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How Steroids Steer T Cells

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Recent papers from Mahata et al. and Bereshchenko et al. reveal how steroids steer immune responses by tipping T helper (Th) subset balances and activities. Pregnenolone produced by Th2 cells mediates immunosuppressive responses, and glucocorticoids stimulate regulatory T cell development via the induction of GILZ expression.

Steroids are hormones that are involved in diverse physiological functions ranging from regulation of metabolism, behavior, and fertility to inflammation and immune control. The different forms of steroids (progesterone, mineralocorticoids, glucocorticoids [GCs], androgens, and estrogens) all (1) form by a synthesis pathway that starts with conversion of cholesterol into pregnenolone, (2) are to some degree anti-inflammatory and immunosuppressive, (3) interact with a specific nuclear receptor, and (4) can act on distant tissues. Steroid synthesis has historically been associated with organs such as the testes, ovaries, and the adrenal glands, but recent evidence points to synthesis in other organs. GC synthesis, for example, has been detected in the gut, lungs, and skin (Noti et al., 2009). Although low in concentration in these organs, these steroids may be important for local control of biological processes.

We know that infections and other challenges to homeostasis are controlled by our innate (fast and poorly specific) and adaptive (slow and highly specific) immune systems. The specificity of the adaptive immune response is guided in part by the action of T helper (Th) cells that differentiate into a subset of effectors (Th1, Th2, Th17, memory Th, and regulatory T [Treg] cells) on the basis of the nature of the antigen and external stimuli. Two recent *Cell Reports* papers reveal groundbreaking details about how steroids regulate the differentiation of Th cell subsets, in particular Th2 cells that regulate host immunity to helminths and Treg cells that protect against excessive immune responses.

In a paper published in this issue of *Cell Reports*, Mahata et al. (2014) performed single-cell RNA sequencing on Th subsets and discovered that Th2 cells express the enzyme Cyp11a1, which is essential for transforming cholesterol into the steroid pregnenolone. This expression is clearly associated with a block in Th cell proliferation and immunomodulating activities of these Th2 cells, such as B cell immunoglobulin class switching, suggesting that steroids produced by the Th2 cells themselves may be novel immunomodulators. These results suggest that "lymphosteroids" may act not only on other cell types such as innate immune cells and structural cells but also on the local production of and/or further metabolism of steroids in these cells. This type of cascading effect could potentially lead to a generalized immunosuppression. Additional study of lymphosteroid regulation, as well as their impact on the whole organism versus local tissues, would likely also reveal if/how they cause or exacerbate side effects, such as those seen with GC treatment of chronic inflammation (Dejager et al., 2014). For instance, how would local stimulation or inhibition of Cyp11a1 impact mouse models of Th2-mediated colitis (Noti et al., 2009) or other inflammatory conditions? Moreover, lymphosteroids may play a role in escape from immune suppression of the hypothalamic-pituitary-adrenal axis that can occur during sepsis and/or may allow affected individuals to overcome reduced steroid production in cases of adrenal insufficiency or necrosis (Cohen and Venkatesh, 2010).

GCs are predominantly produced by the adrenal cortex and are potent modulators of inflammation and immunosuppression. GCs bind and activate the GC receptor (GR), which functions in the nucleus by two binding mechanisms: (1) as a homodimer to promoters of a wide range of genes, including anti-inflammatory genes (such as *Tsc22d3*, which codes for the anti-inflammatory protein GC-induced leucine zipper [GILZ]), or (2) as a monomer to inflammatory transcription factors, such as nuclear factor κB (NFκB), AP-1, and IRF3, thereby diminishing their transcriptional activities.

A second new mechanism by which steroids (GCs, in this case) regulate Th subsets is reported by Bereshchenko et al. (2014), who describe the molecular mechanism through which GILZ strongly impacts Treg cell proliferation. The binding of GILZ to NFκB is considered to be its major immunosuppressive activity. Now, Bereshchenko et al. (2014) show that GILZ binds to SMAD2, an essential signal transducing molecule in the pathway initiated by Treg-cell-activating cytokine TGF-β. The authors find that GILZ leads to SMAD2 phosphorylation and consequent optimal induction of Foxp3, a typical marker of Treg cells that is responsible for Treg cell proliferation. The authors provide a physiological context for the role of GILZ in peripheral Treg (pTreg) cell proliferation by examining the effects of GILZ overexpression or knockout in a mouse model of inflammatory bowel disease. However, given that the depletion of GILZ does not completely impair the production of pTreg cells, it might be interesting to study which additional mechanisms contribute to their development and whether GCs are involved in these processes.

The results also raise the question of whether enhanced Treg cell proliferation is involved in the reported protective effects of GILZ in other inflammatory settings, such as endotoxemia (Pinheiro et al., 2013) and arthritis (Beaulieu et al., 2010; Ngo et al., 2013). The reported strong anti-inflammatory role of GILZ undermines the dogma that GR-dimer-dependent actions are dispensable for the beneficial immunosuppressive function of GCs (Vandevyver et al., 2013). Therefore, the current development of dissociated compounds that act only on GR-monomer-dependent actions might not mimic all anti-inflammatory actions of GR because they don't induce GILZ.

On the basis of the findings of Mahata et al. (2014) and the reported local production of GCs in intestinal epithelial cells (Noti et al., 2009), it is worth investigating whether local GC production in Treg cells also occurs and whether such locally produced GCs contribute to the production of GILZ and to the development of pTreg cells. In addition, additional research will likely elucidate whether inflammatory stimuli enhance these effects, given that proinflammatory cytokines can promote local steroidogenesis by directly inducing steroidogenic enzymes in epithelial cells (Noti et al., 2010). On the other hand, it is not clear yet how the immunosuppressive effects of the lymphosteroids described by Mahata et al. (2014) are exerted. It is important to investigate which steroid nuclear receptor is engaged during immunosuppression and whether nongenomic or genomic actions are involved. In the latter case, it would be interesting to study whether steroid-induced anti-inflammatory effectors such as GILZ are involved.

These insights may lead to new therapeutic strategies that enhance local steroid or GILZ production to stimulate restoration of immune homeostasis or improve immune tolerance while potentially avoiding side effects that are typically associated with steroid-based therapies.

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