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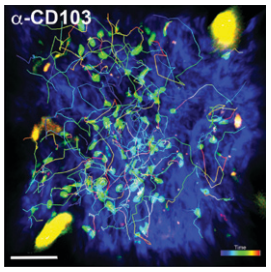
CD103 Restrains Treg Migration in Inflamed Skin



In this Top Read, Norman et al. (p. 551) used multiphoton intravital microscopy in a mouse model of contact hypersensitivity to understand how the integrin CD103 mediates regulatory T cell (Treg) migration and interaction with other immune cells during skin inflammation. Whereas CD103 expression by dermal Tregs was consistently high from the onset of inflammatory challenge, CD103 blockade led to an increase in Treg migration only at later stages of inflammation. The expression of E-cadherin, the major ligand of CD103, increased in the dermis of inflamed skin and was expressed mainly on dermis-infiltrating myeloid leukocytes. Inflammation also induced more numerous, albeit shorter-lived, interactions between dermal dendritic cells and dermal Tregs. Altogether, the data suggest that skin homeostasis is maintained by altered motility of dermal Tregs and adhesion between CD103-expressing Tregs and E-cadherin–expressing myeloid cells that infiltrate the dermis during inflammation.

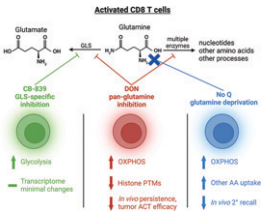
Suramin Neutralizes Histones

Endotheliopathy is a histone-mediated acute thromboinflammatory response of the vascular endothelium resulting from extensive tissue injury. In this Top Read, Villalba et al. (p. 648) show that the polyanionic drug suramin mitigates endotheliopathy by binding histones. In vitro, suramin decreased histone-induced thrombin in endothelial cell cultures and rescued vasodilatory dysfunction in isolated mouse vessels. Mice treated with suramin prior to sublethal doses of histones showed decreased ICAM-1 expression on pulmonary endothelial cells and reduced pulmonary neutrophil recruitment. Suramin treatment protected mice from lethal doses of histones by decreasing lung endothelial cytotoxicity, lung edema, and intra-alveolar hemorrhage. The electrostatic interaction between suramin and individual histones neutralizes the effects of individual histones; however, suramin has less affinity for citrullinated histones from neutrophil extracellular traps. Together, these data demonstrate the therapeutic potential of suramin in conditions characterized by elevated histone levels.

Ablating CCR8$^+$ Tregs Enhances CD8$^+$ T Cell Tumor Response

The chemokine receptor CCR8 is selectively expressed on tumor-infiltrating regulatory T cells (Tregs). In This Top Read, Ueyama et al. (p. 673) demonstrated that ablating tumor-specific Tregs with anti-CCR8 Ab resulted in tumor regression mediated by a more effective CD8$^+$ T cell response. In mouse models of multiple cancers, anti-CCR8 Ab treatment resulted in increased naive and nonexhausted effector CD8$^+$ T cells within the tumor environment, compared with the control treatment. CD8$^+$ T effector cells had decreased expression of inhibitory receptors following anti-CCR8 Ab treatment. Similarly, when human tumors were assessed for CCR8$^+$ Tregs and CD8$^+$ T cells, increased numbers of the former correlated with decreased naive CD8$^+$ T cells and increased exhausted CD8$^+$ T cells. These data show that anti-CCD8 Ab treatment effectively ablates tumor-specific Tregs, leading to a robust CD8$^+$ effector response, and suggests that anti-CCR8 Ab treatment could be an effective tumor immunotherapy.

Glutamine Inhibition Affects CD8 T Cell Outcomes



In this Top Read, Madden et al. (p. 563) showed that three commonly used strategies to inhibit glutamine–the glutaminase-specific inhibitor CB-839, the pan-glutamine inhibitor 6-diazo-5-oxo-L-norleucine (DON), and glutamine depletion (No Q)–can have different effects on murine CD8 T cell function. Adoptive transfer experiments showed that glutamine inhibition during activation leads to different levels of CD8 T cell proliferation and function depending on the inhibition strategy used. Whereas transcriptomic analysis revealed that all treatments increased CD8 T cell dependence on glucose metabolism, anabolic pathways became activated in CB-839 and control groups. No Q cells upregulated both autophagy transcripts and utilization of other amino acids besides glutamine. CB-839 caused greater reliance on glycolysis than on oxidative phosphorylation relative to DON and No Q treatment. DON treatment had the highest negative impact on the ability of adoptively transferred cells to control tumor growth. Altogether, the data show that the mode of glutamine inhibition changes the way that CD8 T cells metabolize and react in the tumor microenvironment and suggest that these features should be considered when designing cancer treatments targeting glutamine pathways.

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