A systems immunology approach to GVHD defines skin-autonomous control of donor T cells.

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The use of allogeneic hematopoietic stem cell transplantation to treat blood cancers is severely restricted by the development of acute graft-versus-host disease (aGVHD). aGVHD is characterized by the entry of activated donor T cells into target organs such as the skin where they attack and destroy healthy tissues.

We have adopted a systems immunology approach to address the hypothesis that cellular interactions within tissues drive the differentiation of GVHD effector T cells (T_{eff}). We exploited transplantation models in which $CD8^+$ T cells are transferred to minor H antigen-mismatched recipients. T_{eff} were purified from lymphoid organs and peripheral tissues and their gene expression compared by microarray. Computational analyses of these data demonstrate that T_{eff} from lymphoid organs are transcriptionally distinct from those in peripheral tissues. In the skin, transition of T cells from the dermis to the epidermis is associated with up-regulation of a unique gene signature.

To investigate the cellular mechanisms that determine sub-compartmental differences between T_{eff}, we focused on Langerhans cells (LC), which uniquely reside in the epidermis. In the absence of LC the transition to expression of a full T_{eff} profile no longer occurs, and mice depleted of LC do not develop cutaneous GVHD. Our data demonstrate that direct interactions between T_{eff} and LC leads to the establishment of a pool of resident memory T cells which are activated to cause tissue pathology. We further show that LC provide both Notch-dependent signals to enhance cytokine production by epidermal T cells, and Notch-independent signals leading to enhanced T cell survival. Together, these interactions result in the accumulation of pathological T cells in the epidermis.

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