

DC control of immunopathology: Interaction with tissue DC drives a unique transcriptional response in effector T cells

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Interactions between dendritic cells (DC) and primed effector T cells (T_{eff}) within tissues have been shown to mediate the balance between control of disease and immunopathology. In order to further investigate the role of tissue DC in driving CD8 T_{eff} function, we adopted a systems biology approach. We exploited a transplantation model in which monoclonal CD8⁺ T cells are transferred to antigen-mismatched recipients. T_{eff} were purified from lymphoid organs and peripheral tissues and their gene expression compared by hybridisation to the Affymetrix Gene 2.0 Array. Computational analyses of these data demonstrate that T_{eff} from lymphoid organs are transcriptionally distinct from those in peripheral tissues. In particular, T_{eff} in the skin and gut share a distinct gene signature, suggesting that specific interactions occurring at these sites are driving T cell function. In the skin, expression of this signature is determined by the transition of T cells from the blood to the dermis then epidermis, the major site of skin pathology in this model.

To investigate the role of tissue DC in driving the tissue signature of T_{eff} , we used the Langerin-DTR mouse, from which epidermal Langerhans cells (LC) can be inducibly depleted *in vivo*. Transcriptional profiling demonstrates that in the absence of LC the transition to expression of a full effector profile no longer occurs. Correlation of genes differentially expressed by T_{eff} in the LN, dermis and epidermis of LC-replete or -depleted mice with datasets from the Immunological Genome project (Immgen) showed that the epidermal datasets had the most differentially expressed genes. These genes are significantly associated with coarse module 5 (C5), that is genes associated with T cell proliferation and changes in metabolic activity. In summary we have used a systems biology approach to demonstrate that LC drive T cell-mediated immunopathology in the skin by switching on a transcriptional effector programme.

1. Bennett, C. L. & Chakraverty, R. Dendritic cells in tissues: in situ stimulation of immunity and immunopathology. *Trends in immunology* **33**, 8-13 (2012).
2. Honda, T. *et al.* Tuning of antigen sensitivity by T cell receptor-dependent negative feedback controls T cell effector function in inflamed tissues. *Immunity* **40**, 235-247 (2014).