

Helicobacter Pylori Infection Induces Gastric Cancer and the Cancer/Testis Antigens Expression

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Abstract

Helicobacter pylori (HP) are known to induce gastritis, atrophy, intestinal metaplasia, dysplasia, and stomach malignancy. HP infection also induces cancer/testis antigens (CTAs) during or after gastric malignancy. This study aims to elucidate the relationship between HP and CTAs, especially melanoma antigen -A3 and Kitakyushu lung cancer antigen-1.

Keywords: *Helicobacter pylori*; gastric cancer; tumor antigen; cancer/testis antigen; KK-LC-1; MAGE

Abbreviations: HP: *Helicobacter pylori*; KK-LC-1: Kitakyushu Lung Cancer Antigen-1; MAGE: Melanoma Antigen Gene; NY-ESO-1: New York Esophageal Squamous Cell Carcinoma-1; CTL: Cytotoxic T Lymphocyte; TIL: Tumor-Infiltrating Lymphocyte.

Introduction

Helicobacter pylori (HP) are a rare Gram-negative bacterium, which is pathogenic and exists in the stomach. It colonizes the gastric mucosa of more than half of the world's population. Owing to its colonization, a majority of infected individuals exhibit histological signs of chronic gastritis. Furthermore, 20% of individuals develop HP-associated diseases such as peptic ulcers, intestinal metaplasia, dysplasia, and gastric cancer [1].

After lung and liver cancers, gastric cancer is the third leading cause of cancer-related death worldwide [2]. In Japan, however, gastric cancer has the second highest incidence rate among all cancers, and almost all cases are caused by HP infection [3]. Perhaps, detection and eradication of HP infection might reduce the risk of gastric cancer. Furthermore, ABC diagnosis using an anti-HP antibody and measurement of pepsinogen I/II serum level could be an approach for identification of the risk of gastric cancer [4]. However, these approaches lack precision and can indicate only 1%–5% occurrence of gastric cancer in high-risk groups, thereby necessitating the development of more precise methods for risk diagnosis [5].

Several tumor-associated antigens are identified as tumor-specific phenomena in various human cancers [6]. These antigens are classified into four categories, excluding extrinsic viral antigens, as follows: cancer/testis antigens (CTAs), differentiation antigens, amplification or overexpression antigens, and tumor-specific mutated antigens recently defined as neo-antigens. Of these, CTAs are especially attractive targets for immunotherapy because they are not or minimally expressed in normal tissues except for the testis and are aberrantly expressed in

various human cancers [7]. Hence, immune targeting of these antigens is considered to have negligible adverse effects. Furthermore, they might be advantageous molecules for systemic diagnosis of cancer because of their specific expression patterns.

A recent study suggested that γ -radiation, which is used for standard cancer therapy and is a tumorigenic factor, induces the expression of specific CTA [8]. Here we suggest that HP, a tumorigenic factor, also induces specific CTAs.

CTA induction by HP

We co-cultured HP strain NCTC11637 with Meth-A, a cell line of mouse fibrosarcoma, in vitro to prove the HP's potential for CTAs induction. Meth-A induced the expression of the melanoma antigen (MAGE)-A3-encoding gene and retained its expression without HP [9]. Notably, the ability of CTAs to express permanently is crucial for the diagnosis and therapy of cancer. Reportedly, epigenetic alteration promotes the expression of CTAs in gastric cancer [10]. HP alters epigenetic alterations of host cells, which might be both temporary and permanent [11]. MAGE-A3 expression might be induced by permanent epigenetic alterations.

Cancer/Testis antigen	Gene expression (%)					Reference
	Lung	Breast	Colon	Ovary	Stomach	
MAGE-A1	20.8	11.8	4.2	11.1	32.5	[13-15]
MAGE-A3	23.8	11.3	14.6	1.9	39.7	[12,14,15]
MAGE-A4	20.1	4.6	2.6	25.6	20	[12,14,16]
NY-ESO-1	10.5	4.4	1	14.5	15.7	[12,14,15]
KK-LC-1	32.6	13.7	5.2	1.9	79.5	[12,14,15]

Table 1: The expression frequency of each cancer/testis antigen in cancer from each organ.

