature, but not completely immature DC loaded with encephalitogenic myelin oligodendrocyte glycoprotein (MOG) self-peptide induced IL-10-producing CD4 T cells and protected mice from subsequent induction of experimental autoimmune encephalomyelitis (EAE) with the same peptide (14). This led to a new concept suggesting that immature DC—the in vitro-created counterparts of naturally occurring steady-state DC in lymphoid organs—can tolerate naive CD4 T cells (15).

In the present study, we investigated whether this concept is applicable also 1) to CD4 T cells specific for foreign Ag and 2) to tolerize CD8 T cells directly or 3) to tolerize CD8 T cells via IL-10-producing bystander CD4 T cells. Here we demonstrate that the same semimature DC loaded with several different antigenic peptides simultaneously induce MHC II-restricted IL-10-producing T cells responsible for protective tolerance to MHC II-restricted Ag as well as immunity toward class I-restricted Ag. Our data indicate that the same semimature DC can induce simultaneously tolerance and immunity, depending on the type of T cell responding to the presented Ag.

Materials and Methods

Mice

Rip-OVA\textsuperscript{tm} (16), OT-I (17), and OT-II (18) mice have been described previously and were kindly provided by C. Kurts (Institute of Molecular Medicine, University Clinics, Bonn, Germany). All mice were bred and maintained at the Institute for Immunology, Ludwig-Maximilians-Universität München (Munich, Germany) and were used between 6 and 10 wk of age. All donors and recipients were sex-matched.

Adoptive transfer

CD8\textsuperscript{+} cells from lymph nodes and spleen of OT-I or OT-II mice were prepared as single cell suspensions. Spleen RBC were removed using ACK
buffer (0.15 M NaCl, 1 mM KHCO₃, 0.1 mM Na₂EDTA, pH 7.4) for 4 min at room temperature. The percentage of OT-I or OT-II TCR transgenic T cells among CD8⁺ or CD4⁺ T cells, respectively, was controlled via FACS analysis with anti-TCR Vβ5.1/5.2 and Vα2-specific mAbs. Before injection, cells were washed in PBS and filtered through nylon mesh (Reichert Chemie Technik; pore size 51 mm). For adoptive T cell transfer, 1 × 10⁸ OT-I and 2.8 × 10⁹ OT-II T cells were injected i.v. into the lateral tail vein of recipient mice.

**Dendritic cells**

DC were generated from C57BL/6 bone marrow progenitors using GM-CSF as described previously (19). On day 8 of culture, DC were tested for purity by staining with anti-CD11c and anti-MHC II. Purity of DC was routinely around 80%. DC were pulsed for 4 h in complete medium (RPMI 1640 supplemented with 5% FCS, 50 mM 2-ME, and 1% penicillin/streptomycin) with 20 μg/ml OVA257–264, 10 μM OVA323–339, 10 μM MOG35–55 (Neosystem) or mixtures of these. TNF-α (500 U/ml) and LPS (1 μg/ml) were added for 4 h while DC were loaded with peptide. The cells were then washed extensively in PBS, and 2.5–4 × 10⁶ DC were injected i.v. into the lateral tail vein of recipient mice.

**T cell restimulation and ELISA**

Supernatants from spleen cell restimulations were collected after 96 h, and cytokines produced from spleen cells were detected using ELISA kits for IL-10 and IFN-γ (BD Pharmingen).

**Immunostaining and flow cytometry**

mAbs used in this study were anti-Vβ5.1/5.2-FTTC (MR9-4), anti-Vα2-biotin (B20.1), anti-CD8-PerCP (53-6.7), and streptavidin-PerCP. All Abs were purchased from BD Pharmingen. A FACS Calibur flow cytometer and CellQuest Software from BD Biosciences were used to collect and analyze the data. Nonviable cells were excluded using forward and side scatter electronic gating.

**Induction of EAE and diabetes**

MOG35–55 peptide (Biotrend Chemikalien) was used to induce EAE in C57BL/6 mice as described before (14). Briefly, C57BL/6 mice were injected s.c. with 50 μg of MOG35–55 peptide in 50 μl of PBS emulsified in 50 μl of CFA that was further enriched with 10 mg/ml Mycobacterium tuberculosis (H37Ra; Difco/BD Pharmingen). In addition 200 ng of Pertussis toxin (List/Quadratech) were injected i.p. at days 0 and 2. Mice were observed daily for clinical signs of disease. Mice were scored according to their clinical severity of disease as follows: grade 0, no abnormality; grade 1, limp tail; grade 2, limp tail and hind limb weakness (waddling gait); grade 3, partial hind limb paralysis; grade 4, complete hind limb paralysis; and grade 5, moribund. The data are plotted as the mean daily clinical score for all animals in a particular treatment group.

