Bacterial translocation in colorectal cancer patients

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Abstract
Bacterial translocation is the penetration of intestinal bacteria through the intestinal mucosa into usually sterile tissues and internal organs. Commensal bacteria, despite their presence in the intestine in extremely large numbers, rarely cause local or systemic inflammation, because the unicellular epithelial layer of the intestinal mucosa prevents the migration of these bacteria from the intestine. For years, researchers have wondered how a single layer of intestinal epithelial cells can prevent microorganisms from entering the systemic circulation. Today, the phenomenon of bacterial translocation is considered as one of the main mechanisms of endotoxemia and systemic inflammatory response syndrome in various pathologies, including colorectal cancer and acute bowel obstruction. This narrative review is devoted to the search for factors promoting to bacterial translocation from the intestine in colorectal cancer and acute malignant bowel obstruction.

Key words: bacterial translocation, gut microbiota, intestinal barrier, colorectal cancer, bowel obstruction

Introduction
As per the statement of A. Alexopoulou, bacterial translocation (BT) is the invasion of intestinal bacteria, bacterial endotoxins (ex., bacterial lipopolysaccharide, peptidoglycan, lipopeptide) from the intestinal lumen into the mesenteric lymph nodes and extraintestinal areas [1]. These days, the phenomenon of bacterial translocation is considered one of the main mechanisms of endotoxemia and systemic inflammatory response syndrome (SIRS) in various pathologies, including colorectal cancer (CRC) and acute bowel obstruction (ABO).

Colorectal cancer takes the 3rd place among all diagnosed malignancies. CRC holds the third position among lung and prostate cancer in men (10% of the total) and the 2nd position after breast cancer in women (9.2% of the total) [2, 3]. CRC is the 4th leading cause of cancer deaths in the world [2, 4].

In Kazakhstan, colon and rectal cancers occupy the 5th and 6th places respectively in the oncological diseases’ hierarchy. If compared with the data from 2018, there has been an increase in the detection of new cases in 2019 by 1.4% for colon cancer and 2.9% for rectal cancer. In the mortality rate from malignant neoplasms in 2019, colorectal and rectal cancers are on the 5th and 8th places, respectively [5].

More than 66% of patients with CRC are admitted to the hospital with complications, and in most cases these complications are the first symptoms of the disease [6]. Despite the improvement in diagnostic and screening programs, some complicated forms of CRC are diagnosed in 88.9% of newly diagnosed patients, where about 40% of them already have metastases [7]. The most common complication in CRC is acute bowel obstruction, which accounts for about 80-85% of the emergencies related to this pathology [8-10].

Despite the improvement in diagnostic and treatment, there are currently high rates of postoperative complications (46-50% of cases) and mortality (up to 25-52% of cases) in patients with malignant ABO. According to numerous researchers, in case of malignant ABO, both mortality and postoperative complications are 2 to 3 times higher than in operated patients with uncomplicated colon cancer. Additionally, a 5-year survival rate after planned surgeries is 20% higher than after urgent surgeries [11-13]. Today, a number of researchers believe that bacterial translocation is a trigger mechanism for development and enhancement of the SIRS, which can lead to the infectious-inflammatory complications, sepsis and multiple organ dysfunction [14-16]. Thus, a closer look shall be taken to the factors contributing to bacterial translocation in CRC patients and malignant ABO.
Gut bacterial translocation factors

Presently, several factors have been identified as those contributing to bacterial translocation from the intestine.

**Imbalance of normal intestinal microbiota and bacterial overgrowth**

The intestinal microflora is involved in maintaining homeostasis, playing a crucial role in nutrition and energy metabolism [17], as well as immune modulation [18, 19]. Trillions of commensal microorganisms living in the gastrointestinal tract can compete for adhesion sites with pathogenic bacteria. These microorganisms are the first line of defense against bacterial translocation [20]. According to the latest data, in patients with various diseases (acute pancreatitis, severe trauma, burns, surgical interventions), the composition of the intestinal microbiota is changing. It is characterized by a decrease in the number of commensals and an excessive growth of opportunistic proteobacteria, including Escherichia coli, Pseudomonas spp., Klebsiella spp., Clostridium difficile and Vancomycin-resistant Enterococcus [21-28]. Dysbiosis has been associated with severe complications in critical conditions, including sepsis, multiple organ failures, and even deaths [29, 30].