Expression of CTAs in clinical cancer tumor

To date, several laboratories have researched the expression of CTAs in clinical cancer tissues. The expression rate of the CTAs-encoding gene is commonly less than 40% (Table 1) [12-16], except for the specific CTA in the specific tissue cancer such as 80% expression of MAGE-A1 in hepatic cell carcinoma [17]. Although the expression rate of Kitakyushu lung cancer antigen-1 (KK-LC-1) was typical in other tissue cancers (Table 2), it was highest among the CTAs in gastric cancer [18], implying that KK-LC-1 would be induced by specific tumorigenic factors, such as HP, in the stomach.

Expression of CTAs in clinical gastric cancer tumor with HP infection

With or without the expression of each CTA-encoding gene, the IgG titer against HP in the serum was assessed in patients with gastric cancer as an indicator of HP infection. The titer was significantly higher in the group with expression of KK-LC-1 than in those without the expression. There was no difference observed between the groups with and without CTA (Table 1) [16], which implied that HP infection induces the expression of the specific CTA, KK-LC-1, with tumorigenesis. In addition, the discrepancy in the effect of HP between mouse Mage-A3 induction in vitro and human MAGE-A3 of clinical gastric cancer was attributed to the fact that homology between human and mouse MAGE-A3/Mage-A3 is 42% [19] and that HP directly induces mouse Mage-A3 expression. However, the direct induction of the MAGE-A3 expression by HP remains unclear. HP infection induces an immune response in vitro, which in turn induces tumorigenesis [20]. In fact, HP did not induce the expression of KK-LC-1 in human gastric cancer cell lines.

KK-LC-1

KK-LC-1 is frequently expressed in gastric cancer with 79% expression reported during the early stage of gastric cancer (Table 3),

Stage	The expression rate of each CTA (%)			
	KK-LC-1	MAGE-A1	MAGE-A3	NY-ESO-1
	p=1	p=0.162	p=0.044	p=0.222
Early (I)	79.4	23.5	26.5	8.8
Advanced (II-IV)	79.6	38.8	49.0	20.4

P value was calculated by chi-square test

Table 3: The expression rate of cancer/testis antigens in early gastric cancer.

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indicating that the expression of KK-LC-1 occurs at the beginning of malignancy and is maintained after that [14]. Hence, KK-LC-1 seems a potential candidate for the diagnosis of early gastric cancer. In addition, KK-LC-1 is frequently expressed in 75% of patients with triple-negative breast cancer [21]. KK-LC-1 therapy would be an attractive option for patients with TNBC because no existing hormone or antibody therapy is employed. KK-LC-1 has multiple epitope peptides recognized by cytotoxic T lymphocytes (CTLs) [22,23]. When CTLs against KK-LC-1 predominantly accumulate among tumor-infiltrating lymphocytes (TILs), adaptive immunotherapy using TILs leads to a good response [23]. In future, immunotherapy against KK-LC-1 could be considered as the first option for cancer treatment for pre-cancer patients or patients with cancer of the stomach caused by HP and TNBC.

CTA	IgG titer (Average)		p-Value
	Negative expression	Positive expression	
MAGE-A1	59.6 ± 10.0	43.3 ± 11.2	0.2503
MAGE-A3	60.9 ± 10.3	43.3 ± 10.7	0.2109
MAGE-A4	48.3 ± 8.3	69.1 ± 16.7	0.3415
NY-ESO-1	56.8 ± 8.6	38.8 ± 15.3	0.2794
KK-LC-1	15.7 ± 14.8	61.6 ± 7.4	0.0098

P value was determined by Wilcoxon rank-sum test.

Table 2: Anti-*Helicobacter pylori* IgG titer in each cancer/testis antigen-expression group.

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