International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 3, No. 1, 2023

Research Progress on the Relationship between Gastric Microorganisms and the Occurrence and Development of Gastric Cancer

Dan Song [1], Peilong Wang [2, *], Wanbin Zhao [1]

[1] Changzhi Medical College, Changzhi Shanxi 046000, China
[2] Department of Gastroenterology, affiliated Heji Hospital of Changzhi Medical College, Changzhi Shanxi 046000, China
*** Corresponding author:** Peilong Wang (Email: peilongwang06@163.com)

Abstract: The changes of composition and function of gastric microflora are closely related to the occurrence and development of gastric cancer (Gastriccancer, GC). Gastric microflora has great potential as a biomarker for diagnosis and risk assessment of gastric cancer. There is a complex flora structure in the stomach. The changes of gastric microenvironment caused by Helicobacter pylori (H. pylori HP) may change the flora structure and mainly participate in the early process of gastric carcinogenesis. Gastric microflora other than Helicobacter pylori may play a role in the last steps of gastric carcinogenesis. Exploring the mechanism of gastric microorganisms in the occurrence and development of gastric cancer is helpful to provide a basis for early diagnosis and treatment of gastric cancer. This article mainly reviews the role of Helicobacter pylori and other microorganisms in the occurrence and development of gastric cancer.

Keywords: Flora; Gastric Cancer; Gastric Microorganisms; Helicobacter Pylori.

1. Introduction

Gastric cancer (Gastriccancer, GC) is one of the most common major cancers that threaten human life and health. According to the latest global cancer burden data released by the International Agency for Research on Cancer (WHOIARC) of the World Health Organization (WHOIARC) in 2020, there are 1.089 million new cases and 768000 deaths of GC in the world in 2020, ranking fifth in the global cancer incidence spectrum and fourth in the death cause spectrum. Among them, 478000 (43.9%) were new cases of GC and 373000 (43.5%) were GC deaths in China. China accounts for nearly half of the new cases and deaths of GC with a population of 20% [1]. The occurrence and development of GC is a complex process involving many factors, among which the main risk factors are HP infection, environment, genetic factors, smoking, long-term consumption of pickled food and so on. The emergence of high-throughput sequencing technology, as well as the emergence of large-scale international and interdisciplinary projects, have greatly promoted our understanding of the structure and function of microbiome. More and more studies have shown that there are a variety of microbial communities in the stomach. This is different from the microbial community in the mouth and intestines. The bacterial density in the stomach is about 102-104cfu/ml, which is much lower than that in the intestinal tract (1010-1012cfu/ml) [2]. The composition of microflora is closely related to human health and diseases. Studies have shown that the imbalance of intestinal flora is closely related to colorectal cancer, pancreatic cancer, hepatocellular carcinoma and so on [3][4]. HP has been confirmed to be a class I carcinogen, and more than 90% of non-cardiac GC in the world is associated with HP infection [5]. Although the worldwide colonization rate of HP is more than 50%, only about 1% of those infected with GC eventually develop into GC, indicating that GC is a heterogeneous disease and the final result of a series of events in a small number of patients with Helicobacter pylori colonization. And eradication of HP cannot completely prevent the occurrence of GC [6]. In the experiment with insulin-gastrin (INS-GAS) transgenic mice, aseptic INS-GAS mice with only HP and three intestinal symbiotic bacteria (ASF356Clostridium, AFS361LactobacillusMurinus, ASF519Bacteroides) developed GC faster than aseptic INS-GAS mice infected with H. pylori alone, and the expression of pro-inflammatory factors and tumor-related genes in gastric mucosa of INS-GAS mice supplemented with restricted bacteria increased [7]. These evidences suggest that bacteria other than HP play a potential role in the occurrence and development of GC.

Some people think that whether there is HP infection or not, there is a core flora in gastric mucosa [8]. The dominant bacteria at the phylum level are thick-walled bacteria, Bacteroides, Proteus, actinomycetes and Clostridium; at the genus level, the common dominant bacteria are Prussiella, Streptococcus, Vellococcus, Rosella, Neisseria, Haemophilus and so on [8] [9] [10] [11] [12] [13]. There is a flora imbalance during the development from SG to GC, which is characterized by the decrease of the abundance of HP, the increase of the abundance of other bacteria, such as Lactobacillus, Streptococcus, Prussiella, etc., or the change of the composition of flora, which is characterized by the enrichment or depletion of some bacteria. At present, most studies have shown that the diversity and richness of gastric mucosal flora in patients with GC are decreased, and there is an obvious imbalance of microflora, which is significantly different from that of pre-GC lesions [14] [15] [16].However, some studies have shown that GC patients have the highest diversity of gastric mucosal flora [17] [18].There are two viewpoints in the study of gastric mucosal microflora in patients with GC: one is that the enriched flora belongs to intestinal symbiotic bacteria, characterized by nitrosation bacteria, such as clostridium, Neisseria, Escherichia coli, etc., which can increase the production of N-nitroso compounds, lead to progressive genetic instability, and finally lead to the

