Host versus *Helicobacter pylori*: Insights into Novel Host-Immune Response Mechanism

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*Helicobacter pylori* (*H. pylori*), which evolved together with its human hosts over thousands of years, was first identified by Marshall and Warren in 1982 [1]. Epidemiological studies suggest that approximately 50% of the world’s human population is infected by *H. pylori*. Once acquired, *H. pylori* infection persists lifelong and may produce gastroduodenal diseases [2]. *H. pylori* can induce several severe gastric disorders such as peptic ulcers, chronic gastritis, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma. The disorder resulting from the *H. pylori* infection depends on some combination of bacterial virulence factors, environmental factors, and host-immune responses [3]. *H. pylori* have developed effective methods to evade host-immune responses, facilitating its long-term survival within the hostile gastric environment. An understanding of intracellular mechanisms related to host-immune responses against *H. pylori* may help in developing effective strategies to overcome chronic *H. pylori* infection.

Host gastric epithelial cells respond to *H. pylori* infection by releasing various anti-microbial peptides, such as human β-defensins (hBD). Gastric cell releases hBD3 as a first-line innate defense against *H. pylori* infection. This hBD3 is known to possess most potent anti-*H. pylori* activity compared to other hBDs. *H. pylori* infection induces the expression of hBD3 via epidermal growth factor receptor (EGFR) activation. During late-phase of infection *H. pylori* suppresses the release of hBD3 via CagA-dependent activation of Src Homology Phosphatase 2 (SHP-2) leading to EGFR de-phosphorylation facilitating the long-term survival of *H. pylori* [4]. However, precise details of the intracellular mechanisms of *H. pylori*-induced hBD3 expression remain unknown.

Previously, *H. pylori* were known to induce transactivation of EGFR in gastric epithelial cells by increasing the expression and release of membrane bound heparin binding-epidermal growth factor (HB-EGF). However, later I and my research group at University of Toyama, Japan, showed that *H. pylori* infection of gastric epithelial cells can also phosphorylate a specific serine residue of EGFR via activation of transforming growth factor β-activated kinase-1 (TAK1) and p38α, which was independent of HB-EGF pathway, leading to the internalization of EGFR [5]. However the functional significance of this pathway was not elucidated.

Recently, for the first time we reported that this novel intracellular EGFR activation pathway and the consequent internalization of EGFR were functionally linked to the release of hBD3 in *H. pylori*-infected gastric epithelial cells [6].

In our study, we demonstrated that the phosphorylation of serine residue of EGFR via TAK1 and p38α activation is essential for *H. pylori*-induced hBD3 release from gastric epithelial cells. We showed that this pathway was independent of CagA or peptidoglycan derived from *H. pylori* but was dependent on *H. pylori* type IV secretion system. *H. pylori* infection induced the phosphorylation of specific serine residue (pS1046/7) of EGFR followed by internalization of EGFR; and released hBD3 at an early-phase of the infection. In the presence of TAK1 or p38α inhibitors, synthesis of hBD3 was completely inhibited. These results were also confirmed using EGFR, TAK1 or p38α knock-down gastric epithelial cells. This study highlighted the mechanism of how *H. pylori* infection stimulates hBD3 expression from gastric epithelial cells as host immune response towards early-phase infection [6]. Such precise molecular studies related to host-pathogen interactions will provide clearer understanding to how *H. pylori* survive in the hostile gastric mucosa. Findings from studies like this and other similar studies will help in the development of effective strategies to overcome persistent and chronic *H. pylori* infection.

REFERENCES

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