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REVIEW ARTICLE

헬리코박터 파일로리 관련 만성 위축성 위염 및 위암 발생의 진행

임나래, 정우철
가톨릭대학교 성빈센트병원 내과

Helicobacter pylori-associated Chronic Atrophic Gastritis and Progression of Gastric Carcinogenesis

Na Rae Lim and Woo Chul Chung
Department of Internal Medicine, St. Vincent Hospital, The Catholic University of Korea, Suwon, Korea

Chronic inflammation due to a *Helicobacter pylori* (*H. pylori*) infection is a representative cause of gastric cancer that can promote gastric carcinogenesis by abnormally activating immune cells and increasing the inflammatory cytokines levels. *H. pylori* infections directly cause DNA double-strand breaks in gastric epithelial cells and genetic damage by increasing the enzymatic activity of cytidine deaminase. Eventually, gastric cancer is induced through dysplasia. Hypermethylation of tumor suppressor genes is an important cause of gastric cancer because of a *H. pylori* infection. In addition, the changes in gastric microbiota and the mucosal inflammatory changes associated with a co-infection with the Epstein-Barr virus are associated with gastric cancer development. DNA damage induced by *H. pylori* and the subsequent responses of gastric stem cells have implications for gastric carcinogenesis. Although the pathogenesis of H. pylori has been established, many uncertainties remain, requiring more study. **(Korean J Gastroenterol 2023;82: 171-179)**

Key Words: *Helicobacter pylori*; Inflammation; Gastric cancer

INTRODUCTION

Helicobacter pylori (*H. pylori*) infections cause persistent infection, affecting approximately 50% of the world's population.[1] This article discusses the mechanism of *H. pylori*-associated chronic atrophic gastritis (CAG) and the progression of gastric carcinogenesis. Some mechanisms published in the previous year are summarized. PubMed was searched for all articles indexed for *'Helicobacter'* and published from April 2022 to March 2023. The titles were then screened, and all studies that presented a novel part of mechanisms involved in the pathogenesis of *H. pylori*-associated conditions were selected.

MAIN SUBJECT

1. *H. pylori*-associated CAG

Chronic inflammation induced by *H. pylori* infections can damage cells and cause them to undergo multiple stages of cancerous transformations. Epidemiologically, *H. pylori*-positive patients with CAG show a 4.9-fold increased incidence of gastric cancer compared to *H. pylori*-positive patients with-

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교신저자: 정우철, 16247, 수원시 팔달구 중부대로 93, 가톨릭대학교 의과대학 성빈센트병원 소화기내과
Correspondence to: Woo Chul Chung, Division of Gastroenterology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea. Tel: +82-31-249-7138, Fax: +82-31-253-8898, E-mail: jwchulkr@catholic.ac.kr, **ORCID:** https://orcid.org/0000-0003-1044-0440

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out CAG and 14.5-fold compared to *H. pylori*-negative patients without CAG.[2,3] In assessing the gastric cancer risk based on the Kyoto classification, open-type atrophy, and intestinal metaplasia associated with *H. pylori* infection are considered significant risk factors that are used to predict the risk of gastric cancer.[4,5]

Initially, an innate immune response occurs against *H. pylori,* reaching the surface of gastric epithelial cells. In addition to bacterial pathogen-associated molecular patterns, various components of the innate immune system, such as the pattern recognition receptor nucleotide-binding oligomerization domain protein I and Toll-like receptors, induce an immune response. Subsequently, *H. pylori* causes strong humoral immunity and cell-mediated immunity, and *H. pylori* interacts with dendritic cells, T cells, and B cells to form an acquired immune response.[6] This assists in the asymptomatic course and can cause tissue damage. In a recent study, in vitro and ex vivo experiments identified a novel mechanism through which *H. pylori* actively suppresses STING (stimulator of interferon genes) and retinoic acid-inducible gene I (RIG-I) signaling via downregulation of interferon regulatory factor-3 (IRF-3) activation.[7] This novel mechanism of immune suppression by *H. pylori* is a critical component that regulates the initial innate immune response and drives chronic gastric inflammation and injury. During the immune process, abnormally activating immune cells induced inflammatory cytokines, such as IL-1β, tumor necrosis factor α (TNF-α), and IL-10. In particular, the induction of IL-1β expression by *H. pylori* infection can induce the activation of nuclear factor-κB (NF-κB), inducing IL-6 and TNF-α expression. The changes in NF-κB-dependent cellular processes and their associated maladaptation lead to a deleterious gastric pathophysiology.[8] Furthermore, age is one of the main factors influencing the gastric inflammatory pattern during an infection with *H. pylori*.[9] The activated inflammatory cells initiate, promote, and metastasize cancerous changes by producing cytokines, reactive oxygen species, and reactive nitrogen. These substances can be converted into cells through chemical reactions, such as oxidation, nitrogenation, and halogenation. These reactions damage DNA, RNA, and proteins, promotes cell mutation, and modify the functions of tissue enzymes and proteins, contributing to cancerous changes in several stages.

