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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 paligenosis.[1]

Despite emerging understanding of the roles of those epithelial cell types, little is known about the functional and structural organization 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 al[4] 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 (PKAc$\alpha$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 paligenosis; 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.

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**Conflicts of interest**
The authors disclose no conflicts.

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