Long Term GI Damage in Celiac Disease

Gluten consumption in Celiac patients drives long term damage.

Cogence Clinical Pearl

In this Cogence clinical pearl, we look at mechanisms underlying long term or permanent GI damage from gluten consumption by patients with Celiac disease.

What the research says…

This paper, from the journal *Cell*, shows that patients with celiac disease who continue to have gluten exposure develop permanent changes in their intraepithelial lymphocyte populations. This is distinct from those with celiac disease who maintain strict avoidance of gluten.

Application…

We've all had conversations with patients who have said, "I do a great job of avoiding gluten," or, "I'm almost completely gluten free," or, "I'm gluten free except for my birthday," and so on. **This paper shows that, without complete, sustained gluten avoidance, changes in the patient's GI immune function take place that cannot be undone.** Interestingly, one feature of the shift in intraepithelial lymphocytes involves an increase in the production of interferon gamma (IFNγ). You will often see this kind of self-protective mechanism come into the picture when there is persistent damage to tissue, as the immune system tries to down-regulate pathogen burden.

The Research…

Chronic Inflammation Permanently Reshapes Tissue-Resident Immunity in Celiac Disease.
Mayassi T, Ladell K, Gudjonson H, et al. Cell. 2019 Feb 21;176(5):967-981.e19.
(color and bold added)
Abstract
Tissue-resident lymphocytes play a key role in immune surveillance, but it remains unclear how these inherently stable cell populations respond to chronic inflammation. In the setting of celiac disease (CeD), where exposure to dietary antigen can be controlled, gluten-induced inflammation triggered a profound depletion of naturally occurring Vγ4+/Vδ1+ intraepithelial lymphocytes (IELs) with innate cytolytic properties and specificity for the butyrophilin-like (BTNL) molecules BTNL3/BTNL8. Creation of a new niche with reduced expression of BTNL8 and loss of Vγ4+/Vδ1+ IELs was accompanied by the expansion of gluten-sensitive, interferon-γ-producing Vδ1+ IELs bearing T cell receptors (TCRs) with a shared non-germline-encoded motif that failed to recognize BTNL3/BTNL8. **Exclusion of dietary gluten restored BTNL8 expression but was insufficient to reconstitute the physiological Vγ4+/Vδ1+ subset among TCRγδ+ IELs. Collectively, these**

data show that chronic inflammation permanently reconfigures the tissue-resident TCRγδ+ IEL compartment in CeD.

Consistent inhibition of cyclooxygenase drives macrophages towards the inflammatory phenotype.

Na YR, Yoon YN, Son D, Jung D, Gu GJ, Seok. Plos One. 2015 Feb 13;10(2):e0118203.

(Color and bold added.)

Abstract

Macrophages play important roles in defense against infection, as well as in homeostasis maintenance. **Thus alterations of macrophage function can have unexpected pathological results.** Cyclooxygenase (COX) inhibitors are widely used to relieve pain, but the effects of long-term usage on macrophage function remain to be elucidated. Using bone marrow-derived macrophage culture and long-term COX inhibitor treatments in BALB/c mice and zebra fish, we showed that chronic COX inhibition drives macrophages into an inflammatory state. Macrophages differentiated in the presence of SC-560 (COX-1 inhibitor), NS-398 (COX-2 inhibitor) or indomethacin (COX-1/2 inhibitor) for 7 days produced more TNFα or IL12p70 with enhanced p65/IκB phosphoylation. Yml and IRF4 expression was reduced significantly, indicative of a more inflammatory phenotype. We further observed that indomethacinorNS-398 delivery accelerated zebra fish death rates during LPS induced sepsis. **When COX inhibitors were released over 30 days from an osmotic pump implant in mice, macrophages from peritoneal cavities and adipose tissue produced more TNFα in both the basal state and under LPS stimulation. Consequently, indomethacin-exposed mice showed accelerated systemic inflammation after LPS injection. Our findings suggest that macrophages exhibit a more inflammatory phenotype when COX activities are chronically inhibited.**