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**EDITORIAL**

- 6009** Helminths as an alternative therapy for intestinal diseases

Sipahi AM, Baptista DM

REVIEW

- 6016** Dextran sodium sulfate colitis murine model: An indispensable tool for advancing our understanding of inflammatory bowel diseases pathogenesis

Eichele DD, Kharbanda KK

- 6030** Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments

Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D

MINIREVIEWS

- 6049** Colorectal cancer, screening and primary care: A mini literature review

Hadjipetrou A, Anyfantakis D, Galanakis CG, Kastanakis M, Kastanakis S

- 6059** Behavioral gastroenterology: An emerging system and new frontier of action

Jia L, Jiang SM, Liu J

ORIGINAL ARTICLE**Basic Study**

- 6065** Pharmacological evaluation of NSAID-induced gastropathy as a "Translatable" model of referred visceral hypersensitivity

Hummel M, Knappenberger T, Reilly M, Whiteside GT

- 6077** High yield reproducible rat model recapitulating human Barrett's carcinogenesis

Matsui D, Omstead AN, Kosovec JE, Komatsu Y, Lloyd EJ, Raphael H, Kelly RJ, Zaidi AH, Jobe BA

- 6088** Changes in expression of inhibitory substances in the intramural neurons of the stomach following streptozotocin- induced diabetes in the pig

Bulc M, Palus K, Zielonka L, Gajęcka M, Calka J

- 6100** HOX transcript antisense intergenic RNA represses E-cadherin expression by binding to EZH2 in gastric cancer

Chen WM, Chen WD, Jiang XM, Jia XF, Wang HM, Zhang QJ, Shu YQ, Zhao HB

- 6111 Ca^{2+} /calmodulin-dependent protein kinase II regulates colon cancer proliferation and migration *via* ERK1/2 and p38 pathways

Chen W, An P, Quan XJ, Zhang J, Zhou ZY, Zou LP, Luo HS

- 6119 Aberrant DNA-PKcs and ERGIC1 expression may be involved in initiation of gastric cancer

Wang FR, Wei YC, Han ZJ, He WT, Guan XY, Chen H, Li YM

Retrospective Cohort Study

- 6128 Real world treatment patterns of gastrointestinal neuroendocrine tumors: A claims database analysis

Benson III AB, Broder MS, Cai B, Chang E, Neary MP, Papayan E

Retrospective Study

- 6137 Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases

Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Koch-Hansen L

- 6147 Suspicious brush cytology is an indication for liver transplantation evaluation in primary sclerosing cholangitis

Boyd S, Vannas M, Jokelainen K, Isoniemi H, Mäkilä MA, Arola J

- 6155 Management of gastric mucosa-associated lymphoid tissue lymphoma in patients with extra copies of the *MALT1* gene

Iwamuro M, Takenaka R, Nakagawa M, Moritou Y, Saito S, Hori S, Inaba T, Kawai Y, Toyokawa T, Tanaka T, Yoshino T, Okada H

- 6164 Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy

Xie G, Zhou Q, Qiu CZ, Dai WK, Wang HP, Li YH, Liao JX, Lu XG, Lin SF, Ye JH, Ma ZY, Wang WJ

Observational Study

- 6172 Definition of colorectal anastomotic leakage: A consensus survey among Dutch and Chinese colorectal surgeons

van Rooijen SJ, Jongen ACHM, Wu ZQ, Ji JF, Slooter GD, Roumen RMH, Bouvy ND

CASE REPORT

- 6181 How to treat intestinal obstruction due to malignant recurrence after Whipple's resection for pancreatic head cancer: Description of 2 new endoscopic techniques

Mouradides C, Taha A, Borbath I, Deprez PH, Moreels TG

- 6187 Arteriportal shunt incidental to treatment with oxaliplatin that mimics recurrent gastric cancer

Kim HB, Park SG

LETTERS TO THE EDITOR

- 6194** Comment on "Effect of biofilm formation by clinical isolates of *Helicobacter pylori* on the efflux-mediated resistance to commonly used antibiotics"

