ONCOGENIC MECHANISMS OF THE GUT MICROBIOTA THROUGH DISRUPTION OF THE GUT BARRIER

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ABSTRAK
Mikrobiota saluran cerna merupakan komponen penting dalam mengatur kondisi homeostasis tubuh manusia secara keseluruhan. Namun, dalam kondisi disbiotik, mikrobiota saluran cerna juga berkontribusi pada proses patologis mulai dari gangguan pada dinding saluran cerna, merangsang proses peradangan, hingga menyebabkan infeksi tersebar ke seluruh sistem tubuh. Studi sebelumnya telah menunjukkan bahwa mikrobiota saluran cerna berkontribusi pada proses onkogenik kanker melalui berbagai mekanisme seperti peradangan kronis dan gangguan dinding saluran cerna. Namun, interaksi molekuler antara mikrobiota saluran cerna dan dinding saluran cerna, baik dalam konteks homeostasis maupun onkogenik, belum terungkap dengan jelas. Tinjauan ini menunjukkan bahwa berbagai metabolit dan komponen bakteri disbiosis seperti asam lemak rantai pendek, protein efektor termasuk Esps dan Maps, asam empedu sekunder, dan lipopolisakarida menargetkan komponen dinding saluran cerna, termasuk hubungan antar sel, komponen terkait sistem kekebalan tubuh, dan komponen terkait mukus. Dalam konteks onkogenik, gangguan dinding saluran cerna merupakan tahap penting yang membuka jalan onkogenik lebih lanjut seperti peradangan kronis dan translokasi bakteri onkogenik. Mengungkap interaksi molekuler ini memberikan wawasan tentang potensi pencegahan dan pengobatan terkait efek onkogenik bakteri disbiotik pada saluran cerna.

Kata kunci **:** dinding saluran cerna, disbiosis mikrobiota usus, kanker, mekanisme onkogenik

ABSTRACT
The gut microbiota is an important component in regulating the overall homeostatic conditions of the human body. However, in dysbiotic conditions, gut microbiota contributes to a pathological process ranging from disrupting the gut barrier, stimulating an inflammatory process, to causing a disseminated infection to the whole-body system. Previous studies have shown that the gut microbiota contributes to the oncogenic process of cancer via various mechanisms such as chronic inflammation and gut barrier disruption. However, the molecular crosstalks between the gut microbiota and the gut barrier, both in homeostatic and oncogenic contexts have not been elucidated. This review showed that various metabolites and components of dysbiotic bacteria such as short chain fatty acids, effector proteins including Esps and Maps, secondary bile acids, and lipopolysaccharides target gut barrier components, including tight junctions, immune-related components, and mucus-related components. In the oncogenic context, gut barrier disruption is a crucial step, opening further oncogenic pathways such as chronic inflammation and oncogenic bacterial translocation. Elucidating these molecular crosstalks showed insights into potential prevention and treatment related to the oncogenic effects of dysbiotic gut bacteria.

Keywords ***:*** *gut dysbiosis; oncogenic mechanisms; gut barrier; cancer*

INTRODUCTION

The gut microbiota is a collection of microorganisms consisting of viruses, bacteria, fungi, and protozoa that live in the digestive tract (Fan et al., 2020). There are over one hundred

trillion microbiota in the intestines (Leviatan and Segal, 2020). Bacteria are the most dominant microbiota in the intestines, and more than a thousand species of bacteria have been found, consisting of three major phyla: Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria (Khanna and Tosh, 2014).

The gut microbiota has various roles related to normal body functions, as well as roles in pathological processes. The gut microbiota plays an important role in body homeostasis, such as metabolizing the food that enters the digestive tract into nutrients, maintaining the barrier function of the digestive tract, and also playing a role in modulating the body's immunity (Belkaid and Naik, 2013).

The role of the gut microbiota in body homeostasis indicates the presence of an ideal composition of gut microbiota needed to maintain that homeostatic condition. The connection between the gut microbiota and the modulation of the body's immunity shows a reciprocal activity that leads to an ideal composition called eubiosis (Zheng et al., 2020). In addition to the body's immunity, various factors such as age, genetics, geography, antibiotic use, and diet can also affect the composition of the gut microbiota. Changes in the composition and function of the gut microbiota that are associated with a disease are defined as dysbiosis (Levy et al., 2017).