Glucose levels in the urine were checked every day by glucose test strips (Diabur-Test 5000) from Roche Diagnostics. Mice were considered diabetic when glucose concentration was ≥ 5.5 mmol/L.

**In vivo CTL assay**

This assay was performed as described before (20). Syngeneic C57BL/6 spleen and lymph node cells were depleted of erythrocytes by osmotic lysis. Cells were washed and split into two populations. One population was pulsed with 10⁻⁶ M OVA257–264 peptide (or in some experiments OVA323–339) for 1 h at 37°C, washed, and labeled with a high concentration of CFSE (2.5 μM: CFSEhigh cells). The second control population was labeled with a low concentration of CFSE (0.25 μM; CFSElow cells). For i.v. injection, an equal number of cells from each population (CFSEhigh and CFSElow) was mixed, such that each mouse received a ratio percentage CFSElow/percentage CFSEhigh; percentage specific lysis = (1 – (ratio unprimed/ratio primed)) × 100.

**Results**

**Semimature DC can induce IL-10-producing CD4 T cells specific for self and foreign Ag**

Semimature DC are indistinguishable from fully mature DC according to surface expression of typical DC maturation markers. However, they lack the ability to produce cytokines and, therefore, induce IL-10-mediated regulatory responses rather than IFN-γ-producing T effector cells. To investigate tolerance induction by TNF-α-treated semimature DC, we incubated DC from GM-CSF bone-marrow cultures with either LPS or TNF-α as described previously (14). Both, LPS and TNF-α-treated DC were similarly mature according to surface expression of MHC II, CD80, CD86, CD25, MHC class I (MHC I), and CD40 (data not shown). However, as we reported previously (14), in contrast to LPS-DC, semimature TNF-DC did not produce IL-6, IL-12p40, or IL-12p70 (data not shown) and were able to prevent EAE via an IL-10-dependent mechanism, when loaded with MOG35–55-peptide and injected into C57BL/6 mice (Ref. 14, data not shown, and see Fig. 3).

To further assess the immunostimulatory capacities of the differentially matured DC, we immunized mice three times with LPS- or TNF-DC loaded with either the class II-restricted MOG35–55 or OVA323–339 peptide. Restimulation of T cells with the relevant peptide showed in general weaker proliferative T cell responses in those mice injected with TNF-DC as compared with fully mature LPS-DC (Fig. 1A). Also the produced cytokine-patterns were different: while T cells from LPS-DC immunized mice produced both IFN-γ (Fig. 1B) as well as IL-10 (Fig. 1C) in response to antigenic peptide, the TNF-DC pretreatment lead to strongly diminished IFN-γ production (Fig. 1B). Therefore, TNF-DC induced Ag-specific IL-10-producing T cells specific for MOG self-Ag (as described previously (14)), but also for the foreign model-Ag OVA.

