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Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1 on Murine Dendritic Cells Is a Potent Regulator of T Cell Stimulation

Robert Kammerer,* Detlef Stober,∗ Bernhard B. Singer, † Björn Öbrink, † and Jörg Reimann‡

Dendritic cells (DC) are important APCs that play a key role in the induction of an immune response. The signaling molecules that govern early events in DC activation are not well understood. We therefore investigated whether DC express carcinoembryonic Ag-related cell adhesion molecule 1 (CEACAM1, also known as BGP or CD66a), a well-characterized signal-regulating cell-cell adhesion molecule that is expressed on granulocytes, monocytes, and activated T cells and B cells. We found that murine DC express in vitro as well as in vivo both major isoforms of CEACAM1, CEACAM1-L (having a long cytoplasmic domain with immunoreceptor tyrosine-based inhibitory motifs) and CEACAM1-S (having a short cytoplasmic domain lacking phosphorylatable tyrosine residues). Ligation of surface-expressed CEACAM1 on DC with the specific mAb AgB10 triggered release of the chemokines macrophage inflammatory protein 1α, macrophage inflammatory protein 2, and monocye chemotactic protein 1 and induced migration of granulocytes, monocytes, T cells, and immature DC. Furthermore, the surface expression of the costimulatory molecules CD40, CD54, CD80, and CD86 was increased, indicating that CEACAM1-induced signaling regulates early maturation and activation of dendritic cells. In addition, signaling via CEACAM1 induced release of the cytokines IL-6, IL-12 p40, and IL-12 p70 and facilitated priming of naive MHC II-restricted CD4+ T cells with a Th1-like effector phenotype. Hence, our results show that CEACAM1 is a signal-transducing receptor that can regulate early maturation and activation of DC, thereby facilitating priming and polarization of T cell responses. The Journal of Immunology, 2001, 166: 6537–6544.

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Dendritic cells (DC) are the most potent APCs that can induce T cell responses (reviewed in Refs. 1–3). Immature, tissue-resident DC capture Ag and respond to other, not yet well-defined, signals derived from either the pathogen (e.g., LPS, bacterial DNA, viral double-stranded RNA) or from tissue lesions induced by the pathogen (e.g., stress proteins), before they develop into competent DC. To achieve this, they migrate to regional lymph nodes where they differentiate into presentation-competent DC. Hence, DC prime naive T cells remote from the site of initial Ag contact (4, 5). In the maturing process leading to presentation-competent cells, several signaling events triggered by soluble ligands as well as specific cell-cell interactions play a crucial role. An important theme in cell signaling is signal regulation by costimulation and coinhibition. In the immune system, a large number of both coinhibitory and costimulatory receptors are known, many of which belong to the Ig superfamily. Several of these receptors have immunoreceptor tyrosine-based activation motifs or immunoreceptor tyrosine-based inhibitory motifs (ITIM) in their cytoplasmic domains and operate by recruiting and activating SH2 domain-containing protein tyrosine kinases and protein tyrosine phosphatases. Among the ITIM-containing receptors signal-regulatory proteins and killer cell-inhibitory receptors are well known. Carcinoembryonic Ag-related cell adhesion molecule 1 (CEACAM1), also known as CD66a, BGP, or C-CAM, is an ITIM-containing Ig superfamily receptor abundantly expressed on the cell surface. CEACAM1 is the receptor for a variety of microorganisms. Because it is involved in both cell-cell communication and pathogen-host interactions, we analyzed its putative expression and functional role in DC.