Dysbiosis of the gut microbiota has been found to be associated with various diseases, including cancer. Cancer is a group of diseases that fundamentally occur due to uncontrolled cell proliferation (Hassanpour and Dehghani, 2017). Cancer is one of the diseases with the highest mortality rates worldwide, known to cause approximately ten million deaths in 2020 (Sung et al., 2021).

Cancer is a condition preceded by a complex process consisting of various stages of oncogenesis. Various studies have shown a link between dysbiosis of the gut microbiota and cancer, with the microbiota composition varying depending on the stage of oncogenesis (Sadrekarimi et al., 2022). For example, before gastric cancer occurs, there are several stages of oncogenesis, such as superficial gastritis, gastric intraepithelial neoplasia, and eventually gastric cancer. Previous studies have shown variations in the composition of the gut microbiota during these stages of oncogenesis (Zhang et al., 2021). This indicates a causality between the gut microbiota and the oncogenic process that leads to cancer. This article will discuss various mechanisms of this causality, as well as research opportunities and clinical applications related to the gut microbiota and its oncogenic role in cancer.

Dysbiosis and Intestinal Barrier Dysfunction in Cancer

The gut microbiota is an important part of the gut homeostasis mechanism. Dysfunction of the gut microbiota can lead to a significant effect, leading to various pathological gut processes, including cancer. One of the mechanisms is dysfunction of the gut barrier caused by gut microbial dysbiosis. The gut barrier is composed of various components, including tight junctions, mucus-related components, and immune-related components. Previous studies showed significant relationships between gut microbial dysbiosis, dysfunction of the gut barrier, and cancer.

A study by Bertocchi et al. analyzed liver metastasis of colorectal cancer related to impairment of the gut vascular barrier. This study focused on the gut vascular barrier, which acts as a deeper barrier compared to the gut epithelial barrier, controlling the access of molecules from the gut system to the systemic blood circulation. In this study, plasmalemma vesicle-associated protein-1 (PV-1) was used as a biomarker for gut vascular barrier disruption. PV-1 is a transmembrane protein specific to the fenestrated endothelium. In this study, patients with high PV-1 are determined by a ratio of PV1+ cells to CD31+ cells of >65. Cancer patients with high PV-1 were associated with lower progression-free survival and a higher mean bacterial count. Further study with tumor-bearing mice model showed significantly similar gut-

liver microbiota landscape in tumor-bearing mice compared to healthy mice (Bertocchi et al., 2021). Furthermore, a previous study demonstrated that various microbiota, such as *S. typhimurium* are capable of regulating PV-1 levels, strongly suggesting a relationship between gut microbiota, gut vascular barrier, and cancer (Spadoni et al., 2015).

Table 1. Summary Of Previous Studies Relating Gut Dysbiosis and Gut Barrier Dysfunction

Author	Year	Barrier Component	Findings
Bertocchi	2021	PV-1	Gut vascular barrier damage was indicated by an increase of PV-1, barrier damage was found to be correlated with bacterial translocation to the liver, causing carcinogenic lesions.
Liu	2020	LPS-D-lactate, DAO	Increased various gut barrier biomarkers were significantly correlated with gut dysbiosis in early colorectal cancer.
Li	2019	ZO-1, occludin, claudin3, goblet cell, paneth cell, Muc2, cryptidin, reg3y	Exposure of CRC patients' microbiota to mice led to tight junction, goblet cell, and paneth cell disruptions.
Koh	2020	ZO-1, occludin	Exposure to P. distasonis led to improvement in colon cancer and gut barrier tight junctions.