Several randomized prospective studies have examined the preventive effect of eradication therapy on gastric cancer, but each had a different target population and sample size. In addition, each study showed significant differences in the quantitative effect because the follow-up period and the status of the basal gastric mucosa were different. Nevertheless, there are some questions as to the effectiveness of eradication treatment. Therefore, long-term verified research results are required. Recently, a previous study conducted a randomized, placebo-controlled prospective study to examine the effects of *H. pylori* eradication treatment on gastric cancer prevention and mortality in the high-risk areas of gastric cancer.[10] During a follow-up period of up to 26.5 years, 56 cases of gastric cancer were diagnosed. Of these, 21 (2.57%) and 35 (4.31%) cases occurred in the eradication and placebo control groups, respectively. Converting these results to a standardized risk compared with the general population revealed the eradication treatment and placebo control groups to be 0.72 and 1.20, respectively. According to the subgroup analysis conducted according to the results of baseline gastric tissue sample analysis, the difference in the gastric cancer prevention effect between the two groups was significant only in cases without underlying precancerous gastric lesions (normal mucosal or superficial gastritis, p=0.03). Cases with basal atrophic gastritis, intestinal metaplasia, and dysplasia were not statistically significant (p=0.42). In addition, the gastric cancer preventive effect of an *H. pylori* eradication treatment was consistent, regardless of the intra-gastric location (cardia or non-cardia) of the tumor or the follow-up period. Therefore, it can be seen as a research result highlighting the importance of early eradication treatment. This paper provides important evidence that active dissemination of early *H. pylori* eradication treatment in Asian countries with an exceptionally high *H. pylori* carrier rate and high gastric cancer incidence can help reduce the incidence of advanced gastric cancer and improve public health.

1) Is CAG 'reversible' after *H. pylori* eradication?

Histologically, the gastric body consists of oxygen glands, parietal cells, chief cells, surface mucous cells, and mucous neck cells. The gastric unit of the antrum is composed mainly of mucous cells, including surface mucous cells and antral gland cells. Gastric epithelial cells can renew from multipotent gastric stem cells (GSCs) and progenitor cells residing in the isthmus of gastric glands.[11] When parietal cells are lost, GSCs

can expand laterally around the gland circumference, indicating the 'reversibility' of atrophy. CAG appears reversible in these clinical and basic studies after removing chronic stimuli, such as eradicating *H. pylori*, even though atrophy improvement is not always reached. Indeed, reversibility is regeneration from the proliferation and differentiation of GSCs or progenitors in the gastric gland.[12]

H. pylori infections cause an increase in the pepsinogen II (PG II) levels, possibly due to an inflammatory response and cytokine secretion.[13] In particular, in non-atrophic gastritis caused by *H. pylori* infection, PG II is a reliable marker of gastric mucosal inflammation. A decrease of at least 25% (within two months after completion of eradication therapy) downregulates the patient's inflammatory lesions. On the other hand, PG II serology is inconsistent in distinguishing patients whose *H. pylori* eradication treatment is successful from those who remain infected. When combined with the PG I levels, the PG II levels are useful indicators of gastric inflammation and *H. pylori* re-infection.

2) Why does CAG progress after *H. pylori* eradication?

