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Highlights

Helicobacter pylori's road to colonization

Emma Louise Walton

Staff Writer at the Biomedical Journal, 56 Dronningens Gate, 7012 Trondheim, Norway

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ABSTRACT

In this issue of the *Biomedical Journal* we learn about the virulence factors that have made *Helicobacter pylori* such a successful pathogen. We also highlight some *in vitro* findings that may shed light on epithelial–mesenchymal transition that occurs during renal fibrosis. This issue also includes the findings of clinical trials testing the effectiveness of drugs to limit nausea in chemotherapy patients and the symptoms of alcohol withdrawal syndrome.

Spotlight on reviews

Helicobacter pylori*'s road to colonization*

Around half of the world's population is infected with *Helicobacter pylori*. Although the infection is asymptomatic in most cases, *H. pylori* can cause stomach ulcers and even gastric cancer [1]. With increasing antibiotic resistance, *H. pylori* is becoming more difficult to eradicate [2]. In this issue of the *Biomedical Journal*, Kao and colleagues [3] take us on a journey with *H. pylori*, from ingestion to colonization, and describe the virulence factors that could represent future therapeutic targets.

For any ingested pathogen, the first step to colonization is a big one: surviving a bath in gastric acid. With a pH as low as 1.5, this is no mean feat. *H. pylori* copes with these harsh acidic conditions by expressing urease, a nickel-dependent enzyme that breaks urea down into carbon dioxide and neutralizing ammonium ions. Under acidic conditions the proton-gated urea channel Ure1 on the inner bacterial membrane opens to allow urea into the bacterium [4]. What is more, bacteria that succumb to these conditions help their neighbors by releasing urease into their microenvironment, which enables other *H. pylori* to pass safely through gastric juices [5]. Urease is so important to the life of *H. pylori* that strains lacking it could colonize the gastric epithelium in an animal model of *H. pylori* infection [6], and a nickel free diet improves the eradication rate of *H. pylori* [7].

Despite these amazing acid-neutralizing abilities, *H. pylori* prefers to reside on the epithelial surface of the stomach, where the pH is close to neutral. This epithelium is covered in a thick layer of mucus and *H. pylori* must use its flagella to burrow into the mucosal lining and reach underlying epithelial cells. The flagellar is a complex piece of machinery, with more than 40 proteins involved in its biosynthesis and operation [8]. The motility it confers is also essential to infection [9], and flagella proteins have been investigated as a vaccine target [10].

To avoid being displaced by the forces generated as food passes through the digestive tract, *H. pyroli* expresses several adhesin molecules that interact with receptors on host cells, enabling the bacteria to latch onto to the gastric epithelium and endure the bumpy ride. Some of the most well-studied adhesins include blood-antigen binding protein A (BabA), which binds to fucosylated Lewis B blood group antigen [11]

E-mail address: ewalton86@gmail.com.

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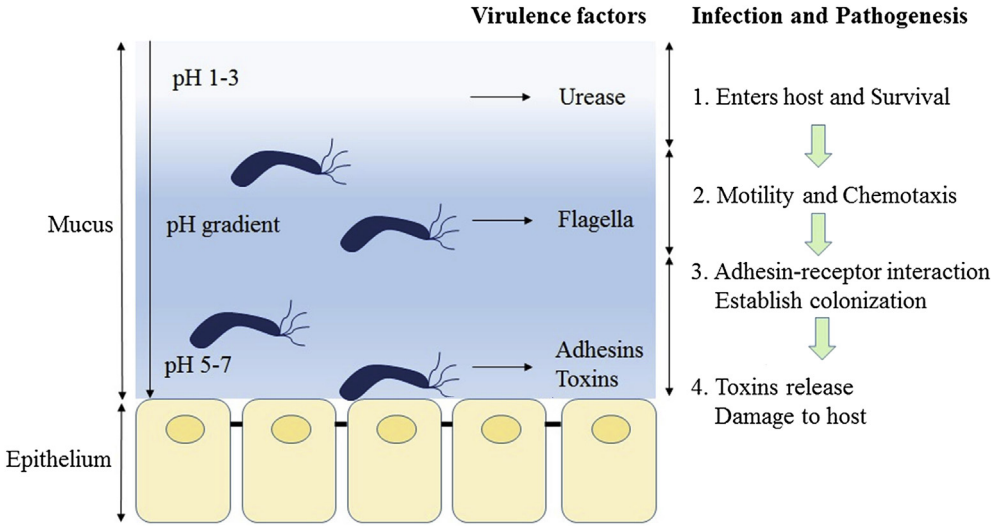