A study by Liu et al. showed a change in the microbiota landscape in colorectal cancer patients compared to healthy controls. Various bacteria that were known to be carcinogenic, such as *Fusobacterium* and *Enterobacteriaceae* were found to be more prevalent in colorectal cancer patients. Various biomarkers of gut barrier dysfunction, such as lipopolysaccharide (LPS), D-lactate, and diamine oxidase (DAO) were found to be increased. LPS is an endotoxin found in the outer membrane of bacteria. D-lactate is a biomarker for bacterial fermentation. Both LPS and D-lactate are biomarkers for gut bacterial translocation caused by a dysfunctional gut barrier. DAO is an enzyme produced in the small intestine, that commonly increases in the case of gut epithelial damage. Dysbiosis and gut barrier dysfunction in early stage colorectal cancer patients found in this study suggested the relationship between dysbiosis, dysfunction of the gut barrier, and cancer (Liu et al., 2020).

A study by Li et al. analyzed the effects of mice fed with colorectal patients compared to healthy control feces. This study showed that exposure to colorectal cancer gut microbiota led to increased proliferation of intestinal adenoma. The levels of ZO-1, claudin3, and occludin were decreased, suggesting gut barrier dysfunction. Additionally, various inflammatory markers such as NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), interleukin-1B (IL-1B) and tumor necrosis factor-a (TNF-a) were found to be increased. Microbiota analysis showed a decrease in *Roseburia* and *Clostridium*, and an increase in *Akkermansia* compared to healthy control, suggesting dysbiotic changes in the microbiota environment. This study's findings suggest a relationship between dysbiosis, gut barrier dysfunction, inflammation, and cancer (Li et al., 2019).

A study by Koh et al. showed the importance of the gut microbiota in modulating tumorigenesis and improving gut barrier integrity. In this study, freeze-dried *Parabacteroides distasonis* (Pd) was given to colon cancer mouse model. Pd-fed mice showed a significant decrease in colon tumors compared to the control group. Various inflammatory biomarkers such as IL-4, toll-like receptor 4 (TLR-4), and TNF-α showed a 40% to 58% decrease in Pd-fed mice. Various gut barrier proteins such as occludin and ZO-1 were also increased. This showed the important relationship between gut microbiota, gut barrier integrity, inflammation, and cancer (Koh et al., 2020). However, none of the previous study explored the molecular mechanisms of the microbiota and the gut barrier. This will be further explored in the next section.

Homeostatic Molecular Pathways Between Gut Microbiota and Gut Barrier

The gut barrier integrity is comprised of various components, such as the gut epithel itself, tight junctions, mucus-related component, and immune-related component. The gut microbiota can affect the gut barrier either via its component, such as lipopolysaccharide (LPS) or via its derived metabolites such as short chain fatty acid (SCFA). These components and metabolites can regulate the tight junction, induce antimicrobial peptide secretion, and regulate the gut barrier via various pathways (Parada Venegas et al., 2019).

SCFAs are one of the gut microbiota metabolites that contribute to gut barrier homeostasis. SCFAs are the result of gut microbiota fermentation process. SCFAs are esentially carboxylic acids, comprised of butyrate, acetate, and propionate as the most common fermentation end products. Various studies have shown the importance of SCFAs in promoting gut barrier tight junction integrity. A previous study by Miao et al. showed the effect of sodium butyrate on improving the gut barrier tight junction. This in-vitro study used the calcium switch assay in Caco-2 cell model. In this study, it has been found that sodium butyrate activated the calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ) pathway, resulting in the phosphorylation of AMP-activated protein kinase (AMPK). This resulted in the phosphorylation of protein kinase C β (PKCβ), which is known to block the reassembly of tight junctions. This activation of the AMPK phosphorylation pathway resulted in the promotion of the tight junction reassembly process, improving the overall gut barrier tight junction function (Miao et al., 2016).

A previous study by Yan et al. showed other molecular mechanisms of SCFA in improving gut barrier tight junction function. This study utilized the LPS-induced inflammation model in IPEC-J2 cells. In this study, butyrate was found to increase the levels of tight junction-related proteins, such as claudins-3 and claudins-4. Additionally, butyrate was found to have protective mechanisms against LPS-induced inflammation in tight junctions by preventing the downregulation of Akt phosphorylation. This showed the potential mechanism of tight junction homeostasis by butyrate via activation of Akt/mTOR pathway. This was shown in the study by the effect of butyrate on reducing the impairment of tight junction permeability induced by LPS (Yan and Ajuwon, 2017).