**Semimature DC elicit diabetes in RIP-OVAlow mice**

To analyze if semimature DC might be used to either directly or indirectly tolerate CD8⁺ T cells and have therapeutic effects in CD8⁺ T cell-mediated autoimmune diseases, we used the OT-I adoptive transfer model to induce diabetes in RIP-OVAlow mice. Transgenic RIP-OVAlow mice, which express OVA as model autoantigen under control of the rat insulin promoter, are tolerant to OVA, which is expressed on the β cells of the pancreatic islets (16). Upon transfer into these hosts, naïve “autoreactive” OVA-specific CD8⁺ CTL from TCR-transgenic OT-I mice, are ignorant to their specific Ag due to low amounts of OVA expression in RIP-OVAlow recipients (16, 21–23). However, when OT-I T cells become activated in vivo, they expand and destroy the OVA-expressing pancreas inducing diabetes as measured by high urine glucose levels (16, 21–23). To examine the tolerizing capacity of semimature DC in this system, OVA257–264-pulsed TNF-DC or LPS-DC were injected into RIP-OVAlow mice reconstituted with 1 × 10⁶ OT-I cells. To monitor T cell expansion, blood was analyzed and the percentage of OT-I T cells determined by flow cytometry (Fig. 2A). After i.v. immunization OT-I T cells expanded to over 70% of CD8⁺ PBL (Fig. 2A). The kinetic of OT-I expansion induced by mature or semimature DC was similar in all mice, peaked at day 4 postinfection (Fig. 2A) and was comparable, when PBL (Fig. 2A) and spleens (data not shown) were analyzed. However, because T cell expansion not only accompanies activation but also tolerization of T cells (24, 25), we determined diabetes induction as a sign for CTL activation in vivo. Although all mice treated with mature or semimature DC were clinically scored as diabetic (Fig. 2B, left panel), the urine glucose levels in the group treated with TNF-DC was in average 2- to 3-fold lower (Fig. 2B, left panel). In addition, while LPS-DC-treated animals did not clinically improve, the TNF-DC-treated mice fully recovered from diabetes after 27 days (Fig. 2B, left panel). However, after complete recovery of the animals vaccinated with TNF-DC (day 27,
FIGURE 1. OVA233–339-pulsed TNF-DC induce identical peptide-specific CD4⁺ T cell response as TNF-DC pulsed with MOG35–55. C57BL/6 mice received three i.v. injections (days −7, −5, −3) of TNF-DC or LPS/CD40-DC pulsed either with OVA233–339 or MOG35–55 peptide. Splenocytes from these mice were restimulated at day 0 with 2 μM of the respective peptide (■, OVA, left graphs or MOG, right graphs) or without peptide (□). T cell responses were assessed after 72 h of culture, B and C. Cell supernatants were harvested and their cytokine content measured by ELISA. A. Proliferation was assayed by [³H]thymidine incorporation for an additional 18 h.

Semimature DC induce CTL function in C57BL/6 mice and simultaneously protect from CD4 T cell-mediated EAE

To exclude that absence of tolerance induction by TNF-DC was due to the transgenic nature of OT-I or OT-II T cells, or their artificially elevated precursor frequencies, we next compared polyclonal CTL responses induced by mature and semimature DC. To analyze the cytotoxic activity induced by the different DC, we performed “in vivo killer assays” (20) in normal C57BL/6 mice. DC-treated mice were injected with a 1:1 mixture of differently CFSE-labeled spleen cell targets, either pulsed with OVA257–264 peptide (CFSE high) or unpulsed (CFSE low) (Fig. 3A). CTLs generated by immunization of the mice with mature OVA257–264-loaded DC, selectively killed the peptide-loaded (CFSE high) target cell population (Fig. 3A) within a few hours, allowing calculation of specific lysis (20). As shown in Fig. 3A, killing of injected OVA257–264-pulsed spleen cells was not statistically different in mice treated with OVA257–264-loaded LPS- or TNF-DC. Furthermore, when CD4 T cell epitopes of MOG or OVA or both were provided together with the OVA257–264 MHC I epitope on DC as well as on the targets, similar specific killing was observed in each group (Fig. 3A). These results indicate, that neither OVA- nor MOG-specific IL-10-producing DC cells (Fig. 1) suppressed the CD8 T cell responses as bystanders.

We next analyzed cytokine production of CD8 T cells induced by mature or semimature DC. Restimulated splenocytes from mice treated with OVA257–264-pulsed LPS-DC produced mainly IFN-γ, but no or little IL-10, while semimature TNF-DC did not elicit any significant cytokine responses at all (Fig. 3B). The absence of IFN-γ secretion by CD8 T cells from mice immunized with TNF-DC (Fig. 3B) in contrast to those treated with fully mature DC indicates incomplete induction of CTL responses in vivo. However, these IFN-γ negative CD8 T cells do show cytolytic functions (Figs. 2B and 3A).

