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Review

Cellular and molecular mechanisms underlying aging-related gastric neuromuscular dysfunction

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Abstract

Aging is linked to a gradual decline in the gastric motor function, contributing to reduced food intake, and its association with frailty and sarcopenia. A key cellular change in the gastric neuromuscular apparatus is the loss of interstitial cells of Cajal (ICC), pacemaker cells of the gut. The ICC function as pacemakers that generate electrical slow waves and mediate enteric neurotransmission, playing a critical role in gastric motility. Aging-related ICC depletion leads to impaired gastric compliance and reduced slow wave activity, which contributes to early satiety and reduced food intake. Recent studies have elucidated the molecular and epigenetic mechanisms underlying aging-related ICC decline, highlighting the roles of ICC stem/precursor cells (ICC-SCs), transformation-related protein 53 (TRP53), extracellular signal-regulated kinase (ERK), and insulin-like growth factor 1 (IGF1) pathways, and epigenetic regulation mediated by the histone methyltransferase enhancer of zeste 2 (EZH2). By synthesizing the current findings, this review aims to provide a comprehensive understanding of the mechanisms driving ICC decline and to explore potential therapeutic strategies for preserving gastric motility in aging populations. Future research should aim to translate these discoveries into clinical applications to improve the gastric motor function and overall health in the aging population. Identifying effective interventions targeting ICC maintenance may ultimately help to alleviate age-related gastric motor dysfunction and its associated health burdens, including frailty, malnutrition, and impaired quality of life.

Key words: aging, interstitial cells of Cajal, gastrointestinal tract, motility

Introduction

The global population is aging rapidly, owing to increased longevity and declining fertility rates. This demographic shift has profound implications for families and society. Although aging itself does not directly cause diseases or disorders, age-related biological defects are significant contributors, and aging is a major

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risk factor for numerous health conditions (1). The growing elderly population imposes a substantial burden on healthcare systems worldwide. As a result, all countries inevitably face significant challenges in managing the diseases and conditions that are prevalent among older adults (2). In general, aging is associated with a gradual decline in the function of most organs and tissues, including the stomach (1, 3). Age-related gastric motor dysfunction is characterized by reduced nitrergic relaxation, impaired gastric compliance, and decreased accommodation, ultimately leading to a decline in food intake (3). Although these motor functional changes are often subtle and underestimated due to nonspecific symptoms, complex underlying mechanisms, and insufficient medical attention, they have been shown to contribute to early satiety, increased satiation, and a subsequent reduction in caloric and dietary intake (4, 5). Reductions in food intake caused by gastric motor dysfunction may adversely affect the quality of life, exacerbate sarcopenia and frailty, contribute to disability, and increase the mortality risk in older adults (3, 6, 7). This phenomenon is commonly referred to as “anorexia of aging” (8). Given the increasing burden of age-related gastric motor dysfunction and its far-reaching consequences, it is critical to gain a deeper understanding of its pathophysiology. However, progress in this field has been hindered by the nonspecific nature of the symptoms and complex underlying mechanisms. In this review, we discuss the cellular and molecular changes associated with aging in the stomach as well as external factors that influence the gastric motor function. By elucidating these mechanisms, we aimed to provide insights into potential therapeutic strategies to mitigate gastric neuromuscular degeneration and improve health outcomes in the aging population.

Overview of Aging-related Cellular and Functional Changes

Gastric motility is a complex process regulated by multiple specialized cell types including interstitial cells of Cajal (ICC), smooth muscle cells, platelet-derived growth factor receptor alpha-positive interstitial cells (PICs), and enteric neurons in the gastric tunica muscularis (9, 10). ICC are mesenchymal cells derived from the mesoderm that function as pacemakers of gut motility, generating electrical slow waves to coordinate smooth muscle contractions (11). ICC also mediate both cholinergic and nitrergic neural control (12–14). Smooth muscle cells are the primary contractile components that respond to excitatory and inhibitory inputs to generate coordinated peristalsis (9). PICs are also mesenchymal cells derived from the mesoderm; these play a complementary role in transducing inhibitory signals and modulating smooth muscle relaxation, forming an integrated network known as the smooth muscle cell, ICC, and PIC (SIP) syncytium (15). Enteric neurons, including both cholinergic excitatory and nitrergic inhibitory motor neurons, regulate gastric tone and motility through neurotransmitter release (12). Disruptions of any of these cellular components can impair the gastric motor function, leading to impaired digestion and reduced nutrient absorption. Understanding the pathological mechanisms underlying age-related gastric motor dysfunction is essential for developing targeted therapies. The decline of enteric neurons with age in the lower gastrointestinal (GI) tract has been reported (16–18), but age-related changes in enteric neurons in the stomach remain unclear. Notably, although a decline in enteric neurons was consistently observed in the lower GI tract, no significant changes were detected in the stomachs of the same animals (16, 19, 20). This suggests that certain cellular or molecular differences between the lower and upper GI tracts may influence the maintenance of enteric neurons during ageing.

