SOCIETY FOR MUCOSAL IMMUNOLOGY

COMMENT

α4β7 expression guides B cells to front lines of defense in the gut

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One of the main characteristics of a functional immune system is the ability to limit specific pro- or anti-inflammatory responses to a designated site, without systemic or off-target effects. Integrins are cell surface glycoproteins that play a key role in mediating leukocyte migration, through specific binding to their receptors, expressed at the respected site. More than 20 different integrins have been identified that vary according to their expression pattern and specificity of ligand binding. These processes are further strengthened by the expression of various chemokine receptors on immune cells that are involved in stabilizing the interaction between the immune cells and the vessel walls during the extravasation process at peripheral sites. The α4β7 integrin complex binds mucosal addressin cell adhesion molecule 1 (MAdCAM-1), expressed exclusively on intestinal endothelial cells, leading to leukocyte extravasation into intestinal high endothelial venules and is therefore considered gut-selective.

Most data until recently on α4β7-mediated homing to the intestine was focused on different subsets of T cells. Here Christopher Tyler and colleague assess through in-depth immune profiling of different mouse models how α4β7 directs B cells to the gut in the setting of intestinal inflammation.[1] Although B cells are abundant throughout the gastro-intestinal tract, and it is well established that secretory IgA plays a key role in the defense against different pathogens, the role of B cells in sustaining mucosal hemostasis is not well defined.

The authors initially show through mass cytometry in *Il10*$^{-/-}$ mice that B cells predominately express α4β7 in the colonic lamina propria, in contrast to T cells that express α4β1.[1] Along these lines, the *Il10*$^{-/-}$*β7*$^{-/-}$ mice developed a more severe form of spontaneous colitis, compared to *Il10*$^{-/-}$ or *β7*$^{-/-}$ mice. Despite severe inflammation, B cell numbers were unchanged in the colons of *Il10*$^{-/-}$*β7*$^{-/-}$ mice, while the concentrations of intestinal antibody secreting cells (ASC) were significantly lower, compared to *Il10*$^{-/-}$. Strikingly, an increase in CD3^{+} T cells was observed in colitic *Il10*$^{-/-}$*β7*$^{-/-}$ mice. These results were strengthened by additional observations in *Il10*$^{-/-}$ mice that administration of MECA-367, an antibody targeting MAdCAM-1, the ligand of α4β7, led to development of severe colitis with similar immunophenotyping data in the gut, including a decrease in B cells and ASC and an increase in T cells. The *Il10*$^{-/-}$*β7*$^{-/-}$ mice, similar to the IgA-deficient *Il10*$^{-/-}$ mice that also developed worsened colitis, were shown to exhibit a decrease in intestinal microbiome diversity, including expansion of clostridiales species and a decrease in bacteroides, similar to microbiome metagenomic profiles observed in patients with active inflammatory bowel diseases (IBD).[2] Collectively, the authors show how blocking α4β7 or MadCAM-1 expression results in severe colitis in a predisposed model of IL10 deficiency. Moreover, their data highlights an important role for α4β7 expression on B cells for their migration to the gut, including generation of local ASC. Loss of α4β7-MAdCAM-1 interactions results in a relative decrease in intestinal B cells and a colonic deficit of ASC, predisposing to severe colitis (Fig. 1).

One of the main questions arising from this work is how to reconcile the data with clinical observations on the effectiveness of different anti-integrin drugs for both patients with Crohn's disease (CD) and those with ulcerative colitis (UC). The first anti-integrin drug that was approved for patients with CD was natalizumab, a humanized monoclonal antibody targeting α4. Although shown effective in treated patients, it had a severe side effect profile of progressive multifocal leukoencephalopathy, and its use was discontinued. Vedolizumab, a monoclonal antibody targeting α4β7, was approved in 2014 for treatment of patients with moderate-severe CD or UC,[3,4] and is widely used in the clinic for patients with IBD with overall good efficacy and safety profile given its selectivity to the gut. Currently there are many other anti-integrin drugs in different stages of development for patients with active IBD with promising results, such as etrolizumab, targeting β7 (including α4β7 and αEβ7 integrins) and also ontamalimab, a monoclonal antibody targeting MAdCAM-1.

Despite the well-established efficacy of vedolizumab in the clinic, how blocking α4β7 suppresses intestinal inflammation is not entirely clear. Until recently the driving hypothesis was that vedolizumab targets homing of effector T cells, as α4β7 is upregulated on activated cells.[5] However, this dogma has been challenged by recent studies that other immune cells also express α4β7 and therefore might similarly be targeted by the drug. β7 expression was shown to facilitate intestinal migration of different innate immune cell populations, including inflammatory monocytes, macrophages and retinoic acid-producing dendritic cells.[6,7] Moreover, Zeissig et. al. compared systemic and mucosal immune profiles of 18 IBD patients treated with vedolizumab to 20 patients treated with anti-TNFα.[8] While they were unable to show differences in the frequency or phenotype of mucosal T cells in patients treated with vedolizumab, they did identify marked changes in macrophage abundance, phenotype and pattern recognition receptor expression.[8] We also

