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LETTER TO THE EDITOR

Ability of *Helicobacter pylori* to internalize into *Candida*

Zheng-Hong Chen, Jian-Chao Sun, Ting-Xiu Yang, Gu-Zhen Cui

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Abstract

The following are our views regarding the "letter to the editor" (*Helicobacter* is preserved in yeast vacuoles! Does Koch's postulates confirm it?) by Alipour and Gaeini, and the response "letter to the editor" (*Candida* accommodates non-culturable *Helicobacter pylori* in its vacuole-Koch's postulates aren't applicable) by Siavoshi and Saniee. Alipour and Gaeini rejected the methods, results, discussion, and conclusions summarized in a review article by Siavoshi and Saniee. The present article reviews and discusses evidence on the evolutionary adaptation of *Helicobacter pylori* (*H. pylori*) to thrive in *Candida* cell vacuoles and concludes that *Candida* could act as a Trojan horse, transporting potentially infectious *H. pylori* into the stomach of humans.

Key Words: *Helicobacter pylori*; *Candida* yeast; Intracellular presence; *Helicobacter pylori*-specific gene; *Helicobacter pylori* transmission

Core Tip: The authors of the "letter to the editor" (*Helicobacter* is preserved in yeast vacuoles! Does Koch's postulates confirm it?) described "shortcomings" of the review article "Vacuoles of *Candida* yeast behave as a specialized niche for *Helicobacter pylori*" published in the *World Journal of Gastroenterology*. Here, we present our view that *Candida* spp. can indeed serve as reservoirs for *Helicobacter pylori*.

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TO THE EDITOR

We read with interest the December 2017 letter to the editor "*Helicobacter* is preserved in yeast vacuoles! Does Koch's postulates confirm it?" by Alipour and Gaeini[1], and the February 2018 response letter "*Candida* accommodates non-culturable *Helicobacter pylori* in its vacuole-Koch's postulates aren't applicable" by Siavoshi and Saniee[2]. The argument originated from the review article "Vacuoles of *Candida* yeast behave as a specialized niche for *Helicobacter pylori*" by Siavoshi and Saniee[3]. To ensure clarity and comprehension, we have designated the authors of this review[3] and the response letter[2] as proponents, while referring to the authors of the December 2017 letter[1], who hold a contrasting viewpoint, as opponents.

The review article[3] presented the research findings on *Helicobacter pylori* (*H. pylori*) infection in *Candida* cells. Moving bacterium-like bodies inside the vacuoles of *Candida* spp. isolated from feces[4], vaginal discharge, and oral samples[5] were observed by light microscopy. Because bacterial cells can't be cultured from disrupted *Candida* cells, *H. pylori*-specific *16S rRNA*, *ureAB*, *vacA s1*, and *ahpC* genes from the whole DNA of *Candida* isolates similar in size to those of the control *H. pylori* were amplified[5,6] by PCR to reveal their bacterial nature. *H. pylori*-specific proteins in the protein pool of Candida cells were assessed by Western blot analysis using IgY-*H. pylori* raised in hens and IgG1-*H. pylori* infections in mice[7]. Antigen of *H. pylori* within the vacuoles of *Candida* was detected using direct immunofluorescence[8]. To avoid bacterial contamination, *H. pylori*-specific gene- or protein-positive *Candida* isolates were passaged several times on yeast extract-glucose agar with chloramphenicol. The presence of *H. pylori* genes and proteins persisted in the subcultures of *Candida* isolates, indicating that the transmission of the bacterium is integral to the transfer of *Candida* vacuolar content. The proponents concluded that *Candida* yeast serves as a host that protects *H. pylori* against stress outside the stomach, provides nutrients for the survival of *H. pylori*, and mediates its transmission[3].

The opponents[1], however, have argued that the review article[3] was not prepared in a scientific manner, and the methodology used was inadequate; therefore, they felt that the conclusion reached was incorrect. Subsequently, 11 months later, the proponents published a "letter to the editor" in response to all comments by the opponents[2].

The internalization of *H. pylori* into *Candida* may be crucial for *H. pylori* transmission and potentially change our understanding of the transmission route of this bacterium; therefore, most of our experiments focused on the internalization of *H. pylori* into *Candida* reported in the review[3]. Our results are consistent with those reported in the articles[4-8] analyzed by the proponents[3]. In the present study, *Candida*, including gastric, intestinal, and vaginal isolates from patients diagnosed with *H. pylori* infection were subcultured for more than 10 generations. *H. pylori*-specific 16S rDNA, *cagA* gene fragments, and *H. pylori*-specific antigens were still detectable, and some *H. pylori* 16S rDNA-positive *Candida* strains exhibited urease activity. We previously published a paper titled "Intracellular presence and genetic relationship of *Helicobacter pylori* within neonates' fecal yeasts and their mothers' vaginal yeasts"[9].

Hence, we agree with Farideh Siavoshi's (proponent) opinion that the establishment of *H. pylori* inside the ubiquitous yeast might explain why such fastidious bacteria can survive outside the stomach and remain highly prevalent in certain human populations, with yeast acting as a Trojan horse, carrying the potentially infectious *H. pylori* into the stomach[2,3]. Moreover, based on our experimental results, we present our opinion on the "shortcomings" of the article written by the opponents[1].