Mild or moderate CAG is 'reversible' because the loss of parietal cells and principal cells/enzyme cells can be regenerated from stem or progenitor cells after eradicating *H. pylori* and the resolution of inflammation. On the other hand, severe CAG is usually accompanied by localized fibrosis in the gastric gland, which means that atrophy is not restored to its original state, even though stem cells from the adjacent gastric glands migrate to the site of loss of the gland, proliferate, and differentiate. Whether CAG with metaplasia is reversible is not as straightforward as regular CAG because it can be further divided into spasmolytic polypeptide-expressing metaplasia (SPEM) and intestinal metaplasia.[14] If metaplasia is recovered from clinical study results, SPEM can be referred to and considered to originate from mucous neck cells. It is reversible after removing stimuli. If metaplasia is irreversible, it may be an incomplete intestinal metaplasia because the origin of intestinal metaplasia is believed to be from stem cells or SPEM.[15] *H. pylori*-induced chronic inflammation rather than *H. pylori* infection per se appears to trigger the progression to gastric cancer, which is believed to persist even in the absence of *H. pylori* (Fig. 1).

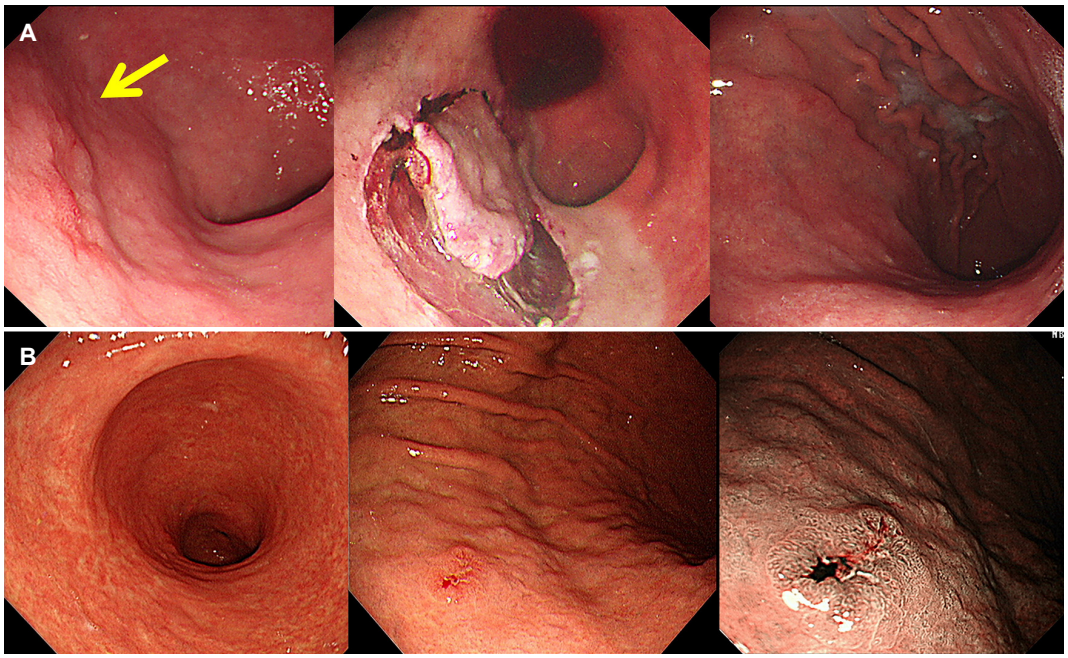

Fig. 1. Metachronous gastric cancer after *Helicobacter pylori* eradication. (A) A 2.0 cm elevated mucosal lesion with a central depression (arrow) is identified on the anterior wall of the proximal antrum on the initial endoscopy. After endoscopic submucosal dissection, successful *Helicobacter pylori* is performed. (B) After six years of endoscopic treatment, surveillance endoscopy shows a surgical scar on the anterior wall of the proximal antrum. A 1.4 cm elevated mucosal lesion with central depression is shown on the greater curvature side of the high body. It is a metachronous lesion.

2. Mechanism of *H. pylori* Causing Stomach Cancer

Generally, *H. pylori* causes gastric cancer, and various hypotheses exist about the mechanism for the abnormal activation of inflammation-related immune cells. *H. pylori* can induce inflammation and an increase in cytokines, inactivate tumor suppressor genes or activate oncogenes, and induce the generation of gastric cancer stem cells.

