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T cell addiction: can pathogenic T cells be controlled using dopamine receptors?

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Summary

Crosstalk between the immune system and the nervous system, via neurotransmitters such as dopamine, is increasingly of interest as we begin to learn how lymphocytes in peripheral tissues can both produce and respond to these molecules. This crosstalk can modulate immune responses by influencing the local tissue environment and can, for instance, influence the activation status and migration of T cells. Immune cells also use neurotransmitters to communicate with each other. Understanding how neurotransmitters influence the immune system may provide novel approaches for targeting diseases associated with tissue-specific inflammation, such as psoriasis.

Dopamine is a catecholaminergic neurotransmitter that is crucial for many central processes including sleep, memory, the reward system, hormone regulation and cardiovascular function.[1] Dopamine is not only produced by cells of the central nervous system, but also in peripheral tissue and in the immune system; even bacteria inhabiting our intestine make it. It has been known for some time that dopamine can directly influence immune cells. T cells, dendritic cells and other leukocytes express dopamine receptors. The immune system interacts with dopamine released by nerve endings, but dopamine can also be synthesised by T cells and dendritic cells. Dopamine can, therefore, influence T cell function in an autocrine-paracrine feedback loop. The expression of dopamine receptors by multiple immune cells means that it will take some time to unravel the complexity of these interactions. In the case of T cells, for instance, dopamine-mediated actions are context dependent. Dopamine can drive activation of naïve T cells,[2] but conversely, it also supresses T cells that have already been activated.[3] These observations and others[4] demonstrate how the local environment plays a fundamental role in modulating the functions of T cells in tissues.

In this issue of *Immunology*, Keren *et al.* report on the suppressive effects mediated by dopamine on activated T cells, and describe the potential for modulating this communication to target T cell-mediated inflammation in psoriasis.[5] Dopamine has been shown to increase cytokine release by keratinocytes[6] and dopamine levels are raised in serum of psoriasis patients.[7] Here, the authors report a 20-fold increase in T cells expressing the dopamine receptor D1R in a humanised mouse model of psoriasis, and this observation is consistent with observations in lesional skin from psoriasis patients.[5] The authors demonstrate that dopamine causes rapid depolarisation of activated T cells, and that the dopamine receptor agonist, Fenoldopam, supresses *in vitro* activated T cells from psoriasis patients. Suppressive effects were characterised by reduced secretion of inflammatory cytokines (including TNFα, IL-6 and IL-1β) and reduced expression of activation markers (CD69 and CD28). Psoriasis immunopathology is dominated by the IL-17/-23 axis, predominantly driven by dendritic cells and Th17 cells.[8] Therefore, identifying novel ways to supress pathogenic T cells in lesional skin is potentially very important.

The skin functions as a physical barrier against a multitude of potentially harmful and innocuous antigens, but is also very responsive to stressful stimuli. Thus, mechanisms maintaining immune regulation are crucial to avoid over-active immune responses in the skin[9] that may lead to chronic inflammation associated with diseases including psoriasis and atopic dermatitis. This paper highlights how dopamine can contribute to immune regulation, highlighting a novel contribution to the fast-growing list of immune mechanisms that modulate potentially harmful immune responses in barrier tissues.

Clinically, understanding how dopaminergic pathways drive and suppress T cells presents a potential novel strategy for a psoriasis treatment. Psoriasis, and many other inflammatory diseases, are strongly associated with stress and psychological comorbidities, which therefore implicate dopamine pathways.[10] Additionally, murine dermal endothelial cells exposed to norepinephrine produce IL-6

that can drive IL-17A production in $CD4^+$ T cells.[11] Therefore, when thinking about the bigger picture, it is becoming increasingly important to investigate how stress-associated dysregulation of neurotransmitters and their receptors contribute to chronic inflammation. This understanding will be vital if we are to restore homeostatic immune regulation in affected patients.

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