The opponents stated that the criteria established by Robert Koch for identifying a specific microorganism or pathogen were not adopted in the methodology used in the proponents' study[1]. However, the proponents[3] have mentioned that their study aimed to show that yeast cells can serve as a specialized niche and environmental reservoir for *H. pylori*. Because *H. pylori* in *Candida* cells is not culturable, Koch's postulates were not applicable. Moreover, we took into account the perspective highlighted by Fredricks and Relman[10]: "The power of Koch's postulates comes not from their rigid application, but from the spirit of scientific rigor that they foster. Proof of disease causation rests on the concordance of scientific evidence, and Koch's postulates serve as guidelines for collecting this evidence". Evans[11], who interpreted Koch's postulates with a modification describing the use of immunologic evidence for proof of disease causation, noted that "failure to fulfill the Henle-Koch postulates does not eliminate a putative microorganism from playing a causative role in a disease. Postulates of causation must change with the technology available to prove them and with our knowledge of the disease". These postulates have been invoked for sequence-based identification of bacterial pathogens, for resolving outbreaks of infectious diseases, and for defining the causation of certain noninfectious diseases[12]. Although no live *H. pylori* have been cultured from *Candida* cells positive for *H. pylori*-specific genes, released *H. pylori* from *Candida* cells can be grasped using magnetic beads coated with anti-*H. pylori* antibody[13]. Moreover, in our study,

Table 1 Divergent perspectives about the intracellular occurrence of *Helicobacter pylori* in *Candida*

Experimental facts and conclusions from Siavoshi and Saniee (proponents)[2-8]	The opposing view from Alipour and Gaeini (opponents)[1]	Experimental facts and conclusions from our lab[9]
The yeast cell can serve as a specialized niche and environmental reservoir for *H. pylori*. Koch's postulates are not applicable	Since Koch's postulates were not practiced in the study of *H. pylori* internalizing *Candida*, the hypothesis that the yeast can act as a vehicle to transfer *H. pylori* into humans is incorrect	Although no live *H. pylori* have been cultured from *Candida* cells, *H. pylori*-specific genes, antigens, and urease activity are positive in these *Candida* strains. The potency of *H. pylori* -internalized *Candida* in disease transmission and pathogenicity can be determined by molecular Koch's postulates
The IgY-*H. pylori* antibody has been used as a marker for localizing *H. pylori* inside yeast vacuoles	The presence of *H. pylori* in yeast cells demonstrated by IgY-*H. pylori* is inaccurate	The presence of *H. pylori* in vaginal and fecal *Candida* has been determined through immunofluorescence microscopy with IgG-*H. pylori*
The intracellular occurrence of *H. pylori* in the vaginal yeast of pregnant mothers provides potency for the transmission of *H. pylori* to newborns through vaginal yeast	The intracellular occurrence of *H. pylori* inside yeast is not reliable. If yeast can host *H. pylori*, the prevalence of *H. pylori* infection should be higher in females than in males owing to the higher yeast infection rate in the female population. However, the situation is the other way around	The intracellular occurrence of *H. pylori* in vaginal *Candida* of mothers and fecal *Candida* of newborns has been determined and suggests the transmission of *H. pylori* to newborns through vaginal yeast

Our experimental results and perspectives are consistent with Siavoshi and Saniee (proponents). *H. pylori*: *Helicobacter pylori*.

H. pylori-16S rDNA- and *ureA*-positive *Candida* strains isolated from vaginal or fecal samples expressed urease activity, whereas *H. pylori*-negative *Candida* strains were urease-negative. Therefore, the significance of *H. pylori*-internalized *Candida* in disease transmission, latency, and pathogenicity cannot be excluded.

The opponents stated that IgY is not accurate enough for such an experiment. To our knowledge, we agree with the proponents that IgY-*H. pylori* demonstrated precise and specific interactions with *H. pylori* antigens. Our current study utilized IgG-*H. pylori* to detect *H. pylori* antigens in vaginal *Candida* and fecal *Candida* isolated from mothers and their newborns, respectively[9], as well as in gastric *Candida* strains isolated from patients. Our results showed that *H. pylori* antigen in *Candida* subcultures could be detected using immunofluorescence microscopy.

The opponents believe that the prevalence of *H. pylori* infection should be higher in women than in men because of the higher yeast infection rate in the female population. However, actual scenarios contradict this expectation[1]. As refuted by the proponents[2], the relationship between yeast-positive individuals and frequency of *H. pylori* infection has not been discussed in their articles. Therefore, we agree with their hypothesis. In our experiment, *Candida* was isolated not only from vaginal discharge but also from feces, and no difference in the positivity rate was noted for *H. pylori*-specific genes or antigens in gastrointestinal *Candida* isolated from males or females infected with *H. pylori*.

Table 1 presents the divergent perspectives of the proponents and opponents, along with the viewpoints derived from the outcomes of our experiments. In conclusion, based on our experimental results, we agree with the proponents Siavoshi *et al*[6] that *Candida* could be a reservoir for *H. pylori*. Nevertheless, more in-depth studies are needed to elucidate the internalization process of *H. pylori* in *Candida* cells, its significance in the spread of *H. pylori* among humans, and long-term colonization of *H. pylori* in the gastric epithelium.

FOOTNOTES

Author contributions: Chen ZH analyzed the literature and wrote the letter; Sun JC and Yang TX performed the research mentioned in the letter; Cui GZ proposed the idea and revised the letter; and all authors have read and approved the final manuscript.

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