Indole is a gut microbial metabolite that is used as a common, interkingdom signaling molecule. Previous studies have shown the homeostatic effect of indole in gut barrier tight junctions. A previous study by Wang et al. utilized in vitro LPS-induced Caco-2 cells treated with indole metabolites of *Latilactobacillus curvatus*. In this study, indole has been found to activate the aryl hydrocarbon receptor (AhR), resulting in an increase in various tight junction proteins. Additionally, administration of indole also resulted in an anti-inflammatory effect, suppressing the nuclear factor-κB (NF-κB) pathway (Wang et al., 2022).

A previous study by Bansal et al. utilized the human colon-cancer cell line HCT-8 exposed to indole. This study showed that 24 hours of indole exposure led to an increase in various tight junction proteins and gap junction proteins as a result of the increased expression of claudin. Exposure to indole was also found to increase various cytoskeleton gene expressions such as cingulin and actinin. These molecular effects of indole in relation to the gut barrier resulted in an increase in transepithelial resistance, showing improvement in gut barrier tight junction integrity (Bansal et al., 2010).

In addition to SCFAs and indole, the gut microbiota can also produce bile acid metabolites that have been proven to homeostatically regulate the gut barrier. A previous study by Li et al. utilized an aspirin-mediated intestinal damage mouse model supplemented with *Parabacteroides goldsteinii* and its bile acid metabolite, 7-keto-lithocholic acid (7-keto-LCA). This study showed a significant reduction in gut barrier damage caused by aspirin. It has been found that 7-keto-LCA acts as an antagonist of the farnesoid X receptor (FXR), resulting in the

suppression of Wnt pathway, improving the self-repair process of intestinal stem cell (Li et al., 2024).

