Helicobacter pylori, Induced Gastric Cells Apoptosis

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ABSTRACT

Gastric epithelial cells apoptosis induced by Helicobacter pylori depends on microbial and host factors. Apoptosis on mitochondrial level by Bcl2 family protein is the main pathway for Helicobacter pylori induced gastric epithelial cells apoptosis, though there are roles for apoptosis through Fas receptors or TNF. Imbalance between proliferation and apoptosis gastric epithelial cells determines the risk for neoplastic transformation. Increase of gastric epithelial cells apoptosis seems to have an obligation for initiating secondary hyperproliferative response. If altruistic cellular death fails to oppose this process, uncontrollable cellular growth leading to neoplastic transformation will occur.

Keywords: *Helicobacter pylori, gastric cells, apoptosis*

INTRODUCTION

Colonization of gastric mucous membrane by *Helicobacter pylori* induces local inflammation in most hosts. It is an on going process that will increase the incidence of atrophic gastritis, intestinal metaplasia and non-cardiac gastric adenocarcinoma.[1] Apoptosis (programmed cell death) is cellular response to internal or external signals resulting in "cellular suicide". This is a part of efforts for maintaining stable cell population by assuring a balance between cellular proliferation and destruction.[2]

HELICOBACTER PYLORI INDUCED APOPTOSIS PATHWAYS

Apoptotic cellular death has been considered as a cause of death to most of the gastrointestinal tract cells, but little is known about the intracellular signal conduction leading to this event.[3] Apoptosis index in *Helicobacter pylori* infection increases if the density of *Helicobacter pylori* reaches more than 1.6×10^4 CFU/ml.[4] Imbalance between proliferation and apoptosis of the gastric epithelial cells is a risk factor for atrophic gastritis and neoplastic transformation.[5] Substantial apoptosis induced by *Helicobacter pylori* provokes secondary hyperproliferative response of the mucosa in order to maintain its cellular mass. If this event continues, cell cycle velocity increases, making gastric epithelial cells more vulnerable to genotoxic damage and altruistic cellular death. If the altruistic pathway fails, uncontrollable cellular proliferation occurs.[1] Chronic infection of *Helicobacter pylori* seems responsible for genomic instability on some cases of chronic active gastritis with positive *Helicobacter pylori*.[6]

There are two pathways for apoptosis,[2] the first is death receptor mediated apoptosis pathway, such as CD95 (Fas) and tumor necrosing factor (TNF) receptors. If Fas ligand attach to Fas receptor, a signal complex will be generated. This complex then activates caspase-8, processes effector caspases (caspase-3,-6,-7) and induces apoptosis. Other pathway is various apoptotic signals converging to mitochondrial level which provoke cytochrome C translocation from mitochondria into cytoplasm. Inside cytoplasm, cytochrome C joins with Apaf-1 and initiates recruitment of procaspase-9. Activated caspase-9 is released and in turn activates procaspase-3, which results in apoptosis.

Caspases are apoptosis' final phase protease. They exist inside cytoplasm as larger forms called procaspases. If other caspase cleaves the procaspase, it becomes active and in turn activates one another, initiating self amplifying proteolitic cascade.

Mitochondrial apoptosis seems to be the main pathway for gastric cell apoptosis induced by *Helicobacter pylori*.[1,3] On this case cytoplasmic protein from Bcl2 family plays a very important role.[1,3,4] Bcl2 protein family is a group of cytoplasmic protein which related to oncoprotein Bcl2, which closely monitors apoptosis at mitochondrial level. This protein family consists of proapoptotic protein (such as Bak and Bax) and antiapoptotic protein (such as Bcl2, BclX and p53).[2] Alterations in expression of Bcl2 family is a key factor on gastric cell apoptosis due to *Helicobacter pylori*.[4]

In *Helicobacter pylori* induced apoptosis there is translocation of BaX protein from cytoplasm onto mitochondrial membrane, which releases cytochrome C into cytoplasm and initiate caspases cascade.[3,7] Cytoprotective oncoprotein Bcl2 stabilizes barrier function which protects mitochondria, on the contrary tumor suppressor protein Bax induces permeabilization of mitochondrial membrane.[7] Bak (suicide gene related to Bcl2) expression increased by moderate-expression of another Bcl2 family (such as Bcl2, BclX). This explains *Helicobacter pylori* induce gastric cell apoptosis is partly mediated by Bak dependent pathway.[1,4]

P53, an oncosuppressor gene which continuously monitors chromosomes DNA integrity, also have important role in apoptosis. On vitro *Helicobacter pylori* infection, there is a decrease in p53 expression which indicates p53 alteration appears before gastric carcinoma and accelerates tumor progression.[1,2,8]

