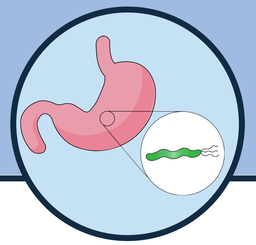

Helicobacter pylori: in the deregulation of p53, and involvement in Gastric Cancer development

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Introduction

How does *H. pylori* deregulate host tumor suppressor protein p53 signalling pathways?

Helicobacter pylori–a bacterial pathogen that colonizes the stomachs of **half the world's human population**–is the leading risk factor for gastric cancer. By downregulating the tumour suppressor protein p53, *H. pylori* is able to prevent the renewal of the gastric mucosa, thereby ensuring the survival of its replicating niche. However beneficial the ability of p53 suppression is to *H. pylori*, the host pays the price. This literature review explores the mechanisms by which *H. pylori* deregulates host p53 signalling, and how it contributes to the survival and proliferation of cells potentially harbouring genetic aberrations–thus, promoting gastric cancer development.

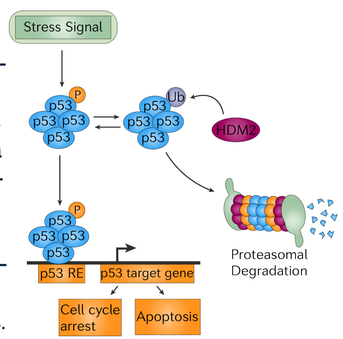
Why is this important?

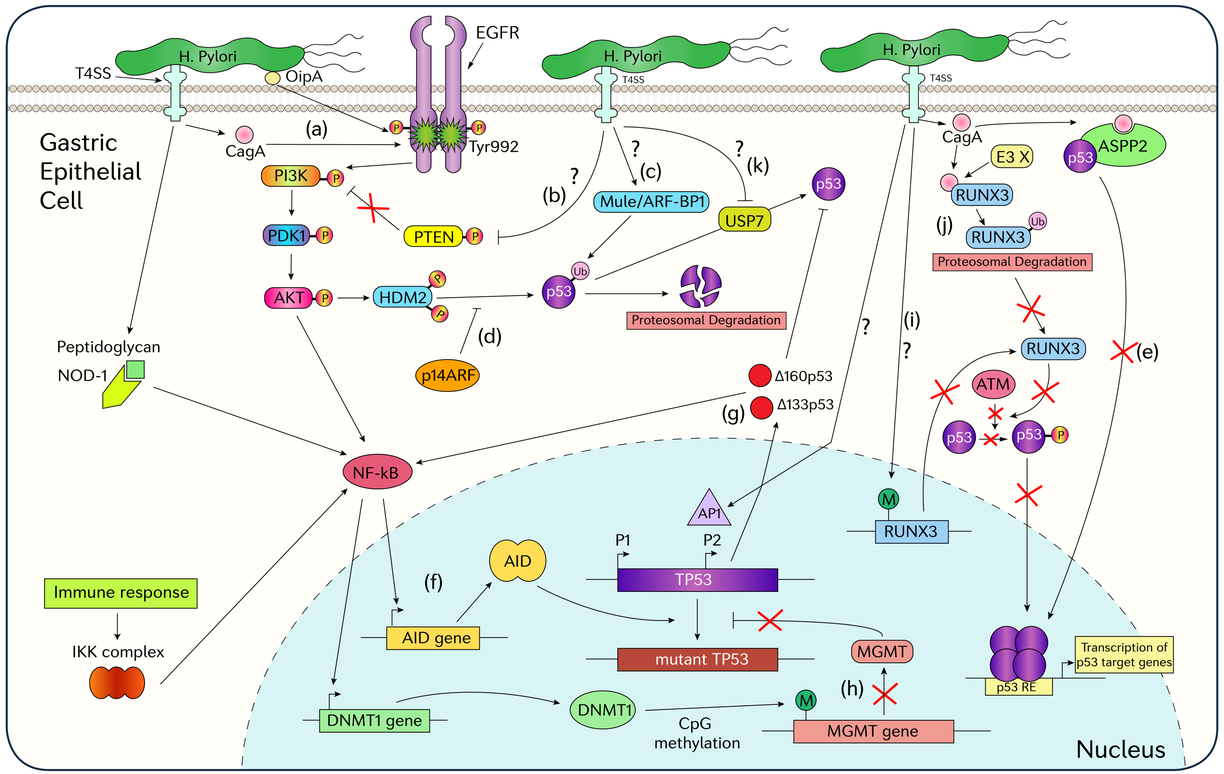
The Problem:
- Currently, *H. pylori* infection is treated with antacids/acid-reducing drugs in combination with antibiotics.
- This treatment increases the risk of antibiotic resistant infections, making recurrent infections difficult to treat .
- Most individuals are asymptomatic until the progression of the gastric cancer.