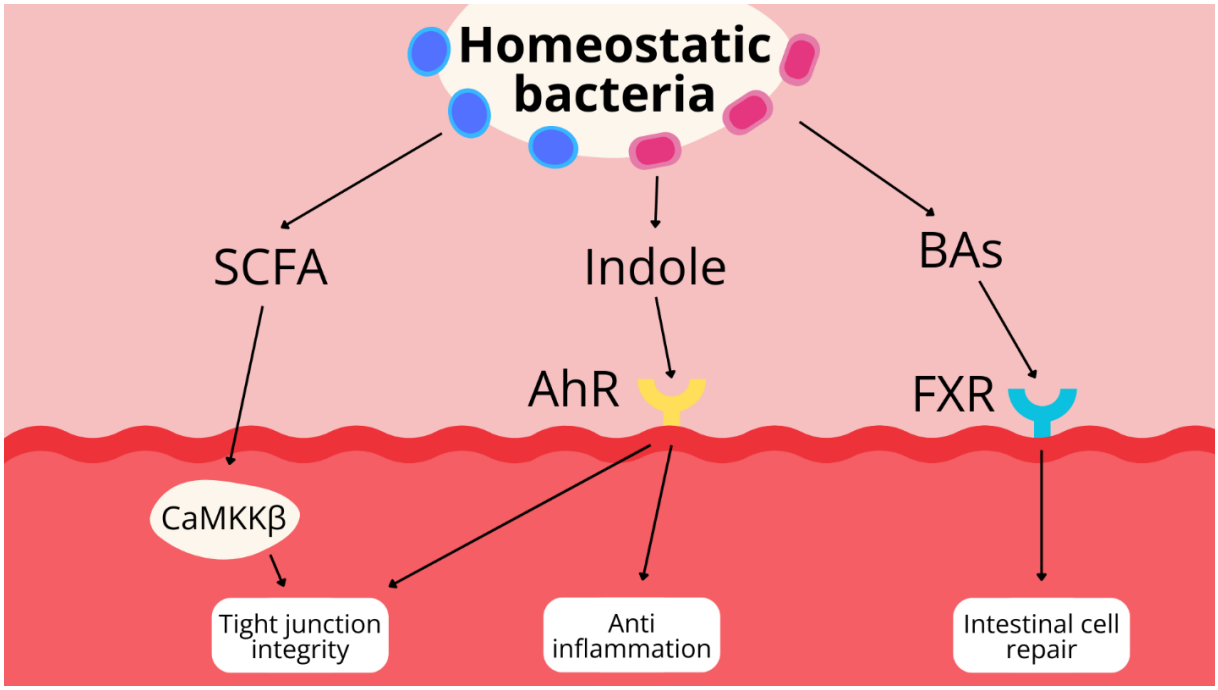

Figure 1. Molecular crosstalks between the gut microbiota and the gut barrier in homeostatic conditions. SCFA: short chain fatty acid; CaMKKβ: calcium/calmodulin-dependent protein kinase kinase β; AhR: aryl hydrocarbon receptor; FXR: farnesoid X receptor; BAs: bile acids

Pathogenic Molecular Pathways Between Gut Microbiota snd Gut Barrier

The gut microbiota can both cause homeostatic as well as pathogenic effects on the gut barrier. Similar to the homeostatic effects, the gut barrier can also pathogenically affect various gut barrier components, including the tight junction, mucus-related components, and immune-related components. A study by Singh et al. showed the pathogenic effect of *E. coli* and various mechanisms mediating the effect. This study utilized an in vitro model involving *E. coli* effectors, EspF and Map. This study showed that both effectors act as inhibitors of tight junction protein recruitment, as well as causing lysosomal degradation of tight junction protein. EspF was found to downregulate ZO-1, occludin, and claudin-1. Map was found to downregulate only claudin-1 (Singh et al., 2018).

A previous study by Morampudi also showed other pathogenic mechanisms of the gut microbiota on the gut barrier. This study utilized Caco-2 cells exposed to enteropathogenic *E. coli* (EPEC). This study showed that EPEC exposure significantly reduced tricellulin protein levels in conjunction with the loss of transepithelial resistance. Further analysis with a confocal microscope also confirmed that epithelial cells overexpressing tricellulin are more resistant to a decrease in transepithelial resistance and overall gut barrier disruption caused by EPEC exposure. Further analysis of knockout-gene EPEC showed the importance of an EPEC effector, EspG1 in modulating the expression of tricellulin (Morampudi et al., 2016).

Gut microbiota can contribute to pathogenic mechanisms via disruption of gut mucus production. A previous study by Sheikh et al. showed a degradation of the mucin barrier by enterotoxigenic *E. coli*. In this study, heat labile *E. coli* was found to stimulate the production of MUC2 by the goblet cells, suggesting an increase in the protective gut barrier. However, further study in the human small intestine showed that a virulence factor in *E. coli*, EatA autotransporter protein degrades the MUC2, enhancing bacterial access to the intestinal wall, leading to the promotion of inflammatory and oncogenic process (Sheikh et al., 2022).

A previous study by Ruas-Madiedo also showed that other bacteria can cause gut mucus degradation. This study showed that *Bifidobacterium* isolates that contain 1,2-α-l-fucosidase (*afcA*) or endo-α-N-acetylgalactosaminidase (engBF) can degrade high molecular weight mucin. In this study, 22 strains of *Bifidobacterium* were tested for the genes afcA and engBF. These strains were inoculated in a specific medium with or without mucin from a porcine stomach type III cell. In this study, two species of bacteria (*B. longum* and *B. breve*) were found to significantly degrade the mucin. afcA and engBF are genes related to the encoding of extracellular glycosidases, contributing to the higher capability of mucin degradation (Ruas-Madiedo et al., 2008).

