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RESEARCH HIGHLIGHT

Aspirin-based chemoprevention of colorectal cancer: The role for gut microbiota

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1 | MAIN TEXT

Despite improvements in the surveillance, diagnosis, and multimodal therapies for colorectal cancer (CRC), its mortality is persistently high worldwide [1-3]. Continuing efforts for controlling CRC using similar strategies seems not sufficient given the persistent threats of CRC on human health. Prevention, in the form of chemoprevention, may provide another cost-effective way to enhance the outcomes of individuals at risk of developing CRC. In this regard, aspirin is emerging as a promising agent in the chemoprevention of CRC, especially for those at risk of cardiovascular diseases. However, the overall efficacy (~30%) reported from multiple randomized controlled trials is still limited [4-6]. The reasons for the limited efficacies of aspirin are elusive. Genetic and epigenetic factors are thought to be critical in relation to drug responses [7, 8]. Cyclooxygenase-2 (COX-2) has been identified as one of the important factors affecting aspirin response. In one study by Chan et al. [9], the authors demonstrated that aspirin could reduce the risk of CRC in individuals that overexpressed COX-2 but not in those with a weak or absent expression of COX-2. The percentage of COX-2 overexpression in that study was 67%, much higher than the observed responsive rate in clinical trials [9]; suggesting that the status of COX-2 expression cannot fully explain the responsiveness to aspirin-based chemoprevention. Other factors associated with the chemopreventive efficacy of aspirin are still needed to be explored and elucidated.

Apart from host factors, a new research published in *Gastroenterology* by Zhao et al. delineates the instrumental role of the gut microbiota, one of the environmental factors, in modulating the chemopreventive effectiveness of aspirin [10]. The authors found that depletion of the gut microbiota by antibiotics cocktail enhanced the suppressive effect of aspirin on COX-2 and tumorigenesis in adenomatous polyposis coli gene-mutated ($APC^{min/+}$) mice and on mice supplemented with azoxymethane (AOM) and dextran sulfate sodium (DSS). This finding was then validated in germ-free mice which were treated with AOM/DSS, and aspirin was found to significantly inhibit COX-2 and tumorigenesis. The inhibitory effect was, however, abolished by the conventionalization of the germ-free mice. Further analysis revealed that microbiota depletion was associated with an elevated level of aspirin in the plasma. Co-incubation of microbes with aspirin demonstrated the aspirin-degrading effect of commensal bacteria. Through high-throughput functional screening of the commensal bacteria, the authors identified *Lysinibacillus sphaericus* (*L. sphaericus*) as a microbe that could degrade aspirin. Increase abundance of *L. sphaericus* in the gut not only reduced the plasma level of aspirin but also dampened the efficacy of aspirin on CRC chemoprevention. These findings indicated that some microbes, such as *L. sphaericus*, possessed a degrading effect on aspirin and could impair aspirin-base chemoprevention by reducing

Abbreviations: AOM, azoxymethane; APC, adenomatous polyposis coli; COX-2, cyclooxygenase-2; CRC, colorectal cancer; DSS, Dextran sulfate sodium; *L. sphaericus*, *Lysinibacillus sphaericus*

