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Letter to the Editor

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The Importance of Molecular Immune Investigation in Therapeutic Clinical Development for Biomarker Assessment

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We thank Roosenboom *et al*. for their interest in our paper exploring the relative expression of αE integrin in the colon and ileum in inflammatory bowel disease [IBD] patients and in healthy subjects. The αE integrin [CD103] is a cell surface molecule that forms a heterodimer with β7 integrin and, through interactions with E-cadherin, serves to retain αEβ7-expressing cells at mucosal surfaces.[1] Therapeutic treatment with etrolizumab, which binds to β7 integrin and blocks both α4β7:MAdCAM-1 as well as αEβ7:E-cadherin interactions, led to a reduction in crypt-associated αE+ cell numbers in a phase 2 clinical trial.[2] Baseline levels of colonic αE expression were also associated with remission in a post-hoc analysis of the same study.[2] Our present study was designed to evaluate the prevalence and localization of αE+ cells in the colon and ileum and the potential impact of inflammation and concomitant medication on αE expression.[3] We found αE expression to be stable and not dependent on either concomitant medications or degree of inflammation. These findings are of importance given the future potential of biopsy-based predictive biomarker assessment for etrolizumab treatment.

Roosenboom *et al*. suggest that the role of αE+ cells in IBD pathobiology is not currently understood.[4] While studies are on-going, previous work from our labs and others using enzymatic digestion of intestinal biopsies has shown that αE integrin is expressed on approximately 90% of intraepithelial lymphocytes in the intestine, 40% of T cells in the lamina propria, and <3% of circulating T lymphocytes.[5,6] As many αE+ cells are intra-epithelial, appropriate digestion of tissue prior to analysis is critical and studies that have used only mechanical isolation of cells have shown lower levels of αE+ cells with high variability.[7] Mechanical isolation techniques have been demonstrated to result in low cell yield, functional alterations[8] and inversion of the CD4:CD8 ratio[9] that may affect the interpretation of studies that have not used enzymatic digestion.[7,10] Our previous studies using enzymatic digestion have shown a potential inflammatory role for CD4+αE+ T helper cells,[6,11] more interferon-γ in αE+ CD8+ T cells,[6] and a striking increase in tissue αE+ CD4 T cells during inflammation in ulcerative colitis.[12] Other groups have shown that αE is induced on Th9 cells, a key CD4 helper T cell population *in vitro*, and blockade of both αEβ7 and α4β7 is superior to blockade of α4β7 in inhibiting homing of these cells, as well as CD8 T cells, to the inflamed intestine.[13] Taken together, these data implicate αE+ T cells in the pathophysiology of IBD.

Personalized medicine has been identified as a major unmet research need of importance to patients and clinicians in IBD,[14] and has the potential to direct the right treatment to the right patient at the right time, thereby maximizing the likelihood of a positive clinical outcome whilst aiming to minimize risk of side effects and cost. The potential utility of αE or other genes[11] as predictive biomarkers for etrolizumab is being tested prospectively in on-going phase 3 clinical trials. To reach the goal of personalized medicine for IBD patients, predictive biomarkers such as αE for etrolizumab must be prospectively tested as well as evaluated in patient datasets to move the field forward.

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