Dendritic cells in peripheral blood of patients with breast and lung cancer - a pilot study

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Abstract: Dendritic cells (DCs) are regarded as the most potent antigen presenting cells that are well suited to activate T cells toward various antigens, such as tumor-associated antigens, due to their costimulatory activity. There is evidence that DCs are of diverse origin, with at least two types of myeloid and lymphoid precursors implicated in their generation. The recent reports demonstrated that the number and function of dendritic cells might change dramatically in cancer patients. In the present study we evaluated the percentage of myeloid and lymphoid DCs in patients with breast cancer, non-small cell lung cancer (NSCLC) and in the healthy donors. The percentage of both DC populations was significantly lower in patients with NSCLC than in the control group. In patients with breast cancer, the number of lymphoid DCs was significantly higher than in NSCLC patients. The obtained results suggest influence of pathological states on host immune system. The decrease in the number of DCs in the peripheral blood from cancer patients may be closely correlated with the type of tumour.

Key words: Dendritic cells - Immunophenotype - Breast cancer - Lung cancer

Introduction

Dendritic cells (DCs) constitute a family of professional antigen presenting cells (APC) defined by their morphology and their unique capacity to generate and regulate primary immune responses and maintain immunological memory [2, 7]. The main functions of DCs include the ability to take up, process and present antigens, to migrate selectively through tissues, and to interact with, stimulate and direct T- and B-lymphocytes [2, 9]. DCs represent a system of hematopoietic cells that are rare but ubiquitously distributed throughout the peripheral tissues. Their journey starts in the bone marrow where, at least, two DC lineages have been identified so far, namely the conventional myeloid-related DCs and the newly defined lymphoid-related DCs [11, 12]. Both populations migrate to the blood and become immature DCs, which wander through tissues where they monitor the invading pathogens [9, 12]. Upon pathogen capture, immature DCs receive activation signals, which initiate their maturation and migration to secondary lymphoid organs in order to induce antigen-specific immune responses [9, 12].

In this report we focused on subpopulation of DCs circulating in peripheral blood. We investigated circulating myeloid- and lymphoid-related DCs using markers specific for blood dendritic cells: BDCA-1 and BDCA-2, respectively. BDCA-1 (blood dendritic cell antigen), which in cluster differentiation corresponds to CD1c antigen, is expressed on human myeloid subpopulation of peripheral blood dendritic cells (PBDCs), which are CD4+, CD2+, Lin-, CD123 dim and CD45RO+ [2, 7, 9]. BDCA-1-positive cells express myeloid markers (CD11c+, CD13, CD33), are able to phagocytose because of the high expression of Fc receptors (CD32, CD64, FcεRI) and have monocytoid morphology [9, 12]. It is thought that BDCA-1-positive cells express CD1a and after entering tissues give rise to DCs resembling Langerhans cells and epithelial DCs[12]. BDCA-2 is specifically expressed on human plasmacytoid (lymphoid) dendritic cells [3, 4]. This apparently corresponds to a cell type that previously has been erroneously designated plasmacytoid T cell or plasmacytoid monocyte due to its peculiar morphology [4]. BDCA-2-positive cells are CD4+, Lin-, CD11c- and CD45RA+ [4]. They express CCR5 (CD195) receptor and CD123 (IL-3Rα), just as activated lymphocytes, and critically depend on IL-3 [4, 8]. These cells express neither myeloid lineage markers (CD13, CD33) nor Fc receptors and show low phagocytic potential compared to myeloid DCs. The
Flow cytometric analysis was performed using CellQuest software.

**Statistical analysis.** Statistical analysis was performed using Wilcoxon-non-parametric test, U Mann-Whitney test and Statistica 5.0 software.

Results

In our study we defined subpopulation of myeloid dendritic cells as BDCA-1-positive and CD19-negative cells and lymphoid DCs as BDCA-2 and CD123 double positive cells. The count of DCs was expressed as percentage of the peripheral blood mononuclear cells (PBMC).

In the control group, the total number of myeloid and lymphoid dendritic cells was 0.402% ± 0.23 and 0.22% ± 0.14, respectively, of peripheral blood mononuclear cells. The percentage of myeloid DCs was significantly higher (p<0.01) than that of lymphoid DCs (Figs. 1, 2).

In the group of patients with breast cancer, the percentage of myeloid DCs (0.403% ± 0.325 of PBMC) was significantly higher (p<0.01) than that of lymphoid DCs (0.23% ± 0.11 of PBMC) (Figs. 1, 2).

In patients with non-small cell lung cancer, the percentage of myeloid- and lymphoid-related DCs was 0.253% ± 0.2 and 0.193% ± 0.166 of PBMC, respectively. The percentage of myeloid-related DCs was also significantly higher (p<0.001) than that of lymphoid DCs (Figs. 1, 2).

Comparison of dendritic cell subsets between NSCLC patients and healthy donors demonstrates that the percentage of both myeloid and lymphoid DCs was significantly lower (p<0.05) in patients with non-small cell lung cancer than in the control group (Fig. 3). No statistically significant differences in the percentage of myeloid and lymphoid DCs between control groups and breast cancer patients were found. We also noticed that in blood from patients with NSCLC, the number of lymphoid DCs was significantly lower (p<0.05) than in patients with breast cancer (Fig. 4).

Discussion

It is clear that in cancer patients, the immune response to cancer cells has failed [1]. Cancers probably acquire many characteristics that allow them to evade an effective immune response [6, 9]. The presence of functional, competent DCs is critical for effective antitumor control and for the success of cancer immunotherapy. There is ample evidence of inadequate function of these cells in tumor-bearing hosts [1, 6]. Tumor cells may produce several growth factors and cytokines able to affect hematopoiesis, differentiation and accumulation of effector cells at the site of neoplastic lesion [1, 6].

In our study, we investigated differences in myeloid and lymphoid DCs circulating in peripheral blood of cancer patients. We found that in all examined groups the percentages of myeloid DCs was significantly higher than that of lymphoid DCs. According to the function of myeloid DCs, we conclude that abundance of myeloid DCs in cancer patients may correspond to predominance of Th1 type of immune response what is comparable.
with healthy donors. We found noteworthy unchanged ratio but decrease in percentage of both populations of DCs in NSCLC patients. On the contrary, Almand et al. found increased production of immature myeloid cells in cancer patients and these cells were able to directly inhibit antigen-specific T-cell responses [1]. Gabrilovich et al. isolated DCs from the peripheral blood of patients with breast cancer. They demonstrated significantly reduced ability to cluster and to stimulate immune responses by this population of DCs [5]. We found no significant differences in both populations of DCs between breast cancer patients and healthy donors. The higher percentage of lymphoid DCs in breast cancer patients compared to NSCLC patients may result from different sex of the examined subjects [14]. The level of estrogens, predominant hormones in females, corresponds to higher levels of lymphoid DCs [13].

There is now enough evidence that defective DC function is an important mechanism of tumor escape from the immune system control [6]. Our observation presented in this paper is a pilot study on the quantitative analysis of dendritic cells and allows us to conclude that the amount of DCs in peripheral blood of cancer patients may correspond to the type of neoplasm. It faces us with the necessity to expand the examined groups and to include the other pathological conditions. The further study should be aimed at comparisons of the stage, duration and localization of neoplasm with the number of dendritic cells.

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