occurrence of GC [19]. Meta-genomic analysis showed that the functional composition of gastric microflora in patients with GC increased the functions of nitrate reductase and nitrite reductase, and nitrate reductase increased the concentration of nitrite and N-nitroso compounds [20]. Another view is that the enriched flora belongs to oral symbiotic bacteria, and its specific pathogenic mechanism needs to be further studied, but it can be found that these symbiotic bacteria are overexpressed in inflammatory bowel disease, pancreatic cancer and colorectal cancer. It has a potential pathogenic effect [21] [22] [23].

2. The Role of HP in the Occurrence and Development of Gastric Cancer

Since the International Center for Research on Cancer (IARC) listed HP as a class I carcinogen in 1994, a large number of studies have been published to prove the causal relationship between chronic HP infection and gastric cancer (IARC2011). However, the type of detection methods used to detect the risk of gastric cancer associated with HP infection is different, and the risk is also different [24].

Recent studies have revealed that it is mainly involved in the early process of gastric carcinogenesis. HP colonization leads to the imbalance of gastric microecology and further leads to changes in the composition of microflora, while the disordered flora dominates the late process of gastric carcinogenesis [25]. At the same time, dysbacteriosis induces changes in gastric functional gene expression and metabolic pathways, and the activation of specific metabolic pathways drives the formation of tumor microenvironment that contributes to the occurrence and development of gastric cancer [26] [27]. The genetic diversity of HP, especially the variation of virulence genes related to the pathogenicity of strains, also affects the risk of gastric cancer. The most common virulence factors of Helicobacter pylori are vacuolar cytotoxin (vacuolatingcytotoxinA, VacA) and cytotoxin associated antigen (cytotoxin-associatedantigenA, CagA) [28]. Among them, the CAG pathogenicity island (CagPAI) encodes a protein that forms the type IV secretory system (T4SS), and the oncoprotein CagA is the first described bacterial oncoprotein, which interacts with different signal pathways once it enters the cytoplasm of epithelial cells. CAGA disrupts the stability of cell connections and activates pro-inflammatory and carcinogenic signaling pathways. Helicobacter pylori injects CagA into the host gastric epithelial cells and activates integrin. CagA activates multiple signal pathways by tyrosine phosphorylation of Src family kinases or Abl kinases [24].

And studies have shown that the occurrence and development of gastric cancer has multiple factors and host genetic susceptibility, that is, the gene polymorphism involved in the inflammatory response of HP infection is related to the risk of gastric cancer. (1) HP weakens the repair mechanism of central DNA, induces transient mutation phenotype, increases the genetic instability of gastric epithelial cells, and induces gastric cancer in infected patients [29]. (2) the polymorphisms of inflammatory factors lead to different intensity and types of inflammatory reaction, gastric acid secretion and different clinical phenotypes after HP infection. (3) it may also be related to genetic modification, including acetylation and methylation of some stomach-specific butler genes. For example, the decreased expression of histone deacetylase 6 caused by HP infection is related to the carcinogenic transformation of gastric cancer. (4) signal transduction pathway: some studies have shown that HP may mediate the PI3K/AKT/GSK3 β signal transduction pathway in HP positive gastric cancer patients. A recent new study suggests that in addition to Wnt signal molecules, R-spondin signal molecules have been found to act on stem cells in the fundus glands, causing them to overrun [30]. (5) other factors, such as HP stimulating the production of reactive oxygen species (reactiveoxygenspeciesROS), lead to the expression of inflammatory mediators and the imbalance of apoptosis and proliferation in infected tissues; hypoxia inducible factor I (hypoxia-induciblefactorI) is a kind of molecule closely related to cell proliferation and apoptosis, and its level is closely related to gastric cancer [31]. The most studied cytokines are IL-1 β, IL-1 receptor antagonists, tumor necrosis factor-α pro-inflammatory cytokines and anti-inflammatory IL-10 cytokines. Genetic variations in the promoters or non-coding regions of these genes are associated with an increased risk of gastric cancer [32]. It is worth noting that among genetically susceptible hosts, infection with stronger HP strains significantly increases the risk of gastric cancer.