1) Epigenetic changes

Epigenetic changes are an essential mechanism associated with the development of almost all types of cancer, the most representative of which is DNA methylation. DNA methylation occurs in approximately 60–70% of human gene promoters. It is a biochemical change in which a methyl group binds to carbon 5 of cytosine located in this CpG island and changes it to 5-methylcytosine. In cancer development, two types of abnormal methylation patterns are largely observed. DNA hypermethylation (regional hypermethylation) occurs in CpG islands in gene promoters and global DNA hypomethylation, where methylation is instead reduced throughout the genome.[16,17]

Since the first report that the E-cadherin gene (CDH1) was hypermethylated in the gastric mucosa of *H. pylori*-infected individuals, DNA methylation induced by *H. pylori* infections has been reported in the promoter region of various tumor suppressor genes, such as p16, MLH1, LOX, and RUNX3. Gastric cancer is induced by suppressing the expression of the corresponding genes (Table 1).[18-53] On the other hand, a *H. pylori* infection contributes to the process of gastric cancer development through a pathway that causes hypomethylation throughout the genome by demethylating in the region of Alu and long interspersed nucleotide element-1 (LINE-1), which are repetitive sequences of the human genes that are usually methylated.[54-56] The DNA methylation changes of gastric cancer-related genes are accumulated because the stomach has been exposed continuously and extensively to *H. pylori* infections for a long time. Multiple stages of gastric cancer can occur anywhere in the exposed mucosa. The hypothesis that an 'epigenetic field for cancerization' is accepted as an important concept.[57] In one study, the cancer-specific methylation gene, cysteine dioxygenase type 1 (CDO1) promotor hypermethylation was observed in tumors and the tumor-adjacent mucosa in cases with metachronous lesions. Identifying molecular alterations could predict the development of metachronous lesions and the early stages of carcinogenesis.[58]

2) Microbiota

One of the most critical aspects of understanding the impact of the microbiome on disease is the diversity of microorganisms present in a particular environment. As atrophic gastritis and intestinal metaplasia progress with a *H. pylori* infection, gastric acid secretion decreases, which alters the composition of the gastric microbial community. In addition, there is a marked difference in the microbiota structure between patients with and without bile reflux.[59] In the gastric microbial community, the diversity decreases and increases as *H. pylori* infection, atrophic gastritis, and intestinal metaplasia progress without a *H. pylori* infection. The gastric flora of patients with intestinal and diffuse type gastric cancer should be different because the changes in the bacterial flora observed during gastric carcinogenesis are determined by intra-gastric pH.[60]

Thus far, there has been no comprehensive study on the gastric flora, including other microflora, viruses, and fungi. It is difficult to determine the influence of microflora other than *H. pylori* on the gastric carcinogenesis process. A recent

Table 1. Genes Regulated by *Helicobacter pylori*-induced DNA Methylation in Gastric Carcinogenesis

Major function	Genes
Cell adhesion/invasion/migration	CDH1, FLNc, VEZT, CX32, CX43, LOX 20-27
Cell cycle regulation	CDKN1C, CDKN2A, PRDM5, TCF4
DNA mismatch repair	hMLH1, MGMT, BRCA1
Apoptosis	DAPK, BNIP3, WWOX, GSTP1, PCDH10, PCDH17, SFRP2
Modulation of inflammation	TFF2, COX-2
Encoding transcription factors	RUNX3, ZIC1, FOXD3, USF1, USF2, GATA4, GATA5
Autophage-related genes	MAP1LC3A, ATG16L1
Signal transduction	RASSF1A, SFRP5, CTNNB1, SOCS-1, RARβ, Dkk-3
Other tumor suppressor genes	HRASLS, THBD, HAND1, TP73, TFPI2, PTEN, CYLD

