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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Improving Gastric Motility in Aging Through EZH2 Inhibition and Preservation of Interstitial Cells of Cajal

Interstitial cells of Cajal (ICC) provide important regulatory functions that generate the patterns of gastrointestinal motility.[1] ICC serve as pacemaker cells generating electrical slow waves that define the frequencies of peristaltic and segmental contractions.[2] ICC also mediate responses to neurotransmitters released from enteric motor neurons.[3] ICC growth and differentiation are regulated by the signaling of the receptor tyrosine kinase, KIT and its ligand, stem cell factor (SCF).[4] Under pathologic conditions, ICC exhibit phenotypic plasticity, potentially leading to their loss or dysfunction. Specifically, ICC loss is notably observed in several gastrointestinal motility disorders, such as diabetic gastroparesis,[5,6] chronic constipation,[7] and intestinal pseudo-obstruction.[8] Furthermore, studies indicate a natural age-related decline in the number of ICC in the stomach and colon, decreasing by approximately 13% per decade in both sexes.[9] One of the most conserved indicators of aging is the alteration in epigenetic markers, such as histone modifications and DNA methylation,[10] which may contribute to the decline in ICC function with age.

In a recent issue of *Cellular and Molecular Gastroenterology and Hepatology*, Taheri et al[11] explore the role of the histone methyltransferase, enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), in aging-induced ICC decline in the stomach. EZH2 catalyzes trimethylation of histone 3 lysine 27 (H3K27me3), resulting in the transcriptional repression of target genes.[12] Overexpression of EZH2 has been observed in a wide range of cancer types, leading to the clinical development of its inhibitors for cancer treatment.[13] The *klotho*-deficient mouse model resembles human aging, characterized by a short lifespan, arteriosclerosis, skin atrophy, osteoporosis, and emphysema.[14] The authors previously reported that gastric ICC were substantially lost in *klotho* mice, leading to reduced gastric slow wave activity and impaired gastric motor functions.[15] The current study found that EZH2 and H3K27me3 were elevated in an age-dependent manner in the gastric tissue of aged mice, including naturally aging and *klotho* mice, and in elderly humans of both sexes. Furthermore, they demonstrated that injection of the EZH2 inhibitor, EPZ6438 (tazemetostat), into *klotho* mice mitigated ICC loss by preserving KIT and SCF stem cell factor, improved gastric slow wave activity, increased food intake, and reduced body weight. Previous studies also noted that SCF stem cell factor is reduced in aged *klotho* mice,[15] and EZH2 epigenetically represses *Scf* expression.[16] The current study confirmed that ICC-specific *Ezh2* knockout in aged $Kit^{CreERT2/+};Ezh2^{fl/fl}$ mice prevented ICC loss by increasing KIT expression. This group previously reported that ICC arise from ICC progenitors or stem cells (ICC-SC: KIT^{low}/$CD44^{+}$/$CD34^{+}$ cells).[17,18] Transformation-related protein 53 (TRP53) plays a pivotal role in cellular senescence and aging[19] and its upregulation by the overactivated Wnt signaling in the stomach of *klotho* mice led to ICC-SC and ICC depletion.[20] Furthermore, this study showed that EZH2 inhibition in organotypic cultures and ICC-SC prevented the aging-like effects caused by TPR53 induction.

Using a comprehensive approach that includes *klotho* mice, ICC-specific *Ezh2* knockout mice, human gastric tissue, gastric muscle organotypic cultures, a murine ICC-SC line, and EZH2 inhibitors (EPZ6438 and GSK126, both Food and Drug Administration–approved drugs, and siRNA-mediated Ezh2 knockdown), this study elegantly demonstrates that EZH2 inhibition, both in vivo and ex vivo, improves gastric slow wave and motor function by preventing aging-induced ICC/ICC-SC loss in the stomach. It provides novel mechanistic insights into the epigenetic regulation of gastric ICC/ICC-SC by EZH2 in aging.

Future studies should confirm alterations in gastric ICC, slow wave activity, fundic relaxation, and appetite pathways in ICC-specific *Ezh2* knockout mice. Additionally, it is imperative to explore the direct regulation of *Kit* gene expression by EZH2 in gastric ICC. Furthermore, investigating the potential of EZH2 inhibition to enhance gastric and colonic motility in gastrointestinal motility disorders would be of significant interest.

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Conflicts of interest
The authors disclose no conflicts.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2024.101382