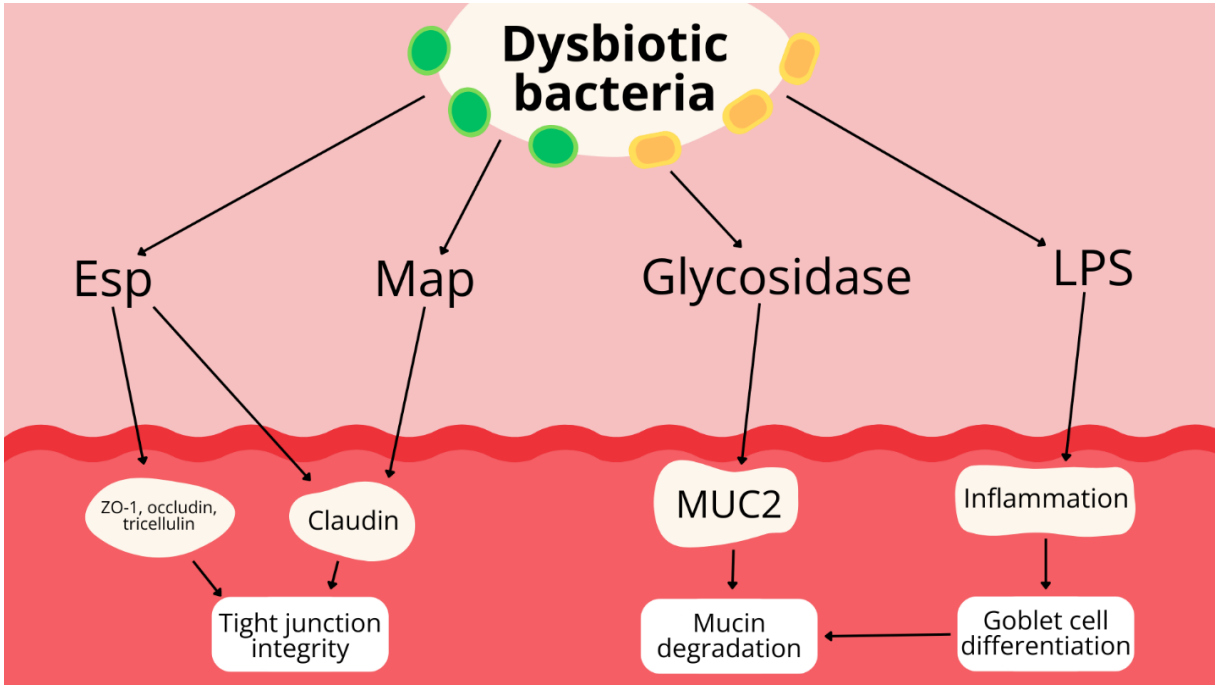

Figure 2. Molecular crosstalks between the gut microbiota and the gut barrier in dysbiotic conditions. ZO-1: zonula occludens 1; LPS: lipopolysaccharide; MUC2: mucin 2

Other than directly degrading mucus, the gut microbiota can indirectly disrupt goblet cell development. A previous study by Atanga et al. showed the effect of inflammation on the disruption of colonic goblet cell differentiation. In this study, a mouse model of spontaneous colitis was utilized. An increase in Notch pathway activity was found in colon epithelial cells, and there was an increase in Notch ligand expression in intestinal macrophages. A further study using a co-culture system utilizing a monolayer of intestinal stem cells. This was then cultured with either anti inflammatory or inflammatory macrophages stimulated with IFNγ, resulting in inflammatory macrophages with a high expression of Notch ligands. Compared to cells cultured with inflammatory macrophages, intestinal stem cells with anti inflammatory macrophages showed a significantly higher goblet cell count. This study also showed that Notch activation led to a decrease in the expression of MUC2 and CHGA genes responsible for gut secretory activity. This suggests that the gut microbiota can indirectly disrupt goblet cell development via the induction of inflammatory activity (Atanga et al., 2023).

CONCLUSION

In summary, various studies have shown a correlation between gut dysbiosis and cancer. The oncogenic mechanisms and crosstalks of the gut microbiota affected various components of the gut, including the tight junction, mucus-related components, and immune-related

components. The molecular crosstalks were done by bacterial metabolites and components such as SCFAs, LPS, and glycosidases requiring specific genes in the bacteria itself. Elucidating these molecular crosstalks showed insights into potential prevention and treatment related to the oncogenic effects of dysbiotic gut bacteria.

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