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Effect of *Helicobacter pylori* and *Porphyromonas gingivalis* on the Correa cascade progression

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In their review, Rokkas and Rugge [1] reported the potential impact of *Helicobacter pylori* (Hp) and autoimmune gastritis on Correa's cascade (CC). Intestinal metaplasia (IM) is a highly heterogeneous condition and, importantly, most individuals with IM will not progress to malignancy [2]. Hp and *Porphyromonas gingivalis* (Pg), both highly prevalent pathogens, may contribute to CC [3,4].

Several emerging risk factors associated with IM and gastric cancer (GC) in the setting of Hp and/or Pg infection warrant particular attention [3,4]: Incomplete IM is more strongly associated with progression to GC. Hp-induced inflammation in both murine models and humans (Houghton's theory), promotes migration of bone marrow-derived stem cells to the gastric mucosa, where, by undergoing metaplastic and dysplastic transformation, they contribute to GC development along CC. Increased mast cells in areas of severe inflammation, gastric atrophy, IM and GC, correlate with Hp-induced gastritis and neoplastic progression. The Hp virulence factors CagA and VacA are closely associated with progression along CC. Hp-related gastrin production with increased expression of anti-apoptotic Bcl-2 protein can contribute to CC progression. Pg can exhibit an oncogenic effect by upregulation of anti-apoptotic Bcl-2 protein. Microbiome classifiers enable accurate GC detection [5]. Mutations in Hp-related p53 tumor suppressor gene are associated with familial GC. Pg has similarly been associated with altered p53 expression. Apart from p53, increased immune expression of the oncogenic markers Ki-67 and cyclin D1 has been implicated in Hp- and Pg-related carcinogenesis through their modulation. Hp eradication induces significant reductions in Ki-67, p53 and cyclin D1 immune expression, suggesting that timely eradication therapy may reverse precancerous gastric alterations [6].

The absence of these alterations in IM indicates a more favorable prognosis. For example, in a randomized controlled trial with a 26.5-year follow up, Hp eradication reduced GC in older patients with baseline IM or dysplasia [7]. Incomplete IM also regresses after 10 years' eradication therapy [8].

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