CEACAM1 is abundantly expressed in epithelia, vessel endothelia, granulocytes, macrophages, T cells, B cells, NK cells, and platelets (6–11). It can mediate intercellular adhesion via homophilic binding (12–14). Work in many laboratories has demonstrated that CEACAM1 has important regulatory functions in cell proliferation, angiogenesis, apoptosis, immune responses, T cell cytotoxicity, differentiation, and polarization and lumen formation of epithelial cells (15–20). It is down-regulated in many types of cancer (21, 22). CEACAM1-dependent signals can inhibit tumor growth in vivo (23). CEACAM1 can influence and regulate signal transduction. It is a molecular system composed of several splice isoforms that can influence cell signaling in both positive and negative ways. CEACAM1 probably operates by recruiting and activating either src-family kinases, or protein tyrosine phosphatases Src homology phosphatases 1 and 2 to the same tyrosine-phosphorylated ITIM motifs in the cytoplasmic domain of the isoform CEACAM1-L (24–26). The two major isoforms are CEACAM1-L and CEACAM1-S, which differ in their cytoplasmic domains. The cytoplasmic domain of CEACAM1-L consists of 73 amino acids...
and has 2 ITIM motifs with tyrosine residues that can be phosphorylated. CEACAM1-S has a cytoplasmic domain of only 10 amino acids and lacks ITIM motifs (27). CEACAM1-L and CEACAM1-S are coexpressed at different ratios in different cell types and in different functional states of cells of one lineage. Both isoforms can dimerize, and there is evidence that the S isoform can regulate the signaling activity of the L isoform (23, 28, 29).

The only well-characterized physiological ligand interaction of CEACAM1 is the homophilic binding to itself; this may represent an important signal input via cell-cell interactions (29). Several pathogenic microorganisms bind to CEACAM1 as their host cell receptor. Murine CEACAM1 is the major receptor for mouse hepatitis viruses (MHV) (30, 31) and human CEACAM1 binds Escherichia coli, Salmonella typhimurium (32), Neisseria gonorrhoeae (33, 34), Neisseria meningitidis (35), and Haemophilus influenzae (36). Both the physiological cell-cell interactions mediated by CEACAM1 and its binding to pathogens may have an influence on the activation of the immune system.

In this investigation, we show that both immature and mature murine (myeloid and lymphoid) DC express CEACAM1 on the surface in vivo and in vitro. Specific binding of a mAb to surface CEACAM1 expressed by immature DC stimulates their maturation including the release of cytokines and chemokines. We demonstrate that CEACAM1 facilitates priming of naive CD4⁺ T cells by Ag-bearing DC in vitro and favors a Th1-type differentiation. These data show that CEACAM1 takes part in the signaling scenario that leads to the induction of Th1 immune responses.

Materials and Methods

Mice

BALB/c (H-2b) and C57BL/6 (H-2b) mice were obtained from Bomboltgard (Ry, Denmark) and kept under standard pathogen-free conditions in the animal colony of Ulm University (Ulm, Germany). BALB/c-derived D011.10 TC-transgenic mice were kindly provided by D. Loh (Roche, Horbony, Ontario, Canada). Furthermore we used the rat anti-mouse DEC205 (NLD-145C) mAb from Biozol (Eching, Germany) and the FITC-conjugated IgG1 mAb R3-34, PE-conjugated IgG1 mAb R3-34, and streptavidin Red 670 (Life Technologies, Eggenstein, Germany).

Cell culture and mAb purification

The mature B cell line L10 and the hybridomas producing the mAbs Decma-1 (38) and AgB10 (39) were cultured in a humidified atmosphere with 5% CO₂ at 37°C in RPMI supplemented with 10% heat-inactivated FCS, 2 mM L-glutamine, 100 IU/ml penicillin, and 100 μg/ml streptomycin. The supernatants were collected, and the Abs were affinity-purified on a HiTrap protein G column according to the manufacturer's instructions (Amersham Pharmacia Biotech, Uppsala, Sweden). Endotoxin content in the Ab preparations was <0.03 endotoxin U/ml as determined using the Endosafe Gel-Clot Assay (Charles River, Sulzfeld, Germany).

Cytokines and cytokine detection by ELISA

The following recombinant mouse cytokines were obtained from Pepro-Tech: IL-4, IL-6, IL-10, IL-18, monocyte chemotactant protein 1 (MCP-1), macrophage inflammatory protein 2 (MIP-2), TNF-α, GM-CSF, and IL-12 p40 and IL-12 p70 were purchased from R&D Systems (Wiesbaden, Germany). IFN-γ and IL-12 p70 were obtained from PharMingen.