In contrast to the lower GI tract, the most prominent age-related cellular change in the gastric neuromuscular apparatus is the loss of ICC (19, 21–25), highlighting a distinct pattern of cellular alterations in the stomach. The stomach serves two major functions in the digestive system (26). The first function is storage of food in the proximal stomach (fundus). When food enters the stomach, the fundus relaxes to store it, allowing

sufficient time for it to be triturated and properly digested. The second function is digestion (26). The stomach triturates food and transfers it to the duodenum, where nutrients are absorbed (26). Reduced gastric slow wave activity and impaired postjunctional neural responses are key indicators of ICC depletion, as demonstrated in genetically ICC-deficient *W/W^v* mice (27), despite preserved nitrergic neural inhibition (28). This finding links ICC loss to gastric motor dysfunction (19). Impaired fundal relaxation and reduced gastric contractile activity impair the ability of the stomach to accommodate and process food, contributing to early satiety and reduced food intake in elderly individuals (19). This association has been experimentally confirmed in both chronologically aged and *klotho* mice, a model of accelerated aging (29). While the focal depletion of the antral ICC has been linked to delayed gastric emptying of solids in patients with type 1 diabetes mellitus and type 1 diabetic mouse models (30–32), gastric emptying of solids remains unaltered in *klotho* mice, aged rats, and elderly humans with diffuse ICC loss (19, 33–35). This may result from the opposing effects of aging-related ICC depletion in the antrum, which is responsible for digestion, and in the fundus, which is responsible for storage. These changes delay and accelerate the gastric emptying of solids, respectively, as summarized in Fig. 1. This interpretation aligns with the variable gastric emptying of solids reported in elderly individuals (19, 25). It is important to note that while these two mechanisms counterbalance each other's effects on the gastric emptying of solids, they collectively impose significant limitations on gastric functions, thereby explaining the

