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AUTHOR'S VIEW

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The extent to which melanoma alters tissue-resident dendritic cell function correlates with tumorigenicity

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ABSTRACT

We have shown that melanoma-derived factors alter the function of differentiated tissue-resident dendritic cells (DC) in a tumorigenicity-dependent manner. Soluble factors, including TGFβ1 and VEGF-A, contributed to dendritic cell dysfunction associated with a highly-aggressive melanoma and conferred a phenotype upon DC likely to favor immune escape and tumor outgrowth.

Abbreviations: DC, dendritic cell; IFN, interferon; IL, interleukin; PD-L1, programmed death-ligand 1; TGFβ1, transforming growth factor beta-1; VEGF-A, vascular endothelial growth factor-A

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DC are master regulators of immune reactivity, and the ability of these cells to promote immune tolerance versus activation is largely controlled by their maturation and activation status. As the role of DC in the induction and regulation of both natural and therapy-induced immune responses has become appreciated, there has been significant interest in understanding how tumors might influence DC function and their capacity to shape the quality of antitumor immune responses. To date, several reports have identified roles for various tumor-derived factors in suppressing the differentiation of DC from bone marrow and monocytic precursors.[1-6] On the other hand, few studies have investigated the influence of tumor-derived factors on the function of already differentiated DC, particularly those that are naturally occurring tissue-resident cells. Because tissue-resident DC are likely to play important roles in the induction and regulation of immune responses elicited by many protein-, peptide-, and DNA-based cancer vaccines, and because these cells are also likely to influence the activity of both endogenous and adoptively transferred antitumor T lymphocytes, we sought to understand how melanomas of differing tumorigenicities influence the maturation and activation of lung-resident and splenic DC.

Using an *in vivo* lung metastasis model of melanoma, we demonstrated that LPS-induced maturation and activation of lung-resident DC were altered in mice bearing highly tumorigenic B16-F1 metastases but not in mice challenged with the poorly tumorigenic D5.1G4 mutated variant of B16.[7] These tumor-altered DC exhibited diminished expression of CD80, IL-12p35, and the chemokine CCL22. B16-F1 melanoma also upregulated lung-resident DC expression of CXCL1, and the altered chemokine expression profile of these cells correlated with an accumulation of $CD115^+$ $CD206^+$ M2-like tumor-associated macrophages in tumor-bearing lung tissue. We observed similar tumor-dependent effects on DC function using freshly isolated splenic DC in an *ex vivo* setting. Although tumor-conditioned media from both B16-F1 and D5.1G4 melanomas altered the maturation and activation of LPS-stimulated splenic DC, the extent of these alterations was far greater for DC stimulated in the presence of soluble factors derived from the aggressive B16-F1 tumor, suggesting that melanoma-altered DC function may contribute to tumor progression. In this light, it has recently been reported in a murine model of ovarian carcinoma that tumor progression corresponds with a shift from immunostimulatory to immunosuppressive splenic, tumor-draining lymph node-resident, and tumor-infiltrating DC.[8] In this system, DC associated with late-stage tumors upregulated expression of both PD-L1 and arginase, and these tumor-altered DC suppressed $CD8^+$ T cell proliferation and IFNγ secretion. Others have shown that pulmonary DC isolated from the mediastinal lymph nodes of mice bearing orthotopic lung tumors also exhibit suppressed IL-12 production and $CD8^+$ T cell stimulatory activity, and these tumor-altered DC promote a shift in helper T cell cytokine production from an IFNγ-dominant Th1 profile to an IL-13/IL-17 pattern of secretion.[9] Interestingly, we did not observe melanoma-associated upregulation of co-inhibitory molecules or immunosuppressive mediators by tumor-altered DC in our study, and we found that melanoma-altered splenic DC retained the capacity to activate naive $CD8^+$ T cells. Therefore, while melanoma-altered DC may still be useful targets for therapies designed to induce antitumor T cell responses in some settings, it will be important going forward to understand how the alterations to endogenous melanoma-associated DC impact other facets of tumor progression and the overall immune response against this tumor.