Smoking, alcohol consumption and salt are recognized as environmental factors affecting the risk of gastric cancer. In fact, past and present smokers have a higher risk of developing stomach cancer than people who have never smoked, and among current smokers, the risk increases with the number of cigarettes per day. Heavy drinkers and heavy drinkers had a higher risk of developing gastric cancer than teetotalers, and these associations were independent of HP infection status. Salt intake is also associated with the risk of gastric cancer, which increases with the increase of intake [33]. Therefore, a high-salt diet accelerates the development of gastric cancer in infected animal models, especially in animals infected with cagA-positive HP strains [34]. On the other hand, consumption of fruits and white vegetables, which is a rich source of vitamin C, is negatively correlated with the risk of gastric cancer [33]. Generally speaking, HP has carcinogenic effect on gastric mucosa through the complex interaction among bacterial factors, host factors and environmental factors.

3. The Role of Other Microorganisms in Stomach in the Occurrence and Development of Gastric Cancer

The emergence of high-throughput sequencing technology, especially next-generation sequencing and meta-genomics, suggests that there may also be diverse microflora in the stomach, including five major gates. HP is an indispensable species, which affects other bacterial communities in terms of richness and balance. Helicobacter pylori is currently recognized as a major risk factor for gastric cancer, especially strains containing CAG pathogenicity island and CagA oncoprotein [24], but the needs of other factors of host and environment can explain the important difference between infection and development of gastric cancer. Several studies have shown that there are differences in gastric microflora among patients with precancerous lesions and malignant lesions at different stages of development, usually the diversity of gastric microorganisms decreases and the existence of intestinal symbionts increases. especially the intestinal symbiote with nitrosation function [35] [36]. Other studies have shown an increase in oral microflora [37]. These

data suggest that gastric microflora other than Helicobacter pylori may play a role in the final steps of gastric cancer. For microbial diversity, different studies have obtained opposite results due to differences in sample types, sorting methods, geographical sources and population environmental exposure.

Nitrite theory is the main theory of the pathogenesis of GC at present. The production of a large number of N-nitroso compounds will lead to cell damage, resulting in genetic instability, and eventually lead to the occurrence of GC. The theory of nitrite is related to the enrichment of intestinal symbiotic bacteria. The intestinal symbiotic bacteria enriched in GC, such as Streptococcus, Puccinia, Clostridium and nitrospirobacteria, are nitrifying bacteria [38] [39]. The analysis of flora metabolic pathway also shows that GC patients increase the function of nitrate reductase and promote the reduction of nitrite by nitrate [40]. This evidence suggests that the enrichment of intestinal symbiotic bacteria in GC increases the formation of nitrite compounds. Oral symbiotic bacteria enriched in GC, such as Micromonomonas, Haemophilus, Weistellosis and Clostridium, play a potential role in the development of GC.

The enrichment of oral microorganisms has been reported in many types of cancers, such as esophageal adenocarcinoma, colorectal adenocarcinoma, breast cancer and so on. TLR4 plays a very important role in their induced inflammation, and the polymorphism of TLR increases the risk of GC in Chinese [41][42]. Lactobacillus can be enriched in all GC tissues, but the role of lactic acid is very different. A study has proved that Lactobacillus is a beneficial bacterium, and some components of Lactobacillus cytoplasm can inhibit GC cells in a time-and dose-dependent manner. Lactobacillus stagnates the cell cycle in G0/G1 phase, which is related to the increase of p53 and P21 expression, the decrease of cyclinD1 expression and the induction of apoptosis. Lactobacillus belongs to probiotics in intestinal tract [43]. However, some studies have confirmed that Lactobacillus is an effective inducer of reactive oxygen species (ROS) in human body, which can induce DNA damage in colon cells. At the same time, Lactobacillus can reduce nitrate to nitrite, resulting in the formation of a large number of N-nitroso compounds, promoting cell carcinogenesis, angiogenesis, proto-oncogene expression and so on [44]. Propionibacterium acne has also been found to be enriched in some GC tissues. Propionibacterium acne is associated with lymphocytic gastritis and can produce pro-inflammatory cytokines such as IL-15 to promote the development of GC [41]. Prussiella can significantly enhance the immune response of helper T cell type 17 (Th17). The increase of its abundance is significantly related to the enhancement of Th17 cell function. It can also produce redox protein, which increases the resistance to host [45].

4. Conclusion and Prospect

The results of different studies on gastric microbiota are different, especially in terms of diversity or population changes, which may be due to different research methods, standards and operating procedures, which makes it difficult to make a proper comparison between prospective and retrospective studies on the changes of gastric mucosal microflora during the development of GC. We look forward to a higher level of cooperation. Agree on common standards, procedures and methods in order to improve the comparability of data, so as to make a breakthrough in the study of the mechanism of gastric cancer and microbial treatment. With the increase of the study of gastric microbiota, some changes of gastric microbiota are expected to be used as biomarkers to monitor the progress of disease.

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