

Candida sp. as a Potential Reservoir and Transmission Facilitator of *Helicobacter pylori*



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Abstract

Helicobacter pylori is a bacterium broadly distributed in the world, colonizing nearly 50% of the human population. Its niche is the human stomach, where it is able to generate several gastric pathologies. A numbers of studies have detected *Candida* sp. together with *H. pylori* in the stomach, condition which could increase the severity of the gastric damage. Nevertheless, the association between these two microorganisms is closer because it has been reported that *H. pylori* can be found active within vacuoles of yeasts belonging to genus *Candida*. This association is present in yeasts isolated from diverse sources including foods as well as human bodies, such as mouth and vagina of pregnant women, suggesting the presence of a novel mechanism of protection and a means of transportation which facilitates *H. pylori* transmission. The aim of the present work is to review the relationship between *H. pylori* and yeasts of the genus *Candida* and the role of yeasts in the persistence of *H. pylori* worldwide infection.

Keywords: *Helicobacter pylori*; *Candida*; Transmission; Reservoir; Persistence

Introduction

Helicobacter pylori is a Gram negative microaerophilic bacterium associated to a series of gastric pathologies, such as duodenal ulcer, gastric ulcer, mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) and gastric adenocarcinoma [1,2]. Despite it is associated to a number of gastric and extra-gastric pathologies [3], *H. pylori* is a labile organism unable to survive under a low pH condition and it must be protected from desiccation, contact with oxygen and ambient temperature [4,5]. Presently, infections caused by *H. pylori* constitute a global health problem, particularly in developing countries where its prevalence exceeds 70% [6]. In *H. pylori* positive patients, the triple eradication therapy, consisting in clarithromycin, metronidazole or amoxicillin and proton-pump inhibitors (PPIs), is recommended as the first line treatment [7,8]. This therapy is modified in accordance with the local resistance and second third or even fourth line treatments can be established [9,10]. Nevertheless, and in accordance with reports of systematic reviews, the effectiveness of the first line therapy has been steadily decreasing [10-12], favoring the persistence of *H. pylori*.

Discussion

Helicobacter pylori as an Intracellular Organism

One of the reasons for the inefficiency of the treatment could be the intracellular facultative nature of *H. pylori*. These observations began in 1984, when “*Campylobacter*-type organisms” were

reported to invade the intercellular spaces in patients with gastritis and ulcers [13-16]. Later on, studies confirmed the invasiveness of this bacterium reporting its presence inside cells of the gastric epithelium [17-20], several cell lines [21] and in cells of the immune system, such as macrophages [22] and dendritic cells [23]. Furthermore, its entry into other eukaryotic cells, such as yeasts, particularly members of the genus *Candida* [24-30], has been reported.

Helicobacter pylori and its relationship with *Candida* sp.

Candida is a genus of unicellular fungi also known as yeasts. Species of the *Candida* genus are considered as normal microbiota of humans and they have been found in the skin, mouth, vagina and gastrointestinal system and they are considered opportunistic organisms [31]. In 1978, the presence of *Candida* in the stomach of patients with gastric ulcer was reported [32]. Later on, its presence was reported in patients with gastric cancer [33], peptic ulcer [34], chronic gastritis and persons without gastric pathologies [35]. The effect of yeast colonization in the development of gastric diseases has not been clarified yet, but the presence of *Candida* has been associated with an active role in the persistence of gastric ulcer, preventing the normal course of healing and generating persistent clinical symptoms in the patients [36]. Karczewska et al. analyzed several disorders of the upper gastrointestinal tract, such as non-

ulcer dyspepsia, gastric ulcer and duodenal ulcer, establishing a relationship between the presence of *Candida* and *H. pylori* and the development of gastric ulcer and suggested a synergism between these microorganisms in the pathogenesis of the disease [37].

Nevertheless, the interest for the presence of *Candida* together with *H. pylori* is not only based on the increased gastric damage severity because studies demonstrate a closer relationship between both microorganisms. These studies started in 1998, when optical microscopy studies revealed the presence of moving "bacteria-type bodies" within the vacuoles of gastric *Candida* [38]. The PCR technique identified these bodies as bacteria belonging to the species *H. pylori* and after subjecting the yeasts to high temperatures, desiccation, acid pH and a biocide, both *Candida* and *H. pylori* maintained their viability (the latter showing active movement) while the control *H. pylori* strain (not localized within *Candida*) was inactivated by these stressing conditions [38]. Further studies allowed visualizing and detecting yeasts belonging to the species *C. albicans* from different body origins, such as mouth, stomach and vagina, containing active non-culturable *H. pylori* within their vacuoles [24-39]. In the years 2005 [24] and 2008 [39], oral *Candida* strains containing *H. pylori* within their vacuoles were identified, providing a precedent to propose *Candida* as a reservoir of *H. pylori* and as a facilitator of the oral-oral transmission of this bacterium. Later on, using PCR, the presence of intravacuolar *H. pylori* in *C. albicans* strains of vaginal origin was detected in pregnant women [25,27] and vaginal yeasts were proposed as the main *H. pylori* reservoir for transmission of this bacterium to newborns [27].

It must be taken into consideration that *Candida* is not only highly widespread in the human body but it is also the main genus of yeasts which contaminate foods [40], being *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. rusei* the main pathogenic species [41]. The first three of them have been frequently isolated from foods such as milk, cheese, juices and salads [42,43]. Regarding intra-yeast *H. pylori* detection in foods, it has been reported within yeasts species of *Candida* isolated from different food sources, such as yogurt, grape juice, bread, preserves, fruits and honey [30,39]. In this sense, food quality yeasts, used to prepare fermented foods or food by themselves or those present as contaminants, may play a crucial role in *H. pylori* transmission [39,44]. It must be considered that yeasts can tolerate manufacturing processes present in the food industry, such as high temperatures, desiccation, acid pH, high saline concentrations, cold chains and sanitization processes [45]. Under these conditions, *H. pylori* has only been identified as non-culturable (coccoid) bacterium and it is unknown if it is viable in foods or if it is able to infect humans [26,46].

This habitat offered by *Candida* could provide protection to *H. pylori*, allowing its survival against the lack of nutrients and the presence of unfavorable conditions. It looks like yeasts, particularly their vacuoles, are appropriate dwellings for bacteria which invade these eukaryotic microorganisms. This is probably due to the diverse functions of the vacuole which includes storage and hydrolysis of glycoproteins and storage of Ca^{2+} , phosphate and amino acids. Also, the membrane of yeast vacuoles are rich in ergosterol, a compound

extensively incorporated by bacteria of the genus *Helicobacter* in their cell membrane and required to colonize hosts [47]. Thus, *H. pylori* could obtain direct benefits within the vacuole of yeasts, namely protection against the lack of nutrients and other stressing environments, such as high or low temperatures, acid pH and the presence of antibiotics [26].

Conclusion

Although the presented findings reveal a new vision of the relationship between *C. albicans*, a yeast widely spread in the human body, with *H. pylori*, a highly prevalent pathogenic bacterium, it is necessary to develop new research. It is essential to elucidate if this *C. albicans-H. pylori* close relationship provides the bacterium protection against unfavorable environments or if it provides a potential example of a model of reservoir and vector facilitating *H. pylori* transmission.

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