Role of Translocation of Pathogen-Associated Molecular Patterns in Sepsis

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Key Words

Pathogen-associated molecular pattern • Toll-like receptor • Sepsis • Organ injury

Abstract

Background/Aim: Unlike animals, the incidence of bacterial translocation and its clinical significance remain to be determined in humans, which may be due to the lack of accurate methods to confirm and monitor bacterial translocation. The literature on the consequences of novel insights of bacterial translocation was reviewed. **Methods:** The Medline databases were searched for publications regarding translocation of bacteria as well as pathogen-associated molecular patterns. **Results:** Although substantial data support the occurrence of bacterial translocation in humans, the lack of data correlating bacterial translocation with its clinical significance has led to confusion among physicians. Toll-like receptors have been implicated in the mediation of systemic responses to the relevant pathogen-associated molecular pattern. The gut is a reservoir of pathogen-associated molecular patterns from microbes, and translocation of pathogen-associated molecular patterns other than endotoxin also induces a systemic inflammatory response through toll-like receptors. **Conclusions:** Pathogen-associated molecular patterns translocation may be at least partly responsible for the development of sepsis under conditions in which bacterial translocation may occur. Detection of bacterial DNA in blood and tissues/organs should be useful as a marker of

translocation of pathogen-associated molecular patterns and/or bacterial translocation, and should have the predictive value for developing sepsis in surgical patients.

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Introduction and Methods

We have substantial evidence of the occurrence of bacterial translocation in animal models. However, the incidence of bacterial translocation and its clinical significance remain to be determined in humans. In order to review the occurrence and clinical consequences of bacterial translocation in humans, the Medline literature databases were searched for pertinent publications relating to bacterial translocation and its clinical role, with emphasis on its pathophysiological importance in sepsis.

In this study, a search strategy was based on the previous guidelines for systematic review [1]. The literature databases such as PubMed Medline National Library of Medicine and EMBASE from 1960 to 2007 were used. The following medical subject headings were searched: 'bacterial translocation' and 'pathogen-associated molecular pattern', or 'toll-like receptor', or 'sepsis', or 'organ injury', or 'mesenteric lymph node'. We found 1,078 manuscripts by the above-mentioned search. Of 1,078 manuscripts, we selected 585 manuscripts for this review; 111 and 382 were excluded because they were not in English and the content did not suit this review, respectively.

Table 1. Studies of bacterial translocation in humans

Author	Clinical condition	Number of patients	Incidence	Relation to morbidity	Methods testing BT	Ref.
MacFie	laparotomy	927	yes (14%)	yes	culture of MLN	14
Sedman	elective surgery	263	yes (10%)	yes	culture of MLN, intestinal serosa	15
Tancrede	hematological malignancies	55	yes (82%)	yes	culture of PB, feces	19
Deitch	intestinal obstruction	17	yes (59%)	yes	culture of MLN	20
LeVoyer	thermal injury	15	yes (NR)	yes	L/M ratio	21
Sagar	intestinal obstruction	36	yes (39%)	yes	culture of MLN, PB, intestinal serosa	22
Woodcock	aortic aneurysm repair	51	yes (10%)	yes	culture of MLN	23
Yeh	liver resection	181	yes (20%)	yes	culture of MLN	24
Rush	trauma	50	yes (56%)	yes	culture of PB, serum Et	25
Kuzu	obstructive jaundice	21	yes (24%)	no	culture of MLN, PB, peritoneal swab, portal blood	16
Ferri	liver resection	14	yes (43%)	no	culture of MLN, PB, portal blood	26
Kanwar	elective surgery	68	yes (NR)	no	L/M ratio, serum Et antibody	27
Ambrose	Crohn's disease	46	yes (33%)	NR	culture of MLN, intestinal serosa	28
Reed	trauma	16	yes (81%)	no	culture of MLN, electron microscopy	29
Moore	trauma	20	no (2%)	no	culture of portal blood, PB	17
Peitzman	trauma	25	no (0%)	no	culture of MLN	18

BT = Bacterial translocation; PB = peripheral blood; MLN = mesenteric lymph node; L/M ratio = lactulose/mannitol ratio; Et = endotoxin; NR = not referred.

