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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Coping With the Stress of Metaplasia

Gastric cancer remains one of the leading causes of cancer-related deaths worldwide. A critical event in the progression to gastric dysplasia is the gradual loss of parietal cells and chief cells from acid-secreting, or oxyntic, glands of the gastric corpus. This oxyntic atrophy induces glandular changes along the corpus unit, characterized by the expression of metaplastic genes. While we continue to expand the catalog of metaplastic epithelial markers, the fundamental intracellular events that underlie cellular reprogramming during the metaplastic injury response remain largely unexplored. How is gastric injury, either acute or chronic, sensed by gastric epithelium? How are these stress signals transduced and regulated intracellularly? More importantly, what are the cell-intrinsic metabolic changes that govern the metaplastic state?

In this issue, 2 groups seek to elucidate some of the metabolic changes that characterize the progression to metaplasia. On one hand, Meyer et al[1] highlight the zymogenic chief cell's capacity to handle intracellular reactive oxygen species (ROS) as a crucial licensing event during metaplastic reprogramming. Various independent lines of evidence had pointed to the reprogramming of chief cells into a population of proliferative, metaplastic cells as driving epithelial regeneration following glandular injury.[2–4] Meyer et al focus on the role of the xCT subunit of the heterodimeric cystine/glutamate antiporter in regulating cystine uptake and intracellular glutathione stores, thereby limiting the detrimental effects of ROS during metaplasia. Pharmacologic inhibition of xCT activity with sulfasalazine prevented cystine uptake, depleted glutathione stores, and increased intracellular ROS, both in vitro and in vivo. Moreover, these metaplastic cells were unable to downscale their secretory machinery through autophagy and instead underwent apoptosis, suggesting that the failure to appropriately handle the accumulation of ROS during metaplastic reprogramming triggers cell death.

The intracellular metabolic changes during metaplastic reprogramming were also explored in this issue by Tsugawa et al.[5] In contrast to Meyer et al, Tsugawa et al focused on the effects of a bacterially derived virulence factor, CagA, on metaplastic gene expression. *Helicobacter pylori* is the most significant risk factor for the development of gastric cancer, and the expression of CagA is known to confer additional oncogenic risk. How gastric epithelium reprograms and progresses to metaplasia in the face of chronic injury with CagA-positive *H pylori* strains remain unclear, however. Here, Tsugawa et al offer a potential mechanism by which the accumulation of translocated CagA in gastric epithelium enhances metaplastic gene expression. Notably, in the face of oxidative stress, gastric epithelial cells increase expression of CAPZA1, an actin filament capping protein that was previously shown to repress autophagy. This results in an accumulation of CagA within infected host cells and an increase in *CD44v9* through an upregulation of β-catenin and the alternative splicing factor ESRP1. Complimenting Meyer et al's evidence that CD44v9 regulates xCT activity, their findings highlight a mechanism by which an oxidative environment promotes the stability of an oncoprotein (ie, CagA) that influences cellular reprogramming and drives metaplastic gene expression.

Taken together, these 2 studies converge on the importance of oxidative stress in determining cellular responses during metaplastic injury. Perhaps most intriguing is that a conserved cellular reprogramming appears to be required for epithelial cells to appropriately respond to either acute or chronic gastric injury. In both cases, the injured cell must be able to degrade its secretion machinery through autophagy, re-express metaplastic genes, and proliferate. The ability of differentiated cells to repurpose themselves into proliferative, metaplastic cells in the face of injury relies in part on appropriately handling the redox changes that accompany metaplasia. Cells incapable of dealing with metabolic fluctuations can undergo apoptosis or, worse yet, accumulate and store mutations induced by oxidative stress, predisposing them to dysplasia. Cellular plasticity is therefore a process that is tightly regulated intracellularly, and we are just beginning to scratch the surface in terms of how oxidative stress is sensed during metaplasia, what other metabolic or microbial factors determine whether a metaplastic gastric epithelial cell will recover from injury or progress toward dysplasia, and whether similar mechanisms are conserved across other gastrointestinal tissues. During chronic injury, for example, it is becoming increasingly clear that metaplasia is not homogeneous across gastric tissue, and it is possible that a subpopulation of injured cells are more susceptible to oxidative stress and could be marked, among other factors, by dysregulated xCT activity or CAPZA1 overexpression, as these two studies would suggest. Future studies should continue to "stress" the intracellular metabolic changes that define cellular plasticity and that dictate metaplastic cell fate during injury as well as during recovery.

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