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Potential implications of *Helicobacter pylori*-related neutrophil-activating protein

Jannis Kountouras, Christos Zavos, Georgia Deretzi, Emmanuel Gavalas, Dimitrios Chatzopoulos, Panagiotis Katsinelos, Elena Tsiaousi, Stergios Gagalis, Stergios A Polyzos, Ioannis Venizelos

Jannis Kountouras, Christos Zavos, Georgia Deretzi, Emmanuel Gavalas, Dimitrios Chatzopoulos, Panagiotis Katsinelos, Elena Tsiaousi, Stergios Gagalis, Stergios A Polyzos, Ioannis Venizelos, Department of Medicine, Second Medical Clinic, Aristotle University of Thessaloniki, Ippokration Hospital, Thessaloniki, Greece

Author contributions: All authors generated the ideas and contributed to the writing of this paper.

Correspondence to: Jannis Kountouras, MD, PhD, Professor of Medicine, Gastroenterologist, Department of Medicine, Second Medical Clinic, Aristotle University of Thessaloniki, Ippokration Hospital, 8 Fanariou St, Byzantio, 55133 Thessaloniki, Macedonia, Greece. jannis@auth.gr

Telephone: +30-2310-892238 Fax: +30-2310-992794

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Abstract

Helicobacter pylori (*H. pylori*) virulence factors promote the release of various chemoattractants/inflammatory mediators, including mainly the neutrophil-attractant chemokine interleukin-8 and neutrophil-activating protein (NAP), involved in *H. pylori*-induced gastric pathologies. Co-administration of Chios mastic gum (CMG), which inhibits *H. pylori* NAP, with an *H. pylori* eradication regimen might add clinical benefits against *H. pylori*-related gastric pathologies, but possibly not CMG as main therapy. Although *H. pylori* NAP and other *H. pylori*-related cytotoxins [i.e., vaculating cytotoxin (VacA)] appear to play a major role in generating and maintaining the *H. pylori*-associated gastric inflammatory response and *H. pylori* NAP is a promising vaccine candidate against *H. pylori* infection (*H. pylori*-I), concerns regarding its potential drawbacks, particularly neurogenic ones, due to possible cross-mimicry, should be considered. Possible cross-mimicry between *H. pylori* NAP and/or bacterial aquaporin (AQP) and neural tissues may be associated with the anti-AQP-4 antibody-related neural damage in multiple sclerosis (MS)/neuromyelitis optica patients. Moreover, the sequence homology found between *H. pylori* VacA and human Na+/K+-ATPase A subunit suggests that antibodies to VacA involve ion channels in abaxonal Schwann cell plasmalemma resulting in demyelination in some patients. A series of factors have been implicated in inducing blood-brain barrier (BBB) disruption, including inflammatory mediators (e.g., cytokines and chemokines induced by *H. pylori*-I) and oxidative stress. BBB disruption permits access of AQP4-specific antibodies and T lymphocytes to the central nervous system, thereby playing a major role in multiple sclerosis pathogenesis. Relative studies show a strong association between *H. pylori*-I and MS. *H. pylori*-I induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with components of nerves, thereby contributing and perpetuating neural tissue damage. Finally, *H. pylori* NAP also plays a possible pathogenetic role in both gastric and colon oncogenesis.

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Key words: *Helicobacter pylori*; Neutrophil-activating protein; Chios mastic gum; Cross-mimicry; Multiple sclerosis; Demyelination; Gastric carcinogenesis

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TO THE EDITOR

In their recent paper published in this journal, Choli-Papadopoulou *et al*[1] consider the development of new drugs targeting *Helicobacter pylori* (*H. pylori*) neutrophil-activating protein (NAP) and this raises some concerns.

With reference to a study[2] focusing on *H. pylori* NAP-mediated neutrophil activation before and 2 mo after *per os* administration of Chios mastic gum (CMG), the authors claimed that "these results indicate a substantial down-regulation of the innate cellular immune effectors, which, according to unpublished clinical data in the context of this study, are accompanied by a significant clinical improvement of the patients' complaints (dyspepsia, epigastric discomfort, distention)"[1]. However, such clinical benefits cannot be deduced from this study[2] and, as mentioned, relative clinical data on CMG as treatment for *H. pylori* and peptic ulcer are controversial[2]. Although *H. pylori* virulence factors promote the release of various chemoattractants/inflammatory mediators including mainly the neutrophil-attractant chemokine interleukin-8 and *H. pylori* NAP involved in *H. pylori*-induced gastric pathologies[3], our clinical experience suggests that only co-administration of CMG with an *H. pylori* eradication regimen might add clinical benefits against *H. pylori*-related gastric pathologies, but possibly not CMG as main therapy, as the authors claimed[1,2]. In particular, co-administration of CMG might be a potential therapy to reduce damage of gastric mucosa induced by *H. pylori* NAP. However, large-scale relative prospective studies are needed to elucidate this field.

The authors, further considering data on the safety and immunogenicity of a vaccine comprising *H. pylori*-induced vaculating cytotoxin (VacA), cytotoxin associated gene and *H. pylori* NAP, suggested that the obtained neutrophil activation by the C-terminal region of *H. pylori* NAP opens new pathways for drug design directed at *H. pylori* inflammation[1]. In particular, both VacA and *H. pylori* NAP play a major role in generating and maintaining the *H. pylori*-associated gastric inflammatory response, and *H. pylori* NAP is a promising vaccine candidate against *H. pylori* infection (*H. pylori*-I). However, concerns regarding potential drawbacks of *H. pylori* NAP, particularly neurogenic ones, should be considered. For instance, possible cross-mimicry between *H. pylori* NAP and/or bacterial aquaporin (AQP) and neural tissues may be associated with the anti-AQP-4 antibody-related neural damage in multiple sclerosis (MS)/neuromyelitis optica (NMO) patients. In this regard, by using histology, the practical gold standard for the diagnosis of *H. pylori*-I, we have shown a strong association between *H. pylori*-I and MS[4]. *H. pylori*-I induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with components of nerves, thereby contributing and perpetuating neural tissue damage[4]. In this respect, *H. pylori* NAP, as a virulence factor, recruits leukocytes from the vascular lumen, and activates neutrophils, monocytes and mast cells, as mentioned by the authors. Besides, the sequence homology found between *H. pylori* VacA and human Na+/K+-ATPase A subunit suggests that antibodies to VacA involve ion channels in abaxonal Schwann cell plasmalemma resulting in demyelination in some patients[5]. Moreover, VacA exhibits chemotactic activities to the bone marrow-derived mast cells (BMDMCs) and induces BMDMCs to produce pro-inflammatory cytokines[5]. A series of factors have been implicated in inducing blood-brain barrier (BBB) disruption, including the aforementioned inflammatory mediators (e.g., cytokines and chemokines induced by *H. pylori*-I) and oxidative stress. BBB disruption permits access of AQP4-specific antibodies and T lymphocytes to the central nervous system, thereby playing a major role in MS/NMO pathogenesis[6]. Therefore, *H. pylori* NAP and *HP*-I itself, by inducing several mediators, may influence MS/NMO (including relapsing type) pathophysiology, thereby raising possible concerns regarding even the C-terminal region of *H. pylori* NAP use as a candidate vaccine. Accordingly, relative studies are also needed to clarify the aforementioned concerns.

Finally, the possible *H. pylori* NAP pathogenetic role in gastric carcinogenesis, mentioned by the authors, may also apply to colon oncogenesis[2,7].

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