Decreased Antigen Presentation by Dendritic Cells in Patients with Breast Cancer

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ABSTRACT

We evaluated T-cell responses to mitogens and to defined antigens in breast cancer patients. Significant defects in responses to tetanus toxoid and influenza virus were observed in patients with advanced-stage breast cancer. To define whether these defects were associated with a defect in antigen presentation [dendritic cells (DCs)] or effector function (T cells), these cells were studied separately. Purified DCs from 32 patients with breast cancer demonstrated a significantly decreased ability to stimulate control allogeneic T cells, but stimulation of patient T cells with either control allogeneic DCs or immobilized anti-CD3 antibody resulted in normal T-cell responses, even in patients with stage IV tumors. These data suggest that reduced DC function could be one of the major causes of the observed defect in cellular immunity in patients with advanced breast cancer. We then tested whether stem cells from these patients could give rise to functional DCs after in vitro growth with granulocyte/macrophage colony-stimulating factor and interleukin 4. Normal levels of control allogeneic and tetanus toxoid-dependent T-cell proliferation were observed when DCs obtained from precursors were used as stimulators. Those cells also induced substantially higher levels of influenza virus-specific CTL responses than mature DCs from the peripheral blood of these patients, although responses did not quite reach control values. Thus, defective T-cell function in patients with advanced breast cancer can be overcome by stimulation with DCs generated from precursors, suggesting that these cells may better serve as allogeneic antigen carriers for cancer immunotherapy than mature peripheral blood DCs.

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INTRODUCTION

Defective function of the host immune system is thought to be a major mechanism by which tumors escape from immune control. Numerous studies have described defective function of T lymphocytes, including tumor-infiltrating cells, in tumor-bearing hosts (reviewed in Ref. 1). The precise mechanism of this dysfunction is not known, but it has been reported that it can be reversed if sufficient stimulation with antigen-presenting cells and support with cytokines (such as IL-2) is provided (2-4). Because host professional APCs are one of the most important elements in the induction of specific antitumor immune responses (5, 6), APC could be partly responsible for the observed defective immune responses in tumor-bearing hosts. This group of cells includes dendritic cells, macrophage/moноocytes, and B cells. DCs are thought to be the most potent APCs, and only these cells are capable of inducing primary immune responses and, therefore, are actively being studied for use as vehicles for delivery of tumor-specific antigens in both animal experimental systems and in patients with cancer (7-9). In our previous study, we showed that the nonresponsiveness of T cells from tumor-bearing mice was reversed after stimulation with antigen-pulsed control DCs, even without additional cytokine support (4). It is not known, however, whether DCs obtained from patients with cancer have sufficient functional activity for use as autologous antigen carriers. In particular, the ability of these cells to present soluble antigens and induce cytotoxic immune responses in patients with cancer is not clear. The clarification of this question is important not only for understanding the mechanisms of tumor progression but also for the development of effective cancer immunotherapeutic strategies.

Previously, we have shown that defects in T-cell function in tumor-bearing mice could be reversed by stimulation with DCs generated from stem cells from the bone marrow of tumor-bearing mice (10). Here we investigated the function of DCs from patients with breast cancer and found that these cells had a considerably lower than normal ability to stimulate allogeneic T cells as well as to present soluble antigen to autologous T cells. To test the hypothesis that sufficient antigen presentation may reverse observed defects in T-cell function, we generated DCs from peripheral blood precursors and showed that those cells were able to elicit an almost normal level of immune response.

The abbreviations used are: IL, interleukin; APC, antigen-presenting cell; DC, dendritic cell; CCM, complete culture medium; GM-CSF, granulocyte/macrophage colony-stimulating factor; NK, natural killer; FLU, influenza virus; TT, tetanus toxoid; MLR, mixed leukocyte reaction.
PATIENTS AND METHODS

Patients. Thirty-two patients aged 33–69 years with histologically confirmed breast cancer were enrolled into the study. All patients were newly diagnosed with no prior therapy. Staging was performed in accordance with American Joint Committee on Cancer criteria. Four patients had stage I tumors, 10 had stage II, 13 had stage III, and 5 had stage IV. Fourteen healthy volunteers were used as controls. Informed consent was obtained from all individuals.