To gain mechanistic insight into the tumorigenicity-dependent effects of melanoma-derived factors on tissue-resident DC

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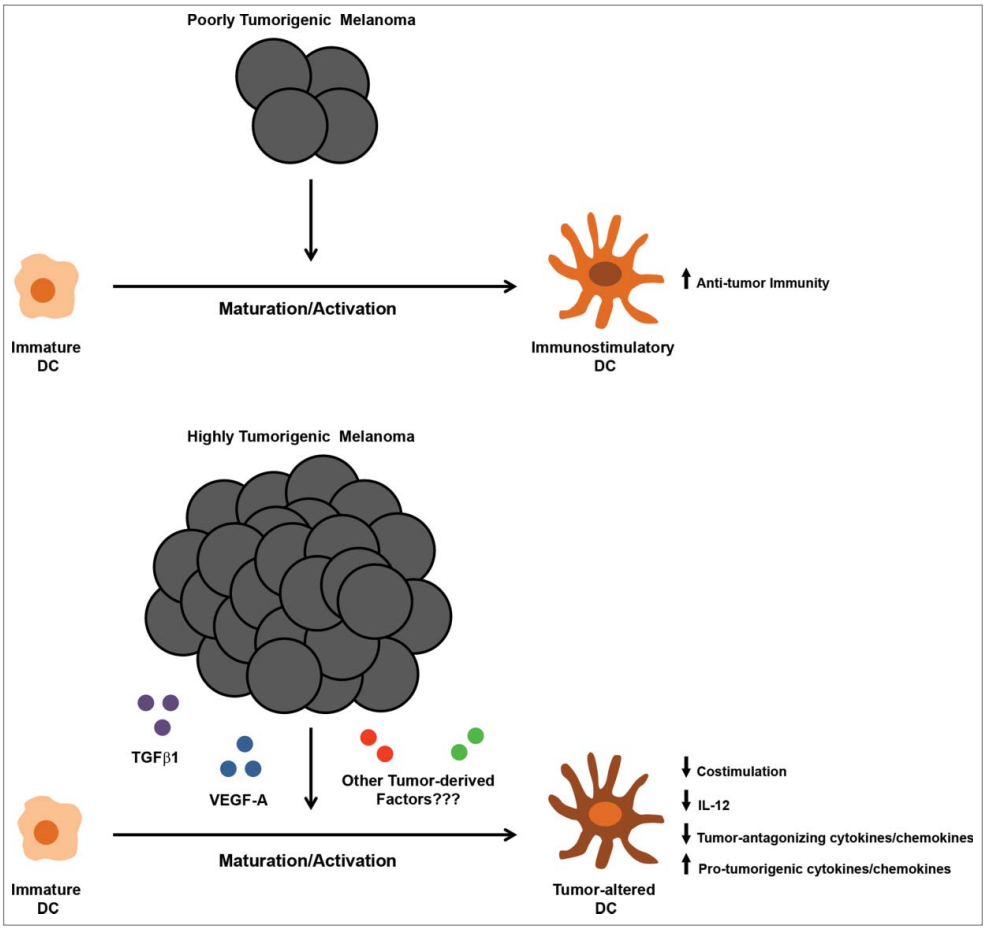

Figure 1. Model for melanoma tumorigenicity-dependent alterations to DC function. Highly-tumorigenic melanomas overexpress soluble factors that alter the maturation and activation of DC, conferring a pro-tumorigenic phenotype to DC that may promote tumor outgrowth, metastasis, and immune escape.

maturation and activation, we used a gene silencing approach to knock down expression of immunosuppressive factors we found to be overexpressed in the highly tumorigenic B16-F1 melanoma. We found that tumor-derived TGFβ1 and VEGF-A (as well as other unidentified soluble factors) both contributed to melanoma-altered DC function, as knockdown of either of these factors partially restored splenic DC cytokine/chemokine expression patterns to those of DC stimulated with LPS in the absence of tumor-conditioned media. While it is likely that these and other tumor-derived factors contributed to the dysfunction of lung tissue-resident DC in our *in vivo* studies as well, it is possible that proteins expressed on or secreted by other suppressive cells infiltrating the tumor microenvironment also influenced the phenotype and function of these DC. Indeed, it has recently been reported in a murine mammary carcinoma model that IL-10 derived from tumor-associated macrophages suppresses IL-12 expression by tumor-infiltrating DC.[10] Based on our findings that M2-like macrophages also accumulate in the lungs of mice bearing B16-F1 metastases, future studies that address the role of both tumor-derived and non-tumor-derived factors within the tumor microenvironment will be important to determine the full complement of mediators that drive melanoma-altered DC function, and it will be interesting to address the interactions between lung-resident DC and tumor-associated macrophages and how potential cross-talk between these cells might promote melanoma progression.

In summary, we have demonstrated melanoma tumorigenicity-dependent alterations to the maturation and activation of tissue-resident DC, and we propose that the progression of aggressive melanomas may be augmented by their promotion of a pro-tumorigenic phenotype in DC (Fig. 1). Because of the vast immunoregulatory activities of DC, the impact of the tumor microenvironment on endogenous DC must therefore be considered in the design of immune therapies, and combinatorial strategies that aim to neutralize the deleterious effects of tumor-derived factors on tissue-resident DC in the host may significantly improve the immunogenicity and clinical outcome of cancer immunotherapies in the future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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