
Staying on Top of Things Right from the Start: The Obsessive-Compulsive Disorder of Regulatory T Cells

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Our choice of partners, so they say, is subconsciously directed by an immune system aiming to making itself more diverse and robust. This strategy seems to work quite well if one looks at the highly complex structures that underlie human immunology, which still surprises with unexpected enigmas even after decades of intense research. Another recent proof of this phenomena is the study by Eller et al.¹ in this issue of JASN that describes a surprisingly aggravated course of glomerulonephritis in mice lacking the chemokine receptor CCR7.

The family of chemokines and their receptors are important mediators of directional leukocyte trafficking under inflammatory and homeostatic conditions. Given the complexity of the immune system and the multitude of different leukocytes, guidance by the chemokine family is much needed to facilitate the interaction of the right leukocyte subsets at the right time and in the right location. CCR7 is particularly crucial in the initiation of antigen-specific immune responses.²

Upon encountering a danger signal, antigen-bearing dendritic cells upregulate CCR7 and become responsive to the corresponding ligands CCL19 and CCL21, which are expressed in secondary lymphoid organs. Likewise, naïve T helper cells bear CCR7 on their surface and are similarly directed to lymph nodes and spleen. Here, these two cell types interact in a favorable environment to initiate a T cell response.

Given that Eller’s nephrotic nephritis (NTS) model of glomerulonephritis is strongly T cell dependent, one would assume that interference with this CCR7-mediated T cell activation pathway might result in amelioration of disease; it did not. To understand why, it is necessary to look further at recently identified functions of CCR7.

First, the groups of Butcher and Luster³,⁴ convincingly showed in the past few years that CCR7 is involved in the egress of T cells from peripheral tissues; therefore, lack of CCR7 might result in the renal accumulation of T cells that have entered the kidney and no longer can leave in an orchestrated manner. Indeed, spontaneous lymphocyte accumulation and subsequent tissue injury are reported in several organs in CCR7-deficient mice.⁵

Second, Schneider et al.⁶ reported yet another function for CCR7. They showed that not only effector T cells but also regulatory T cells (Treg) need this receptor to be guided to sites of antigen-specific activation. Lack of CCR7 resulted in exacerbated experimental colitis, demonstrating that activation of effector T cells was achieved by alternative mechanisms. On the contrary, effector T cell suppression by Tregs was insufficient, suggesting dependence of this process on CCR7.

Eller et al.¹ further underscore the importance of these findings in their current article. Having already demonstrated some years ago that Tregs ameliorate the kidney-directed immune response in the NTS model, they now show that lymph nodes and spleens of nephritic CCR7 null mice contain significantly fewer Tregs than those of wild-type controls. Importantly, adoptive transfer of CCR7⁺ Tregs into CCR7 null mice restores Treg numbers in lymphoid organs and ameliorates disease, whereas transfer of Tregs from CCR7 null mice does not.

These findings once more highlight the potential role of Tregs as therapeutic targets in autoimmune disease and make them a rewarding subject to study. Two very important aspects of their biology are how and where they exert their anti-inflammatory actions.⁸ It has become evident over the past few years that Tregs are by no means a singular population; to the contrary, they form many different subsets.⁹ Each of these subsets seems tailor-made for suppression of a distinct type of immune response. In analogy to the development of Th1, Th2, or Th17 helper responses, corresponding Treg populations expand concordantly. How closely related these two counterregulatory arms of the immune response are is highlighted by the fact that programming of lineage-specific T effector and T regulatory responses relies on several of the same key transcription factors.¹⁰–¹²

This is an arrangement, like most biologic processes, that makes perfect sense. Tregs need to be present at the site of ongoing immune responses to exert their anti-inflammatory actions; therefore, they need similar properties and trafficking receptors as effector cells. It has indeed been shown that lineage-specific che-
mokine receptors, such as CXCR3 for Th1 and CCR6 for Th17 cells, are similarly present on some Tregs. As a result, Tregs home to the same regions in inflamed organs as their proinflammatory targets to control exuberant immune responses. This notion is suggested by several studies in the recent years13,14; however, Eller et al.1 did not find Tregs in inflamed kidneys of wild-type animals. This observation is surprising because it contradicts previous studies in other organs as well as our own unpublished data, which show regular presence of Tregs in kidneys of mice with NTS, and in various human renal pathologies.

A possible explanation for this discrepancy is that numbers of infiltrating Tregs depend on the severity of disease, which was mild in the study by Eller et al.,1 a common issue with NTS in mice on the BALB/c background. Furthermore, modulation of an immune response by Tregs might follow a certain time course in which Tregs are first found in secondary lymphoid tissues and only then infiltrate inflamed target organs at later stages. The current study supports this latter hypothesis.

Eller et al.1 show that Tregs have the potential to downregulate the immune response directly at the systemic site of antigen-specific T cell priming, namely the lymph node. Tregs are guided to this location, in analogy to activated dendritic or naïve T helper cells, by the chemokine receptor CCR7. Thus, there are not only Tregs matching committed T cell lineages of the effector arm but also a population designed to monitor the activation of naïve T cells. As a result, it is guaranteed that every step of a potentially hazardous T cell response, from priming within secondary lymphoid organs to damaging the parenchyma of target organs, is under the control of Tregs. The most common form of obsessive-compulsive disorder in humans, compulsive checking, therefore seems to be an issue for Tregs as well.

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REFERENCES


See related article, “CCR7 Deficiency Exacerbates Injury in Acute Nephritis Due to Aberrant Localization of Regulatory T Cells,” on pages 42–52.

**Sorting out Lysosomal Trafficking of the Thiazide-Sensitive Na-Cl Co-transporter**

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The aldosterone-sensitive distal nephron is a key site for regulated renal sodium reabsorption and, hence, plays a critical role in the long-term control of arterial BP and extracellular fluid volume. Coupled Na⁺ and Cl⁻ transport across the luminal surface of the most proximal portion of the aldosterone-sensitive distal...