patients. Both papers support the accumulating evidence that to avert the risk of HCC, viral replication needs to be inhibited early during the chronic HBV infection, preferably before the stage of advanced fibrosis.

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Conflicts of interest
The authors disclose no conflicts.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2014.05.026

Studies in Human Intestinal Tissues: Is It Time to Reemphasize Research in Human Immunology?

See "A CD3-specific antibody reduces cytokine production and alters phosphoprotein profiles in intestinal tissues from patients with inflammatory bowel disease," by Vossenkämper A, Hundsrucker C, Page K, et al, on page 172.

Inflammatory bowel diseases (IBD) arise largely owing to an inappropriate mucosal immune response to luminal antigens.[1,2] Our understanding of the pathogenesis of these diseases and many of our current and future therapeutic approaches, have evolved from studies of human tissues and animal models. In this issue of *Gastroenterology*, Vossenkämper et al,[3] reported on their investigation of the ability of an antibody targeting CD3 to inhibit T-cell–mediated inflammation in intestinal tissues from patients with ulcerative colitis (UC) or Crohn's disease (CD). This interesting study illustrates the potential benefit of studying

human intestinal tissues directly in the evaluation of the potential benefit of a biological therapy. In addition, new insights into the pathogenesis of disease can be achieved by understanding how therapies work.

At the risk of oversimplifying a vast literature, IBD is associated with genetic polymorphisms that impact the host response to microbial and metabolic stress, including the innate cytokine responses mediated by macrophages, dendritic cells, and epithelial cells.[1,2] As a consequence of the transition from innate to adaptive immunity, there are increased numbers of lamina propria T and B lymphocytes.[4] T cells are among the central sources of cytokines and together with those produced by innate cells, they target virtually all lineages within a tissue resulting in changes in gene transcription and function. For example, tumor necrosis factor-α and interferon-γ induce chemokine responses by the epithelium, myofibroblasts, and endothelium, leading to the recruitment and activation of neutrophils, monocytes, and lymphocytes from the peripheral blood. T cells also drive the expansion of B cells and the selection of the immunoglobulin (Ig)M and IgG isotypes that can activate complement[5] and contribute further to the inflammation and tissue damage (Figure 1).

Advances in understanding immune-mediated diseases such as rheumatoid arthritis, psoriasis, and type I diabetes have led to the development of useful biologics, and others show substantial promise. Curiously, most drugs used currently for treating IBD were pioneered in other disorders. For example, corticosteroids, methotrexate, and tumor necrosis factor inhibitors were developed and used in rheumatoid arthritis before IBD. From an immunologic perspective, this speaks to a significant degree of overlap in key pathways that drive inflammation. However, these diseases are complex. For example, interleukin (IL)-17 has been implicated in IBD through phenotyping intestinal T helper cells, genetic studies in humans, and murine models of intestinal inflammation.[6] Although clinical trials utilizing therapeutic approaches that targeted IL-17 were efficacious in psoriasis, these were ineffective in IBD, and exhibited a trend toward harm.[7] Another paradox in the efficacy of biological therapy was identified in studies showing that some of the TNF-α neutralizing antibodies that were effective in rheumatoid arthritis or other disease failed to work in IBD, whereas others worked in both.[8,9] Somewhat surprisingly, TNF-α inhibition worked in UC as well as CD. Clearly, there remain significant gaps in our knowledge of how immune responses function and how they can best be manipulated therapeutically.

There are several reasons why a seemingly similar approach may work in one immune-mediated disease and fail in another. The issues of dose, bioavailability, or the

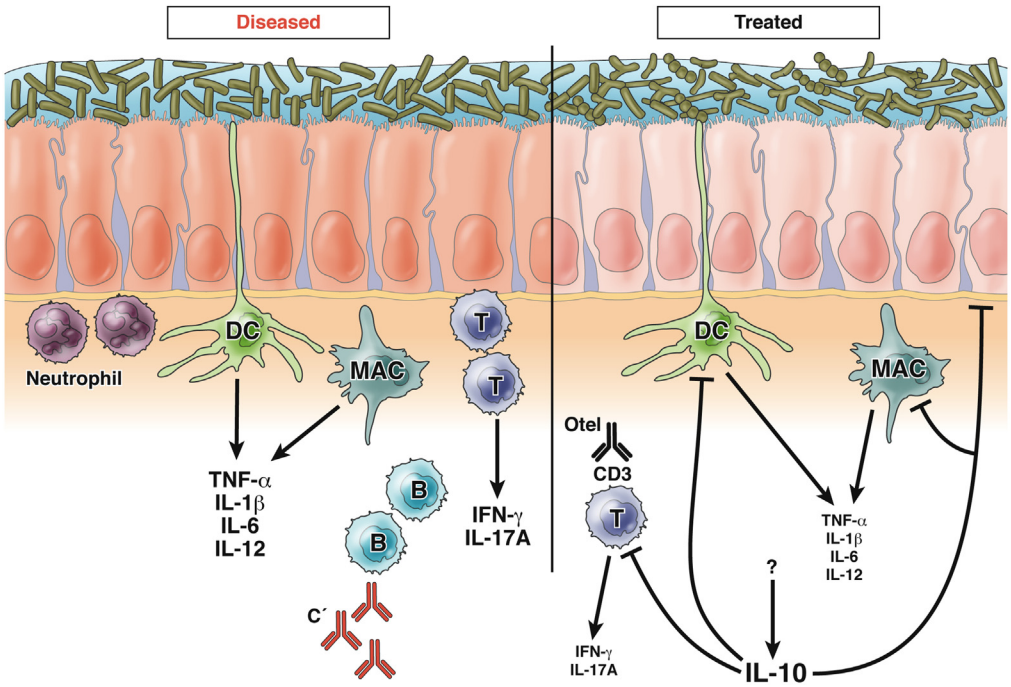

Figure 1. Inflammatory bowel disease is associated with genetic polymorphisms that impact the innate responses to bacteria mediated by macrophages (MAC), dendritic cells (DC), and epithelial cells. As a consequence of the transition from innate to adaptive immunity, there are increased numbers of T and B lymphocytes within the lamina propria. The simplified model shows the primary sources of some key cytokines associated with both Crohn's disease and ulcerative colitis (*left panel*). T cells are among the central sources of cytokines and change the function of many cell lineages. T cells also drive the expansion of B cells and the selection of the more pro-inflammatory immunoglobulin (Ig)M and IgG isotypes that can activate complement (C'). In response to the otelixizumab anti-CD3 antibody (otel, *right panel*), there was an increase in interleukin (IL)-10 that accounted for changes in many of the phosphoproteins as well as pro-inflammatory cytokines and chemokines (see Results, Vossenkämper et al[3]). This approach to model the effect of biologics in explants may prove to have meaningful predictive value for drugs in advance of clinical trials or in tailoring a treatment protocol to an individual patient. IFN, interferon; TNF, tumor necrosis factor.