EDITORIAL

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Reversal of the Methylation-Associated Regulation of miR-200a/b by *Helicobacter pylori* Eradication Contributes to the Chemoprevention of Gastric Carcinogenesis

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See "*Helicobacter pylori* Eradication Can Reverse the Methylation-Associated Regulation of *miR-200a/b* in Gastric Carcinogenesis" by Ji Min Choi, et al. on page 571, Vol. 14, No. 5, 2020

MicroRNAs (miRNAs) are currently considered as crucial post-transcriptional regulators of gene expression.[1] Their roles in development, cell proliferation and differentiation are widely recognized. Furthermore, miRNAs are frequently altered in cancer cells and reveal their functions as either oncogenes or tumor suppressors.[1] The emerging role of miRNAs in diverse and fundamental cellular mechanisms suggests that proper control of these regulatory elements is essential for the maintenance of a nonpathological state.[1] Recent reports have highlighted the regulatory role of miRNAs in *Helicobacter pylori* infection and associated diseases.[2] For example, a strong inflammatory response characterized by the early production of pro-inflammatory tumor necrosis factor (TNF)-α and interleukin (IL)-6 cytokines, followed by IL-10, IL-1β and IL-23 secretion as a consequence of miR-146a up-regulation and strong miR-155 induction, which raised the TNF-α production.[2] In contrast, IL-8, TNF-α and IL-1β could contribute to the induction of miR-146a during *H. pylori* infection.[2] Therefore, miRNAs modulate the *H. pylori* infection and are also affected by these bacteria, as, for example, the synthesis of the transcription factor nuclear factor-κB that can act as a transactivator of miR-200b and miR-200c.[2] Similarly, epigenetic change is one of the mechanisms that regulates the expression of miRNAs and has been known to play a role in *H. pylori*-associated gastric carcinogenesis.[3,4] From this background Choi *et al*.[5] aimed to evaluate the epigenetic changes of miR-200a/b in *H. pylori*-associated gastric carcinogenesis and whether *H. pylori* eradication restore epigenetic changes of miR-200a/b. The miR-200 family is closely linked to the expression of ZEB1 and ZEB2, key regulators of epithelial-mesenchymal transition (EMT), and regulates crucial processes in carcinogenesis, such as tumor initiation, progression, invasion, and metastasis of various types of cancer.[5] Recent studies have shown that miR-200 family were downregulated in gastric cancer (GC), suggesting its role as a tumor suppressor in GC.[6] In addition, hypermethylation of the promoter CpG island was one of the mechanisms of miR-200c/141 downregulation.[6] However, it has not yet been fully elucidated whether epigenetic alterations in the miR-200 family are affected by *H. pylori* infection and/or by its eradication. Choi *et al*.[5] evaluated the expression and methylation levels of miR-200a/b in GC cell lines, human gastric mucosa of *H. pylori*-negative and -positive controls, and *H. pylori*-positive GC patients. They found that the level of miR200a/b methylation decreased and the level of expression increased after demethylation.[5] Furthermore, the miR-200a/b methylation levels in the human gastric mucosa, increased in the order from *H. pylori*-negative control group, *H. pylori*-positive control group, and *H. pylori*-positive GC group.[5] Interestingly the level of methylation decreased and the level of expression of miR-200a/b increased significantly only after 6 months in the *H. pylori*-eradicated group.[5] These results suggest that epigenetic alterations of miR-200a/b may be implicated in *H. pylori*-induced gastric carcinogenesis and *H. pylori* eradication improved the field defect for cancerization.

The causal association between *H. pylori* infection and GC has been firmly established by many epidemiological and clinical studies. Although GC develops in approximately 1% to 3%

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of *H. pylori*-infected subjects, more than 90% of GC patients have a current or past *H. pylori* infection.[7] In addition, a meta-analysis of 11 case-control studies including larger subjects also reported a strong association between *H. pylori* infection and GC (odds ratio for GC in *H. pylori*-infected subjects, 3.00; 95% confidence interval [CI], 2.42 to 3.72).[8] In addition, many studies have demonstrated the beneficial effect of *H. pylori* eradication by reduction of the incidence risk of GC. A meta-analysis of seven randomized controlled trials regarding the effectiveness of *H. pylori* eradication in the prevention of primary GC in healthy asymptomatic individuals showed that overall risk ratio and risk difference were 0.67 (95% CI, 0.48 to 0.95) and –0.00 (95% CI, –0.01 to 0.00).[9] Recently Choi *et al*.[10] nicely showed the chemopreventive effect of *H. pylori* eradication in the first GC family over 9.2 years follow-up in 1,676 participants. Our team also reported the chemopreventive effect of *H. pylori* eradication after multivariable adjustment in a comprehensive manner.[7] However, it remains unclear how *H. pylori* eradication prevents GC. Our team proposed that its underlying mechanism includes reversibility of atrophic gastritis and intestinal metaplasia, methylation, EMT, and stem cells.[7] However, it has not yet been established whether EMT of non-neoplastic gastric epithelial cells is directly associated with *H. pylori* infection.[7] Now Choi *et al*. proposed the methylation of miR-200a/b, which is involved in EMT as one of mechanism of *H. pylori*-induced gastric carcinogenesis.[5] As *H. pylori* eradication improved the field defect for cancerization by methylation of miR-200a/b[5] it might be added as one of mechanisms how *H. pylori* eradication prevents GC. In 2018 Korean Ministry of Health and Welfare extended indications of *H. pylori* eradication including to the conditions when doctors think *H. pylori* eradication is helpful for individuals. Maybe in the future the insurance could be extended into all of *H. pylori*-associated gastritis like in Japan in 2013 because our country has the infamy that the incidence of GC is the first in the world so far.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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