Direct T-cell Presentation by cDC1: The Key Feature for Cancer Vaccine Success?

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In this issue of *Cancer Immunology Research*, Ferris and colleagues demonstrate that type 1 conventional DC (cDC1) vaccines drive tumor rejection through direct antigen presentation, without the need of endogenous cDC1. This suggests that cDC1-based vaccines could represent an optimal strategy to induce antitumor immunity in patients.

See related article by Ferris et al., p. 920 (7).

Dendritic cells (DC) are professional antigen-presenting cells specialized in the uptake, processing, and presentation of antigen to naïve T cells to elicit primary immune responses. DCs are classified as conventional (c)DCs (consisting of two subsets, cDC1 and cDC2) and plasmacytoid DCs, and can be further divided into migratory DCs (mDC) or lymphoid-resident DCs (rDC). mDCs are located in peripheral tissues and comprise cDC1 and cDC2 subsets. They migrate to draining lymph nodes in a CCR7-dependent manner after antigen encounter to induce tolerance in the steady state or immunity toward pathogens or tumor cells. Previous studies suggest cDC1s dominantly prime $CD8^+$ T cells through antigen cross-presentation, whereas cDC2s mainly prime $CD4^+$ T cells. It has also been proposed that mDCs gather local antigen, whereas rDCs acquire antigen from lymphatic drains carrying apoptotic bodies and peptides, as well as cellular sources such as DC vaccines (1). The development of DC subsets depends on FLT3L, and their differentiation states are regulated by multiple factors, including the growth factor GMCSF.

DC vaccines for cancer therapy have been developed using cells generated from culturing peripheral blood monocytes or bone marrow cells with GMCSF (+/− IL4), referred to GMDCs. Multiple clinical studies using GMDC vaccines report modest antitumor immune responses and clinical benefits (2). One limitation of GMDC vaccines is the dependence on host DCs for T-cell activation. Initially, GMDCs were thought to directly stimulate host T cells through *in vivo* presentation of tumor antigen. However, $CD4^+$ T-cell activation by GMDC vaccination requires MHC-II expression by host cDCs (3), and $CD4^+$ or $CD8^+$ antigen-specific T-cell responses induced by GMDCs can be restored by selective MHC reexpression on DCs in the context of MHC deficiency (1). Antigen-specific $CD8^+$ T-cell activation is not observed in mice that lack cDC development (4). These results indicate that GMDCs do not present antigens directly to host T cells, but act as a source of antigen that is transferred and processed by host cDCs (5). In addition, tumor rejection requires MHC-I/-II expression by cDC1 for both direct $CD8^+$ and $CD4^+$ T-cell priming against tumor-derived antigens and for orchestration of their cross-talk for optimal antitumor immunity (5).

Because cDC1 can directly prime both $CD4^+$ and $CD8^+$ T cells, Ferris and colleagues investigated whether cDC1 vaccines, unlike GMDC vaccines, could induce direct tumor antigen presentation to host T cells, independently of host DCs (6). To address this, they develop a new mouse model that lacks endogenous cDC1 and cannot reject immunogenic fibrosarcomas. They compare antitumor responses induced by intratumoral injection of GMDCs and cDC1. Interestingly, they observe that although GMDCs and cDC1 can cross-present cell-associated antigens to $CD8^+$ T cells *in vitro*, injection of GMDCs into tumors does not induce antitumor immunity, consistent with their reported dependence on host cDC1. In contrast, injection of cDC1 into tumors results in their migration to tumor-draining lymph nodes, activation of tumor-specific $CD8^+$ T cells, and tumor rejection, which did not require *in vitro* loading of cDC1 with antigen, indicating that antigen uptake *in vivo* is sufficient to induce antitumor responses. Finally, cDC1 vaccination shows abscopal effects, with rejection of untreated tumors growing concurrently on the opposite flank. These results demonstrate for the first time that cDC1 vaccines drive tumor rejection through direct antigen presentation, without the need of endogenous cDC1. cDC1-based vaccination could represent a promising strategy to induce antitumor immunity in patients and argues for the development of an optimized *in vitro* protocol for cDC1 generation in humans.

Authors' Disclosures

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