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More testosterone, less aggression…at least in the stomach

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Chronic inflammation contributes to the development of several types of cancer, including gastric cancer. Gastric cancer is the fifth most common neoplasm and fourth leading cause of cancer-associated deaths.[1] While many people develop chronic gastritis as a result of infection with *Helicobacter pylori* and autoimmune gastritis, only a subset of those affected will develop gastric cancer.[2] Individuals that develop atrophy and metaplasia have a much higher risk of developing gastric cancer than those with mild gastritis. In the stomach, at least two types of metaplasia develop, spasmolytic polypeptide-expressing metaplasia (SPEM) and intestinal metaplasia, and both may be precursors of gastric cancer.[3, 4] There are many risk factors that influence the progression from gastritis to gastric cancer, including infection with pathogenic strains of *Helicobacter pylori*, genetics, environment, and chronic inflammation.[5, 6] The article by Busada et al. featured in this issue of *Gastroenterology* investigates the role of androgens and glucocorticoids in the development of gastritis and gastric metaplasia.[7]

The fact that sex hormones influence immune cell function and inflammation may account for differences in inflammatory diseases that develop in males and females. For example, it is well-established that the incidence of many autoimmune diseases is much higher in females than males.[8, 9] Glucocorticoids and androgens are reported to have anti-inflammatory effects, so differences in levels of either or both may contribute to inflammatory diseases.[9–12] Busada et al. studied the role of an androgen (testosterone) in protecting from the development of gastritis and gastric metaplasia. To induce disease, cohorts of male and female mice were adrenalectomized (ADX) to remove endogenous glucocorticoids, leading to gastritis. By two months of age, females developed gastritis and gastric metaplasia while male mice remained normal. To investigate whether testosterone was responsible for protecting male mice from disease, male mice were adrenalectomized and a subset were castrated to remove sex hormones. Adrenalectomized and castrated males developed gastritis that appeared identical to the ADX female mice. Additionally, gastric metaplasia developed in both ADX female mice and ADX/castrated male mice, but not ADX male mice that were not castrated. Finally, treating female mice with testosterone protected them from gastritis and gastric metaplasia. These data demonstrate that male sex hormones play a role in suppressing pathogenic gastric inflammation and metaplasia in this model of ADX-induced disease.

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To investigate the mechanism(s) by which glucocorticoids and androgens regulate the development of gastritis and gastric metaplasia, single-cell RNA sequencing was performed on cells isolated from stomachs. These data identified a subset of immune cells, type 2 innate lymphoid cells (ILC2s), that express both glucocorticoid receptors and androgen receptors. Additional support for a role for ILC2s in gastric pathology was provided by showing a reduction in disease severity when ILC2s were depleted using antibodies. Evidence for testosterone acting on ILC2s isolated from small intestines was provided by showing that testosterone injections reduced the expression of mRNA encoding two cytokines, *Il13* and *Csf2*, by ILC2s. These data reveal a possible link between testosterone and protection from disease: testosterone might act on immune cell subsets, including ILC2s, to suppress the production of proinflammatory cytokines that contribute to disease pathology.

Overall, these data add to an evolving understanding of the factors regulating the severity of gastritis and progression to gastric metaplasia. For example, Busada et. al. also implicates IL-33, a cytokine released by gastric epithelial cells, in activating ILC2s in stomach. These data are in agreement with recent studies demonstrating the potential of IL-33 to activate immune cells that contribute to gastric metaplasia.[13, 14] Although each study used a different model system, and many immune cell subsets respond to IL-33, a common theme has emerged; understanding the cytokines secreted by immune and epithelial cells is critical to understanding gastritis, gastric metaplasia, and gastric cancer development.[15, 16] If sex hormones regulate the types and levels of cytokine secretion, it is likely they play a role in regulating disease outcomes. Whether sex hormones affect gastritis and gastric metaplasia in other models needs to be determined, and if they do, this will highlight the importance of considering differences in male and female cohorts when studying inflammation-induced metaplasia.

In summary, the study by Busada et al. implicates a role for sex differences in regulating the severity of stomach inflammation in a mouse model of gastritis and gastric metaplasia. The data demonstrate that androgens likely provide males with additional protection by suppressing immune cell activity. While it remains to be determined whether androgens regulate inflammation and gastric metaplasia in other models *(H. pylori* infection, autoimmune gastritis) and in human with gastritis, these findings provide evidence that glucocorticoids and sex hormones can contribute to inflammatory disease and differences in disease incidence between males and females. For example, this could help explain why men have lower rates of inflammatory and autoimmune diseases than women. However, men are nearly two times more likely than women to develop gastric cancer, indicating that there are other factors that contribute to disease risk.[17] Furthermore, aberrant expression and activation of androgen receptors has been associated with carcinogenesis, cell proliferation, and angiogenesis facilitated by dysregulation of cell-cycle inhibitors and angiogenic factors.[18] This suggests that androgens may function as both protecting from inflammation and autoimmune diseases under normal conditions and promoting carcinogenesis when dysregulated. These findings suggest that attention should be given to differences in the cytokines and immune cells in males and females and offer additional insight into the complex mechanisms that regulate gastric carcinogenesis.

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