cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

The Age of Angiogenesis: A Novel Role of NGF in Gastric Repair

The stomach continually encounters a wide variety of intrinsic and exogenous stress factors. These factors, which can include luminal irritants, *Helicobacter pylori* infection, and ingested therapeutics such as nonsteroidal anti-inflammatory drugs, slow epithelial repair.[1] These insults to the gastric tissue can lead to gastric, or peptic, ulcers and can become persistent or recurring ulcers.[2] In the United States alone, more than 5 million individuals suffer from gastrointestinal ulcers, with approximately 500,000 new cases reported each year.[3] Fortunately, the incidence of gastric ulcers is decreasing in the general population; however, gastric ulcer hospitalization and mortality still remain high in elderly individuals. This is owing, in part, to the increased susceptibility to injury and delayed healing that occur within the aged stomach. The aged stomach has shown decreased gastric acid secretion, motility, and proliferation,[4] which likely result in an increased susceptibility to chronic ulceration in the elderly that can be exacerbated during chronic insults such as *H pylori* infection or nonsteroidal anti-inflammatory drug administration.[5] In the United States it is estimated that the number of individuals age 65 years and older will more than double, reaching 84 million by 2050.[6] Despite the prevalence of gastric ulcers, the ulcer healing process is incompletely understood. In addition, because elderly patients show gastric pathophysiology, a better understanding of repair within the aged stomach is imperative. As a result, the development of strategies to reduce ulcer incidence or accelerate the healing process represents an important goal for gastric research.

Prior studies have described the complex process of gastric wound repair, which involves immune cell infiltration, cell proliferation, re-epithelialization, angiogenesis, and tissue remodeling.[1] Although it is known that growth factors play a critical role in gastric epithelial regeneration, the mechanism has not been well defined. The new study reported by Ahluwalia et al[7] assist our understanding of gastric regeneration by elucidating the role of nerve growth factor (NGF) expressed in gastric endothelial cells during the repair process in the stomach. The investigators observed decreased expression of NGF, which correlated with decreased angiogenesis in an in vitro culture of gastric endothelial cells isolated from aged rats when compared with gastric endothelial cells isolated from young rats. Ahluwalia et al[7] showed an increase in in vitro angiogenesis in aging gastric endothelial cells through NGF gene therapy. In addition, the investigators used inhibitors to show that this response was mediated through the phosphatidylinositol 3 kinase/protein kinase B and mammalian target of rapamycin signaling pathways. This study further provided evidence that silencing of serum response factor abolished NGF-induced angiogenesis in aging gastric endothelial cells in vitro.

The in vivo studies performed by Ahluwalia et al[7] using acetic acid to induce focal gastric injury in young and aged rats showed delayed epithelial wound repair, which was the result of decreased angiogenesis in aged rats. Administration of exogenous NGF increased angiogenesis, accelerated repair, and improved mucosal regeneration in the gastric tissue of aged rats. Analysis of human gastric biopsy specimens corresponded to experimental results showing that individuals older than 70 years of age had decreased expression of NGF in gastric endothelial cells compared with individuals younger than 40 years old.

Taken together, the combination of in vitro and in vivo experiments compellingly show that decreased expression of NGF in gastric mucosal endothelial cells in aging gastric tissue resulted in impaired reparative processes. Expression of exogenous NGF was effectively able to reverse impairment of angiogenesis and healing. The investigators thereby showed a novel role of NGF in ulcer healing with specific significance in aging gastric mucosa. Furthermore, Ahluwalia et al[7] suggested a possible therapeutic target for the treatment of mucosal injuries of the gastrointestinal tract. The work by Ahluwalia et al[7] represents an important step forward in understanding gastrointestinal epithelial regeneration. The study highlights the complex nature of epithelial wound repair that is orchestrated between a number of compartments (immune, endothelial, epithelial, and so forth).

The data reported by Ahluwalia et al[7] raises some interesting questions regarding aging gastropathy. Given that gastric cancer is most prevalent in individuals age 60 years and older,[8] what are the consequences of manipulating angiogenesis in elderly patients? The study under discussion showed a decrease in NGF in the aging stomach. However, overexpression of NGF in gastric epithelium promotes gastric carcinogenesis.[9] This suggests a delicate balance of NGF expression to maintain proper homeostasis. It is possible that in the aging stomach, the accumulation of multiple lesions may lead to deregulation of NGF, other angiogenic factors, or cytokines that could result in the development of gastric cancer rather than epithelial regeneration. The data presented by Ahluwalia et al[7] elucidate the pathway of NGF-induced angiogenesis in the setting of wound healing. However, it remains unknown whether NGF also plays a role in cancer progression in elderly individuals. Future studies likely will further illuminate our understanding of gastric ulcer repair, especially with regard to aging.

AMY C. ENGEVIK, PhD
Division of Surgical Sciences
Vanderbilt University Medical Center
Nashville, Tennessee

References

1. Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. Dig Dis Sci 2005;50(Suppl 1):S24–S33.
2. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 2006; 19:449–490.
3. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. Vital Health Stat 10 2009;242:1–157.
4. Saffrey MJ. Aging of the mammalian gastrointestinal tract: a complex organ system. Age (Dordr) 2014;36:9603.
5. Salles N. Is stomach spontaneously ageing? Pathophysiology of the ageing stomach. Best Pract Res Clin Gastroenterol 2009;23:805–819.
6. Ortman JM, Velkoff VA, Hogan H. An aging nation: the older population in the United States. United States Census Bureau, Economics and Statistics Administration, US Department of Commerce. 2014:25–1140.
7. Ahluwalia A, Jones MK, Hoa N, Zhu E, Brzozowski T, Tarnawski AS. Reduced NGF in gastric endothelial cells is one of the main causes of impaired angiogenesis in aging gastric mucosa. Cell Mol Gastroenterol Hepatol 2018;6:199–213.
8. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006;12:354–362.
9. Hayakawa Y, Sakitani K, Konishi M, Asfaha S, Niikura R, Tomita H, et al. Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. Cancer Cell 2017;31:21–34.

Correspondence
Address correspondence to: Amy C. Engevik, PhD, Division of Surgical Sciences, Vanderbilt University Medical Center, 2213 Garland Avenue, 10435 MRBIV 37232, Nashville, Tennessee 37232. e-mail: amy.c.engevik@vanderbilt.edu.

Conflicts of interest
The author discloses no conflicts.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2018.06.001