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Accumulation of Somatic Mutations in TP53 in Gastric Epithelium With Helicobacter pylori Infection

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Abstract **Full Text** References Supplemental Materials

Background & Aims

Helicobacter pylori infection is a risk factor for gastric cancer. To explore the genetic basis of gastric cancer that develops in inflamed gastric mucosa, we investigated genetic aberrations that latently accumulate in nontumorous gastric epithelium with H pylori infection.

Methods

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We performed whole-exome sequencing of gastric tumors, noncancerous tissues with gastritis, and peripheral lymphocytes from 5 patients. We performed additional deep-sequencing analyses of selected tumor-related genes using 34 gastritis mucosal samples from patients with or without gastric cancer. We also performed deep sequencing analyses of gastric mucosal tissues from mice that express transgenic human TP53 and constitutively express activation-induced cytidine deaminase (AICDA or AID) (human TP53 knock-in/AID-transgenic mice).

Results

Whole-exome sequencing revealed that somatic mutations accumulated in various genes in inflamed gastric tissues. Additional deep-sequencing analyses of tissues from regions of gastritis confirmed nonsynonymous low-abundance mutations in TP53 in 15 cases (44.1%) and ARID1A in 5 cases (14.7%). The mutations that accumulated in gastric mucosal tissues with H pylori-induced gastritis, as well as gastric tumors, were predominantly C:G>T:A transitions in GpCpX motifs—a marker of cytidine deamination induced by AID. Constitutive expression of AID in the gastric mucosa of mice led to mutations in the human TP53, at amino acid coding positions identical to those detected in human gastric cancers.

Conclusions

Studies of gastric tumors and tissues from humans and mice indicate that somatic mutations accumulate in various genes in gastric mucosal tissues with H pylori infection. Increased cytidine deaminase activity in these tissues appears to promote the accumulation of these mutations and might promote gastric carcinogenesis in patients with H pylori infection.

Keywords:

Stomach Cancer, Somatic Hypermutation, Pathogenesis, Bacteria

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Abbreviations used in this paper:

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AID (activation-induced cytidine deaminase), Hupki (human TP53 knock-in), indel (insertion and deletion), MSI (microsatellite instability), MSS (microsatellite stability), PCR (polymerase chain reaction), SNV (single nucleotide variant)

Conflicts of interest The authors disclose no conflicts.

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