Cytokines released into culture supernatants were detected by a conventional double-sandwich ELISA. For detection and capture, the following mAbs (from PharMingen) were used: mAb R4-6A2 and biotinylated mAb XM1G2.2 were used for IFN-γ; mAb 2H5 and biotinylated mAb 4E2/MCP1 were used for MCP-1; mAb C15.6 or mAb RedF2G297-289 were used as coating Abs for IL-12 p40 and IL-12 p70 ELISA, respectively; mAb C17.8 was used for detection in both cases. Extinction was analyzed at 405 nm (in a Tecan microplate ELISA reader, Crailsheim, Germany) using EasyWin software (TECAN). The detection limits of the cytokine ELISAs were: 0.2 pg/ml for IL-4; 1 pg/ml for MIP-2; 10 pg/ml for IL-12p40, MIP-1α, and MCP-1; 20 pg/ml for IL-12 p70 and IFN-γ; and 60 pg/ml for IL-18.

Chemotaxis assay

Chemotaxis was assayed by an in vitro two-chamber migration assay followed by FCM. Cells in 100 μl complete medium were added to the upper chamber of Falcon Transwells (6.5-mm diameter, 3-μm pore size, poly-ethylen-terephthalat membrane; Becton Dickinson, Heidelberg, Germany), and chemotactic substances were added to the lower chamber to form a chemotactic gradient. A total of 1 × 10⁵ cells were incubated for 4 h in the upper chamber of the Transwell. After cells were collected in suspension, 0.5 ml 5 mM EDTA was added to the lower chamber for 15 min at 37°C to detach adherent cells such as monocytes and granulocytes from the bottom of the wells. Detached cells were combined with the previously collected suspension cells for cell counting. Migrated granulocytes, monocytes, and lymphocytes were counted by FCM by gating on appropriate populations of cells using forward scatter and side scatter channels. CD4⁺ and CD8⁺ T cells were detected with FITC- or PE-conjugated mAbs to CD4 and CD8. Each chemotaxis experiment was performed in duplicate. The results from three independent experiments were pooled. For statistical analyses, nested ANOVA was performed to compare the mean counts of cells migrating toward supernatants of stimulated vs unstimulated DC. When ANOVA detected a statistically significant difference in mean counts, the Tukey method of multiple comparisons was applied. A p value of <0.05 was considered to be statistically significant for all analyses.

Detection of CEACAM1 splice variants by RT-PCR

Total mRNA was isolated from 5 × 10⁵ cells using the RNeasy kit (Qiagen, Hilden, Germany). The RNA yield was quantified photometrically and 1 μg mRNA was used for cDNA synthesis by reverse transcription using

FCM analyses

Cells were suspended in PBS, 0.3% w/v BSA supplemented with 0.1% w/v sodium azide. Unspecific binding of Abs to FcR was blocked by preincubating the cells with the anti-CD16/CD32 mAb 2.4G2 (1 μg mAb/10⁶ cells; PharMingen, Hamburg, Germany). Cells were incubated with 0.5 μg/10⁶ cells of the relevant mAb for 30 min at 4°C, washed twice, and subsequently incubated with a biotin-streptavidin reagent for 15 min at 4°C. Cells were washed twice and analyzed on a FACSScan (Becton Dickinson, Mountain View, CA). Dead cells were excluded by propidium iodide staining. The following reagents and mAbs from PharMingen were used: PE-conjugated anti-I-Α/Β-E: E; PE-conjugated anti-I-Α, biotinylated anti-H-2D:α; PE-conjugated anti-CD80 (B7-1); PE-conjugated anti-CD40; FITC-conjugated anti-CD86 (B7-2); and PE-conjugated anti-CD1c. FITC-conjugated anti-CD4 (M4-80) and PE-conjugated anti-CD8 were purchased from Cedarlane (Caledon, Ontario, Canada). We furthermore used the rat anti-mouse DEC205 (NLD-145C) mAb from Biozol (Eching, Germany) and the FITC-conjugated IgG1 mAb R3-34, PE-conjugated IgG1 mAb R3-34, and streptavidin Red 670 (Life Technologies, Eggenstein, Germany).

