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EDITORIAL

Deciphering the Role of Mesenteric Fat in Inflammatory Bowel Disease

A well-known feature of inflammatory bowel disease (IBD), especially long-standing Crohn's disease, is mesenteric "creeping fat," which wraps around the intestine. Yet the role of such mesenteric fat in IBD pathophysiology has remained relatively elusive. Some have hypothesized that such fat might serve a protective role, possibly serving to ameliorate disease or offer an additional level of protection in the face of mucosal injury. For example, one might imagine that the wrapping fat might serve as a barrier to bacteria that might have breached the intestinal mucosa. Other investigators have proposed that mesenteric adipose tissue might serve an anti-inflammatory role. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Sideri et al[1] report findings that indicate that mesenteric fat may indeed normally be programmed to dampen inflammation but has acquired a tendency to promote inflammation in IBD.

A major reason the role of creeping fat in IBD has remained enigmatic is that its study is inherently difficult. Specifically, creeping fat generally does not exist in healthy control subjects, which precludes the approach of comparing disease versus control specimens that is typically used in biomedical research. To surmount this problem, Pothoulakis and colleagues isolated and cultured premesenteric adipocytes from healthy individuals and those with IBD, including both Crohn's disease and ulcerative colitis (UC) patients. They observed that, when isolated from healthy subjects, the preadipocytes from the controls released readily detectable levels of the anti-inflammatory cytokine interleukin-10 (IL-10). In contrast, the preadipocytes from IBD patients, both those with Crohn's disease and UC, released elevated levels of IL-1β and showed a dramatic elevation in the levels of IL-17, which were not detectable in the preadipocytes from the controls.

They also studied how such cells responded to the neurotransmitter substance P, which they have shown has immune modulating properties and is present in elevated levels in IBD. A striking disease-related pattern of responsiveness was observed. Specifically, in control preadipocytes, stimulation by substance P resulted in a rapid reduction of expression of a number of proinflammatory cytokines, including IL-17, tumor necrosis factor-α, and interferon-γ, suggesting that substance P ligation of the substance P receptor on mesenteric adipocytes might normally serve to dampen or prevent gut inflammation. In contrast, in the preadipocytes from IBD patients, substance P resulted in a rapid activation of expression in proinflammatory cytokines as assessed at both the mRNA and protein levels. Interestingly, both Crohn's disease and UC displayed markedly distinct patterns in the specific cytokines induced by substance P with the singular exception that the elevations in IL-17 were common to both of these forms of IBD.

These findings are in accord with previous observations that elevations in IL-17 expression are a central feature of IBD, but they suggest that creeping fat may not be a beneficial adaptation. Conversely, creeping fat may be contributing to the immune dysregulation associated with IBD. That the differential responsiveness of control and disease-derived preadipocytes persisted after multiple passages in cell culture suggests that these are stable characteristics of such cells acquired as a result of disease; alternatively, they could represent an inherent alteration in the adipocyte cell signaling of IBD patients.

The view that adipocytes are contributors to inflammation has gained momentum among researchers studying a number of diseases states, including cancer and type 2 diabetes, both of which are thought to be promoted by proinflammatory cytokines released by these cells. Yet inflammation also promotes adipogenesis as evidenced by the existence of creeping fat itself and observations that low-grade inflammation can promote increased adiposity. It will be important for future studies to better understand how inflammation promotes the generation of creeping fat and whether IL-17 and the other cytokines that this tissue generates are driving clinical manifestations of disease. Indeed, the recent failure of antibody-mediated neutralization of IL-17 to ameliorate Crohn's disease cautions against the view that adipocyte production of proinflammatory cytokines is actually detrimental to the host. Nonetheless, thanks to Pothoulakis and colleagues' elegant study, we can at least appreciate that mesenteric fat is certainly not an innocent bystander in gut immunity and inflammation but rather is an active participant in the process.

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Reference

1. Sideri A, Bakirtzi K, Shih DQ, et al. Substance P mediates proinflammatory cytokine release from mesenteric

adipocytes in inflammatory bowel disease patients. Cell Mol Gastenterol Hepatol 2015;1:420–432.

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