Helicobacter pylori and Gastric cancer: recent advance in pathogenesis and eradication therapy

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Helicobacter pylori(H. pylori)infection is strongly involved in the development of gastric adenocarcinoma (Gastric Cancer 12:79-87, 2009). It was reported that transfer of H. pylori-derived CagA to epithelial cells through the type IV secretion system promoted an early trigger event of gastric carcinogenesis. We observed that intracellular CagA was degraded by autophagy. The autophagy causing CagA degradation was induced as follows: VacA of H. pylori-induced glutathione (GSH) deficiency via binding to low-density lipoprotein receptor-related protein-1 (LRP1), a multifunctional member of the LDL receptor family (J. Biol. Chem. 287(37):31104-15, 2012). LRP1 is regulated by proteolytic processing, and then LRP1-intracellular domain (LRP1-ICD) is translocated to nucleus. Nuclear-translocated LRP1-ICD enhanced Lamp1 expressions and enhanced the fusion between autophagosomes and Lamp1-positive lysosomes, leading to the formation of autophagolysosome. On the other hand, VacA-induced glutathione (GSH) deficiency via binding to LRP1 enhanced Akt phosphorylation, Mdm2-mediated p53 degradation and then formation of autophagosome. However, especially in gastric cancer stem-like cells expressing of CD44 variant 9 (CD44v9), that is evident to be suppressed in ROS accumulation by elevating GSH levels, intracellular CagA could be escapedfrom the autophagic degradation, linking to gastric carcinogenesis (Cell Host Microbe 12(6):764-777, 2012). These finding provide a direct molecular link between H. pyloriand gastric carcinogenesis through the specific accumulation of CagA oncoprotein in gastric cancer stem-like cells. We also reported that the recurrence rate of early gastric cancer was significantly higher in the CD44v9-positive cohorts than in the CD44v9-negatives (HR: 21.8; 95% CI, 5.71-83.1), suggesting of CD44v9 positive cells in the primary early gastric cancer tissue as a potential predictive marker for the recurrence (Br. J. Cancer109(2):379-86, 2013).

To solve all of issues related to H. pylori infection, the development of complete eradication technology is the most important. Recent advance in H. pylori eradication would be focused on the novel quinolone (such as sitafloxacin)-based third line (Antimicrob. Agent Chemother. 56(3):1643-45, 2012) as well as novel orally bioavailable potassium-competitive acid blocker (P-CAB) containing primary and secondary eradication regimen would be introduced. Pros and cons of these new eradication regimens should be carefully discussed.