

**EDITORIAL****INFLAMMATORY BOWEL DISEASE AND LYMPHOLOGY:  
A DISCONTINUOUS THREAD REVISITED IN THE MOLECULAR ERA**

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In this issue of *Lymphology*, Becker and colleagues (1) meticulously dissect molecular mechanisms, develop new insights, and review current concepts on the molecular basis, pathophysiologic events, and historical context implicating “lymphatic dysregulation” as a key player in the pathogenesis, defense, and progression of inflammatory bowel disease (IBD). Drawing on the explosion in “molecular lymphology” during the past 15 years, the authors implicate novel regulatory factors and new roles for familiar signaling pathways linked to inflammation-induced lymphatic alterations associated with lymphangiogenesis and tissue remodeling.

While their focus is on non-infectious enteritis, IBD spans a spectrum of intestinal disorders, some of which can be traced to specific microbes as etiologic agents and others, perhaps by default, classified as non-infectious immune disorders, i.e., not linked to a specific microbe. Indeed, in their original description in 1932, Crohn et al (2) distinguished cases of regional ileitis among the “benign granulomatous tumors” which clinically and histologically resembled tuberculous enteritis but where the tubercle bacillus could not be isolated or identified on tissue section.

From the outset, lymphatic system abnormalities – increased lymphatic vessel density and vigorous immune system response –

have provided a backdrop for Crohn’s disease and other inflammatory bowel disorders. In the context of “lymphology” – the study of the integrated function of the lymphatic system – *lymphatic vessels, lymph, lymph nodes, and lymphocytes* acting together – in health and disease, IBD fulfills the definition of a “lymphologic” disorder:

*Lymph* transports causative microorganisms from the infected intestine, for example, tubercle bacilli, through the thoracic duct lymph (and from there to central bloodstream and lungs) as reported after thoracic duct cannulation (3) and on autopsy tissue section in patients with tuberculous enteritis. In addition, Whipple cells – lipid-laden macrophages now known to be infected with the rare and fastidious bacillus called *Tropheryma whipplei*, the elusive cause of intestinal lipodystrophy (Whipple’s disease) – have also been found circulating in thoracic duct lymph (4). Superimposed on lymphogenous spread of intestine-dwelling microbes (and inflammatory biomarkers), immune system involvement (i.e., *lymph nodes and lymphocytes*) is a hallmark of IBD. And Becker et al describe in detail the *lymphatic vessel* abnormalities and dysfunction in IBD investigated increasingly in the past 10 years.

Furthermore, to lymphologists all too familiar with the gross appearance, tissue changes, progression, and complications of chronic lymph stasis manifested in the lymphedematous limb, the “garden hose” intestine of regional ileitis bears a striking

resemblance. Indeed, Reichert (5) in 1936 reproduced the gross and histologic findings of regional ileitis by silica injections in the mesenteric lymphatics leading to chronic lymphedema of the bowel wall, thickening, “string sign” and the “garden hose.” The elegant studies of Kalima et al (6) in the pig further elaborated on these findings, including specific features of the fibrotic process and adipose tissue deposits (“fat wrapping”). These conform to the sequelae of lymphostasis in multiple organs of the body, most strikingly in the elephantine limb of chronic lymphatic filariasis. This general concept of “lymphostasis” was applied throughout the body in Rusznyak, Földi, and Szabo’s seminal text of lymphology (7) and further developed in subsequent years by Földi and colleagues and applied to a wide variety of experimental models and clinical settings. Clinically, surgeon-lymphologists Dumont, Mulholland, and C Witte in the 1960’s at New York’s Bellevue Hospital described at operation the characteristic impaired mesenteric lymphatic drainage after subserosal blue dye injection in the ileum of patients with Crohn’s disease, a finding recently expanded by Tonelli as a valuable operative prognostic feature to assess active disease and guide the extent of resection (8). Other clinical features, specifically susceptibility to recurrent intestinal infection and also greatly enhanced risk of neoplasia (specifically, colorectal cancer), follow in the wake of lymph stasis and chronic inflammation in IBD as they do in peripheral lymphedema.

Thus, the discontinuous threads linking IBD and lymphology over the past century are now being picked up and, with new molecular insights, woven together into the fabric of Becker et al’s convincing story that “lymphatic dysregulation” plays a key and neglected role in IBD pathogenesis and should be targeted in the search for improved treatment modalities. Perhaps lymphatic biologists Yoffey and Courtice posed the most basic of questions (9). While contemplating the “small epithelioma on the back of the hand with axillary metastasis, a small septic

wound with angry red lines running up to the axilla,” they asked, “as far as barrier action is concerned, would the patient perhaps be better off had he possessed neither lymphatic vessels nor nodes?” The challenge ahead is to blend and translate the dramatic advances in molecular, cellular, systemic, and clinical lymphology since Crohn et al’s classic description into new ways to modulate lymphatic system function to the benefit rather than the detriment of patients susceptible to or suffering from IBD.

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