Kazakos EI, Dorrell N, Polyzos SA, Deretzi G, Kountouras J

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Comment on “Effect of biofilm formation by clinical isolates of *Helicobacter pylori* on the efflux-mediated resistance to commonly used antibiotics”

Evangelos I Kazakos, Nick Dorrell, Stergios A Polyzos, Georgia Deretzi, Jannis Kountouras

Evangelos I Kazakos, Stergios A Polyzos, Jannis Kountouras, Department of Medicine, the Second Medical Clinic, Aristotle University of Thessaloniki, Ippokration Hospital, 54642 Thessaloniki, Greece

Nick Dorrell, Department of Pathogen Molecular Biology, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom

Georgia Deretzi, Department of Neurology, Multiple Sclerosis Unit, Papageorgiou General Hospital, 54629 Thessaloniki, Greece

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Correspondence to: Evangelos I Kazakos, MD, PhD, MSc, DTM&H, Department of Medicine, the Second Medical Clinic, Ippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, Biopathology Labs SA, 50132 Kozani, Greece. ekazakos@gmail.com
Telephone: +30-246-1026775
Fax: +30-246-1026475

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Abstract

Attaran *et al*^[1] have recently shown that decreased susceptibility of established *Helicobacter pylori* (*H. pylori*) biofilms to specific antibiotics, was associated with the overtly enhanced transcription of two efflux pump genes, *hp1165* and *hefA*, involved in specific resistance to tetracycline and multiple antibiotics, respectively. Apart from antibiotic exposure, secretion of multiple antimicrobial peptides, such as human β -defensins ($\text{h}\beta\text{Ds}$), by the gastric epithelium upon *Hp* challenge, may act as early triggering events that positively impact biofilm formation and thus, antibiotic resistance. In this regard, we undertook genomic transcriptional studies using *Hp* 26695 strain following exposure to sublethal, similar to those present in the gastric niche, concentrations of $\text{h}\beta\text{Ds}$ in an attempt to provide preliminary data regarding possible mechanisms of immune evasion and selective sensitivity of *Hp*. Our preliminary results indicate that $\text{h}\beta\text{D}$ exposure ignites a rapid response that is largely due to the activation of several, possibly interconnected transcriptional regulatory networks – origins - that ultimately coordinate cellular processes needed to maintain homeostasis and successful adaptation of the bacterium in the gastric environment. In addition, we have shown that both antibiotic and $\text{h}\beta\text{D}$ resistance are mediated by dedicated periplasmic transporters, including the aforementioned efflux pump genes *hp1165* and *hefA*, involved in active export of antibiotics from the cell membrane and/or, as recently suggested, substrate sensing and signalling. Furthermore, it

appears that sublethal doses of h β Ds may enhance biofilm formation by the sustained expression of, mainly, quorum sensing-related genes. In conclusion, we provide additional data regarding the role of specific innate immune molecules in antibiotic cross-resistance mechanisms that may deepen our understanding in the context of the development of novel eradication regimens.

Key words: *Helicobacter pylori*; Human β -defensins; Biofilm; Antimicrobial resistance

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Core tip: In the course of *Helicobacter pylori* infection, epithelium-derived human β -defensins may act as early triggering signals that induce biofilm formation and enhanced expression of antibiotic resistance genes, regardless of prior antibiotic exposure.

Kazakos EI, Dorrell N, Polyzos SA, Deretzi G, Kountouras J. Comment on “Effect of biofilm formation by clinical isolates of *Helicobacter pylori* on the efflux-mediated resistance to commonly used antibiotics”. *World J Gastroenterol* 2017; 23(33): 6194-6196 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i33/6194.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i33.6194>

TO THE EDITOR

Attaran *et al*^[1] concluded that, in biofilm-forming populations, overexpression of two efflux pump genes, *hp1165* and *hefA*, conferring resistance to tetracycline and multiple antibiotics respectively, may favor reduced antibiotic susceptibility of *Helicobacter pylori* (*H. pylori*) *in vivo*.

