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EDITORIAL

T-Cell Specificity Matters in IBD: Impaired IL10 Production Revealed by OmpC-Tetramers

Crohn's disease (CD) is a is a chronic inflammatory disorder of the intestinal mucosa. Uncontrolled cycles of inflammation result in cumulative intestinal damage and there is an urgent need to find better ways to prevent or treat symptoms as early as possible. Effective intervention, however, requires knowledge of the triggers for disease onset and immune cells driving pathology. A key question in the study of CD, and indeed in inflammatory bowel disease (IBD) in general, has been: what are the antigens that drive this inappropriate immunity?

In contrast to classic autoimmune diseases in which immune cells react inappropriately to self-antigens, accumulating evidence suggests that in IBD, the inappropriate response is to antigens from the intestinal microbiome. Early evidence from the seminal studies of Targan and Elson have shown that a significant proportion of CD patients have high levels of antibodies to bacterial flagellin proteins from *Clostridium* cluster XIVa (reviewed in[1]). In support of the concept that bacterial antigens drive IBD, there are associations between the frequency and phenotype of bacterial-specific $CD4^+$ T cells and IBD disease severity.[2–4] However, a limitation of these studies was that specific epitopes were not mapped, meaning that it was not possible to create tetramer reagents, mainstay reagents in the immunology tool box, which allow precise quantification and phenotypic characterization of antigen-specific T cells.

Seeking to overcome this limitation, Uchida et al[5] used tetramer-guided mapping to identify T-cell epitopes within the *Escherichia coli* outer-membrane porin C (OmpC), an antigen previously associated with perforating disease in CD patients.[6] They elected to focus on HLA-DRB1*15:01–restricted epitopes because there was a high frequency of this HLA type in their cohort of individuals with OmpC-specific antibodies. They subsequently identified an HLA-DRB1*15:01–restricted OmpC epitope, $OmpC^{321–340}$, enabling tetramer-based analysis of antigen-specific $CD4^+$ T cells.

Consistent with previous reports[2–4] of bacterial-specific T cells in IBD, Uchida et al[5] found that there was no difference between healthy controls and CD patients in the absolute number of circulating $OmpC^{321–340}$–specific $CD4^+$ T cells. In addition, as previously observed,[2,3] $OmpC^{321–340}$–specific $CD4^+$ T cells had a T-helper 17 cell phenotype, defined as $CD161^+CXCR3^{neg}$. After sorting and clonal expansion, $tetramer^+$ $OmpC^{321–340}$–specific cells retained antigen specificity and, strikingly, clones from CD patients secreted significantly less interleukin (IL)10 than those from healthy controls. Although not significant, there also was reduced production of the T-helper 2 cell cytokines IL4, IL5, and IL13, with no changes seen for IL2, IL6, IL13, IL21, tumor necrosis factor, or interferon γ, illustrating the restricted nature of the IL10-specific effect in CD patients. Moreover, blocking activation of the costimulatory receptor CD226 further enhanced IL10 expression by $OmpC^{321–340}$–specific T cells from healthy controls, but not CD patients.

T-cell–receptor sequencing of $OmpC^{321–340}$–specific $CD4^+$ T-cell clones showed that although the $OmpC^{321–340}$–specific clones were polyclonal, they contained a substantial number of public clonotypes (ie, clonotypes with identical CDR3 amino acid sequences in several individuals). These data suggest that the majority of individuals have $OmpC^{321–340}$ specific T cells and thus that immune responses to this epitope are not inherently pathogenic but rather that in CD the normal function of these cells is altered.

This study advances our understanding of T-cell immunity in CD in several ways. First, it provides a tetramer reagent to study antigen-specific $CD4^+$ T cells in this disease; an important technical advance. Second, it highlights important commonalities between CD and other autoimmune diseases, in which there is similar evidence for functional rather than numeric changes in self-reactive T cells. For example, in type 1 diabetes, most people have islet-reactive T cells, and protection from disease is associated with increased frequencies of islet-specific IL10-producing effector T cells and Forkhead Box protein 3^+ regulatory T cells.[7] Third, it shows the T cell immunoreceptor with Ig and ITIM domains (TIGIT)/CD226 axis may be important in regulating IL10 production in human $CD4^+$ T cells, providing new possibilities for therapeutic manipulation of IL10. Finally, together with recent literature, it solidifies the notion that the development of inappropriate adaptive immunity to intestinal bacterial is a key aspect of the pathogenesis of CD.

Future studies should address why this specific reduction in IL10 secretion occurs and confirm the mechanistic basis. Defective IL10 secretion in cells after in vitro expansion suggests stable epigenetic changes. Understanding how these changes could be reversed will be an important step toward identifying new therapies for CD.

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