Reagents. CCM included RPMI 1640 (Life Technologies, Inc., Gaithersburg, MD) supplemented with 10% FCS and antibiotics. For the generation of DCs from progenitors, medium was additionally supplemented with 5 x 10^{-5} 2-mercaptoethanol. Ficoll-paque was purchased from Pharmacia Biotech, Inc. (Uppsala, Sweden). GM-CSF and IL-4 were obtained from R&D Systems (Minneapolis, MN). Influenza virus strain PR8 (A/Puerto Rico/8/34) was obtained from the American Type Culture Collection (Rockville, MD) and was propagated in the Laboratory of Virology at the University of Texas Southwestern Medical Center (Dr. J. Luby). Anti-HLA DR, CD3, CD14, and CD19 antibodies were purchased from Sigma Chemical Co. (St. Louis, MO). Anti-HLA ABC, B7-1, B7-2, and CD56 antibodies were purchased from PharMingen (San Diego, CA). Anti-CD34 antibody was obtained from Becton Dickinson (Mountain View, CA). Purified anti-CD3 antibody (64.1 hybridoma cell lines produce an IgG2a monoclonal antibody) was a generous gift from The Cancer Immunobiology Center, University of Texas-Southwestern (Dr. E. S. Vitetta). Goat antimouse IgG antibody conjugated with magnetic beads was purchased from Dynal (Lake Success, NY).

Cell Isolation. DCs and T cells were isolated from the peripheral blood of patients or control donors as described (11) with minor modifications. Briefly, mononuclear cells obtained after centrifugation of peripheral blood over Ficoll-paque gradient were incubated with neuraminidase-treated sheep red cells (R). Cells that adhered to the red cells (R⁺) and those that did not (R⁻) were separated on Ficoll-paque gradient. R⁻ cells were then incubated for 18 h in CCM at 37°C, followed by incubation of nonadherent cells for 60 min on Petri dishes coated with human γ-globulin to remove remaining FcR⁻ monocytes. Finally, cells were centrifuged over a metrizamide gradient (14.5 g of metrizamide; Neyegaard, Oslo, Norway, in 100 ml of culture medium). Cells collected from the interface were 50–70% DCs, as estimated morphologically or by flow cytometry after labeling a mixture of monoclonal antibodies (CD3, CD14, CD19, CD56, and HLA-DR). Contaminants were B cells, NK cells, and few T cells. R⁺ cells were further processed to obtain an enriched T-cell fraction by overnight incubation in CCM at 37°C, followed by osmotic lysis of the red cells. Nonadherent cells were >90% T cells, as estimated by flow cytometry. In several experiments, the DC fraction was additionally purified using a magnetic bead separation technique. Briefly, the DC fraction isolated as described above was treated at 4°C with a cocktail of monoclonal antibodies: anti-CD3, anti-CD19, anti-CD14, and anti-CD57/HNK. After a 30-min incubation, cells were washed and labeled for 30 min with goat antimouse IgG antibody conjugated to magnetic beads (Dynal), followed by washing and magnetic separation. Unlabeled cells were more than 95% DCs, as estimated by flow cytometry.

DCs were generated from progenitors in peripheral blood as described previously (12). Briefly, peripheral blood mononuclear cells were incubated for 2 h in six-well plates, nonadherent cells were removed, and adherent cells were incubated with GM-CSF (5 ng/ml) and IL-4 (5 ng/ml) for 6–7 days. After that time, cells were collected, washed, and analyzed. The purity of the DCs was more than 70% with >95% viability.

MLR. The ability of DCs to stimulate allogeneic T cells was tested in MLRs. To minimize the effect of differences in HLA between individuals on allogeneic T-cell proliferation, DCs from each of 14 normal controls were tested independently against allogeneic T cells obtained from another three control individuals, and the pairs giving maximal responses were used. Cells from the patients were similarly tested against the panel of normals, and those giving maximal responses were used. For each experiment, T cells from patients were tested against DCs from three control volunteers. DCs and T cells were cultured at different ratios for 5 days in 96-well plates. Eighteen h prior to harvesting the cells, 1 μCi of [3H]thymidine was added to each well. [3H]Thymidine uptake was counted in a liquid scintillation counter (Beckman, Palo Alto, CA).