Generation of myeloid DC (mDC) from murine bone marrow (BM)

The in vitro generation of mDC from murine bone marrow has been described (37). Briefly, bone marrow cells (BMC) obtained from femurs and tibiae were depleted of CD4⁺ and CD8⁺ T cells, B220⁺ B cells, and MHC class II⁺ maturing myeloid cells by MACS sorting following the manufacturer's instructions (Miltenyi Biotec, Bergisch Gladbach, Germany). These BMC were cultured at a density of 10⁶ cells/ml in UltraCulture medium (BioWhittaker, Verviers, Belgium) supplemented with 5 ng/ml GM-CSF, 30 ng/ml IL-4, and 10 ng/ml Flt3 ligand (FL) (Pepro-Tech, Rocky Hill, NJ), 2 mM glutamine, and antibiotics. BMC from C57BL/6 mice were cultured in serum-free medium; BMC from BALB/c mice required low FCS supplements (0.5% v/v) to the medium to maintain viability and support expansion of mDC. Cultures were incubated at 37°C in humidified air supplemented with 5% CO₂. On days 3 and 5, cells were fed by medium changes. On day 7 of culture, nonadherent cells were harvested; CD11c⁺ cells were purified by magnetic bead separation (Miltenyi Biotec) and re-plated in UltraCulture medium supplemented with GM-CSF, FL, L-glutamine, and antibiotics.

CD11c⁺ cells were analyzed by flow cytometry at day 8–10 of culture. DC harvested from day 8 cultures were seeded into 96-well round-bottom plates at 2 × 10⁵ cells/well in UltraCulture medium with GM-CSF, FCS, and antibiotics. These cultures were stimulated with the indicated cytokines and Abs. In some experiments, 6.6 × 10⁵ cells/well CD40 ligand (CD40L)-transfected J558L cells (or negative control nontransfected J558L cells) were added. After 48–72 h incubation, supernatants were harvested, and cytokine release was detected by ELISA.

Isolation and purification of CD4⁺ T cells

Single-spleen cell suspensions were passed through nylon wool columns. CD4⁺ T cells were selected from the nonadherent cell population by MACS. The purity of the isolated CD4⁺ T cell subset was >96% as determined by flow cytometry (FCM).
the Reverse Transcription System (Promega, Mannheim, Germany). The reverse transcription product was amplified by PCR for 25 cycles with *taq* polymerase (Qiagen). PCR conditions were 95°C for 1.5 min, annealing at 60°C (CEACAM1) and at 58°C (β-actin) for 1 min, extension at 72°C for 1.5 min, and final extension at 72°C for 15 min. The primers used were 5′-AGCGTCAGGAGGACACTCAA and 3′-AGAAGAAGGGGCT GAAGTTGGC, complementary to both sides of exon 7. Thus, an amplified fragment of 268 bp is expected from the short cytoplasmic isoform, and a fragment of 321 bp is expected from the long cytoplasmic isoform. A 569-bp fragment from the β-actin mRNA was amplified using the 5′-primer ATGGATGAGATATCGCT and the 3′-primer ATGGAGTAGTCTGTCAGGT. Ten microliters of each PCR product were analyzed by 1.5% agarose gel electrophoresis and visualized by ethidium bromide staining.

**Results**

**Expression of CEACAM1 by murine DC**

We generated CD11c<sup>+</sup> mDC from BM progenitors in cultures supplemented with GM-CSF and FL. mDC developed from C57BL/6-derived marrow progenitors in serum-free cultures; BALB/c-depleted with GM-CSF and FL. mDC developed from C57BL/6-supplemented medium (data not shown). CEACAM1 surface expression was seen in C57BL/6-derived DC growing in serum-free cultures, and in BALB/c-derived DC cultured in FCS-supplemented medium (data not shown). CEACAM1 surface expression was, however, not preferentially up-regulated in DC with a more mature phenotype, i.e., high surface expression of MHC-II, CD40, CD80, and CD86 molecules (Fig. 2). CEACAM1 is thus expressed on the surface of early DC developing in vitro from BM progenitors, is up-regulated to a limited extent on DC during their in vitro differentiation, but is not preferentially expressed by mature, presentation-competent mDC.

