

Senescence: A Novel Driver of *Helicobacter pylori*-Induced Gastric Atrophy



Helicobacter pylori infection is the main risk factor for gastric cancer, which develops in a multistep process that includes chronic atrophic gastritis, intestinal metaplasia, and dysplasia.¹ This process develops over decades. Progression to gastric cancer can still be observed after bacterial eradication suggesting that once a “point of no return” is reached, mechanisms triggered by the infection perpetuate and drive carcinogenesis. Atrophic gastritis is a complex lesion occurring at early stages of the carcinogenesis cascade. Although, in general, it is considered a benign condition, in some individuals it progresses to gastric cancer.² Therefore, the identification of molecular mechanisms causing atrophy, and more importantly contributing to its progression to cancer, is of major importance to reduce the overall incidence of gastric cancer.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Cai and colleagues report cellular senescence as a new mechanism causing *H pylori*-induced atrophic gastritis. Previous studies showed that *H pylori*, through the Cytotoxin associated gene A (CagA)-dependent activation of p21, can induce cellular senescence.³ Based on this evidence, and considering that senescent cells are still detected in intestinal metaplasia but reduced in gastric cancer,⁴ Cai et al⁵ further investigated the incidence of senescence in various precancerous lesions, and concluded that senescent cells are primarily observed in atrophic gastric mucosa. Importantly, pharmaceutical inhibition of CXCR2 not only decreased senescence, but it also reduced gastric atrophy and delayed its progression to a more severe pathology in a mouse model.⁵ Although this observation may be somewhat counterintuitive because senescence has been classically accepted as one of the main barriers to tumor formation, senescent cells can also contribute to tumorigenesis by secreting several proteins constituting what is known as the senescence-associated secretory phenotype. This senescence-associated secretory phenotype induces several inflammatory cues and signaling events that promote cell proliferation and tumor growth, relapse, and metastasis (reviewed in Reference⁶). Therefore, the results reported by Cai et al⁵ may have important clinical implications for patients presenting with *H pylori*-related atrophic gastritis, because the presence of senescent cells might be used as a marker to identify patients at risk for gastric cancer development who need to undergo endoscopic surveillance. In addition, treatments interfering with cellular senescence represent an attractive therapeutic approach, especially when considering that *H pylori* eradication does not ameliorate atrophy in most cases, and cytokines upregulated by the bacterium and able to signal through NF κ B1 (eg, tumor necrosis factor- α , interleukin-1 β) may trigger

CXCR2 signaling, and thereby induce senescence, even in the absence of an active infection.

Further analysis of the molecular mechanisms leading to enhanced senescence after *H pylori* infection identified a feedback loop between p53 and CXCR2. Thus, p53 has a major role in the progression of gastric atrophy to other precancerous lesions, such as intestinal metaplasia or dysplasia, and eventually to gastric cancer by regulating cellular senescence in 2 apparently opposing manners. At the early stage, p53 induces senescence by activating the CXCR2 pathway. At later stages, mutations in TP53 induced by *H pylori* infection accumulate and cells are then able to escape from senescence. p53 thus contributes to gastric carcinogenesis by regulating cellular senescence in different ways depending on its mutational status.

An aspect that still remains to be resolved is the involvement of certain *H pylori* virulence factors in the induction of senescence. The presence of a functional type IV secretion system and translocation of CagA may be important for the induction of senescence, as suggested by previous studies.³ CagA-proficient strains are more virulent, induce stronger immune responses, and are significantly associated with the development of gastric cancer. In light of previous observations and the in vivo results by Cai et al⁵ using the CagA-proficient *H pylori* strain PMSS1, it is tempting to speculate that one of the mechanisms by which CagA contributes to gastric carcinogenesis is the induction of senescence in the gastric mucosa. However, further investigations are necessary to clarify this matter.

Together, the involvement of cellular senescence in the progression of gastric atrophy to other precancerous lesions and eventually to gastric cancer may have potential clinical implications that need to be further evaluated.

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Conflicts of interest

The author discloses no conflicts.

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