

Commentary

Dendritic cell defects in patients with cancer: mechanisms and significance

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Abstract

Dendritic cells (DCs) are a complex network of antigen-presenting cells that have an essential role in the modulation of primary immunity. There has been increasing evidence that DCs isolated from patients with malignancy demonstrate functional deficiencies that inhibit the capacity to mount an effective anti-tumor response. In this issue of *Breast Cancer Research*, Pinzon-Charry and colleagues investigate one of the possible mechanisms by which tumors induce DC dysfunction to evade host immune surveillance. They demonstrate that DCs isolated from the circulation of patients with early-stage breast cancer exhibit increased rates of spontaneous apoptosis. *In vitro* studies suggest that a soluble factor secreted by breast cancer cells is responsible for this phenomenon. In contrast, *ex vivo* conditioning of DCs with CD-40 ligand and IL-12 was protective against tumor-induced apoptosis.

Dendritic cells (DCs) are the most potent antigen-presenting cells and are uniquely capable of stimulating primary immune responses by the presentation of antigen in the context of high levels of costimulatory molecule expression [1,2]. The functional characteristics of DCs evolve with their stage of maturation. Immature DCs are found at sites of antigen capture and excel at antigen processing, but lack significant stimulatory capacity. After antigen uptake, DCs undergo further differentiation characterized by the loss of phagocytic capacity and increased expression of costimulatory molecules necessary for T cell activation. DC-based tumor vaccines are being explored as tumor immunotherapy. One approach involves the introduction of tumor-associated antigens or genes that are subsequently taken up by native DCs, which then migrate to the draining lymph node. An alternative strategy involves the administration of DCs manipulated *ex vivo* to express tumor antigens [3-7].

DCs isolated from cancer patients exhibit quantitative and functional deficiencies [8-11]. Decreased numbers of mature DCs have been demonstrated in the tumor bed, draining lymph nodes, and circulation in multiple tumor models. In patients with head and neck squamous cell carcinoma (HNSCC), numbers of DCs were halved in early-stage patients, with a further decrease in patients with more advanced disease [10]. DC subset analysis in patients with breast cancer and HNSCC has revealed that decreases in cell numbers are confined to DCs of the myeloid in comparison with those of the plasmacytoid or lymphoid lineage. Surgical debulking of breast and prostate cancer results in a corresponding increase in myeloid-derived DCs [10,12]. Minimal DCs are recruited to the tumor bed in patients with renal and prostate cancer. Those present have low levels of costimulatory molecules and a decreased capacity to stimulate allogeneic T cell proliferation [11,13]. Similarly, DCs isolated from patients with colon cancer lack expression of CD80 or CD86. *In vitro* culture with granulocyte/macrophage colony-stimulating factor (GM-CSF) and CD40 ligand (CD40L) or tumor necrosis factor (TNF) did not result in the upregulation of costimulatory molecule expression, suggesting that tumor cells cripple the capacity of DCs to undergo normal differentiation [14]. In concert with these findings is the relative predominance of immature DCs in cancer patients that potentially induced tolerance by presenting tumor antigens in the absence of costimulatory signals.

In their study, Pinzon-Charry *et al.* [15] demonstrate that circulating DCs isolated from early-stage breast cancer have higher rates of spontaneous apoptosis than those from healthy controls. Whereas previous studies have demon-

CD40L = CD40 ligand; DC = dendritic cell; GM-CSF = granulocyte/macrophage colony-stimulating factor; HNSCC = head and neck squamous cell carcinoma; IL = interleukin; PBMC = peripheral blood mononuclear cell; TNF = tumor necrosis factor.

strated that tumor cells induce apoptosis of blood DCs *in vitro*, this report suggests that the reduction in circulating DC populations arises from their increased rate of clearance *in vivo*. The authors argue that this phenomenon results in a lack of effective antigen presentation and contributes to a permissive environment for tumor growth. They demonstrate that a soluble factor contained in supernatant derived from cultured breast cancer cell lines induces DC apoptosis. Pinzon-Charry *et al.* show that 24-hour culture with tumor-derived supernatant caused an increase in Lin⁻HLA-DR⁺ apoptotic cells as in comparison with DCs cultured with peripheral blood mononuclear cell (PBMC)-derived supernatant, supporting the authors' hypothesis that tumor products were responsible for the elevated proportions of apoptotic blood DCs in the patients with breast cancer. A variety of tumor-derived factors have been identified that disrupt DC maturation and function, including IL-10 and vascular endothelial growth factor [16,17]. IL-10, for example, irreversibly blocks DC differentiation and induces CD4 and CD8⁺ T cells that suppress antigen-specific responses [17].

It has been shown that IL-12 enhances the function of DCs and promotes the differentiation and maturation of DCs indirectly by the production of proinflammatory cytokines such as interferon- γ , TNF- α , IL-6 and GM-CSF [18]. DCs express IL-12 receptors, and their occupation initiates the nuclear localization of members of the NF- κ B family of transcription factors [19]. IL-12 has also been reported to be an anti-apoptotic factor for DCs, and a lack of production of IL-12 by DCs may lead to early cell death. Pinzon-Charry *et al.* demonstrate that incubation of DCs with CD40L was protective against tumor-associated apoptosis. CD40 ligation induced a modest increase in TNF- α and more marked increases in IL-12 production. Culture with IL-12 alone also reversed the pro-apoptotic effects of tumor supernatant. It is noteworthy that exposure to tumor supernatant resulted in a downregulation of Bcl-2 expression, which was reversed by preincubation with IL-12 or CD40L. IL-12 has been reported to protect *in vitro* derived DCs from apoptosis in prostate cancer [20]. In contrast, IL-12 did not prevent tumor-associated apoptosis when added to PBMCs during early DC development.

Significance for immunotherapy

The findings presented by Pinzon-Charry *et al.* [15] help to further define the immunologic milieu that fosters tumor immune tolerance and carry important implications for the design of immunotherapeutic strategies. The increased susceptibility of blood DCs to apoptosis may result in a diminished capacity to respond to tumor vaccines that depend on *in vivo* antigen loading of native DCs. One strategy to circumvent this limitation is through the use of DCs generated *ex vivo* that are loaded with tumor antigens. Another strategy involves the administration of adjuvant cytokines such as IL-12 to reverse the tumor-associated inhibition of DCs. IL-12 has been shown to augment the efficacy of cancer vaccines. IL-12

enhances the response to vaccination with DC/tumor fusions in animal models and clinical studies [21].

Competing interests

The author(s) declare that they have no competing interests.

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