

Clinical Perspectives™

Highlights from the Perspectives in Melanoma XII Conference

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IMMUNOTHERAPY

Novel improvements in dendritic cell-based vaccines for melanoma

James J. Mulé of the Moffitt Cancer Center in Tampa, Florida, talked about 2 strategies to improve dendritic cell (DC)-based melanoma vaccines. Preclinical studies pointed to the promise of DC-based vaccines for melanoma treatment, but clinical results from melanoma trials have been less encouraging. In his presentation, Dr. Mulé discussed some of the potential limitations of conventional DC-based vaccines, and novel approaches to enhance their antitumor activity. These strategies have been evaluated in the laboratory and are now ready to be explored in the clinical setting.

The first approach Dr. Mulé discussed involves the use of secondary lymphoid tissue chemokine (SLC)/CCL-21 to create functional lymph node-like structures under the skin at vaccination sites with tumor-loaded DCs. Through molecular techniques, human DCs employed in vaccines can be modified to produce biologically active SLC, which has chemoattractant properties for human naïve T cells. The hypothesis is that concomitant expression of SLC at the immunization site of tumor-loaded DCs will result in increased tumor reactivity through elevated levels of host T cell recruitment and activation (ie, by the creation of a functional ectopic “lymph node”). Part of the reason for the heretofore disappointing results in trials of DC-based vaccines is, in part, due to poor migration of intradermally injected, tumor antigen-pulsed DC from the injection site to secondary lymphoid organs, where they encounter naïve T cells for initiation of a primary immune response.¹

The novel approach discussed here brings the naïve T cells to the injection site (via SLC expression), thereby removing the trafficking issue. In vitro studies showed SLC-producing DCs primed naïve T cells to the known melanoma-associated antigen, MART-1.¹ Moreover, in mouse melanoma models, intratumoral injection of SLC-expressing DCs inhibited tumor growth in a CD8⁺/T cell-dependent manner and produced regression of established tumors.² There is also some suggestion that, once the lymph node structure disappears, some of the primed antitumor T cells enter the systemic circulation and can eliminate metastatic disease at distant sites. Dr. Mulé said he and colleagues are now embarking on a clinical trial in melanoma patients to further evaluate this approach to enhancing the effectiveness of DC-based vaccines.

The second approach discussed by Dr. Mulé makes use of the finding that macrophage receptor with collagenous structure (MARCO) is highly expressed by killed tumor cell loaded DCs.³ MARCO appears to play an important role in immune function by affecting binding and phagocytosis, cell trafficking, and the formation of lamellipodia-like structures and dendritic processes. In preclinical studies, blockade of MARCO is associated with enhanced migration of DCs from the tumor vaccination site to peripheral lymphoid tissues (sentinel and nonsentinel lymph nodes, as well as the spleen) and enhanced vaccine potency.³ In mouse models, vaccine alone was unable to inhibit tumor growth, whereas tumor growth was significantly impacted when the mice were injected with anti-MARCO antibody-treated, tumor-loaded DCs. Future clinical vaccine trials in melanoma will incorporate this strategy as well.

References

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2. Kirk CJ, Hartigan-O'Connor D, Nickoloff BJ, et al. T cell-dependent antitumor immunity mediated by secondary lymphoid tissue chemokine: augmentation of dendritic cell-based immunotherapy. *Cancer Res.* 2001;61:2062-2070.
3. Grolleau A, Misek DE, Kuick R, Hanash S, Mule JJ. Inducible expression of macrophage receptor Marco by dendritic cells following phagocytic uptake of dead cells uncovered by oligonucleotide arrays. *J Immunol.* 2003;171:2879-2888.