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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

β7 Gives Tregs a Gut Area Code

Biologics have revolutionized the treatment of inflammatory bowel diseases (IBDs), which include Crohn's disease and ulcerative colitis. Although many biologics (eg, infliximab) are targeted against tumor necrosis factor, blocking of lymphocyte-expressed integrins represents an important and widely used alternative. Vedolizumab is a key weapon in the therapeutic arsenal and consists of a humanized monoclonal antibody that binds heterodimeric α4β7 integrins, which are expressed primarily on lymphocytes that home to gut lymphoid and mucosal tissue. Blocking the extravasation of T lymphocytes, through inhibition of the interaction between α4β7 integrins and their endothelial receptor mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), prevents T-cell intestinal infiltration and inflammation in IBD, while sparing the patient of systemic immunosuppression, because the α4β7 integrin target is not expressed in immune cells that home to other organs. Vedolizumab improves IBD symptoms and induces remission in many patients, including in those who have not responded to other biologics.[1]

Despite the promise of α4β7-targeted therapies, the use of vedolizumab, similar to many other biologics, is associated with a high rate of clinical nonresponse. The reasons for this nonresponse are generally not known. There could be technical issues related to dosing and human variation in drug pharmacokinetics. However, could there be a deeper reason?

In this issue, Sun et al[2] show that genetic ablation of β7 integrin (*Itgb7*), one half of the integrin heterodimer inhibited by vedolizumab, paradoxically worsens colitis in mice. Understanding this phenomenon, and the role of β7 in the body, could help to build a biological framework to explain why some patients either do not respond or actually fare worse with vedolizumab.[1] The findings are replicated in 2 different mouse models of colitis. The first, the *Il10*$^{-/-}$ model, involves the genetic deletion of the immunosuppressive cytokine interleukin 10 (IL10). IL10 is secreted by immunoregulatory cell types, including regulatory T cells (Tregs) and M2-polarized macrophages, and its loss predisposes animals to spontaneous, microbiome-targeted colitis. Sun et al[2] have shown that the *Il10*$^{-/-}$ *Itgb7*$^{-/-}$ mice have reduced numbers of colonic Tregs relative to *Il10*$^{-/-}$ *Itgb7*$^{+/+}$ mice. The immunosuppressive function in vitro and homing of *Itgb7*$^{-/-}$ Tregs to other organs in vivo appeared normal, suggesting that β7-mediated homing of Tregs to the gut is needed to prevent severe disease. To support this phenomenon in an adoptive transfer colitis model with functional IL10, Sun et al[2] co-transferred naive CD4+ conventional T cells and β7-expressing or β7-deficient Tregs to *Rag1*- (ie, T-cell– and B-cell–) deficient recipients. A key advantage of the adoptive transfer model is that genetic alterations to T-cell subpopulations can be evaluated in a recipient animal that has not harbored a lifelong mutation in the specific gene of interest (ie, *Itgb7*), which can help distinguish developmental vs acute causes of colitis. Similar to the *Il10*$^{-/-}$ models, Sun et al[2] found more severe disease with transfer of β7-deficient Tregs and a reduced ability of *Itgb7*$^{-/-}$ Tregs to home to the gut.

Moving forward, these elegant experiments raise important questions. Genetic deletion of *Itgb7* and antibody-mediated blocking of α4β7 integrins are not the same thing. In particular, blocking of β7 also would disrupt αEβ7 integrins, which mediate interactions between immune cells and epithelia. Sun et al[2] partly address this by showing similar results with blocking of MAdCAM-1. Nonetheless, preliminary results[3] from human IBD treated with etrolizumab, a β7 blocker, suggest clinical efficacy. Thus, it remains to be seen whether Treg homing is affected in patients whose disease resists treatment with vedolizumab or etrolizumab. The data presented here additionally would seem to contradict previous work[4,5] showing that homing is dispensable for Treg-mediated immunosuppression in the gut. It is possible that some of these discrepancies are the result of differences in the microbiome at various study locales. The finding that some Treg function is preserved in the absence of IL10 also is interesting, and identification of these other immunosuppressive molecules will advance Treg biology in colitis.

However, the thousand-foot view is that there may be some collateral damage that occurs with inhibition of the integrin β7 subunit. The balance between desired and undesired effects probably depends on the individual patient. A key goal should be to predict who would be a good candidate for integrin-targeted therapies, given that these therapies could fundamentally alter immune function and might not provide the anticipated outcome. One should note that this is true for all IBD therapies, including biologics, because no medicine has yet proven to be a magic bullet.

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Conflicts of interest
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