To proof that TNF-DC loaded with either MOG35–55 or both OVA257–264 and MOG35–55 were similarly tolerogenic for MOG-specific T cells and able to protect mice from EAE, we induced EAE in mice treated as in Fig. 3A. As published before (14), immunization with semimature MOG35–55-loaded DC protected C57BL/6 mice from EAE, while mice without DC-treatment or injected with mature MOG35–55-pulsed LPS-DC developed severe EAE (Fig. 3C, MOG). However, the same semimature DC loaded with both, MOG35–55 and OVA257–264, that induced specific CTLs...
against the MHC I peptide OVA<sub>257–264</sub> (Fig. 3A) protected mice from MOG-induced EAE (Fig. 3C). These data suggest that the same semimature DC, which induce MOG-specific IL-10-producing CD4 (regulatory) T cells triggers simultaneously cytotoxic effector T cells, which kill targets (Fig. 3A) in absence of IFN-γ production. The latter were not inhibited by bystander regulatory T cells triggered most likely in their vicinity, because efficient cytolitic activity was induced also by double-, and triple-loaded semimature DC (Fig. 3B).

Taken together, these data suggest that the tolerizing capacity of semimature DC is restricted to Ag-specific CD4 T cells, but ineffective to suppress TCR transgenic (Fig. 2) as well as polyclonal CD8 T cells (Fig. 3) specific for OVA.

Discussion

In vivo counterparts to the in vitro-generated TNF-DC used in this study could be DC in the lymphatics, which migrate from non-lymphoid organs to peripheral lymph nodes, transporting apoptotic cells (26) or tissue (self-)Ag (8, 9, 27). In the lymph node and spleen, these migrated DC are crucial to induce peripheral tolerance (2, 28, 29). The semimature stage of these “steady-state” DC was revealed to be dependent on IL-10-producing regulatory T cells (14), a mechanism that has been demonstrated to operate also by double- and triple-loaded semimature DC (Fig. 3B).

Therefore, we investigated the tolerizing capacity of semimature DC to CD4 T cells specific for nonself Ag and CD8<sup>+</sup> T cells in addition to the described MOG-self Ag specific CD4 T cell response (14). We show that semimature DC induce a similar IL-10-biased cytokine pattern in foreign Ag (OVA)-specific CD4 T cells as observed for self-Ag-specific MOG T cells (Fig. 1).

When adoptively transferred transgenic OT-I or endogenous polyclonal CD8<sup>+</sup> T cells were exposed to MHC I specific peptide-loaded semimature DC in vivo, T cell expansion (Fig. 2) as well as MOG35–55 peptide induce MOG35–55-specific tolerance and protect C57BL/6 mice from MOG35–55-induced EAE (Ref. 14 and Fig. 3C). As experiments with semimature DC from IL-10<sup>−/−</sup> mice showed, DC do not have to produce IL-10 themselves to exert tolerogenic capacity (14). This is in contrast to IL-10-producing DC protecting from EAE (32, 33) or inducing mucosal tolerance (11) in other studies. Similar to immature human DC (34, 35) the mechanism of MOG-tolerance induction by semimature DC was revealed to be dependent on IL-10-producing regulatory T cells (14), a mechanism that has been demonstrated to act also through bystander suppression (36, 37).

In vitro-cultured TNF-α-treated semimature DC loaded with MOG<sub>35–55</sub> peptide induce MOG<sub>35–55</sub>specific tolerance and protect C57BL/6 mice from MOG<sub>35–55</sub>-induced EAE (Ref. 14 and Fig. 3C). As experiments with semimature DC from IL-10<sup>−/−</sup> mice showed, DC do not have to produce IL-10 themselves to exert tolerogenic capacity (14). This is in contrast to IL-10-producing DC protecting from EAE (32, 33) or inducing mucosal tolerance (11) in other studies. Similar to immature human DC (34, 35) the mechanism of MOG-tolerance induction by semimature DC was revealed to be dependent on IL-10-producing regulatory T cells (14), a mechanism that has been demonstrated to act also through bystander suppression (36, 37).