The Approach:
- Understand the mechanisms involved in *H. pylori* pathogenesis to improve treatment options and prevention of infection: e.g. vaccine development.

The guardian of the genome: p53

In a normal cell, the levels of p53 protein are maintained at low levels by HDM2, which ubiquitinates p53 targeting it for degradation. In response to stress signals (e.g., DNA damage), p53 is stabilized (by phosphorylation) in the cell. Active p53 forms a homotetramer, enters the nucleus and carries out its role as a transcription factor, inducing transcription of target genes. This results in the inhibition of cell growth either by cell-cycle arrest or the induction of apoptosis.





Mechanisms of p53 deregulation by *H. pylori*

(a) The CagA protein secreted by the T4SS, and the *H. pylori*-membrane bound OipA protein promote the phosphorylation and activation of EGFR at Tyr992. This is followed by successive activation of the PI3K-AKT pathway and phosphorylation of HDM2, promoting the proteasomal degradation of p53.
(b) PTEN, a negative regulator of PI3K is inhibited by *H. pylori* through phosphorylation at Ser380 and Thr382/383.
(c) *H. pylori* causes the upregulation of the p53 E3 ubiquitin ligase Mule/ARF-BP1.
(d) p14ARF is essential for neutralizing the downregulation of p53 due to the upregulation of HDM2 upon *H. pylori* infection.
(e) CagA sequesters ASPP2 to the plasma membrane, which retains p53 in the cytosol. The retention of p53 in the cytosol prevents p53 from entering the nucleus and carrying out its transcriptional activity.
(f) The activation of NF-kB promotes the aberrant expression of AID, which contributes to mutations in TP53.
(g) *H. pylori* infection induces expression of inhibitory isoforms of p53: Δ133p53 and Δ160p53.
(h) The activation of NF-kB during *H. pylori* infection induces the expression of DNMT1 which leads to the hypermethylation of the CpG promoter of MGMT. This leads to reduced expression of MGMT and increased accumulation of mutations in TP53.
(i) *H. pylori* induces hypermethylation of the RUNX3 gene, **(j)** as well as promotes the ubiquitination and subsequent degradation of the RUNX3 protein. The interaction between CagA and RUNX3 promotes the recruitment of an unknown ubiquitin ligase (E3 X).
(k) *H. pylori* infection induces the downregulation of USP7 in an unknown manner.

The Cag Pathogenicity Island

More virulent *H. pylori* strains harbour a 40-kb region of DNA known as the cytotoxin-associated gene (cag) pathogenicity island (PAI) which contains ~28 genes, and encodes for virulence factors such as the CagA protein and the type IV secretion system (T4SS)–a multisubunit syringe-like pilus that injects CagA from the bacteria to the host cell. Patients infected with CagA-(+) strains of *H. pylori* exhibit more severe inflammation of the gastric epithelium, as well as a 4-fold increased chance of developing mutations in TP53 in comparison to CagA-(-) *H. pylori* infections.

What's in it for *H. pylori*?

H. pylori infection activates immune system responses which lead to inflammation of the gastric mucosa. Prolonged inflammation induces multifaceted cellular stress, such as activation of oncogenic signalling, and generation of DNA damage-both strong inducers of p53-mediated cell cycle arrest and apoptosis. Therefore, dampening p53 signalling is essential to ensure host cell survival and prevent renewal of the gastric mucosa. Ultimately prolonging the survival of the bacteria.

Conclusions

The ability of *H. pylori* to elicit various mechanisms to disrupt regular p53 function, implies the importance of p53 inhibition for successful bacterial invasion. Although it is well established that *H. pylori* is capable of deregulating p53, many of the mechanisms remain unknown. Exploration of the mechanisms may lead to the identification of new drug targets and therapeutic interventions. This is especially important due to the rapid spread of antibiotic resistance, accompanied by the ineffectiveness of current treatment options.

DID YOU KNOW?

The 2005 Nobel Prize in Physiology or Medicine was awarded to Barry J. Marshall and J. Robin Warren "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease." Before their discovery ulcers were thought to be caused by eating spicy foods, or being too stressed. To prove *H. pylori* was the culprit, Dr. Mashall drank a Petrie dish containing cultured *H. pylori*, and published the experiment in the *Medical Journal of Australia*.