Tetanus Toxoid-specific T-Cell Proliferation. DCs were cultured with autologous T cells in the presence of 0.5 μg/ml tetanus toxoid (this concentration was selected after preliminary testing). [3H]Thymidine uptake was measured 5 days later. The background level of T-cell proliferation stimulated by autologous DCs was subtracted from all experimental values.

FLU-specific CTL Responses. DCs were cultured in serum-free medium with influenza virus strain PR8 (A/Puerto Rico/8/34) for 2 h, washed, and cultured with autologous T cells at a ratio of 1:5 in 24-well plates (Costar, Cambridge, MA). Seven days later, the cells were harvested and distributed at various dilutions to 96-well plates. CTL activity was measured against FLU-infected and uninfected 51Cr-labeled autologous phytohemagglutinin blasts in a standard 6-h assay. At the termination of the assay, 51Cr release into the supernatants was measured using absorption cartridges (Skatron Instruments, Inc., Sterling, VA) and counted in a gamma counter. The percentage of specific 51Cr release was calculated from the following formula:

% specific 51Cr release =

\[
\text{Release by CTL - spontaneous release} \times 100
\]

Spontaneous release was equal to or less than 25% of the total release.

RESULTS

Defective Responses to Mitogenic and Antigenic Stimulation in Patients with Breast Cancer. We first examined antigen- and mitogen-driven T-cell proliferation in patients with breast cancer. Because this required the presence of APCs, DCs and T cells were isolated from the peripheral blood of breast cancer patients and mixed at different concentrations with var-
ious stimulators. Interestingly, patients with advanced breast cancer demonstrated a substantially reduced yield and purity of DCs, as assessed by flow cytometry and light microscopy. The proportion of DCs in the fractions isolated from patients with stages I and II was the same as that from control individuals (55–70%), but samples from patients with stages III and IV tumors yielded a substantially lower DC purity than control (25–35%). Because of these differences in the purity of DCs, DC numbers were always carefully adjusted to equal concentrations before any assays were performed. Significant decreases in the ability of T cells to respond to ConA stimulation were seen in patients with progressively advanced stages of breast cancer (Fig. 1A). This was accompanied by a dramatic reduction in the response to the soluble antigen TT (Fig. 1B). Defects in TT-dependent T-cell proliferation were seen in patients at earlier stages (stage II) than the defects in responses to mitogens (stage III; Fig. 1B). The majority of patients with stage II breast cancer demonstrated normal or only slightly decreased levels of influenza virus-specific CTL responses. However, a significant decrease in this response was observed in patients with more advanced disease (Fig. 2).

Defective Function of DCs but not T Cells in Breast Cancer Patients. These data are consistent with defective function of either T cells or APCs. To characterize the mecha-

Fig. 1 Function of DCs and T cells in patients with breast cancer. A, T-cell responses are decreased in response to ConA but maintained for anti-CD3 stimulation. For ConA stimulation, DCs and T cells were isolated as described in “Patients and Methods” and cultured together at a ratio of 1:50 (2 × 10^3 DCs and 10^3 T cells) in the presence of 10 μg/ml ConA. Averages (bars, SE) of [H] uptake on day 3 are shown. □, statistically significant differences from control (P < 0.05). For anti-CD3 stimulation, 96-well plates were coated with 5 μg/ml anti-CD3 antibody and washed; then 10^3 T cells were added to each well. [H] uptake in triplicates was measured on day 3. □, control (n = 11); □, stage 1–2 (n = 5); □, stage 3–4 (n = 4).

B, TT-stimulated T-cell proliferation is decreased in patients with breast cancer. DCs and T cells were isolated as described in “Patients and Methods” and mixed at different ratios (from 1:20 to 1:160). TT-driven T-cell proliferation was tested as described in “Patients and Methods.” Averages (bars, SE) of [H]thymidine uptake at 1:40 DC:T cell ratio are shown. Similar patterns of the results were found for all DC:T cell ratios. □, statistically significant differences from control (P < 0.05).

