Immunomodulatory Material for the Attenuation of Multiple Sclerosis

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Introduction: An immune response towards myelin antigens found in the central nervous system (eg. MOG) defines multiple sclerosis[1]. Treatments for autoimmune diseases typically are delivered systemically, which results in the nonspecific circulation of therapeutics throughout the vascular system. This approach permits non-surgical administration; however, the efficiency of the strategy may be limited by the lack of therapeutic localization. To minimize this issue, we use an *in situ* gelling material to localize immunomodulatory dendritic cells via subcutaneous injection to superficial lymph nodes that have previously been shown to play a role in the progress of multiple sclerosis[2,3].

Methods: Dendritic cells were derived from the bone marrow of female C57Bl/6 mice using interleukin-10/IL-10 to induce a tolerogenic phenotype. Cells were compared to both activated (matured using lipopolysaccharide/LPS) and immature (no IL10, no LPS) dendritic cell phenotypes.

0.5-2 x 10^6 cells were injected and encapsulated with poly (ethylene glycol) hydrogel containing maleimide ends that were crosslinked with bi-cysteinated protease-sensitive linkers and were functionalized with RGD previously characterized by the García lab (GaTech)[4]. Subcutaneous sites examined were the flank, where multiple sclerosis is induced in the EAE model, and the neck, where the cervical lymph nodes reside.

All animals were treated according to the animal care and use committee at Emory University. In brief, to induce EAE, a booster protocol was used, where the antigen MOG_{35-55} was injected on days 0 and 7 in complete Freud's adjuvant and pertussis was injected on days 0 and 2 into female C57Bl/6. Mice were monitored daily for presentation of paralysis as in previous studies[5].

Results: Tolerogenic dendritic cells were distinguishable from immature and activated phenotypes using novel cell markers, but not traditional markers (**Figure 1a-b**). Delivery of tolerogenic dendritic cells using in situ gelling PEG hydrogel resulted in a delay in multiple sclerosis onset. Length of delay depended on the delivery site, with dendritic cells that were delivered to superficial cervical lymph nodes performing better than those delivered to the vaccination site, the flank (**Figure 1c**).

Conclusions: Using this strategy, we were able to deliver dendritic cells locally to immunogenic sites known to play a role in the progression of multiple sclerosis and reveal the importance of location in the efficacy of therapeutics. Furthermore, the use of materials allow for the creation of defined cellular environments that can in future be tailored to enhance our therapy for eventual translation.

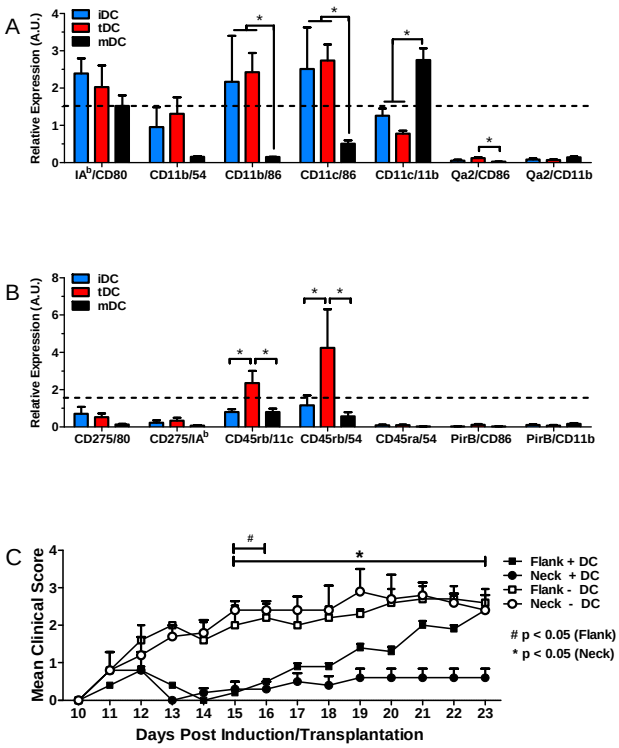

Figure 1. Tolerogenic dendritic cells for the attenuation of multiple sclerosis. Surface profile of tolerogenic dendritic cells (tDC) compared to immature (iDC) and activated (mDC) phenotypes using (a) traditional and (b) novel markers. (c) Assessment of multiple sclerosis progression using clinical score when tolerogenic dendritic cells (+DC) were delivered on day 0 of disease induction to the superficial cervical lymph nodes (neck) or the flank and compared to hydrogel only controls (-DC) according to the following scale: 0, no disease; 1, flaccid tail; 2, hind limb weakness; 3, hind limb paralysis; 4, forelimb weakness; 5, moribund.

References:

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