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Is intestinal metaplasia the point of no return in the progression of gastric carcinogenesis?

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Gastric cancer (GC) is one of the most common malignant tumors worldwide. In China, GC is the second most common malignant tumor, and it is the second leading cause of cancer mortality.[1] Correa model showed that the development of intestinal-type GC was a consecutive cancerous process including normal gastric mucosa, non-atrophic gastritis, atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia and intestinal-type GC in sequence.[2] Epithelium-resembling intestinal morphology replaced gastric mucosa which was defined as IM.[3] Among these precancerous conditions, IM was demonstrated to be a vital risk factor for GC, especially incomplete IM and extensive IM.[4,5]

Point of no return in the progression of gastric carcinogenesis: The point of no return in the progress of gastric carcinogenesis was expanded to discussions since the late 1990s. *Helicobacter pylori* (*H. pylori*) eradication could stabilize risk and delay the progression of GC.[6] However, many meta-analysis studies demonstrated that *H. pylori* eradication could reverse the atrophy of gastric mucosa, whereas it did not show the similar effect in regression of IM.[7,8] Chen *et al*[9] found that patients with IM or dysplasia could not benefit from eradication treatment compared with non-atrophic or atrophic gastritis patients. Hence, IM was defined as the point of no return in the progress of gastric carcinogenesis by some researchers. However, other studies drew different conclusions.

IM may be reversed: In fact, the spontaneous reversal of IM was actually observed. Correa *et al*[10] found that among 1400 residents in a high-risk area the rate of transition from IM to atrophy (0.044 person-years) was less than that from atrophy to IM (0.067 person-years). The conclusion can both be supported among residents less than 40 years of age or 40 years and older. Some cohort studies showed cumulative risk of regression to improved global histology at 1-, 3-, and 5-year follow-up in patients with gastric intestinal metaplasia (GIM) ranged from 19.4% to 29.7%.[11]

H. pylori eradication also showed effect on the reversal of IM. Hwang *et al*[12] conducted a prospective study for up to 10 years. IM was reversed in 60% of the gastric antrum and gastric body. In a cohort of patients with gastric premalignant lesions (GPLs) randomized to either *H. pylori* eradication group or placebo group, about 20% regression rate of IM was found similar with that of AG in the 20-year follow-up.[13] In another 12-year follow-up cohort study, the AG and IM in eradicated patients was significantly improved compared with non-eradicated patients.[14] A study including 2025 patients demonstrated that patients without *H. pylori* infection had higher IM regression rate than patients with persistent infection (60.4% vs. 39.4%).[15] These results indicated that the effect of *H. pylori* eradication could be observed in studies with long-term follow-up and large population.

Some chemical drugs showed great effect of IM regression. Overexpression of cyclooxygenase-2 (COX-2) was found in the tissue of GC and GPLs even after *H. pylori* eradication.[16-18] In recent years, the number of studies on the antineoplastic effects of celecoxib (selective COX-2 inhibitor) has increased considerably.[19] Both long-term and short-term application of celecoxib showed effect in reversal of IM and AG. In rats, treatment with celecoxib decreased GC incidence and development.[20] Yang *et al*[21] found that chronic celecoxib users had a lower mean IM score and a higher regression rate of IM than nonusers. Hung *et al*[22] found among IM patients with 8-week

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celecoxib treatment the mean IM scores in the antrum decreased, and 28% of patients achieved complete IM regression. Sheu *et al*[23] found that after 1-year celecoxib treatment the IM regression rate was higher in the celecoxib group than in the control group (without celecoxib treatment).

H. pylori eradication resulted in recovery of vitamin C secretion which inhibited the Correa cascade. Zullo *et al*[24] found that 31% of patients with 6-month vitamin C treatment and 3.4% of patients with no treatment achieved complete IM regression. In a screening program from Japan, less vitamin A intake increased the extent of IM in men.[25] A 1-year double-blind intervention trial revealed that 57% of patients treated with 6-month high-dose vitamin E and 71% of patients treated with 12-month high-dose vitamin E experienced small IM reversal in the antrum.[26] In addition to chemical drugs mentioned above, a few chemical drugs have been reported to be effective in IM regression such as tamoxifen, the methylethylketone inhibitor smetinib and so on.[27,28]

Some traditional drugs have been proven to be effective in IM reversal. Some herbal drugs could reverse AG and IM.[29-31] Meantime they worked in clinical symptom disappearance. Other animal-originated drugs like Lamb tripe extract vitamin B_{12} capsule also have been proven to reverse AG and IM even after *H. pylori* eradication.[32,33]

Other risk factors of intestinal metaplasia: After spontaneous reversal, *H. pylori* eradication, chemical drugs and traditional drugs, there are still some patients with IM. Genetic factors are a vital aspect. In GC and GPLs, a family history of GC could still be viewed as an independent risk, even for IM.[34,35] In a Chinese case-control study, the toll like receptor 4 (*TLR4*) rs11536889C allele increased the risk of GC.[36] However, Nieuwenburg *et al*[35] indicated that *TLR4* rs11536889C allele was inversely associated with the progression of IM. Li *et al*[37] suggested that overexpression of miR-92a-1-5p and downregulation of forkhead box D1 (*FOXD1*) promoted the progression of IM. Wang *et al*[38] found that the histone deacetylase 6 (HDAC6)/hepatocyte nuclear factor 4α (HNF4α) loop regulated by miR-1 plays a critical role in IM. Older age, male sex, nonwhite race/ethnicity were also proven to independently be associated with IM, which remained statistically significantly even after adjusting for *H. pylori* infection.[39]

Environmental factors could be intervened in clinical practice to reduce the risk of IM. Studies suggested that smoking showed trends toward the progression of IM.[35,39] A retrospective cohort study included 142,832 Korean adults found that obesity was independently associated with an increased incidence of endoscopic AG and IM[40]. A multicenter, cross-sectional and observational study showed that bile reflux and dietary habits were independent risk factors for the development of GPLs and GC.[34]

Prospect: The controversial perspective, IM was viewed as the point of no return, could be attributed to many different reasons. First, the short-term follow-up after *H. pylori* eradication was insufficient. Patients with IM would remain without malignant transformation for decades. Second, the researchers disregarded the effect of IM regression by chemical and traditional drugs except *H. pylori* eradication. In East Asia, developed countries applied regular endoscopic screening and *H. pylori* eradication as vital methods to prevent development. But in China traditional drugs have affected IM regression and digestive symptoms in clinical practice. Third, the method to evaluate the reversal of IM was not comprehensive and systematic. The operative link for gastric intestinal metaplasia assessment (OLGIM) should be applied for assessment.[11] Last but not least, there were still some other factors promoting the occurrence and malignant progression of IM.

Conclusion: According to many controversial studies, IM may not be defined as the point of no return among GPLs, this issue should be addressed. IM can be reversed spontaneously or by other clinical interventions. The effects of *H. pylori* eradication and chemical and traditional drugs in IM reversal still require further study with long-term follow-up to obtain high-quality evidence. In addition, it is important to address other risk factors for IM.

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Conflicts of interest

None.

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