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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Parietal Cell Death by Cytokines

Parietal cell atrophy in the human stomach occurs along a continuum of gastric inflammation, atrophy, and then metaplasia, a preneoplastic lesion. In mice, and to a lesser extent in human beings, the best-characterized type of metaplasia is spasmolytic polypeptide-expressing metaplasia. Inflammation in the stomach generally arises in response to autoimmune gastritis or an infection from *Helicobacter pylori*. Although relatively rare, autoimmune gastritis is known to occur in response to autoantibodies to parietal cell proteins, specifically the α and β subunits of the proton pump H^+, K^+-adenosine triphosphatase. New studies from Bockerstett et al[1] used a mouse model of autoimmune gastritis and gastric organoids from the corpus to show a seminal role for cytokines in contrast to the antiparietal cell antibodies (APCAs) in the mechanism of parietal cell death. Transgenic expression of the T cell receptor from a T helper cell 1 (Th1) clone on the BALB/c genetic background mice were genetically engineered to generate antibodies against parietal cells, ultimately triggering gastric atrophy, a mechanism reminiscent of pernicious anemia. Parietal cells produce intrinsic factor, which is required for the absorption of vitamin B12. Therefore, autoimmune destruction of parietal cells reduces B12 levels, causing pernicious anemia. Although APCAs are present in the serum of other autoimmune disorders (eg, type 1 diabetes, vitiligo, autoimmune thyroid disease, and celiac disease), APCAs also are found in *H pylori*–induced atrophic gastritis.[2] Thus, immune-mediated destruction of parietal cells might prove to be the most common mechanism triggering gastric atrophy.

Prior studies have focused on Th1-mediated proinflammatory cytokines such as interleukin (IL)1β and tumor necrosis factor-α as mediators of parietal cell atrophy in the setting of *H pylori* gastritis.[3,4] More recently, both Th1 and Th17 immune responses have been implicated.[5,6] However, the cytokines mediating autoimmune destruction of parietal cells have not been well defined. The findings by Bockerstett et al[1] begin to fill this gap in our understanding by using immune cell analysis to identify a time-dependent increase in IL17A that correlated with gastric atrophy and metaplasia in the TxA23 mice. Bockerstett et al[1] hypothesized that IL17A might exert a direct effect on parietal cells to initiate their demise. They used gastric organoids to show a direct effect of this proinflammatory cytokine on nontransformed gastric cells by treating organoids with IL17A. As a result, primary gastric epithelial cells underwent apoptosis, and complemented the immunohistochemical analysis identifying the IL17 receptor on parietal cells. Taken together, the combination of tissue analysis and organoid cultures linked this IL17 cytokine-ligand interaction to the cascade of caspase-3 activation, culminating in parietal cell apoptosis, ultimately resulting in gastric (corpus) atrophy.

Similar to IL1b, which also exerts a suppressive effect on parietal but not gastric mucous cells,[7] IL17A is one of a few proinflammatory cytokines known to directly induce parietal cell death. Perhaps not surprisingly, proinflammatory cytokines are not all created equal and do not exert the same destructive effect. Although interferon-γ is a Th1 proinflammatory cytokine released during *H pylori* infection, this cytokine does not induce parietal cell death.[7] Thus, distinguishing between the effects of specific cytokines on parietal cells will enhance our ability to develop more precise small-molecule and monoclonal antibody therapies, which could be administered prophylactically if precursor lesions are detected.

Perturbations in the resident microbiota mirror variations in proinflammatory cytokine profiles, a subset of which are procarcinogenic because of their impact on stem cells and epithelial cell proliferation.[8] Thus, an imbalance in commensal bacteria may promote transformation even in the acid-producing stomach by inducing inflammation. Recent studies comparing the microbiota of the hypochlorhydric stomach in *H pylori*– vs autoimmune-mediated gastritis and proton-pump inhibition showed that these 3 mechanisms of hypochlorhydria vary substantially in how they perturb the microbiota.[9] Accordingly, the most extensive microbiota changes observed, that is, *H pylori* and autoimmune gastritis, induce parietal cell death.

Demonstration of how parietal cells die has until this report remained elusive, but can be summarized as ligand-receptor mediated. The current study is one of a few that has directly shown parietal cell death via apoptosis.[1] Huh et al[10] also showed cell death but in the setting of tamoxifen, which uses a noninflammatory ligand-receptor–mediated mechanism. Moreover, we have shown that damage-activated molecular patterns also trigger parietal cell apoptosis via caspase activation, presumably through interferon-α.[11] Showing that parietal cells undergo ligand-receptor–mediated cell death—rather than a block in terminal differentiation as previously proposed—provides an opportunity to target the specific signaling pathways regulating these processes. Presumably, blocking inflammation-mediated parietal cell atrophy would ultimately prevent neoplastic transformation of the stomach.

The current report raises 2 interesting questions for further contemplation. First, what is the significance of specific antimicrobial cytokines on parietal cells compared with other epithelial cell types? After all, destruction of the parietal cells eliminates one of the body's most important innate antimicrobial effects: the production of hydrochloric acid. Both IL1β and IL17A mediate their effect through the formation of an inflammasome, which requires caspase activation.[12] Accordingly, some reports have suggested that

Th17 regulates the production of mucosal IL1β.[13,14] Second, is parietal cell atrophy the only mechanism leading to metaplasia and ultimately transformation? Indeed, Burclaff et al[15] recently reported that targeted apoptosis of parietal cells was not sufficient to induce metaplasia, perhaps emphasizing the impact of cytokines on additional processes that facilitate transformation.

In summary, the mechanism of cytokine-induced parietal cell death is considered a critical step in the pathway to neoplastic transformation. In addition, autoimmune-mediated inflammation appears to exert more extensive destruction by affecting a sufficient enough number of parietal cells resulting in hypochlorhydria, calcium and vitamin B12 malabsorption, as well as pernicious anemia. Decreased acid production also impacts the microbiota, leaving the gut more susceptible to organisms that normally would be eliminated by the acid. Thus, for multiple reasons, understanding the mechanisms related to inflammation and parietal cell health are paramount.

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