C, DCs from breast cancer patients show decreased stimulation of control allogeneic T cells. Patients’ DCs and donors’ T cells were isolated, and allogeneic MLR was performed as described in “Patients and Methods.” The means (bars, SE) of [H]thymidine uptake at 1:40 DC:T cell ratio are shown. Similar patterns of the results were found for all DC:T cell ratios. □, statistically significant differences from control (P < 0.05). D, DCs from control individuals effectively stimulate breast cancer patients’ T cells. Experimental protocol was as described in “Patients and Methods.” Means (bars, SE) of [H]thymidine uptake at a 1:40 DC:T cell ratio are shown. Similar patterns of the results were found for all DC:T cell ratios.
nism of the observed effects, we purified DCs and T cells from patients and controls and tested the ability of both patient and control DCs to stimulate allogeneic T cells. As shown in Fig. 1C, a reduced activity of DCs (not statistically significant, \( P = 0.07 \)) was observed in patients with stages I and II breast cancer. A significant decrease in stimulation was observed in patients in stages III and IV. In contrast, no differences were found in the isolated T cells of these patients, for stimulation of patient T cells with either control allogeneic DCs or immobilized anti-CD3 antibody resulted in normal T-cell proliferation, even in patients in stage IV (Fig. 1A and D). These data indicate that defects in the functional activity of DCs could be one of the major reasons for the observed decreased cellular immune responses in patients with advanced breast cancer. Because the purity of the DC preparation obtained from patients with advanced disease was lower than that from control individuals, there is always the possibility that described effects could be due to contamination of DC fractions by other cells. To evaluate this, several experiments were performed using highly purified DCs. In these experiments, DCs were additionally purified using magnetic bead separation, and their ability to stimulate control allogeneic T cells was compared with that of the partially purified DCs described previously. Even the highly purified DCs isolated from patients with stage III tumors showed the same low level of activity as those from partially purified fractions (Fig. 3).

In the next group of experiments, we tested the hypothesis that changes in the level of expression of molecules on the surface of DCs might contribute to their defective function. DCs were isolated from four control donors and five patients with stage III breast cancer. Cells were double labeled with a cocktail of monoclonal antibodies against T, B, and NK cells and monocytes and with antibodies against MHC class I, class II, and B7 molecules. Only DC ("cocktail-negative" cells) were analyzed. As shown in Fig. 4, no differences were observed in the level of expression of MHC class I molecules (HLA A, B, and C), whereas a substantial decrease in the expression of MHC class II (HLA DR and HLA DQ) was seen. A decline in the expression of B7-1 and B7-2 was also notable, albeit less profound than that of MHC class II molecules.

**Function of DCs Generated from Progenitors.** The above data demonstrate serious defects in the function of peripheral blood DCs in patients with advanced breast cancer. We, therefore, investigated the mechanisms of this dysfunction. Previously, we have shown that soluble factors released by animal and human tumor cells affected the maturation of DCs but did not impair the function of mature DCs from peripheral blood (4). We, therefore, hypothesized that DCs generated *in vitro* from precursors from advanced cancer patients, without the influence of any tumor-produced factors, could be functionally intact. To test this hypothesis, peripheral blood from patients with stage III and control donors was processed to obtain T cells and DCs as described before. In parallel, DCs were generated from precursors using GM-CSF and IL-4. Generation of DCs from precursors requires at least 7 days of *in vitro* culture. Mature DCs isolated from peripheral blood are optimally functional on the day after harvest. To use autologous T cells and to standardize experimental conditions, T cells from each patient were cryopreserved in aliquots immediately after isolation and thawed before testing. DCs generated from precursors showed high levels of expression of MHC class II and costimulatory molecules consistent with phenotype of relatively mature DCs.
**DISCUSSION**

The effective function of APCs is an integral part of immune responses in general, and antitumor immune responses in particular. Defects in antigen presentation would make the development of specific immune responses almost impossible. However, until now it was not clear whether the function of APCs was normal or suppressed in tumor-bearing hosts, and if suppressed, whether methods could be developed to restore function. The few reports in this field are controversial and incomplete. It has been shown, for example, that a subset of I-A$^+$ epidermal APCs may be capable of inducing tolerance to tumor antigens and that activated macrophages might induce structural abnormalities of the T-cell receptor/CD3 complex (13, 14). Zou et al. (15) have reported normal and even increased function of APCs (mostly macrophages) in tumor-bearing mice (15). However, defective function of macrophages in patients with cancer has also been described in several reports (16, 17).