Normal intestinal microflora plays a critical role in resisting bacterial pathogen colonization, overgrowth and invasion. This phenomenon has been termed as "colonization resistance" [31]. In addition to competing for nutrition and adhesion to the epithelium, normal gut microbiota can indirectly fight the entry of pathogens by enhancing immunity (immune-mediated resistance to colonization) [32, 33].

The composition of normal intestinal microbiota is affected by various factors: diet, gastric and intestinal secretions, bile salts, lysozyme, secretory IgA, antibacterial drugs, endotoxin shock, parenteral nutrition, bowel obstruction, and much more [34]. All these factors can lead to microbiota imbalance and bacterial overgrowth, which in its turn, contributes to BT, as it is been proven in animal models [35] and in humans [36].

The intestinal microbiota takes part in the metabolism of lipids, carbohydrates, proteins. The metabolites of these reactions can be useful or toxic to the body [37]. Lactic acid, fatty acids, bacteriocins are antimicrobial factors for pathogenic flora [38]. However, for example, phenolic and sulfur-containing compounds formed as a result of protein metabolism are toxic to intestinal epithelial cells [39]. They cause an increase in paracellular permeability by destroying intercellular dense junctions [40]. If the normal composition of the microbiota is disturbed, an increase in the production of toxic metabolites is possible, which leads to a disruption of the intestinal epithelial barrier and subsequent BT [41].

**Immunity disorders**

The gut is an important organ of the immune system that contains all types of white blood cells involved in both innate and adaptive immune responses. As a rule, the innate immune system does not respond to most commensal microorganisms [42]. At the same time, it can also respond quickly to invasion of pathogens and prevent their migration from the intestinal lumen into the systemic circulation. In immunocompetent people, after passing through mucous and epithelial barriers, pathogenic bacteria in mesenteric lymph nodes are recognized and neutralized by macrophages and dendritic cells [43]. Thus, these cells don’t produce proinflammatory cytokines, and no inflammatory response occurs. If, at this stage, macrophages fail to neutralize all pathogens, bacteria or their toxins enter the liver through the portal vein system, where they are neutralized by the Kupffer cells. Since critically ill patients are usually accompanied by systemic immunodeficiency or immunosuppression, innate and adaptive immune mechanisms are unable to destroy pathogenic microorganisms. Therefore, surviving bacteria or their components (lipopolysaccharides and peptidoglycans), as well as cytokines and chemokines, pass through the mesenteric lymph nodes, and ultimately enter the systemic circulation through the thoracic duct. Consequently, immunity disorders can lead to increased bacterial translocation [44, 45].

**Circulatory hypoxia of the intestinal wall and impaired antioxidant defense**

Hypoperfusion, ischemia, and subsequent reperfusion of damaged areas of the intestine enhances the inflammatory response and leads to oxidative stress, which contributes to the death of enterocytes and disruption of tight junctions, thereby increases the intestinal wall permeability and disrupt the intestinal barrier function [46].

**Violation of the barrier function of the intestinal mucosa**

The first line of defense against bacterial invasion is the intestinal mucosa, which contains mucin and antimicrobial peptides. The mucus produced by the intestinal goblet epithelial cells forms a thick, continuous layer, which prevents bacteria from penetrating through the intestinal wall. Mucous secretions are rich in secretory IgA, which neutralizes toxins and microorganisms and prevents their adhesion and colonization [47]. Any disturbances in microcirculation of the intestinal mucosa lead to hypoperfusion, edema of the mucous membrane, its ischemia, an increase in free oxygen radicals that destroy the cytoskeleton of the mucous membrane, which contributes to the disruption of the integrity of the intestinal barrier and subsequent bacterial translocation [48-52].

As known, colorectal cancer leads to disorders of the immune system. The normal intestinal microflora gets out of balance with the intestinal barrier violated, which occurs at the site of the tumor growth as the tumor causes dysplasia of the epithelium. In the case of ABO, microcirculation disorders occur in the area of obstruction, and subsequent ischemia and hypoxia of the intestinal wall. Therefore, the ongoing changes in CRC and ABO can lead to BT.

**Changes in the intestine in malignant ABO**

Colon tumors at the site of their growth cause epithelial dysplasia, changing the structure of the intestinal wall, and causing the violation of the intestinal barrier. With ABO, this situation is aggravated by the presence of an obstruction and the disorders caused by it. The intestinal microcirculation disturbances occur both at the site of tumor growth and above the obstruction. There are edema, ischemia and hypoxia of the intestinal wall in place, which results in even greater violations of intestinal permeability.

