Regulatory T Cells Cease Fire at the Right Place

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Abstract

Since the characterization of CD4+CD25+ regulatory T cells (Tregs) as a specific T-cell lineage with immune regulatory function in the 1990s, approaches manipulating Treg expansion and activities have been proved potential therapeutic strategies for immune-mediated diseases. On the other hand, harnessing leukocyte migration during inflammation as a therapeutic modality for immunologic diseases has not only supported by theoretical basis but also clinically shown potential. Whilst advances have been made in the understanding of the effector mechanisms of Treg-mediated immune suppression, the migration phenotypes as well as the anatomic sites where Tregs exert immune regulation remain obscured.

In a recent study by using the foot-pad inflammation model and adoptive Treg-cell transfer, Huang et al. demonstrated that blockage of Treg lymph node localization abrogated the immune suppressive function of Tregs, suggesting an indispensable role of lymph node trafficking in Treg-mediated immune regulation. Important messages have arisen from this study that migration pattern, i.e. lymph node localization vs. tissue trafficking, matters in the context of Treg-mediated immune regulation and Treg-based cell therapy.

Whilst inflammatory response can be regulated by modulating the migration property of inflammatory leukocytes and be a feasible therapeutic modality, the impact of altered Treg migration phenotypes on the overall inflammatory outcome and the effectiveness of therapy of this kind should be taken into account.

Keywords: Regulatory T cells; Immune regulation; Leukocyte migration

Abbreviations: Tregs: Regulatory T cells; Teff: Effector T cells; LNs: Lymph Nodes; IBD: Inflammatory Bowel Disease

Commentary

Therapeutic measures to induce peripheral tolerance have been in the central stage for treatment of various immunological diseases in the past two decades [1,2] and Tregs are the most well-known key player in this novel therapeutic modality [3,4]. Tregs exert immune suppression via direct cell-cell contacts with APC or effector T cells. Although the effector mechanisms underlying Treg-mediated immune regulation have been thoroughly studied (Figure 1A), where the immune suppression takes place in vivo is unclear. It is conceivable that this unsolved issue is crucial for the feasibility and effectiveness of Treg-based cell therapy as well as treatments targeting inflammatory leukocyte migration. Huang et al. investigated the migration characteristics of Tregs by using a shear-stress flow assay and envisaged the relationship between Treg migration phenotypes and their immune regulatory function in a footpad inflammation model [5]. Both anergic T cells generated by CD80/CD86 blockade and FoxP3-expressing Tregs exhibited decreased adhesion to endothelial cells compared to antigen-activated effector T cells. It was speculated that a sessile phenotype rendered Tregs less tissue-trafficking and hence inefficient to suppress inflammation, which suggested the lymph nodes (LNs) as the anatomic site for optimal Treg immune regulation. In accordance with this speculation, inhibition of Treg LN entry by using CCR7 or CD62L blocking Ab abrogated the suppressive effects of adoptively transferred Tregs in footpad inflammation.

Tregs have been recovered from both lymphoid organs and peripheral tissues at either homeostatic state or during inflammation. It is therefore conceivable that Tregs exert immune regulation in both the draining LNs and the peripheral tissues, i.e. at immune induction stage as well as the effector phase of an immune reaction. However, studies of different experimental conditions have yielded contradictory and mutually exclusive results regarding the anatomic sites of optimal Treg immune regulation [6-9]. CD62L and CCR7 are two main molecules orchestrating LN trafficking of leukocytes. Inhibition of CCR7 or CD62L impairs LN trafficking of both inflammatory leukocytes and Tregs. In the context of immune regulation, LN positioning of Tregs has been shown essential for Treg-mediated immune suppression by using CCR7 blockade, in CCR7-deficient mice [10] as well as by CD62L blockade [11,12]. Whist enhanced graft rejection or exacerbated inflammation developed in these animals, the pathology can be rescued by adoptive transfer of Tregs with LN-trafficking ability [13]. Additionally, the essential role of LN trafficking in Treg immune regulation was demonstrated in studies of autoimmune disease which showed that strategic LN positioning of Ag-specific Tregs induced long-term inhibition of autoreactive T-cell expansion in the draining LNs [14,15]. Nonetheless, studies using fucosyltransferase VII-deficient mice have shown an indispensable role of tissue localization in Treg-mediated immune regulation. Deficiency
of P/E-selectin ligands hampered tissue trafficking of Tregs and prevented these cells from mitigating skin inflammation [8]. However, in studies using β7 integrin-deficient mice, impaired Treg tissue localization did not prevent these Tregs from suppressing intestinal inflammation [9]. These seemingly contradictory findings that Tregs regulate immune responses in both the LNs and peripheral tissues plausibly reflect the in vivo scenario that Tregs regulate immune reaction not only at the induction phase of the immune response, but also during the effector phase of the reaction. These findings also uncovered the “division of labor” for Tregs wherein individual Treg properties of the Treg subpopulations can be attributed to the elicitation and magnitude of the immune response vs. the induction of immune tolerance, can be achieved by modulating leukocyte migration. Novel therapeutic strategies exploiting blocking antibodies in inflammatory reactions have been approved for clinical trials of P-/E-selectin ligands hampered tissue trafficking of Tregs [9]. However, there are at least two Treg subpopulations that re-circulate through the LNs and the effector-like Tregs that traffic to the inflammatory tissues. The distinct homing/ transmigration properties of the Treg subpopulations can be attributed to the differential expression profile of chemokine receptors and adhesion molecules of the particular Treg subpopulation (Figure 1B). It is conceivable that distinct Treg subpopulations are selectively expanded in response to situations that emerge along the course of an inflammatory reaction.

Extravasation of leukocytes from the blood vessels and migration into the peripheral tissues are highly orchestrated and crucial processes during immune surveillance and inflammation. It is theoretically feasible that the nature and outcome of an immune reaction, i.e. the elicitation and magnitude of the immune response vs. the induction of immune tolerance, can be achieved by modulating leukocyte migration. Novel therapeutic strategies exploiting blocking antibodies against integrins or integrin ligands to regulate leukocyte migration have been approved for clinical trials of inflammatory bowel disease (IBD) [16,17]. Whilst success have been claimed in some studies, there were reports of aggravated disease in a small population of patients treated with α4β7 Ab (vedolizumab) [18] or β7 integrin Ab (etrolizumab) [19] for ulcerative colitis. Since Treg migration phenotypes affect the effectiveness of their immune suppressive function, it is possible that blockage of integrin-mediated adhesive function inhibited tissue trafficking of not only the inflammatory leukocytes but also the immune regulatory Tregs. The impact of altered Treg migration may override the disease-alleviating effects of decreased leukocyte recruitment that cumulated in exacerbated colitis.

Huang et al. and recent studies have demonstrated the necessity for Tregs to traffic to the right anatomic sites to exert optimal immune regulation. The Treg subpopulations with distinct migration phenotypes, the stage of the immune response that Tregs encounter and the strategies undertaken to combat the diseases are decisive factors to favorable outcome. Based on current experiences in therapies by harnessing leukocyte migration in IBD, this therapeutic modality can be potentially applied to other inflammatory diseases. The overall outcome of immune regulation attributed to altered Treg migration phenotypes should be taken into consideration.

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Conflict of Interest Disclosure

The authors declare no commercial or financial conflict of interests.

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