We tested whether surface expression of CEACAM1 by DC can be modulated by proinflammatory cytokines that induce DC maturation, i.e., TNF-α, IL-4, IFNs, or LPS. When DC were treated with these agents from day 7 to day 10 of culture, surface expression of MHC II and costimulator (CD40, CD54, CD80, and CD86) molecules was strikingly induced or up-regulated (data not shown). In contrast, the surface expression of CEACAM1 was not modulated (data not shown). Hence, CEACAM1 expression is not up-regulated by exogenous cytokines during maturation of DC.

**CEACAM1-dependent signaling of mDC triggers release of chemokines that attract granulocytes, monocytes, T cells, and DC**

Because early signaling in the immune system involves production and release of chemokines, we investigated the secretion of MIP-1α, MIP-2, and MCP-1 by DC stimulated by CEACAM1 ligation.
Fig. 3A). Signaling through CEACAM1 strikingly enhanced the low “spontaneous” MIP-1α and MIP-2 release by DC. Ligation of surface CEACAM1 was more potent in triggering release of these chemokines by DC than the other stimuli tested. It also enhanced the release of MCP-1 although to a lesser extend. Isotype-matched control mAb, mAb to E-cadherin (DC generated in the BMC cultures expressed the adhesion molecule E-cadherin on the cell surface), or heat-inactivated mAb AgB10 (to exclude a contaminating LPS effect) had no measurable effect on chemokine release by DC (Fig. 3A and data not shown). The chemokine response of DC to CEACAM1 ligation was rapidly inducible and showed a different kinetic for MIP-1α and MIP-2 (Fig. 3B).

Chemokines stimulate the migration of leukocytes. We analyzed cellular migration in a Boyden chamber assay. From nonfractionated spleen cell populations, supernatants conditioned by DC stimulated through CEACAM1 ligation attracted granulocytes and monocytes (Fig. 3C, a). From splenic T cell populations, the migration of both CD4+ and CD8+ T cells was enhanced 2-fold by supernatants from CEACAM1-stimulated DC (Fig. 3C, b). CEACAM1-stimulated DC also enhanced the migration of DC (Fig. 3C, c). Hence, CEACAM1-dependent signals of DC recruit myeloid and lymphoid cells into the immune response, most likely through increased chemokine release.

**Ligation of surface CEACAM1 on DC by mAb AgB10 induces maturation**

Purified CD11c+ DC harvested from day 7 BMC cultures were cultured for 2 days in serum-free GM-CSF/FL-supplemented medium with the mAb AgB10. Either isotype-matched control mAb or the mAb Decma-1 specific for murine E-cadherin was added to the medium in control cultures. The anti-CEACAM1 mAb AgB10 but neither the anti-E-cadherin mAb Decma-1 nor an isotype-matched control mAb up-regulated surface expression of CD40, CD54, CD80, and CD86 costimulator molecules by DC that was comparable with that induced by TNF-α treatment (Fig. 4). Induction of DC maturation may result either directly through CEACAM1 signaling or indirectly through cytokines/chemokines released by CEACAM1-triggered signals.
CEACAM1 Ab did not trigger release of TNF-α by DC (data not shown).

**Signaling through CEACAM1 triggers release of IL-6 and IL-12**

We tested whether mDC stimulated by mAb AgB10 release cytokines. Purified mDC from both mouse strains spontaneously released low amounts of IL-12 p40 (0.3–1.0 ng/10⁶ cells/ml), IL-12 p70 (20–60 pg/10⁶ cells/ml), and IL-18 but no IFN-γ or IL-6 into the supernatant during a 2- to 3-day incubation (Fig. 5 and data not shown). CEACAM1-mediated stimulation of DC strongly enhanced the release of IL-6, IL-12 p40, and IL-12 p70. Ligation of CEACAM1 was as effective as LPS in stimulating release of IL-6 by DC (Fig. 5A). CEACAM1-dependent signals were more efficient than TNF-α or LPS in triggering release of IL-12 p70 but less potent than CD40 ligation (Fig. 5A). Release of IL-18 or IFN-γ by DC was not induced by CEACAM1 ligation (data not shown). Treatment of DC with isotype-matched control mAb, the anti-E-cadherin mAb Decma-1, or heat-inactivated mAb AgB10 did not stimulate IL-6 or IL-12 release by DC (Fig. 5B and data not shown). We detected no synergy among CEACAM1-, CD40-, or TNF-α-dependent signals in stimulating the release of IL-6, IL-12, or IL-18 release by DC (Fig. 5C and data not shown).

