Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related death globally; its etiology is still not established. CRC has a strong association with certain hereditary gene mutations, but only 3-5% of cases are due to these known mutations alone. Epidemiological data has established an association between CRC development and various environmental factors, such as high-calorie diet and obesity; however, these are not high-risk factors and there is apparently contradictory evidence. Besides host genetic and environmental factors, chronic inflammation, induced by bacteria, viruses or parasites, can also cause gastrointestinal tract (GIT) cancers. The human intestine is rich in nutrients and is a habitat for over 500 different bacterial species and viruses, with the highest concentration of bacteria found in the colon. The long list of infectious microbes, potentially implicated in the pathogenesis of CRC, includes Streptococcus bovis, Helicobacter pylori (H. pylori), Escherichia coli, Bacteroides, polyoma viruses (JC and SV40), human papillomavirus, Epstein Barr virus and cytomegalovirus. Among these microorganisms, H. pylori-induced carcinogenesis involves inflammation, as well as deregulation of the cell cycle via CagA, a bacterial oncoprotein that binds and activates SHP2 (a human oncogenic phosphatase), resulting in cell proliferation and motility. Due to the strong association between H. pylori and gastric cancer, the bacterium is classified as a class I carcinogen. Given that H. pylori is strongly associated with carcinogenesis in the human stomach, it may also be relevant to the pathogenesis of other GIT cancers, including CRC. However, the association between H. pylori infection and the development of CRC had been highly contentious.

Zumkeller et al. (2006), who conducted a systematic review and meta-analysis of 11 published studies (between 1991 and 2002) involving 899 CRC patients and 1,476 controls, concluded that there is a possible small increase in the risk of CRC because of H. pylori. Similarly, in a recent large-scale retrospective population-based case-control study, conducted in the Rhine-Neckar region southwest of Germany involving 1,712 histologically confirmed CRC cases and 1,669 controls, H. pylori seropositivity was also reported to be associated with small but relevant increased risk confined to left-sided CRC. While these epidemiological studies showed a correlative relation, the association between H. pylori and CRC remained weak. Moving beyond epidemiological data, another recent study using the Helicobacter hepaticus-infected mice lacking the recombinase-activating gene-2 (rag2) – emulating many aspects of human inflammatory bowel disease (including the development of colitis and CRC) – supported the hypothesis of Helicobacter-related inflammation-mediated carcinogenesis by demonstrating that Helicobacter induced molecular damage and altered gene expression during disease progression in vivo.

In this issue of Immuno-Gastroenterology, Kapetanakis et al. went further to demonstrate that H. pylori may cause chronic inflammatory damage in the colonic mucosa, stimulating cancer stem cells and/or recruiting bone marrow-derived stem cells, thereby affecting oncogenesis and immune surveillance. The authors suggest that this may have an impact on the sequential transformation of colon epithelium to adenoma, leading to moderate-severe dysplasia and eventually CRC development and progression. Here, Kapetanakis et al. detected the presence of H. pylori in histological colonic tissue samples using cresyl violet staining further confirmed by immunohistochemistry (IHC) using anti-H. pylori. Previously, Jones et al. (2007) has also visualized H. pylori in human colonic tissues using IHC. Can H. pylori truly colonize the human colon? Serological detection of antibody against H. pylori indicates only past or current infection with no information on the site of colonization. Polymerase chain reaction and immunohistochemical detection of H. pylori in colonic tissues are sensitive, specific and correlate to present infection but are still limited by their inability to distinguish transient H. pylori infection from a true colonization of the colon or dead from viable bacteria. We need further direct and indirect evidence of extra-gastric colonization of H. pylori before passing a verdict.

Despite having a clearer understanding of the potential role of H. pylori in the progression of pathological events leading up to CRC, many questions still remained to be answered. The development and progression of CRC is likely to be a multi-factorial process, involving a delicate interplay between factors such as host genetics, infectious agents (including but not limited to H. pylori or a combination of multiple agents), gut microbiome and environmental factors. The microbial pathogens-cancers relationship is indeed a complex one. Clarification of the role of infectious agents in carcinogenesis will strongly influence the clinical management of various cancers in the future.

Conflicts of interest

The authors declared no conflicts of interest.
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