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meta-analysis showed that successful *H. pylori* eradication could reverse gastric microbiota dysbiosis and benefit the gastric microbiota.[61] Hence, the abundance of various bacterial taxa increases after a *H. pylori* eradication treatment, and the metagenome function also shows many changes after a *H. pylori* eradication treatment. On the other hand, according to the currently available research results, eight bacterial taxa, including *Veillonella, Dialister, Granulicatella, Herbaspirillum, Comamonas, Chryseobacterium, Shewanella* and *Helicobacter*, were observed predominantly in the gastric mucosa of gastric cancer patients. Therefore, exploring the metagenome function that changes after a *H. pylori* eradication treatment can help identify the pathogenesis of gastric cancer.[62] Non-*H. pylori* is altered throughout various stages of the Correa cascade of gastric carcinogenesis. As a result, early microbial changes associated with gastric carcinogenesis result in the enrichment of Proteobacteria microorganisms (e.g., the genus Proteus), whereas Bacteroidetes microorganisms (e.g., S24-7 family) are depleted in gastric mucosal samples from patients with early gastric tumors.[63]

Patients with atrophic gastritis or intestinal epithelial metaplasia have a different microbiome than those without, even after eradication.[64] It is unclear if the microbial community in the stomach can be restored to the pre-*H. pylori* infection level through *H. pylori* eradication treatment. Research has obtained different results because the diversity of microorganisms can change depending on the stage of *H. pylori* infection, whether there is eradication treatment, atrophic gastritis, or intestinal metaplasia. Considering what is currently known, it is difficult to determine the effects of microflora other than *H. pylori* on the gastric carcinogenesis process. Therefore, further studies are needed to elucidate the detailed carcinogenic mechanisms of the gastric microbiome.

3) Co-infection with Epstein-Barr virus (EBV)

EBV-associated gastric cancer (EBVaGC) is the most common EBV-related malignancy. Approximately 75,000–90,000 such cases occur annually worldwide, accounting for 10% of all gastric cancers. EBVaGC is classified as a separate type according to the molecular classification of gastric cancer because of its notable lymphocytic infiltration, particularly CD8+ tumor-infiltrating T cells. EBV DNA methylation precedes host cell DNA methylation, including the immune response gene. Excessive methylation can lead to adverse consequences, such as suppressing latent-phase genes, transitioning to the lytic phase, and silencing tumor suppressor genes. In the process, the above factors induce local triggering of the host immune responses and make a difference in lymph node metastasis and the prognosis of EBVaGC.[65,66] An EBV and *H. pylori* co-infection may synergistically induce severe inflammatory responses in the stomach tissue, increasing the risk of developing gastric cancer.[67] Previous studies have suggested that a history of gastric ulcer can increase the risk of EBVaGC.

In a recent study, an EBV and *H. pylori* co-infection was significantly associated with male sex, proximal location, and gastric carcinoma with a lymphoid stroma (GCLS) morphology, but a co-infection was not a significant predictor for overall survival.[68] Regardless of *H. pylori* infections, the EBV infection status can influence the clinicopathological characteristics of all types of gastric cancer. Although the survival rates were not significantly different in the EBV+ and EBV− groups in non-GCLS, a better trend was observed in the EBV+ group. The co-infection was not a significant predictor of the oncologic outcome. This suggests that co-infection with EBV and *H. pylori* is more likely to be associated with the development of gastric cancer, but it does not significantly affect disease progression or prognosis.

4) GSC

Stem cells are undifferentiated cells with self-renewal and differentiation capabilities and exist in small numbers in the body. Most stem cells exist in a dormant state. When tissues age and some are shed or damaged by external factors, they replace tissues with new cells and play a role in recovery. Cancer stem cells that exist in small numbers in cancer tissues have self-renewal and differentiation abilities, which are the stem cell characteristics. These cells originate from primary cancer generation, metastasis, and recurrence. Thus far, the origin of cancer stem cells has not been clarified, but various hypotheses have been proposed. The first hypothesis is that mature cells become cancer stem cells by acquiring the ability of cell division and differentiation through self-renewal, which is the property of stem cells, through genetic mutations in DNA accumulated in mature cells. The second hypothesis is that normal stem cells in the body lose their ability to regulate growth because of DNA genetic mutations

and become cancer stem cells. Stem cells have a semi-permanent life span owing to their self-renewal ability, so they are easily exposed to continuous genetic mutations and are suitable for producing cancer cells generated by continuous accumulation of genetic mutations.

