Use of Antibodies to MARCO for Enhanced Dendritic Cell Vaccine Efficacy

Treatment of tumor-lysate pulsed dendritic cells (DCs) with anti-MARCO antibodies resulted in better trafficking of the DCs from the skin injection site to the lymph node, enhanced generation of tumor-reactive T cells, and improved therapeutic efficacy against B16 melanoma as demonstrated by a 50% reduction in tumor growth in mice. These data show that targeting MARCO on tumor-lysate pulsed DCs switches an ineffective vaccine to one that inhibits the growth of a poorly immunogenic, highly aggressive melanoma. This method may also allow DC-based vaccines to be effectively delivered by subcutaneous or intradermal injection.

COMMERCIAL OPPORTUNITY

- There are currently 74 open clinical studies for dendritic cell vaccines yet there is only one approved DC cancer vaccine, Provenge (Dendreon) for metatstatic hormone resistant prostate cancer. In two clinical studies, Provenge increased median overall survival (OS) approximately four months: 25.8 vs. 21.7 (p=0.032) and 25.9 vs. 21.4 (p=0.010). The idea would be that incorporating the MARCO antibody into this vaccine protocol would result an OS increase of greater than four months. This might also result in sales greater than Provenge's current 2013 annualized sales of $272M.
- Our data show that targeting MARCO on tumor-lysate pulsed DCs enhances DC migration to lymph nodes, and may correct one of the significant weaknesses in the use of DC vaccines. Injected DCs must migrate to a draining lymph node to stimulate antigen-specific CD4+ and CD8+ T cells, yet ex vivo generated DCs in both mouse and humans have limited movement from subcutaneous or intradermal injection sites to locally draining lymph nodes and essentially none to spleen.
- This method may also allow DC-based vaccines to be effectively delivered by subcutaneous or intradermal injection. The intravenous route of administration of DCs is ineffective at targeting multiple peripheral lymphoid organs, as these DCs appear to be trapped rapidly in the lungs, spleen and liver where they tend to be cleared. Also the direct intranodal delivery of antigen-loaded DCs is logistically and technically impractical to deliver a large number of DCs to lymph nodes.
- Our method is also easy to implement where the anti-MARCO antibodies are simply an additional component added to the cell culture media.

TECHNOLOGY

T cells from mice immunized with anti-MARCO mAb-treated tumor-lysate pulsed DCs (TP-DCs) produced a greater amount of IFN-γ compared to those from control rat IgG-treated TP-DC immunized mice (6,333 ± 705 pg/ml vs. 4,561 ± 843 pg/ml, respectively, $p < 0.01$). The finding of improved in vitro migration of anti-MARCO mAb-treated murine and human TP-DCs was measured using micro-chemotaxis assays. No anti-tumor effect was evident from control rat IgG-treated TP-DCs (mean tumor diameter at day 25 (mm2 ± SD): PBS, 321.63 ± 40.53; control rat IgG-DC, 298.55 ± 38.90). In contrast, the injection of anti-MARCO mAb-treated TP-DCs resulted in an approximate 50% tumor growth inhibition (167.74 ± 32.82, $p < 0.01$). Moreover, further studies in a MARCO-/- mouse have shown that all enhancement of DC activation and homing are directly correlated to abrogation of the MARCO receptor through antagonistic mAb treatment.

PUBLICATION/PATENT

- Matsushita et al. (2010) J. Immunol. Immunother. & Komine et al. (2013) PLOS ONE
- US patent issued 12/3/13 for Drs. Mulé, Pilon-Thomas, Matsushita, and Grolleau-Julius

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