Dendritic cells are the most potent APCs; therefore, we focused on investigation of their ability to present antigens and

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**Fig. 4** Expression of MHC class I and class II and costimulatory molecules on the surface of DCs isolated from control individuals and patients with breast cancer. DCs were directly isolated from peripheral blood or generated from precursors in peripheral blood as described in "Patients and Methods." Blood was obtained from control individuals and patients with stage III breast cancer. Cells were labeled with a cocktail of phycoerythrin-labeled antibodies (CD3, CD19, CD56, and CD14) and FITC-labeled antibodies against MHC class I, MHC class II, B7-1, and B7-2 molecules. Expression of the FITC-labeled markers was analyzed in phycoerythrin-negative cells (DCs). The means of fluorescence in each experiment are shown. ○, control individuals; ●, patients. □, cells generated using GM-CSF and IL-4 from precursors in peripheral blood from control donors; ■, DCs generated from precursors in peripheral blood from cancer patients.

**Fig. 5** DCs grown from the peripheral blood precursors of patients with breast cancer are capable of normal levels of allogeneic stimulation. A, DCs isolated from peripheral blood; B, DCs generated from precursors in peripheral blood. The experimental protocol was as described in "Patients and Methods." [3H]Thymidine uptake by T cells on day 5 is shown. ●, donor 2; ○, donor 4; ■, patient B; ▲, patient K; ▼, patient L.
induce CTL responses in patients with breast cancer. Previously, we reported defective functioning of DCs in tumor-bearing mice (4), and we speculated that the same defects may occur in patients with cancer. Several other reports have suggested possible DC dysfunction in patients with cancer (16, 18). However, these observations did not answer the main question of whether DCs from patients with cancer are able to stimulate specific immune responses.

In this study, we investigated the immune function of patients with breast cancer and particularly the ability of DCs to present antigens to T cells. Unlike animal experimental models, it is much more difficult to analyze the function of APCs in patients because antigen-specific T-cell lines and clones with the same haplotype are not readily available. Therefore, we chose two antigens (TT and influenza virus) with prevalent immune responses in the general population. We studied a sufficient number of control individuals and patients to reach statistically significant conclusions. A clear inverse correlation between the stage of breast cancer and the level of antitetanus toxoid or FLU immune responses was found. In almost all patients with stages III and IV breast cancer, no FLU-specific CTL responses were observed. These patients' cells also showed a dramatic decrease in T-cell response to mitogenic stimulation with ConA. These data are consistent with defects in either T cells or DCs because in these experimental systems, the presence of APCs is important to getting a maximal T-cell response.

To characterize the contribution of each of these types of cells to the observed decreased function, we studied allogeneic MLR reactions using purified cell fractions. In this system, control allogeneic T cells were stimulated with DCs from patients and vice versa. To minimize the effect of chance MHC matching in the DC-T cell pairs, DCs from each patient were tested against T cells from at least three different control individuals, and the maximum responses were scored. These studies showed that the ability of DCs from patients with advanced breast cancer to stimulate control allogeneic T cells was significantly impaired. Initially, we used partially purified fractions of DCs in all of our experiments. In control individuals and patients with stages I and II, it provided 50-70% pure DCs. However, we found that the purity of identically prepared cells from patients with advanced disease was significantly lower. Because we always adjusted the cell concentration so that the DC numbers were equal, fractions from patients with stages III and IV contained more “non DC cells” than in controls. It was possible that these contaminating cells produced factors or directly interfered with DC function, rather than the defect being an intrinsic property of the DC. To evaluate this possibility, we additionally purified DCs using a magnetic bead separation technique, effectively eliminating all T, B, and NK cells and monocytes from this fraction. The remaining cells had the same low level of activity as those from the partially purified fractions, indicating that the differences we observed were not due to possible contamination of the final DC fractions with lymphocytes or monocytes. However, this approach does not rule out interference from immature cells lacking the markers specific for T, B, and NK cells and monocytes. We have shown previously that supernatants from breast cancer cells inhibited the functional maturation of DCs in vitro and resulted in the production of as yet incompletely characterized immature cells of myelomonocytic lineage (19). These in vitro findings could provide an explanation for the in vivo observations reported here. Decreased expression of MHC class II and some costimulatory molecules on the surface of DCs isolated from the peripheral blood of cancer patients might be one of the possible causes of the observed impaired ability of these cells to stimulate allogeneic MLR and antigen-specific T-cell responses. These molecules are known to be directly involved in T-cell stimulation (20, 21). CD4+ cells engaged through MHC class II molecules play an important role in induction of the CD8+-
specific CTL responses. Depletion of CD4+ cells dramatically decreased CD8+ cell-mediated cytotoxicity against tumor-specific antigens (4).