In case of bowel obstruction, all functions of the large intestine are impaired, including disorders of intestinal motility. Due to the slow evacuation of intestinal contents, there is an increase in pressure in intestine, as a result of which blood circulation in its wall is disrupted with absorption of water, minerals and other substances impaired, and fluid accumulated in intestine. The accumulation of feces above the
tumor localization enhances the processes of putrefaction and fermentation. In addition to fluid in intestine, gas begins to accumulate, the intestinal loops expand, and the disturbance of the regional blood circulation of the intestinal wall is increased. These microcirculation disorders lead to ischemia of the intestinal wall, hypoxia, activation of lipid peroxidation, which ultimately reduces the barrier function of the intestinal wall. As the bowel obstruction progresses, desquamation of the intestinal epithelium and destruction of enterocytes occur, which contributes to the translocation of microorganisms through the intestinal wall and the development of the SIRS and subsequent multiple organ failure. Back in 1971 Dederer Yu.M. described changes in the intestinal wall above the obstruction, which acquired a destructive character: at the first hours of bowel obstruction, the epithelium is exfoliated, after 24-72 hours diffuse leukocyte infiltration is developed, and in later stages, suppuration of the intestinal wall is observed [53].

In the histological examination of resected areas of the colon in patients with ABO Achkasov E.E revealed inflammatory reactions in all layers of the intestinal wall and a significant expansion of lymphatic capillaries [54]. With compensated ABO, there have been signs of myocyte dystrophy with severe neutrophilic infiltration and ulceration of the intestinal wall in areas of tumor obstruction. In the areas above the obstruction there have been microcirculation disorders and interstitial edema. The decompensated ABO has been manifested by the areas of intestinal wall destruction not only in areas of tumor obstruction, but also in the areas remote from the tumor. The microcirculation disorders with interstitial edema have also been present in the small intestine. At the same time, it has been found that with decompensated ABO, the edema of the intestinal wall was less pronounced, which indicated a significant violation of the intestinal barrier permeability. All patients with decompensated and some patients with sub-compensated ABO demonstrated some bacterial translocation into the abdominal cavity, which was confirmed by bacterial cultures of abdominal effusion.

These studies have confirmed that ABO exacerbates changes in the intestinal wall in CRC patients, thereby increasing BT, which may lead to SIRS and infectious and inflammatory complications.

**Postoperative complications after surgery for CRC and malignant ABO**

The antibiotic prophylaxis in 24 hours after surgery is recommended for patients with CRC and malignant ABO, even without signs of infection. Antimicrobial drugs mainly target gram-negative and anaerobic bacteria due to potential bacterial translocation [3].

Postoperative complications include the following: wound suppuration, anastomotic leak, paracolostomy and abdominal abscesses, peritonitis, evagination, intestinal paresis, gastrointestinal bleeding, pneumonia, pulmonary embolism, etc. Numerous studies have noted that infectious and inflammatory complications are one of the main causes of death in patients with cancer [55, 56].

After any surgical intervention in any patient, a cascade of immune responses is triggered with the release of endogenous pro-inflammatory mediators. However, in immunocompromised patients (including cancer patients), these reactions can spill over into the SIRS, which can subsequently cause multiple organ failure and sepsis [57].

One of the reasons for the occurrence of infectious and inflammatory complications is the gut microbiota. The gut microbiota is involved in maintaining homeostasis and plays an important role in nutrition, energy metabolism, immune modulation, and defense, preventing colonization of the intestine by pathogens [58, 59]. Van Praagh by sequencing 16S rRNA in patients after surgery for colorectal cancer confirmed that anastomotic leak and inflammatory reactions were associated with low microbial diversity: a decrease in the number of normal microbiota and an overgrowth of pathogenic bacteria [37]. Thus, dysbiosis of the intestinal microbiota can lead to a loss of "colonization resistance", metabolic disorders and impaired barrier function of the intestinal wall. As a result, translocation of pathogenic flora is increased with the endotoxins in the mesenteric lymph nodes and systemic blood flow, causing systemic inflammatory response syndrome (SIRS) [60]. Also, the main cause of postoperative infectious and inflammatory complications in malignant ABO is the violation of the intestinal wall barrier, the mechanism of which was described above.

