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Metabolomics evidence on *Helicobacter pylori* infection related hydroxytryptophan induced delayed immune response; an immunopathological process that increase the risk of cholangiocarcinoma

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Abstract

Background: *Helicobacter pylori* infection is an important bacterial infection that is related to chronic gastritis and gastric carcinogenesis. Recently, there is an observation that *H. pylori* infection can increase the risk of cholangiocarcinoma, another important gastrointestinal cancer in tropical Asia.
Methods: The authors perform a comparative metabolomics analysis to find the common metabolomes between *H. pylori* infection and cholangiocarcinoma. In addition, cross interaction analysis among identified specific metabolomes from *H. pylori* infection and cholangiocarcinoma is done and the expression analysis to find the possible pathway relating to the carcinogenesis is done.
Results: There are identified specific metabolomes from *H. pylori* infection and cholangiocarcinoma but there is no common metabolome. Further cross interaction analysis shows no interaction. From expression analysis, the tryptophan, a specific metabolome in *H. pylori* infection has the interrelationship with increased expression of tryptophan hydroxylase 1 in cholangiocarcinoma. The resulted increased hydroxytryptophan might relate to the delayed immune response that might be the underlying factor leading to the increased risk for cholangiocarcinogenesis.
Conclusion: From analysis, the identified *H. pylori* infection related hydroxytryptophan induced delayed immune response is an explanation for the increased risk of cholangiocarcinoma.
Keywords: Metabolomics, Helicobacter pylori, cholangiocarcinoma, Hydroxytryptophan

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Introduction

Helicobacter pylori infection is an important bacterial infection. This infection is common in several developing countries including to those countries in tropical Asia (1,2). An important clinical consideration on this infection is its relationship to chronic gastritis and gastric carcinogenesis (1,2). The screening for infection and early management for *H. pylori* infection is an important public health policy against gastric cancer in several tropical Asian countries at present (1, 2).

Recently, there is an observation that *H. pylori* infection can increase the risk of cholangiocarcinoma, another important gastrointestinal cancer in tropical Asia. In animal model, the co-infection between *H. pylori* infection and liver fluke, which is a known etiology pathogen relating to cholangiocarcinoma, result in increased abnormalities in hepatobiliary tract (3). Kaewpitoon et al noted that extrahepatic type cholangiocarcinoma was associated with *H. pylori* infection (4). Nevertheless, the clear pathological process that *H. pylori* infection contributes to increased risk of cholangiocarcinoma is largely unknown and it requires further study on this issue (4).

Objectives

Here, the authors perform a comparative metabolomes assessment with additional expressional analysis to clarify this interesting research issue.

Materials and Methods

This work is a bioinformatics study. First, the authors performed a comparative metabolomics analysis to find the common metabolomes between *H. pylori* infection and cholangiocarcinoma. The data from the previous studies on specific metabolomes in *H. pylori* infection (5) and cholangiocarcinoma were referred too (6).

Then, cross interaction analysis among identified specific metabolomes from *H. pylori* infection and cholangiocarcinoma was

Core tip
In Tropical Indochina, both *H. pylori* infection and cholangiocarcinoma are common. *H. pylori* infection related hydroxytryptophan can caause delayed immune response and increase risk of cholangiocarcinoma.

done by standard expression analysis. Also, an additional expression analysis to find the possible pathway relating to the cholangiocarcinogenesis was done.

Results

Based on the metabolomics data searching, there are three specific metabolomes for *H. pylori* infection, tryptophan, kynurenine, and phenylacetylglutamine whereas there are various specific metabolomes for cholangiocarcinoma; 21-deoxycortisol and bilirubin.

Focusing on the identified specific metabolomes, there is no cross interaction among those 5 identified specific metabolomes.

From further additional expression analysis, there is no possible pathway relating to the cholangiocarcinogenesis for kynurenine, and phenylacetylglutamine, but there is a possible pathway for tryptophan. The mentioned identified pathway is shown in Figure 1.

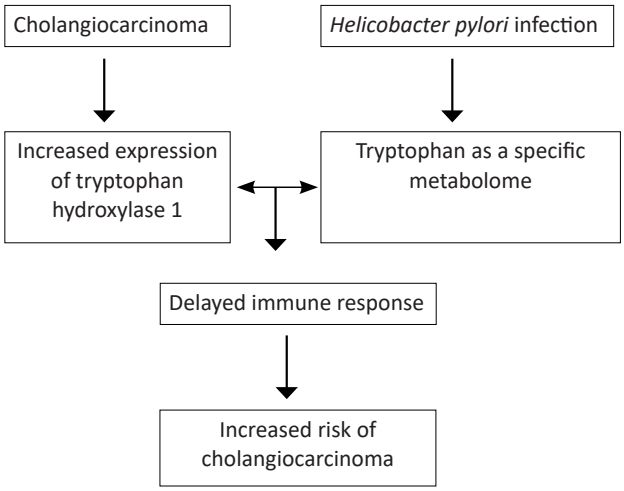

Figure 1. Identified possible pathway that *H. pylori* infection might contribute to increased risk of cholangiocarcinoma based on comparative metabolomes assessment with additional expressional analysis.

Discussion

Cholangiocarcinoma is an important hepatobiliary tract cancer. It is highly prevalent in tropical Asia (7). The liver fluke, *Opisthorchis viverrini*, infection is an important etiology of this cancer. In the same endemic area, another important cancer is the *H. pylori* infection related gastric cancer. The concurrence between *H. pylori* infection and liver fluke infection is possible. As noted by Saltykova et al, "*Opisthorchis viverrini perturbs the microbiome of the gastrointestinal tract* (8)." The co-infection might have the clinical implication.

The possible effect of the coinfection is the increased risk of the cholangiocarcinoma in the endemic area. Here, the authors perform standard metabolomics study and it can show that there are some specific metabolomes in *H. pylori* infection related gastric cancer and cholangiocarcinoma but there is no common metabolome. Nevertheless, the identified metabolomes show no cross-interaction. Hence, there is no common pathological metabolic process in both *H. pylori* infection and cholangiocarcinoma.

Nevertheless, the authors can hereby demonstrate a possible immunopathological process that results in increased risk of cholangiocarcinoma in case with *H. pylori* infection.

Immunopathologically, the tryptophan, an important specific metabolome in *H. pylori* infection is proven to have interrelationship with a pathological pathway in cholangiocarcinoma, an increased expression of tryptophan hydroxylase 1 (9). The increased expression of tryptophan hydroxylase 1 might result in increased metabolism of tryptophan that can further result in an important final product, hydroxytryptophan that can induce delayed immune response. In case that, *H. pylori* coinfection existed, the increase tryptophan as metabolome from infection can be expected. Therefore, in case with concurrent *H. pylori* infection and cholangiocarcinoma, there will be more production of hydroxytryptophan due to both increased substrate and metabolic process. As noted by Devoino et al, hydroxytryptophan is related to "*latent period of the IgM and IgG primary responses, decreased response intensity, delayed the response peak and suppressed IgG immunological memory* (10)". They mentioned immunopathology implies the defect in cancer immunity. It is no doubt that there will be an increased risk and increased severity of the cholangiocarcinoma.

Authors' contribution

Both authors wrote the manuscript equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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