

World Journal of *Gastroenterology*

World J Gastroenterol 2017 September 7; 23(33): 6009-6196



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, Papoyan 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, Mäkisalo H, Färkkilä 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

ABOUT COVER

Editorial Board Member of World Journal of Gastroenterology, Mostafa Sira, MD, Associate Professor of Pediatric Hepatology, Gastroenterology and Nutrition, National Liver Institute, Menofiya University, Menofiya 32511, Egypt

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports[®] cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

FLYLEAF

I-IX Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li-Juan Wei*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
 ISSN 1007-9327 (print)
 ISSN 2219-2840 (online)

LAUNCH DATE
 October 1, 1995

FREQUENCY
 Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

EDITORIAL BOARD MEMBERS
 All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE
 Jin-Lei Wang, Director
 Yuan Qi, Vice Director
 Ze-Mao Gong, Vice Director
World Journal of Gastroenterology
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: editorialoffice@wjgnet.com
 Help Desk: <http://www.fpublishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: bpoffice@wjgnet.com
 Help Desk: <http://www.fpublishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE
 September 7, 2017

COPYRIGHT
 © 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
 Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.fpublishing.com>

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

Author contributions: Kazakos EI, Polyzos SA, Deretzi G and Kountouras J wrote the letter; Dorrell N and Kountouras J revised the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

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

Received: May 1, 2017

Peer-review started: May 3, 2017

First decision: June 5, 2017

Revised: June 27, 2017

Accepted: July 22, 2017

Article in press: July 24, 2017

Published online: September 7, 2017

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 ($\text{h}\beta$ 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 $\text{h}\beta$ DS in an attempt to provide preliminary data regarding possible mechanisms of immune evasion and selective sensitivity of *Hp*. Our preliminary results indicate that $\text{h}\beta$ 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 $\text{h}\beta$ 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

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

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

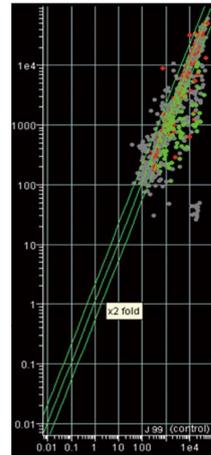


Figure 1 Representative scatter analysis of the general patterns of *H. pylori* genomic response to human β -defensin 3 (h β D3) revealed by transcriptional profiling. Scatter plots (log₂ ratio) of average normalized intensities representing Cy5-red channel versus Cy3-green channel are shown for experiments 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.

REFERENCES

1 Attaran B, Falsafi T, Ghorbanmehr N. Effect of biofilm formation

by clinical isolates of *Helicobacter pylori* on the efflux-mediated resistance to commonly used antibiotics. *World J Gastroenterol* 2017; **23**: 1163-1170 [PMID: 28275296 DOI: 10.3748/wjg.v23.i7.1163]

- 2 Kountouras J, Deretzi G, Gavalas E, Zavos C, Polyzos SA, Kazakos E, Giartza-Taxidou E, Vardaka E, Kountouras C, Katsinelos P, Boziki M, Giouleme O. A proposed role of human defensins in *Helicobacter pylori*-related neurodegenerative disorders. *Med Hypotheses* 2014; **82**: 368-373 [PMID: 24472867 DOI: 10.1016/j.mehy.2013.12.025]
- 3 Pero R, Coretti L, Nigro E, Lembo F, Laneri S, Lombardo B, Daniele A, Scudiero O. β-Defensins in the Fight against *Helicobacter pylori*. *Molecules* 2017; **22**: pii: E424 [PMID: 28272373 DOI: 10.3390/molecules22030424]
- 4 Bessa LJ, Grande R, Di Iorio D, Di Giulio M, Di Campli E, Cellini L. *Helicobacter pylori* free-living and biofilm modes of growth: behavior in response to different culture media. *APMIS* 2013; **121**: 549-560 [PMID: 23237527 DOI: 10.1111/apm.12020]
- 5 Anderson JK, Huang JY, Wreden C, Sweeney EG, Goers J, Remington SJ, Guillemin K. Chemorepulsion from the Quorum Signal Autoinducer-2 Promotes *Helicobacter pylori* Biofilm Dispersal. *MBio* 2015; **6**: e00379 [PMID: 26152582 DOI: 10.1128/mBio.00379-15]

P- Reviewer: Ahmed Said ZN, Gonzalez-Reimers E, Slomiany BL, Zamani M **S- Editor:** Qi Y **L- Editor:** A **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

