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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

MicroRNAs as Commanders-in-Chief

The progression to gastric cancer, one of the leading causes of cancer-related deaths worldwide, is driven by chronic inflammation and marked by a sequence of histologic changes. One of the earliest events in this oncogenic cascade involves the gradual loss of acid-secreting parietal cells and digestive enzyme-secreting chief cells from the gastric corpus, followed by the reprogramming of differentiated, postmitotic chief cells into a population of proliferative metaplastic cells. This process, termed *spasmolytic polypeptide-expressing metaplasia* (SPEM), normally represents a transient alteration in the glandular architecture to facilitate repair but can lead to a preneoplastic progression in the face of chronic injury. It is becoming increasingly clear that the gastric corpus, like other gastrointestinal organs, exhibits significant reparative capacity after acute or chronic injury, in part because of the cellular plasticity of glandular epithelial cells. This is perhaps best exemplified by the chief cell, a differentiated cell that can heed the call for repair by autodegrading its secretory machinery, re-expressing metaplastic markers, and re-entering the cell cycle.[1] However, the intracellular mechanisms by which this process unfolds warrant further investigation. How is chief cell reprogramming activated and modulated during injury? What chief cell–specific genes and pathways characterize the initiation and progression to SPEM?

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Shimizu et al[2] identify a novel role for microRNA (miRNA) miR-148a in the cellular reprogramming of chief cells during SPEM. MiRNAs represent an expanding class of non-coding RNA molecules that can exert regulatory effects on the post-transcriptional expression of multiple gene targets. Multiple miRNAs and their targets have been implicated in various aspects of gastric cancer progression, including tumor growth, invasion, metastasis, and apoptosis.[3] Because of the crucial role of chief cells in fueling glandular repair, the authors identified a suite of chief cell–specific miRNAs by using an elegant miRNA profiling technique. Among the miRNAs most abundant in normal chief cells was miR-148a, whose expression was lost early during SPEM. Relying on established in vivo inducers of SPEM (eg, DMP-777, L635, sulfasalazine, chronic *Helicobacter felis* infection), as well as a recently developed genetic murine model of xCT inactivation,[4] the authors demonstrated that loss of miR-148a coincided with the development of SPEM and up-regulation of the early metaplastic marker CD44v9. Moreover, the expression of the DNA methyltransferase Dnmt1, a direct target of miR-148a, was significantly increased in SPEM, implicating DNA methylation as a possible regulatory mechanism for the initiation of this form of metaplasia. As in vitro validation of their findings, the authors leveraged the use of their previously developed immortalized chief and SPEM cell lines[5] to confirm that miR-148a was down-regulated in the latter relative to the former and that pharmacologic inhibition of miR-148a in immortalized chief cells recapitulated metaplastic gene expression observed in vivo. Taken together, these findings would place miR-148a as a post-transcriptional regulator of metaplastic gene expression during the initial stages of SPEM development.

In sum, the authors have expanded our mechanistic understanding of chief cell plasticity, as implicating miRNAs in SPEM adds a layer of complexity to the initiation, transduction, and regulation of the stepwise reprogramming of chief cells during gastric injury. Going forward, it will be important to determine the intracellular and/or paracrine signals that trigger the loss of miR-148a and to identify other gene targets that might be involved. If the loss in miR-148a identifies an early intracellular event in chief cell reprogramming, as the authors suggest, what other miRNAs are involved in licensing chief cells to activate downstream cellular reprogramming events? Along those lines, does miRNA expression (or lack thereof) mark specific cell states during the gastric epithelial injury response? Through modulation of miRNA expression, can chief cells interconvert between homeostasis and SPEM, and can this be modeled by using immortalized cell lines or perhaps an in vivo inhibitor of mi-148a? Although this study has provided a more granular understanding of chief cell reprogramming during gastric injury, it should prompt renewed emphasis on the role of miRNAs in epithelial plasticity and reprogramming in other gastrointestinal injury models.

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Conflicts of interest
The author discloses no conflicts.


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