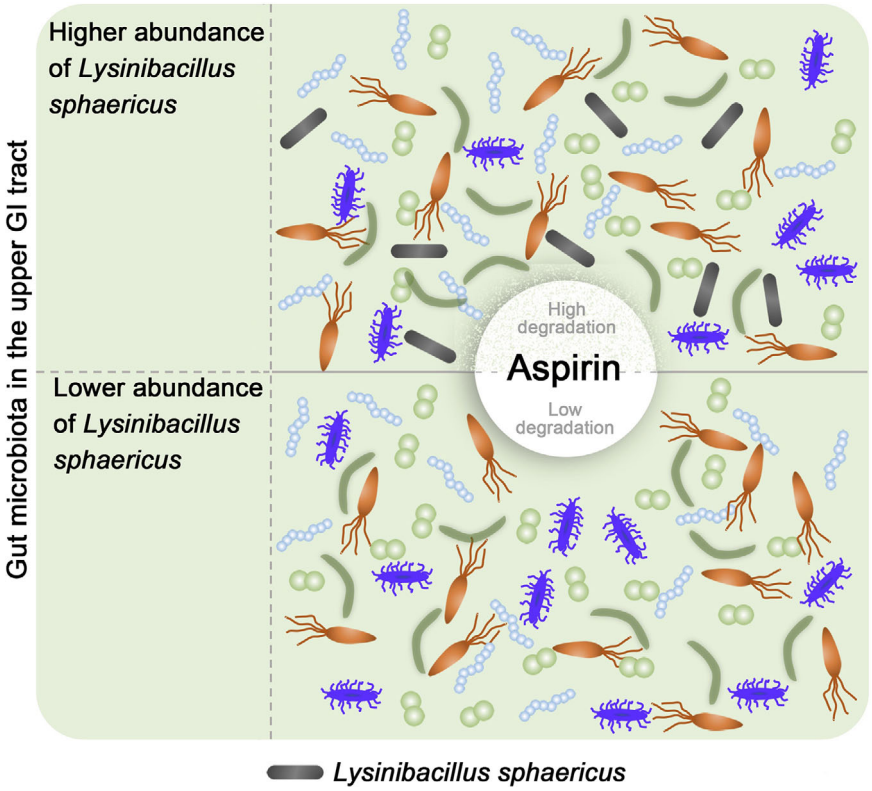

FIGURE 1 *Lysinibacillus sphaericus* promotes the degradation of aspirin in the upper GI tract. Upper panel: the upper GI tract containing a high abundance of *Lysinibaccillus sphaericus*. Lower panel: the upper GI tract containing a low abundance of *Lysinibaccillus sphaericus*.
Abbreviation: GI, gastrointestinal

the aspirin level in the plasma. On the other hand, the authors profiled the composition of microbial communities in the feces of $APC^{min/+}$ mice with aspirin use and discovered that aspirin could enrich the abundance of *Bifidobacterium and Lactobacillus* in the fecal microbiota. By culturing the fecal microbiota, containing a higher abundance of *Bifidobacterium and Lactobacillus*, under aerobic and anaerobic conditions followed by transplantation of these microbiotas into germ-free mice supplemented with AOM and DSS, the authors found that tumorigenesis was markedly reduced in mice gavaged with anaerobic fecal culture, but not in those gavaged with aerobic fecal culture; indicating direct protection from parts of the aspirin-modulated microbiota in CRC development.

Thus, *L. sphaericus* in the gut microbiota degraded aspirin and reduced the intended effect of chemoprevention. Aspirin, in turn, could enrich *Bifidobacterium and Lactobacillus*, which provide some protective effect against CRC development. This is a timely and interesting study for uncovering the bidirectional interactions between the gut microbiota and aspirin for aspirin-based chemoprevention in CRC. On one hand, the gut microorganisms attenuated the preventive effect of aspirin by biotransformation of aspirin into its inactive metabolites, and on the other hand, aspirin enriched the abundance of some probiotics in the gut microbiota, which in turn provided some protections against CRC development (Figure 1). Although the deactivation of aspirin by the gut microbiota, which can compromise the antithrombotic effect of aspirin, has already been previously reported [11], the study by Zhao et al. [10] is novel for identifying the bacterial species responsible for deactivating aspirin and potentially affecting aspirin CRC chemoprevention efficacy. The findings in this study have potential clinical relevance. For instance, if someone harbors a higher abundance of aspirin-degrading microbes, such as *L. sphaericus*, health care providers should be cautious when considering aspirin as the chemopreventive agent for CRC. Otherwise, *L. sphaericus*-mediated deactivation of aspirin could dampen the preventive effect of aspirin, while the gastrointestinal bleeding risk induced by aspirin could mountingly increase [12]. Although this study revealed that a higher abundance of *Bifidobacterium and Lactobacillus* lowered CRC risk, it may not mean to predict CRC risk with the abundance of probiotics or prevent CRC by increasing the colonization of probiotics. The enrichment of *Bifidobacterium and Lactobacillus* was merely one of the alterations induced by aspirin. Other bacteria modulated by aspirin may also have pros and cons impacts on CRC risk, which are still needed to be determined in further studies.

Since all the observations in the study by Zhao et al. [10] were conducted in mice, it is a long way to go towards clinical translation and human studies are still needed to validate these findings. Despite *L. sphaericus* was detected in the stool samples of some adenoma and healthy subjects, whether the bacteria could be colonized in the upper gastrointestinal tract, the main absorption site for aspirin, is yet to be determined. Although only *L. sphaericus* was

shown to possess an aspirin-degrading effect in this study, whether other microbes exert similar functions are still uncertain. Future researches on aspirin-based prevention for cardiovascular diseases or CRC should pay more attention on the aspect of the gut microbiota for discovering more microbial species with aspirin-degrading effect. Advanced sequencing techniques can equip us with more effective tools for deeper investigation of the gut microbiota; leading to the identification of specific microbial species, following long-term use of aspirin, in individuals developing CRC as compared to those not developing CRC. These species might be potential candidates in aspirin degradation. Additionally, further attempts should be taken to pinpoint the microbial enzymes deactivating aspirin. If we can find these functional enzymes, specific antibodies can be developed to block their catalytic activities.

In the future, capsuled aspirin with these antibodies may protect aspirin from rapid degradation and thus, enhance the efficacy of aspirin in patients. These efforts would undoubtedly contribute to better guidance of personalized medicine using aspirin.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

Feiyu Diao and Shirong Cai wrote the manuscript. All authors read and approved the final manuscript.

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