In patients with CRC the imbalance of the intestinal microbiota, immunosuppression, microcirculation disorders, hypoxia and ischemia of the intestinal wall results in the production of a large number of pro-inflammatory mediators. The inflammatory response increases and oxidative stress occurs. These changes contribute to the death of enterocytes, disruption of intercellular tight junctions, which increases the intestinal wall permeability. Bacteria or their endotoxins penetrate the damaged mucous barrier and further enhance the immune response, which becomes systemic, and ultimately, leads to systemic inflammatory response syndrome (SIRS), multiple organ dysfunction and sepsis [56].

In patients with colorectal cancer after resection of colon, M. Schietroma et al. confirmed an increased permeability of the intestinal wall and a significant increase in endotoxemia on the very 1st postoperative day, which subsequently correlated with the development of sepsis [60]. Destruction of the intestinal barrier promotes the translocation of bacteria and endotoxins into the mesenteric lymph nodes and further into the systemic circulation [58, 60]. In a number of studies, researchers have found that bacterial translocation into mesenteric lymph nodes occurs in 65% of patients with colorectal cancer, with predominance in patients with III and IV stages [60].

High rates of postoperative infectious and inflammatory complications in patients with CRC (46-50% of cases), despite the ongoing treatment, are potentially associated with the BT phenomenon, which increases in this group of patients, especially those with ABO.

**Bacterial translocation detection methods**

As of today, BT takes one of the main roles in the development of infectious and inflammatory complications. Various methods are used and studied for the early diagnosis of such complications, as well as the detection of BT, which are as follows:

1. Direct methods, which determine bacteria in the mesenteric lymph nodes (MLN), through which bacteria then enter the systemic circulation and other organs and tissues. These methods include using cultures of MLN and determining the microbial 16S rRNA in MLN by utilizing a polymerase chain reaction in "real time" (RT-PCR). In experimental studies on modeling bowel obstruction, radioactively labeled bacteria are also used, but this technique is not applicable for humans.
2. Indirect methods are aimed at determining bacteria or BT markers in blood and other biological fluids. These methods include blood culture, detection of bacterial genes by RT-PCR in blood and ascitic fluid, determination of markers of impaired intestinal barrier in blood (zonulin, citrulline, intestinal fatty acid-binding protein), determination of endotoxin (lipopolysaccharide) and markers of inflammation and BT in the blood (C-reactive protein, procalcitonin, interleukins, tumor necrosis factor, presepsin and lipopolysaccharide-binding protein).

The growing interest in the BT phenomenon is gaining its momentum among scientists all over the world. BT is being studied for various pathologies: liver cirrhosis, HIV infection, pancreatitis, burns, parenteral nutrition, renal diseases and other. However, there are few works on the study of BT in CRC and ABO.

In Kazakhstan, insufficient attention is paid to the study of the BT phenomenon. In the Scopus database we found only six articles written by the Kazakhstani scientists, which are devoted to BT from the intestine. In one of the experimental studies, the researchers modeled obstructive and strangulated intestinal obstruction using their own method. Various biomarkers in the rats’ blood by immunological and molecular genetic methods (procalcitonin, lipopolysaccharide-binding proteins and interleukin-6) have been detected at different stages of the development of intestinal obstruction. The maximum BT frequency was revealed on the first day of the development of obstruction. There have been no statistically significant differences in the groups with strangulated and obstructive intestinal obstruction, which may indicate the similarity of the pathological mechanisms of intestinal obstruction, leading to BT. Also, some authors found that procalcitonin and lipopolysaccharide-binding proteins are the most valuable markers of BT at intestinal obstruction [61]. In a clinical study of patients with acute surgical pathology, including acute intestinal obstruction, some correlation has been found between an increase in intraabdominal pressure and an increase in the level of presepsin. Moreover, some researchers found that presepsin can be used to stratify the risk of abdominal sepsis [62].

To date, most of the work on BT is experimental, and a large part of clinical studies have been carried out on HIV-infection and liver cirrhosis. BT in CRC and ABO has insufficiently been studied, as its role in the development of SIRS and infectious and inflammatory complications. The questions of the diagnostic value of the proposed biomarkers, their study in dynamics, as well as the relationship between direct and indirect BT markers remain open. These unsolved problems require further in-depth study.

Conclusion
Recently, the studies of bacterial translocation phenomenon have been attracting more and more interest among scientists around the world. Disturbance of the intestinal barrier and subsequent BT is the first step, which ultimately leads to the fact that the intestine becomes the main pro-inflammatory organ that controls the systemic inflammatory response. As of today, many questions remain unresolved, including those on the study of this phenomenon in CRC patients and on the diagnostic value of BT biomarkers. Therefore, further studies are required to be conducted.

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