**Stimulation of DC through CEACAM1 enhances their T cell-stimulatory function**

The secretion of IL-12 by DC in response to CEACAM1 suggests that these DC can efficiently prime Th1 T cell responses. To test this hypothesis, we cocultured naive splenic CD41 T cells from TCR-transgenic DO11.10 donor mice (40) for 5 days with OVA-pulsed DC. The OVA-pulsed DC were pretreated with either mAb AgB10 to signal through CEACAM1 or an isotype-matched control Ab. IL-4 and IFN-γ release by T cells was measured after 5 days of culture. As shown in Fig. 6, CEACAM1-stimulated, OVA-presenting DC stimulated IFN-γ release by specifically primed CD41 T cells. Release of IL-4 by in vitro-primed CD4+ T cell populations was strikingly reduced when these cells were cocultured with CEACAM1-stimulated, OVA-presenting DC. Hence,
DC activated through CEACAM1-dependent signals facilitate priming of Th1-like CD4+ T cell responses.

Discussion

We show that murine DC express two major splice isoforms of the signal-regulating cell adhesion molecule CEACAM1 and that CEACAM1-triggered signaling facilitates T cell priming. A combination of enhanced recruitment of responding and presenting cells enhanced Ag presentation as a result of increased MHC and costimulator molecule expression, and increased release of cytokines may be involved in facilitating the efficient priming and Th1-biased polarization of CD4+ T cell responses by DC stimulated by CEACAM1-mediated signals.

CEACAM1 is related to the inhibitory receptor family (IRF) because it contains ITIM motifs in the cytoplasmic domain similar to NK cell-inhibitory receptors or Ig-like transcript receptors (ILT). Identification of CEACAM1 expression on DC is important, because the only members of the IRF that have been described on murine DC thus far are the paired Ig-like receptors (PIR) (41). In contrast, human DC express several members of the IRF, namely IIT, leukocyte-associated Ig-like receptor, DC immunoreceptor, and signal-regulatory protein (42–45). Recent findings indicate that some of these molecules are involved in Ag uptake and presentation by human DC (46). To our knowledge, our work is the first to demonstrate that receptors of the IRF family transmit maturation-inducing signals to DC that facilitate Th cell priming.

Perturbation of DC-expressed CEACAM1 by Abs recognizing its extracellular domain induced chemokine secretion, particularly MIP-1α and MIP-2. Chemokine release associated with the development and activation of DC (47–55) facilitates recruitment of presenting, regulating, and responding myeloid and lymphoid cells into an immune response; e.g., MIP-1α attracts DC and MIP-2 recruits granulocytes to the site of inflammation (53). In agreement with these observations, we found that Ab-induced CEACAM1 signaling in DC triggered migration of granulocytes, monocytes, T cells, and DC toward the CEACAM1-stimulated DC. Thus, it appears that the early expression of CEACAM1 on immature DC facilitates the rapid recruitment of other cell subsets into an immune response around the nucleus of the emerging response, the DC. Interestingly, the pattern of chemokine release was unique for immune responses triggered by LPS or TNF-α. It could thus be speculated that pathogen-mediated signal input through CEACAM1 is an important priming event for T cell responses that work in concert with homophilic cell-cell interactions to regulate the CEACAM1 supramolecular organization.

On the basis of the present results and the arguments given above, we propose the following scenario for the role of CEACAM1 during an immune response. The first event would be the recognition of a pathogen that binds to DC via CEACAM1.

![Figure 6](http://www.jimmunol.org/DownloadedFrom/)
This would activate the DC, resulting in the secretion of chemokines, which would recruit cellular components of the innate immune system to the site of infection. In addition, this primary CEACAM1-mediated contact leads to maturation of the DC and their migration to lymphoid organs, where they interact with the adaptive immune system. At this stage, cells expressing CEACAM1, e.g., T cells and B cells, may provide further signal inputs through CEACAM1 into DC signaling. This, in combination with other signals provided by cell-cell contacts (e.g., CD40-CD40L) then stimulate cytokine release by DC, which regulate the Th1/Th2 balance of the response.

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