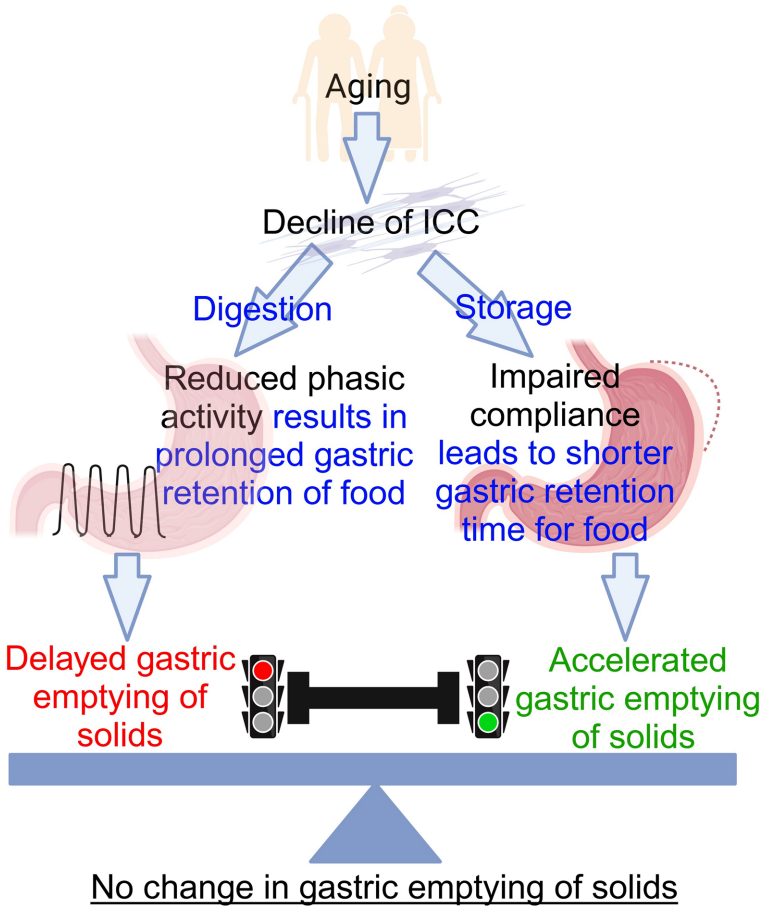

Fig. 1. Aging-related changes in gastric motility. Both proximal and distal gastric functions decline with age, primarily because of the loss of interstitial cells of Cajal (ICC). While reduction of the distal function prolongs gastric retention of food, impaired fundic relaxation accelerates its emptying. As a result, these opposing effects counterbalance each other, leading to no significant changes in the overall gastric emptying of solids.

observed reduction in food intake (Fig. 1). Notably, impaired gastric accommodation (proximal gastric motor dysfunction) alone has been shown to sufficiently reduce food intake in humans (36, 37). However, the relationship between gastric motor dysfunction and organismal aging remains incompletely understood, emphasizing the need for further experimental investigation.

The Molecular and Epigenetic Mechanisms Underlying the Decline of Interstitial Cells of Cajal during Aging

The mechanisms underlying the ICC decline during aging remain complex, multifactorial, and unclear because of controversial and conflicting reports. Here, we review the fundamental aspects of age-related ICC decline, with an emphasis on the molecular and epigenetic mechanisms involved. Notably, relatively few studies have explored the effects of aging on ICC stem/precursor cells (ICC-SCs) (19) despite their critical role in age-related gastric motor dysfunction (22). Understanding these mechanisms is essential for developing targeted therapeutic strategies to mitigate gastric motility disorders in the aging population. Aging of tissue-specific stem cells has been proposed as a major contributor to the decline in tissue and organ integrity and function in elderly individuals (38). Previous studies have identified a subset of cells in the murine gastric tunica muscularis that are immunopositive for cluster of differentiation 34 (CD34) and CD44 with low KIT expression levels as ICC-SCs (39). Unlike mature ICC, which express KIT and CD44 but not CD34, $KIT^{low}CD34^{+}CD44^{+}$ ICC-SCs actively proliferate and continuously replenish ICC (40–42). Recent findings indicate that ICC-SC decline precedes ICC loss with age, suggesting that ICC-SC depletion may play a pivotal role in age-related ICC loss and the associated gastric motor dysfunction (22). The upregulation of transformation-related protein 53 (TRP53), a tumor suppressor and aging-related transcription factor, induces persistent cell cycle arrest in ICC-SCs, leading to ICC loss without increasing senescence, quiescence, or apoptosis (22). This decline in the ICC and ICC-SCs has been linked to gastric motor dysfunction in both *klotho* and aged mice (19, 22). Furthermore, TRP53 inhibits ICC-SC proliferation by suppressing the extracellular signal-regulated kinase (ERK) signaling pathway, suggesting that age-related ICC-SC/ICC depletion could be mitigated through ERK pathway activation (22). Notably, this decline can be reversed by ERK activation via insulin-like growth factor 1 (IGF1), a nutrient-sensitive hormone (38, 43), highlighting the potential of IGF1-targeted therapies to counteract age-related gastric motor dysfunction (23, 43). These findings underscore the critical role of ICC-SCs in sustaining both ICC and the gastric motor function, while also laying the groundwork for developing innovative therapeutic strategies to address aging-related gastric motor dysfunction.

A recent study investigated the role of epigenetic repression in age-related gastric ICC decline (25). The histone methyltransferase enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) catalyzes the trimethylation of histone 3 lysine 27 (H3K27me3), leading to the transcriptional repression of target genes (44). EZH2 overexpression has been observed in various cancer types, prompting the clinical development of its inhibitors for cancer treatment (44). EZH2 and H3K27me3 levels increase with age in gastric muscles, with EZH2 upregulation directly mediated by TRP53, as demonstrated in both *in vitro* and *ex vivo* systems (25). Furthermore, treatment of *klotho* mice with the Food and Drug Administration (FDA)-approved EZH2 inhibitor EPZ6438 (tazemetostat) mitigated ICC loss by preserving KIT and stem cell factor (SCF), the KIT ligand (25). Previous studies have shown a decline in aged *klotho* mice due to EZH2-mediated epigenetic repression of the expression of *Kitl* (19, 45). This treatment also improves gastric slow wave activity, increases food intake, and reduces body weight (25). These findings provide novel mechanistic insights into the epigenetic regulation of gastric ICC/ICC-SCs by EZH2 during aging, and are summarized in Fig. 2.