Does Bacterial Translocation Occur in Humans?

Bacterial translocation was initially defined by Berg et al. [2] in 1979 as the passage of viable bacteria from the gastrointestinal tract through the epithelial mucosa into the lamina propria and then to the mesenteric lymph nodes and possibly other organs. Subsequently, bacterial translocation has been recognized as a possible major contributor to the development of systemic infection and multiple organ dysfunction after shock, mechanical trauma, or thermal injury, as well as in ICU patients. Numerous experimental studies using animal models of trauma [3], thermal injury [4–6], hemorrhagic shock [7, 8], intestinal obstruction [9], obstructive jaundice [10, 11], and liver cirrhosis [12, 13] have shown that bacterial translocation occurs commonly in various situations. In humans, there is also increasing evidence for bacterial translocation under specific conditions as listed in table 1. MacFie et al. [14] cultured mesenteric lymph nodes from 927 patients undergoing laparotomy, and demonstrated that bacterial translocation was identified in 14% of the patients. Postoperative sepsis was more common in patients with bacterial translocation compared to patients without bacterial translocation (42.3 vs. 19.9%, respectively). Sedman et al. [15] examined 267 general surgical patients for evidence of bacterial translocation by culture

of intestinal serosa and mesenteric lymph nodes taken at the time of surgery. Bacterial translocation occurred in 10.3% of patients, and the development of postoperative septic complications was twice as common in patients with bacterial translocation, but the mortality rate was unaffected. The findings from these two studies give support to the presumption that bacterial translocation occurs in patients with surgical stress and that bacterial translocation may cause postoperative septic complications. Kuzu et al. [16] studied 21 patients requiring laparotomy for obstructive jaundice, looking for bacterial translocation by culturing mesenteric lymph nodes, peripheral blood, portal blood, liver wedge biopsy, and bile. Although obstructive jaundice significantly promoted bacterial translocation, no correlation was observed between the incidence of bacterial translocation and the frequency of septic complications. In contrast, Moore et al. [17] obtained peripheral and portal blood cultures and endotoxin concentrations from 20 injured patients requiring emergency laparotomy at 6, 12, 24 and 48 h, and 5 days postoperatively. Only one of 212 portal blood samples was culture positive and no endotoxin was detected in portal or systemic blood. Also, there was no significant elevation of complement activity, tumor necrosis factor α (TNF α), or interleukin (IL)-6 levels in portal or systemic blood in patients who developed multiple organ failure.

In another study, Peitzman et al. [18] reported that 25 trauma patients who required exploratory laparotomy had no positive mesenteric lymph nodes cultures at initial laparotomy or at subsequent operation within 3–5 days after injury. These two reports concluded that bacterial translocation was not a common phenomenon in such patients.

Thus, whether bacterial translocation has any clinical importance in humans remains controversial. The available literature supports the occurrence of bacterial translocation, although there are concerns about its clinical significance [17–29].

Which Is the Best Specific Marker of Bacterial Translocation in Humans?

The most direct method to indicate bacterial translocation is by culture of mesenteric lymph nodes or other tissues. The mesenteric lymph nodes receive its lymphatic drainage from the small intestine, cecum, and proximal colon, and because it is normally sterile, the presence of viable bacteria within the mesenteric lymph nodes is a direct and sensitive marker of gut barrier failure and bacterial translocation. Indirect markers that suggest the occurrence of bacterial translocation are positive peripheral blood culture containing bacteria of intestinal origin, and/or detection of endotoxin in portal or peripheral blood. Increased permeability of the intestinal wall, as measured by the lactulose/mannitol ratio, has also been employed as an indirect verification of bacterial translocation.