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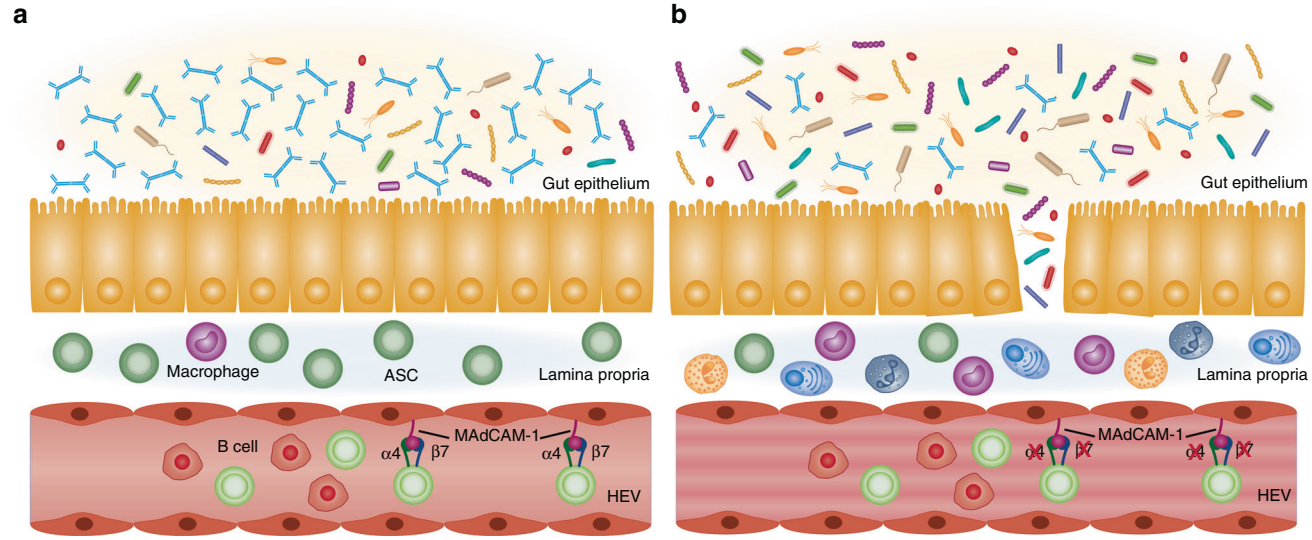

Fig. 1 α4β7-associated B cell intestinal homing is important for maintaining mucosal homeostasis and prevention of colitis in mice. a In steady-state conditions, α4β7 expression on B cells in the high endothelial venules (HEVs) guides their migration to the gut, where they develop into antibody secreting cells (ASC) which take part in mainlining mucosal homeostasis and prevention of intestinal inflammation. **b** Lack of α4β7 expression on B cells leads to diminished intestinal homing of B cells, a decrease in mucosal ASC and decreased production of luminal secretory IgA, resulting in colitis.

showed in sorted circulating α4β7 effector T cells from patients with active CD and UC a polyclonal TCRβ immune repertoire, similar to control subjects.[9] This was initially a surprising observation, since we anticipated to identify expanded gut-directed T cell clones, but might be in line with above observations questioning the importance of α4β7 expression for T cell gut homing. Moreover, α4β7 was shown to direct $CD14^{+}CD16^{high}$ non-classical monocytes migration to the gut, where they develop into $CD163^{+}$ wound healing macrophages.[10] Collectively, these studies, along with Tyler et al. work[1] indicate that vedolizumab most likely targets multiple immune cell populations, including T and B cells, along with different innate immune subsets.

The current study, showing that targeting β7 or MAdCAM-1 worsens colitis in the *Il10*$^{-/-}$ mice contrasts the vast experience with vedolizumab (and other investigational drugs) as being effective in inducing and maintaining remission in patients with IBD. One possibility is the applicability of this mouse strain for human IBD, although inflammation in the *Il10*$^{-/-}$ mice develop spontaneously, without chemical triggers, such as dextran sodium sulfate or 2,4,6-Trinitrobenzenesulfonic acid solution. A different hypothesis might relate to kinetics of vedolizumab. We have learned in the past decade that this is a slow-acting drug, and a clinical response cannot be determined before 14–22 weeks of therapy, much slower than response to TNFα antagonists, such as infliximab. It is possible that innate and adaptive immune populations are affected differently by these drugs, based on the level of expression and the rate of replenishment of mucosal immune compartments. Another possible explanation is that integrin expression levels may fluctuate, and therefore longitudinal serial studies are needed to better define these kinetics. Finally, these drugs might have a direct effect that has not been defined to date on mucosal immune populations that are already in the gut, and not necessarily only on homing properties. It is important to also address Uzzan and colleagues research of six patients with HIV and IBD that were treated with vedolizumab, resulting in a significant decrease in lamina propria B cells and a decrease in lymphoid aggregates.[11] However, this treatment did not lead to worsening of intestinal inflammation, though initial disease severity was very mild and extent of colitis was limited.[11]

In conclusion, this study puts the spot on the role of B cells in mediating intestinal inflammation, and how α4β7- MAdCAM-1 interactions are required to direct B cells to the gut. Nevertheless, it raises more questions on the mechanisms of anti-integrin drugs in restoring mucosal homeostasis among IBD patients. Additional studies are required to better define expression levels of different integrins in the circulation, in gut-associated immune structures and during steady state and different stages of inflammation, in both animal models and in humans. Moreover, although the efficacy of vedolizumab and other anti-integrin medications is well established, studies are required to understand the processes resulting in these beneficial effects.

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AUTHOR CONTRIBUTIONS

D.S.S. conceived this commentary and wrote it.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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