There are investigations on apoptosis pathway through Fas receptor and TNF. Fas pathway apoptosis of gastric cells is characterized by interaction between Fas (CD95) with Fas ligand (CD95L),[9,10] but other investigation revealed Fas, as cellular death receptor, and caspase-8 did not have significant role on *Helicobacter pylori* induced gastric cell apoptosis.[1,3] Tumor Necrosis Factor is a major cytokine produced by gastric mucosa of patients who is infected by *Helicobacter pylori*.[11] Ammonia from hydrolyzed urea by *Helicobacter pylori* urease have major role as accelerator of TNF-α induce apoptosis, but the ammonia molecules or urease itself do not have direct effect in inducing apoptosis.[12]

The role of cagA and vacA expressions

CagA, a unique gene strain of *Helicobacter pylori*, is known as the marker of strains which carry the risk of peptic ulcer and gastric carcinoma.[5] There are different opinions on the role of cagA on gastric cell apoptosis. Studies on cagA$^+$ *Helicobacter pylori* induced gastric epithelial cells shows increasing apoptosis and proliferation of epithelial cells on the antrum and corpus. Even though increasing proliferation does not depend on the *Helicobacter pylori* cagA strain, apoptosis is increased statistically significant in patients with cagA-positive strain. This reveals the possibility of genes in cag pathogenecity island involvement in *Helicobacter pylori* induced gastric epithelial cells apoptosis.[14] Studies revealed cagA$^+$ *Helicobacter pylori* apoptosis depended on expression of vacA and genes inside cag pathogenecity island. This might explains the heterogeneity in proliferation levels and gastric epithelial cells apoptosis on mucosa colonized by *Helicobacter pylori*.[14,15] VacA also has the ability to induce mitochondrial cytochrome C release through N-terminal of 34 kDa fragment from *Helicobacter pylori's* vacA.[16] *Helicobacter pylori* also induces intestinal epithelial cells apoptosis through Fas dependent pathway after a cag PAI dependent process.[17] Hosts response on *Helicobacter pylori* might be important in determining carcinogenity threshold.

Chronic *Helicobacter pylori* infection on gastric epithelial cells also decreases $p27^{kipl}$, a cycling dependent kinase which function as cell cycle controller and a part of apoptosis regulator. A decrease in gastric $p27^{kipl}$ induces gastric carcinogenesis related to *Helicobacter pylori* infection by inhibiting apoptosis pathway.[18,19]

NF-KB, functions as a regulator for genes involved in inflammation, cell proliferation and apoptosis, plays critical part on cellular protection but also has proapoptotic characteristic depending on the strength of the stimulus and variety of cell involved. One study on gastric epithelial cells induced by *Helicobacter pylori* revealed NF-KB antiapoptotic characteristic.[3]

CONCLUSION

Studies showed that *Helicobacter pylory* induced apoptosis of gastric epithelial cells mainly through mithocondrial level involving Bc12 family protein. This apoptosis might provoke secondary hyperproliferatif response of the mucosa and in uncontrollable state may produce neoplastic transformation

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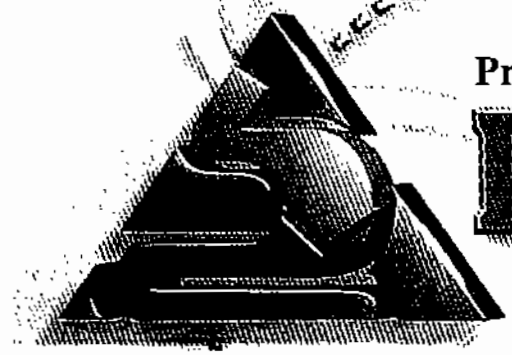

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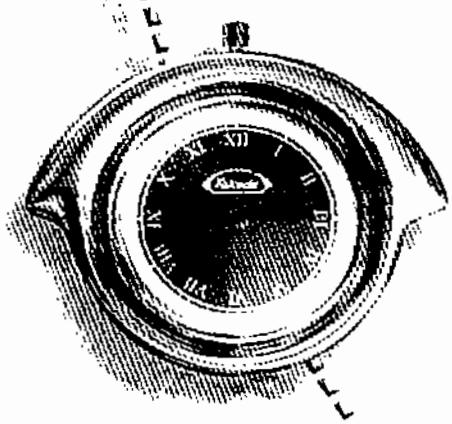

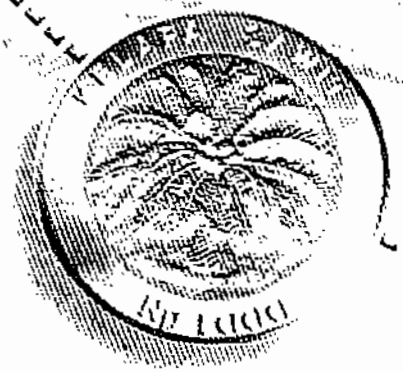

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