

EDITORIAL

Stroma New Tune: Emerging Role of PKA in Maintaining Gastric Homeostasis

The stomach is a complex organ, comprising 2 distinct anatomic compartments (the corpus and antrum) and a diverse array of epithelial cell types that interact by an intricate but poorly understood communications network. In the corpus, isthmal stem cells replenish lost cells in the superficial pit region and cells deeper in the gland (mucous neck and parietal cells) that coordinate acid production. Gastric glands also harbor neuroendocrine cells that secrete hormones, such as ghrelin. At the base of gastric glands reside digestive-enzyme-secreting chief cells that can also serve as reserve stem cells after injury through an evolutionarily conserved program known as palignosis.¹

Despite emerging understanding of the roles of those epithelial cell types, little is known about the functional and structural significance of the mesenchymal components (eg, fibroblasts, myofibroblasts, endothelial cells) that provide structure and support for the glands. It has been shown that the bone morphogenic protein (BMP) and extracellular signal-related kinase (ERK) pathways help maintain homeostasis in the stomach by influencing the mesenchymal-epithelial interaction, and aberrant signaling in these pathways can potentially lead to tumorigenesis. But it is unclear how these pathways are regulated intrinsically and extrinsically.^{2,3}

Puri et al⁴ have now addressed the stromal knowledge gap by unveiling another player in the understudied gastric mesenchymal compartment: protein kinase A (PKA). Using a mesenchymal cell-specific Cre recombinase (Six2-Cre), and a PKA catalytic subunit mutant (PKA α R) that lacks the ability to bind to its regulatory subunit, and hence enables a constitutively active form of PKA, the authors showed that aberrant expression of PKA leads to disruption of key signaling pathways, ultimately resulting in a state of disrupted gastric epithelial homeostasis that may enable tumorigenesis.

The most obvious phenotype of these mice with altered PKA was noted in the epithelial cell compartment of the stomach corpus: a reduction in the number of key mature cell types that constitute the stomach corpus (parietal, chief, pit cells, and, to a lesser degree, neuroendocrine cells). The changes in cell census were associated with an increase (hyperplasia) in mucous neck cells and induction of spasmolytic polypeptide-expressing metaplasia. The glandular metaplasia pattern was accompanied by distinct morphologic alteration (most notably with severe cystic dilatations), chronic inflammatory changes, and aberrant STAT3 activation that has been previously identified as one of the key drivers in tumorigenesis.⁵

This study also provided valuable clues in understanding the mechanism of how aberrant expression of PKA in stromal cells governs BMP signaling. The authors used unbiased mRNA sequencing to show downregulation of multiple BMP pathway ligands and receptors in gastric tissue and downstream transcription factor targets. In contrast, transcripts encoding Gremlin-1, a well-known BMP antagonist, were enriched in the mutant mouse stomach. Furthermore, there was an increase in phosphorylated-ERK signal observed in the mesenchymal compartment. Thus, altering mesenchymal PKA alters 2 of the key pathways known to regulate gastric gland homeostasis.

This new evidence raises several additional questions about how mesenchymal cells contribute to stomach homeostasis and tumorigenesis. Is the phenotype seen because the mice have constitutively active expression of PKA in the mesenchymal cells during development, or would induction in adult tissue lead to a similar phenotype? How does PKA induce Gremlin-1, and which cells and molecular targets interpret that signal? Does this PKA mesenchymal pathway operate in injury, such as playing a role in chief cell palignosis; and if so, at which stage? A broader understanding of how aberrant expression of PKA can be linked to disrupted BMP and ERK signaling pathways will be of great interest to those studying regeneration and tumorigenesis in the stomach.

CHARLES J. CHO

Department of Medicine
Baylor College of Medicine
Houston, Texas

JASON C. MILLS, MD, PhD

Department of Medicine, Department of Pathology and Immunology, and
Department of Molecular and Cellular Biology
Baylor College of Medicine
Houston, Texas

References

- Willet SG, Lewis MA, Miao ZF, Liu D, Radyk MD, Cunningham RL, Burclaff J, Sibbel G, Lo HG, Blanc V, Davidson NO, Wang ZN, Mills JC. Regenerative proliferation of differentiated cells by mTORC1-dependent palignosis. *EMBO J* 2018;37:e98311.
- Shinohara M, Mao M, Keeley TM, El-Zaatari M, Lee H-J, Eaton KA, Samuelson LC, Merchant JL, Goldenring JR, Todisco A. Bone morphogenetic protein signaling regulates gastric epithelial cell development and proliferation in mice. *Gastroenterology* 2010;139:2050-2060.

- 117 3. Kikuchi Y, Kunita A, Iwata C, Komura D, Nishiyama T, 141
 118 Shimazu K, Takeshita K, Shibahara J, Kii I, Morishita Y, 142
 119 Yashiro M, Hirakawa K, Miyazono K, Kudo A, 143
 120 Fukayama M, Kashima TG. The niche component peri- 144
 121 ostin is produced by cancer-associated fibroblasts, 145
 122 supporting growth of gastric cancer through ERK acti- 146
 123 vation. *Am J Pathol* 2014;184:859–870. 147
- 124 4. Pawan Puri GG, Faraj R, Gibson L, Gilbreath E, 148
 125 Yoder BK. Elevated PKA activity in stomach mesen- 149
 126 chyme disrupts mesenchymal-epithelial crosstalk and 150
 127 induces preneoplasia. *Cell Mol Gastroenterol Hepatol* 151
 128 2022;XX:XXX–XXX. 152
- 129 5. Corcoran RB, Contino G, Deshpande V, Tzatsos A, 153
 130 Conrad C, Benes CH, Levy DE, Settleman J, 154
 131 Engelman JA, Bardeesy N. STAT3 plays a critical role in 155
 132 KRAS-induced pancreatic tumorigenesis. *Cancer Res* 156
 133 2011;71:5020–5029. 157
 134 158
 135 159
 136 160
 137 161
 138 162
 139 163
 140 164

Correspondence

Address correspondence to: Jason C. Mills, MD, PhD, Section of Gastroenterology and Hepatology, Departments of Medicine, Pathology & Immunology, and Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, 535E, Houston, Texas 77030. e-mail: Jason.Mills@bcm.edu.

Conflicts of interest

The authors disclose no conflicts.

Funding

Jason C. Mills' laboratory is supported by the National Institutes of Health (awards R01DK094989, R01DK105129, P30 DK056338, R01CA239645, R01CA246208) and the BETRNet (U54CA163060). Charles J. Cho is supported by the Department of Defense, through the PRCRP program (award W821XWH2210327).

© 2022 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2352-345X

<https://doi.org/10.1016/j.jcmgh.2022.06.004>

UNCORRECTED PROOF