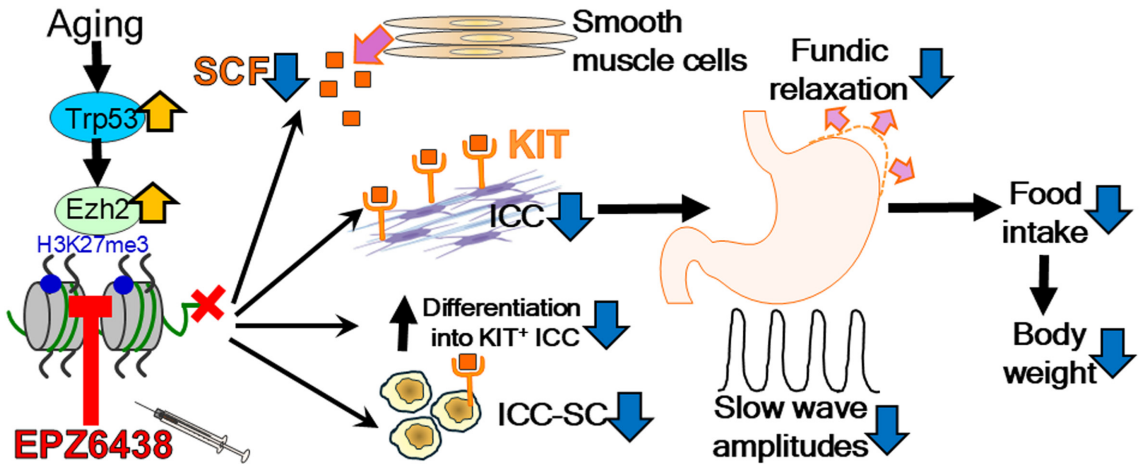

Fig. 2. Molecular and epigenetic mechanisms contributing to age-related decline of interstitial cells of Cajal (ICC) in the stomach. Aging induces the transformation-related protein 53 (TRP53)-mediated upregulation of enhancer of zeste homolog 2 (EZH2), leading to the repression of ICC stem cells (ICC-SC), KIT signaling in ICC, and KIT ligand stem cell factor (SCF). Collectively, these changes impair the gastric slow wave activity and fundic relaxation. Treatment with the Food and Drug Administration (FDA)-approved EZH2 inhibitor EPZ6438, restored ICC populations and improved the gastric motor function, highlighting the therapeutic potential of EZH2 inhibition in alleviating aging-related gastric motor dysfunction.

Conclusion

The increasing prevalence of age-related organ dysfunction poses a significant challenge to global healthcare systems (1). Aging-related changes in the gastric neuromuscular apparatus, particularly the decline in ICC and ICC-SCs, contribute to impaired gastric motility, early satiety, and reduced food intake, ultimately exacerbating conditions such as frailty, sarcopenia, and disability. The complexity of these dysfunctions is underscored by multifactorial mechanisms, including altered neurotransmission, impaired ICC maintenance, and disruptions in cellular signaling pathways. Recent findings highlight the pivotal role of TRP53-induced cell cycle arrest in ICC-SC depletion and demonstrate the potential of therapeutic interventions targeting the ERK and IGF1 pathways. Moreover, epigenetic regulation via EZH2-mediated histone modification has emerged as a critical factor in ICC decline, with preclinical studies showing promising results for EZH2 inhibitors in mitigating gastric neuromuscular degeneration (25). Despite these advances, the precise relationship between gastric motor dysfunction and organismal aging remains unclear. Further research is required to elucidate the complex interplay of molecular, cellular, and environmental factors that influence gastric motility in aging populations. Future studies should focus on translating these mechanistic insights into clinically viable therapeutic strategies aimed at preserving the gastric function, improving the nutritional status, and enhancing the quality of life of older adults. By addressing these challenges, we can pave the way for innovative interventions to mitigate the detrimental effects of age-related gastric dysfunction and support healthy aging.

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Author Contributions

Y.Z.: conception and design, manuscript writing, E.L.C.: manuscript editing, Y.H.: conception and design, financial support, manuscript writing and editing.

Conflicts of Interest

The authors declare no conflicts of interest in association with the present study.

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