Stem cells continuously respond to local changes to maintain tissue homeostasis. The main function of GSCs is to replenish damaged or aged cells and maintain the homeostasis of the gastric epithelium. Therefore, GSCs can actively divide, self-renew, and differentiate into necessary cells and maintain a balance between stem cell division and differentiation into mature cells. The research team recently confirmed that p57Kip2 (p57) plays a vital switch role in maintaining the reserve stem cell state in a mouse model. In a homeostasis situation, p57 is continuously expressed, but its expression decreases rapidly after damage, promoting cell division and proliferation. The results of the present study showed that p57 is a key factor regulating the responsiveness of reserve stem cells in maintaining their homeostasis.[69]

GSCs are identified by the expression of specific molecular markers. Doublecortin-like kinase (Dclk1) is the first known gastric stem cell marker. Spasmolytic polypeptide/TFF2, which is overexpressed in the mucinous metaplasia that precedes intestinal metaplasia, was also a major gastric stem cell marker. Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) is a colonic stem cell marker expressed in the basal portion of the normal gastric glands, and cells expressing Lgr5 are stem cells that can differentiate into all gastric gland cells. Lgr5 is also a major gastric stem cell marker.[70] GSCs activated to regenerate gastric tissue damaged by chronic infection with *H. pylori* are actively undergoing cell division, making them vulnerable to DNA damage and the accumulation of genetic mutations. The probability of inducing a transformation into gastric cancer stem cells is increased significantly. On the other hand, the originating cell type of gastric cancer caused by a *H. pylori* infection is unclear. The gastric epithelial cells present in the gastric mucus layer are converted to stem cells with mobility by an epithelial-mesenchymal transition (EMT) caused by *H. pylori* infections and become the origin of gastric cancer.[71] In particular, in the gastric tissues of gastric cancer patients, Lgr5-positive gastric epithelial stem cells showed more DNA damage by *H. pylori* infection than Lgr5-negative gastric epithelial cells. These results suggest that the accumulation of genetic mutations due to DNA damage can occur more readily in Lgr5-positive gastric stem cells than in Lgr5-negative gastric epithelial cells. Therefore, Lgr5-positive gastric stem cells, which are prone to DNA damage by *H. pylori* infection, show that a *H. pylori* infection is closely related to gastric carcinogenesis.[70,72] Revealing the molecular mechanism controlling the transformation of normal stem cells into cancer stem cells by *H. pylori* infection will help develop methods for preventing or treating gastric cancer caused by *H. pylori* infection.

5) *H. pylori*-negative gastric cancer

The overall incidence of gastric cancer is declining as the *H. pylori* infection rate decreases. On the other hand, the incidence of *H. pylori*-negative gastric cancer will increase as various subtypes of gastric cancer arise from the background mucosa even without *H. pylori* infections. In addition, their histological characteristics are distinct from those of gastric cancer with chronic atrophic gastritis.[73,74] Four types of non-cardiac *H. pylori*-negative gastric cancers exist. The signet ring cell-type poorly cohesive carcinoma is most common, followed by the chief cell-predominant type gastric adenocarcinoma of the fundic gland. There are extremely well-differentiated adenocarcinoma of the corpus and well-differentiated pyloric gland cancers.[75,76] Although there is no unified standard for diagnosing an *H. pylori*-negative stomach, a person who has not received eradication treatment and has a negative *H. pylori* test result in both invasive and non-invasive tests might not be infected. In areas with high numbers of *H. pylori* infections, excluding people with past infection is desirable. Even when *H. pylori* has been eradicated, gastric atrophy and intestinal metaplasia resulting from long-term colonization can occur. It is challenging to determine if patients with gastric cancer have had a previous *H. pylori* infection based on invasive tests. A negative *H. pylori* status indicates poor prognosis in gastric cancer patients[77] because *H. pylori*-negative gastric cancers present with a more advanced pT classification and a more advanced stage than *H. pylori*-positive gastric cancers.

CONCLUSION

Even after *H. pylori* eradication treatment, the risk of gastric cancer is clear. Basic studies explained a large part of the

molecular biological recovery mechanism of the gastric environment after *H. pylori* eradication treatment. In clinical settings, individuals at high risk of developing gastric cancer must be monitored, even after successful *H. pylori* eradication therapy. Furthermore, there is still a need to develop useful biomarkers for selective monitoring.

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