Further to antibiotic exposure, additional, epithelial-derived molecules may function as triggering signals during the dynamic *H. pylori* interaction with the gastric mucosa, provoking overexpression of efflux pumps that in turn, regulate the bacterium's biofilm-producing capacity and promote its virulence. Several studies have unraveled the role of constitutive and/or induced expression of human β -defensins (h β Ds) 1 - 4 in the bacterium's adaptation in the human stomach and *H. pylori* -related pathologies^[2,3].

In this respect, we performed whole genome transcriptome analyses (competitive genomic RNA/RNA hybridisations) using *H. pylori* -specific microarrays based on the *Hp* 26695 and J99 genome sequences and annotation available at the time. Briefly, *H. pylori* 26695 strain was exposed to sublethal, similar to those encountered at the gastric epithelium concentrations of h β Ds, in an attempt to identify possible mechanisms of *H. pylori* immune escape and clarify their role in biofilm development *in vitro*. Our preliminary results have identified profound changes in the transcriptional profile

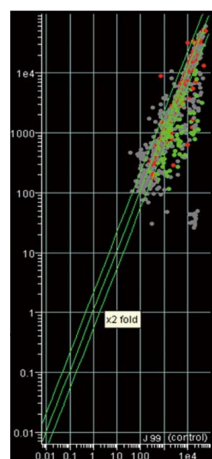


Figure 1 Representative scatter analysis of the general patterns of *H. pylori* genomic response to human β -defensin 3 (h β D3) revealed by transcriptional profiling. Scatter plots (log₂ ratio) of average normalized intensities representing Cy5-red channel versus Cy3-green channel are shown for experiments in the presence of sublethal concentrations of h β D3 compared with “control” conditions (no h β D3). Differential expression of a given gene is reflected by deviation from the central diagonal line. The upper diagonal defines ≥ 2 -fold up-regulation and the lower one defines ≥ 2 -fold down-regulation.

of *H. pylori* 26695 demonstrated by the induction or suppression of multiple gene components of distinct regulatory and signaling cascades activated as a result of environmental stress (Figure 1, unpublished data). Overall, the vast majority of genes affected, encoded components of the cell wall stimulon, possibly as means to prevent h β D-specific binding and proper immune recognition, or could be further assigned to certain origins, essential for colonisation of the gastric niche and long-term adaptation, intracellular metal homeostasis and urease activation that largely determine *H. pylori* pathogenicity. Apart from the marked induction of *hp1165* and *hefA*, also reported by the authors^[1], several other genes coding for transmembrane ABC transporters (*glnP*, *dppF*, *hp1458*, *hp1486*), efflux proteins (*hp0656*, *hp0946*), multidrug and toxic extrusion proteins were found to be significantly up-regulated, thereby indicating their prominent role in the cellular response to h β Ds challenge, membrane detoxification and maintenance of osmotic balance.

Interestingly, enhanced biofilm production by *Hp* 26695, observed in our studies upon exposure to sublethal concentrations of h β D1 and h β D3, was primarily attributed to the down-regulation of *metK* and *luxS* genes, involved in synthesis of quorum-sensing autoinducer-2, in accordance to previously published data^[4,5].

Collectively, our results indicate that sublethal doses of epithelial-secreted antimicrobial peptides such as h β Ds, may select co-resistance to antibiotics commonly used in *Hp* eradication therapies and *vice versa*, considering that they provoke the activation of shared, contact-dependent signaling networks, including efflux pumps. Furthermore, it appears that h β Ds may independently act as triggering stimuli

promoting biofilm formation *in vivo* which in turn, accounts, at least partly, for the observed failure of eradication regimens and the establishment of *H. pylori* -related chronic inflammation.

Given the complexity of *H. pylori* -host epithelial crosstalk aforementioned data warrant further investigation to achieve the development of successful anti-biofilm strategies that will ultimately re-enforce our therapeutic options mainly towards eradication of *H. pylori* -related resistance. Furthermore, future research focus on the polymorphic variability of the human genome that directly affects epithelial dynamics of hβDs expression may reveal important correlation patterns between *H. pylori* pathogenesis, including biofilm formation, and individual disease susceptibility.

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