A normal level of proliferation was observed when T cells from patients were stimulated with DCs from control individuals. To confirm the normal proliferative capacity of the T cells from cancer patients, we tested their responses to immobilized anti-CD3 antibody, which is able to stimulate T-cell proliferation almost independently of the presence of APCs through direct triggering of the CD3/T-cell receptor complex (22). Using this approach, we did not find any differences in the level of proliferative responses between control individuals and breast cancer patients. These data indicate that peripheral blood T cells from these patients are capable of normal responses to these stimuli.

The molecular mechanism of this DC dysfunction is not clear. Previously, we proposed that defects in DC maturation mediated by soluble substances released by tumor cells could be partly responsible (10). DCs generated from bone marrow progenitors from tumor-bearing mice showed a normal level of activity (presentation of the soluble antigen to CTL and stimulation of allogeneic T cells). Recently, we found that vascular endothelial growth factor released by tumor cells was one of the factors responsible for inhibiting the functional maturation of DCs, without affecting the function of the relatively mature cells in peripheral blood (19). The data presented here suggest that defective DC function consistent with the defects observed in vitro can be observed in patients with breast cancer. They further suggest that this defect may be caused by tumor-released soluble factor(s) as seen in vitro.

To explore the latter hypothesis, we generated DCs from peripheral blood precursors from these breast cancer patients using GM-CSF and IL-4. This combination of cytokines promotes the growth of DCs with high activity for taking up and processing soluble antigens (12, 23). Several studies have demonstrated that it is possible to generate DCs from progenitors in patients with cancer using similar combinations of cytokines (24, 25). The cells obtained after this procedure had the phenotype of DCs and were able to stimulate antigen-dependent T-cell responses. However, in all of these cases, the patients were pretreated with chemotherapy and granulocyte-CSF, which could influence the function of the derived cells, and in addition, the function of freshly isolated peripheral blood DCs from the same patient was not investigated. Therefore, from these data it is impossible to conclude whether those patients had any defects in DC function and whether DCs generated from precursors had any functional advantage over those obtained from peripheral blood. To answer all of these questions, we compared the function of DCs isolated from peripheral blood with cells generated from precursors from the same patients. We showed that in control individuals, there were no significant differences between the functional activity of DCs isolated from peripheral blood and of those generated from precursors. TT-specific T-cell proliferation in patients with breast cancer was completely restored when DCs generated from precursors were used as APCs. Increased FLU-specific CTL responses were also observed, albeit not quite to normal levels. Why were DCs generated from precursors in peripheral blood functionally competent whereas those directly isolated from peripheral blood were not? One of the possible explanations could be the fact that the DCs we generated in the presence of GM-CSF and IL-4 were derived not from CD34+ stem cell precursors but from cells which have the phenotypic features of monocytes (26–28). Therefore, it is possible that tumor-derived factors specifically affect the ability of CD34+ cells to different into DCs while not altering the production of these monocytoid cells or their ability to be diverted to a DC phenotype in vitro. A second explanation could relate to the fact that DCs isolated from blood are almost terminally matured cells and do not undergo cell division, whereas cells we generate in vitro in the presence of GM-CSF and IL-4 actively divide (at least during the first 3–4 days in culture). It is possible then that rather than a selective effect on a different lineage of cells, several cycles of cell division in the absence of the tumor-derived factors are required to produce fully functional DCs, regardless of the lineage of the precursor. These questions require additional clarification.

Several major conclusions can be drawn from these findings: (a) cellular immune deficits in patients with advanced cancer can at least partially be explained by a decreased number and potency of DC; (b) defective DC function in patients with advanced stage breast cancer can be at least partially overcome when these cells are generated in vitro from precursors; (c) T-cell hyporesponsiveness to soluble antigens can be overcome by stimulation with functionally potent DCs generated from precursors. These results not only suggest that the antigen presentation function of DCs may be selectively targeted by cancer cells as a means of immune escape but also that DCs generated from precursors can be used as vehicles for antigen delivery in the immunotherapy of cancer.

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Decreased antigen presentation by dendritic cells in patients with breast cancer.

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