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When adoptively transferred transgenic OT-I or endogenous polyclonal CD8<sup>+</sup> T cells were exposed to MHC I specific peptide-loaded semimature DC in vivo, T cell expansion (Fig. 2) as well as...
FIGURE 3. Semimature DC simultaneously tolerize MOG-specific CD4⁺ T cells and activate OVA-specific CD8⁺ T cells. C57BL/6 mice were immunized on days −6, −3, and 0 with mature (A, filled bars) or semimature DC (A, hatched bars), loaded with the peptides indicated below, or no DC (A, open bars). On day 8 after the last immunization, four mice of each group were injected with a 1:1 mixture of CFSE<sup>high</sup> labeled unloaded spleen cells and CFSE<sup>low</sup> labeled spleen cells loaded with the same peptide combinations. After an additional 20 h, mice were sacrificed and spleen cells were analyzed for CFSE-positive cells by flow cytometry (“in vivo killer assay”). A representative example from a FACS-analysis of nonimmunized (left panel) and immunized (right panel) animals from such a killer assay, gated on CFSE<sup>+</sup> spleen cells is shown (A, upper panel). The FACS results are displayed as percent specific lysis (A, lower panel). The specific lysis was calculated as described in Materials and Methods. B, On day 3 postimmunization, spleen cells of another four mice from each group were restimulated with the respective peptides in vitro as shown for OVA<sub>257-264</sub>. Ninety-six hours later supernatants were taken and analyzed by ELISA for IFN-γ (B, left) and IL-10 (B, right) production. Symbols represent data derived from single mice. C, Another four to six mice from each group, which received MOG-loaded DC were used to induce EAE on day 3 after the last immunization. Animals were observed for paralysis and mean disease scores were determined as described in Materials and Methods. C, The kinetic of EAE development after immunization with either MOG<sub>35-55</sub>-loaded (left panel) or MOG<sub>35-55</sub> + OVA<sub>257-264</sub>-pulsed (right panel) differently matured DC is shown.
one could speculate that a reason for this observed cytotoxic activity could be the relatively low threshold signals needed to trigger CTL-activity: one or few specific TCR/peptide-MHC interactions are necessary to induce the cytolytic machinery (38, 39) and even partially activated CD8 T cells can gain cytolitic activity (40, 41). In earlier studies the phenomenon of cytotoxic activity in absence of cytokine production has been called “split energy” (42, 43). Taken together, “CTL” induced by IL-12 - TNF-DC might be severely impaired in their tumor- (44) and virus-clearing (45) efficiencies, but are definitely not tolerated.

Overall our results suggest that one DC can exert different functions on CD4 and CD8 T cells simultaneously: induction of CD4 T cell tolerance as well as CD8 T cell immunity. However, it remains an open question, if such an artificially enforced experimental situation of a double-peptide-loaded semimature DC is at all existing in vivo. A potential restriction for such a scenario could be the intrinsically different Ag uptake, processing, and presentation capacities of distinct DC-subsets; i.e., injected soluble OVA has been shown to be taken up by splenic DC, which after isolation, markedly differed in their capacity to present the processed OVA. Although the CD8α- DC predominately cross-presented OVA to CD8 T cells but showed little stimulation of CD4 T cells, the contrary was observed for the CD8α- DC subsets which readily presented OVA in an MHC II-restricted fashion but poorly on MHC I molecules (46).

However, other examples for a segregation of function within one APC have been published before. It was shown that DC co-pulsed with microbial and helminth Ag were able to prime Th1 responses for the microbial Ag as well as Th2 responses for the helminth Ag (47). Therefore, there is increasing evidence for differential handling of different Ag within the same APC. As a consequence, subsequent induction of qualitatively different immune responses by one and the same DC could appear.

Specifically relevant for the question of maintenance of tolerance to apoptotic self-material were recent findings demonstrating that apoptotic (self-) material and bacterial Ag are handled by discrete intracellular phagosomal maturation and processing pathways in APC, depending on their respective TLR signaling (48). Such a signaling by bacterial material induced phagocytosis and processing pathways, which were independently regulated from constitutive pathways for apoptotic material (48). It seems an attractive hypothesis that DC are equipped with endogenous control mechanisms, allowing them to integrate processing and presentation requirements for different Ags to avoid in vivo situations like the one induced by unphysiological external peptide loading in our study.

Although the physiological occurrence of such a simultaneous induction of tolerance and immunity in vivo seems unlikely, our findings have implications for in vitro-loaded DC as they are currently used for human cancer immunotherapy. When patient-derived DC are loaded with peptides on MHC I and/or II molecules but are improperly matured, the possibility of simultaneous CD4 tolerance and only partial CD8 immunity should be taken into consideration. In addition, these data indicate that CD4 and CD8 T cells have different activation requirements from the side of the APC. Although the semimature state of the presenting DC is suboptimal and therefore still tolerogenic for CD4 T cells, the co-stimulatory and cytokine equipment is sufficient to induce CTL activity, however, with reduced/absent IFN-γ production.

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Disclosures

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References


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