Fig. 1 – The four steps to *H. pyroli* colonization. Figure kindly provided by Kao et al. [3].

and sialic acid-binding adhesin (SabA), which binds to inflammation-associated sialyl-Lewis x antigen [12]. This close proximity to the gastric epithelium also enables the bacteria to scavenge nutrients from host cells, which are released when bacterial toxins like cytotoxin-associated gene A (CagA) damage host tissues. The damage inflicted by such toxins may ultimately lead to the development of gastrointestinal symptoms, and the complement of toxin genes that a particular strain of *H. pyroli* possesses strongly affects its virulence. For example, CagA is a particularly potent bacterial toxin, and is linked to gastric ulcers and cancer [13].

Overall, *H. pylori*'s road to colonization can be summarized in four steps: survive, swim, stick and destroy [Fig. 1]. Targeting any one of these steps could open up new opportunities for vaccine development and antibacterial therapies.

Spotlight on original articles

Recipe for renal fibrosis: TGF-β1 and collagen-I promote transdifferentiation of proximal tubular cells

Since pioneering work in the late 1980s, scientists have been able to manipulate cell fate *in vitro*, turning unassuming fibroblast cells first into muscle [14], and later into liver [15] and even neurons [16]. Such feats of cellular alchemy are called 'transdifferentiation' or 'direct reprogramming' and occur naturally under some circumstances *in vivo*. Take for example the conversion of epithelial cells into mesenchymal stem cells during epithelial–mesenchymal transition (EMT), which is an essential process during development, but contributes to disease progression during metastasis and organ fibrosis. Now, a new study by Yen et al. [17] in this issue of the *Biomedical Journal* bring us one step closer to understanding how EMT occurs during renal fibrosis.

Renal fibrosis is the excessive deposition of extracellular matrix proteins and connective tissue that occurs as the result of a failed wound-healing process in virtually every type of chronic kidney disease. It progresses slowly and ultimately leads to end-stage renal failure, requiring dialysis or transplantation. According to many (but not all [18]) studies, EMT is central to renal fibrosis. In the healthy kidney, a single layer of epithelial cells line the proximal tubule and are attached the tubular basement membrane (TBM) on the basal side. However, in response to inflammation and injury, these proximal tubular cells (PTCs) are thought to produce proteases to dissolve the TBM, allowing them to transit into the renal interstitium where they transdifferentiate into extracellular matrix-producing myofibroblasts [19]. Why and how exactly PTCs undergo this dramatic makeover is not yet fully understood, although the fibrogenic factor transforming growth factor-beta-1 (TGF-β1) plays a major role in this process [20].

To investigate in more detail what directs PTCs to undergo EMT, Yen et al. treated human renal PTC with TGF-β1 and analyzed the expression of cell lineage markers. PTCs exposed to TGF-β1 showed altered morphology, expressed matrix metallopeptidase-9 (MMP9) and the myofibroblastic marker alpha-smooth muscle actin (α-SMA), and the downregulated the epithelial marker E-cadherin. Curiously however, these changes reversed upon the removal of TGF-β1, suggesting that one or more additional factors were required to make the switch from PTCs to myofibroblasts permanent. Hypothesizing that PTCs that break away from the PTM are very likely to encounter collagen I, the most abundant extracellular matrix protein of renal interstitium, Yen et al. tested whether cells grown on collagen-I dishes could undergo a more complete transdifferentiation when temporarily exposed to TGF-β1. Sure enough, these cells stably attained a myofibroblastic phenotype and exposure to both proteins also had a synergistic effect on cell migration and the production of extracellular matrix proteins.

All these findings suggest that transdifferentiation in this case is a two-step process: first, high levels of TGF-β1 induce PTCs to express myofibroblastic markers as well as MMP9, allowing them to break away from the PTM and enter the interstitium. Here, the cells encounter a microenvironment