These methods have several critical problems. First, it is noteworthy that the frequency with which bacterial translocation occurs in humans is much lower than that observed in animal models. Unlike animal models, sequential culture of mesenteric lymph nodes and culture of all mesenteric lymph nodes are not possible in human studies, and direct culture is available only in patients undergoing laparotomy. In addition, most studies have employed the culture of samples of mesenteric lymph nodes, peripheral blood, portal vein, or intestinal serosa to indicate bacterial translocation. Sufficient amounts of microbes and adequate microbial viability are essential to have a positive result using the culture technique, and most of the translocated bacteria may be dead, and thus unable to grow in conventional culture. It has been known that numerous strains of bacteria are able to exist in a ‘viable but nonculturable state’ [30]. Bacteria in viable but nonculturable state cannot be cultured, but remain viable

and potentially able to grow under specific conditions. Indeed, Reed et al. [29] studied mesenteric lymph nodes in 16 trauma patients using conventional culture method and electron microscopy, and demonstrating that 1 patient had a positive culture alone, 9 were positive by electron microscopy, and 3 were positive by both culture and electron microscopy. Therefore, it cannot be concluded that an absence of culturable bacteria in mesenteric lymph nodes and blood means the lack of bacteria. Serum and/or portal endotoxin concentrations have been used frequently as an indirect method to prove bacterial translocation. However, endotoxin measurements are plagued by problems with poorly defined inhibitors of endotoxin activity and are easily affected by anticoagulant, handling, and sample preparation [31]. Alternatively, the measurement of IgM and IgG anti-endotoxin antibody may be reliable to use [32]. Finally, increased permeability of the intestinal wall is not always associated with the occurrence of bacterial translocation, and there are no culture studies correlating increased permeability with bacterial translocation in humans. Thus, there is no simple and accurate method to confirm and monitor bacterial translocation, which may be responsible for the ambiguity regarding the incidence of bacterial translocation or clinical consequence in humans.

Pathogen-Associated Molecular Patterns and Toll-Like Receptors

The innate immune system is phylogenetically conserved and present in almost all organisms [33]. Pathogen-associated molecular patterns are small molecular motifs consistently found on pathogens. They are recognized by toll-like receptors and other pattern recognition receptors in plants and animals. They activate innate immune responses by identifying non-self molecules, protecting the host from infection. Bacterial lipopolysaccharide is considered to be the prototypical pathogen-associated molecular patterns. Other pathogen-associated molecular patterns include bacterial flagellin, lipoteichoic acid from gram positive bacteria, peptidoglycan, and nucleic acid variants normally associated with viruses, such as double-stranded RNA or unmethylated CpG motifs (fig. 1). The mechanism by which innate immunity recognizes non-self remained unknown until quite recently, and the identification of toll-like receptors led to an explosion of research in this field. The toll signaling pathway was described in *Drosophila* for its role in dorsal-ventral patterning during embryogenesis [34]. In hu-

Fig. 1. Microbes, pathogen-associated molecular pattern, and toll-like receptor. Toll-like receptors interact with relevant pathogen-associated molecular patterns and are known to have a specific intracellular signaling pathway. TLR = Toll-like receptor.

mans, Medzhitov et al. demonstrated that constitutively active human toll-like receptors directly activated nuclear factor- κ B (NF- κ B) and pathways that lead to the development of adaptive immunity [35]. The toll-like receptor family includes transmembrane receptors with an extracellular leucine-rich repeat domain that interacts with relevant pathogen-associated molecular patterns, and an intracellular Toll/IL-1 receptor domain that is involved in signaling [36]. At least 11 human toll-like receptors have been identified. Each toll-like receptor is known to detect a specific pathogen-associated molecular pattern and has a specific intracellular signaling pathway [37–39]. Microbes possess various ligands for toll-like receptors in their cellular components, including cell wall, flagella, DNA, and RNA (fig. 1). Each toll-like receptor detects a specific pathogen-associated molecular pattern, including lipopolysaccharide (detected by toll-like receptor-4), bacterial lipoprotein and peptidoglycan (detected by toll-like receptor-2), flagellin (detected by toll-like receptor-5), unmethylated CpG DNA (detected by toll-like recep-

tor-9), double-stranded RNA (detected by toll-like receptor-3), and single-stranded RNA (detected by toll-like receptor-7 and -8). Toll-like receptor-1 and toll-like receptor-6 recognize tri-acyl lipopeptides and di-acyl lipopeptides, respectively, in cooperation with toll-like receptor-2 [40]. Thus, toll-like receptors 1, 2, 4, 5, 6 and 9 seem to specialize in recognizing mainly bacterial products, whereas toll-like receptors 3, 7, 8 and 9 seem to specialize in viral detection. Toll-like receptors are also known to activate macrophages, with production of proinflammatory cytokines including TNF α , IL-1 β , IL-6, and IL-8, via a NF- κ B-dependent mechanism [41]. Therefore, toll-like receptors play a critical role against invading pathogens in the mediation of the systemic responses caused by proinflammatory cytokines [42].

Many studies have reported that endotoxin induces severe inflammatory responses in humans and animals. Wang et al. [43] reported that intravenous administration of peptidoglycan derived from *Staphylococcus aureus* into rats immediately caused hypotension and elevations

Fig. 2. Serum cytokine levels after intraperitoneal injection of CpG DNA. After being anesthetized with diethylether, mice were administered 50 μ g of CpG DNA intraperitoneally. Blood samples were obtained from the retro-orbital plexus of these animals 0, 1, 3, 6, 12, 24, 48 and 72 h after injection ($n = 4$ for each time point) and their sera were stored at -80°C until ELISA assays. Data are expressed as the mean $\pm$ SEM. TNF = Tumor necrosis factor; IL = interleukin; IFN = interferon. Adapted from Tsujimoto et al. [47].

of serum alanine aminotransferase, γ -glutamyl transpeptidase, bilirubin, and creatinine. Moreover, it has been reported that bacterial flagellin induces hypotension, reduced vascular contractility, acute pulmonary inflammation, and death in mice [44, 45]. Hemmi et al. [46] demonstrated that intraperitoneal injection of CpG DNA as well as sublethal doses of D-galactosamine killed all wild-type mice within 10 h, while all toll-like receptor

$9^{-/-}$ mice survived. In addition, we previously examined the kinetics of serum cytokine concentrations in mice after intraperitoneal injection of 50 μ g of CpG DNA (ODN1826; InvivoGen, San Diego, Calif., USA), resulting in a prototypical systemic inflammatory response with increased serum levels of TNF α , IL-12, and IFN γ (fig. 2) [47]. Thus, systemic circulation of various toll-like receptor ligands or pathogen-associated molecular patterns, i.e. 'PAMPemia', may cause systemic inflammation and organ injury, ultimately leading to death [42].

Do Pathogen-Associated Molecular Patterns Translocate from the Gut?

It is well accepted that the gut is the greatest reservoir of pathogen-associated molecular patterns as well as various microbes. Do pathogen-associated molecular patterns translocate to mesenteric lymph nodes and other organs similar to microbes? Translocation of endotoxin from the gut was described more than 30 years ago and termed 'endotoxin translocation' [48, 49]. Alexander et al. [50] demonstrated that 30% thermal injury significantly induced translocation of endotoxin to the mesenteric lymph node in animals with gavage of ^{14}C -labeled endotoxin as measured by radionuclide activity. There is increasing evidence suggesting the occurrence of translocation of pathogen-associated molecular patterns other than endotoxin. Tabata et al. [51] reported that portal peptidoglycan concentrations significantly increased after administration of 20% ethanol in rats, suggesting the translocation of peptidoglycan from the gut. Shimizu et al. [52] demonstrated that patients who underwent non-septic gastrointestinal surgery had increased serum peptidoglycan levels on postoperative day 1, suggesting that surgical stress might induce translocation of peptidoglycan from the gut. Kane et al. [53] detected *Escherichia coli* DNA in peripheral blood using the polymerase chain reaction technique in mice following bacterial gavage and thermal injury, and emphasized the use of this method as a sensitive and specific indirect marker of bacterial translocation. Further, these authors detected bacterial DNA in 64% of clinically ill patients; in particular, all 8 transplant patients receiving anti-CD3 monoclonal antibody, or OKT3, as induction or antirejection therapy had microbial DNA in their peripheral blood, strongly indicating translocation from the gut [54]. Subsequently, many investigators have reported microbial DNA in the blood of patients with liver cirrhosis [55, 56], acute pancreatitis [57–59], and major abdominal surgery, and in septic pa-

Table 2. Expression of microbial DNA detected by PCR in the blood of patients who underwent elective gastrointestinal surgery

Surgery	Number	PCR results with primers for				PCR+ with any primers (%)	Blood culture
		BG	BFR	16S rRNA	Candida		
Esophagectomy	7	–	–	3	3	3 (42.9%)	–
Hepatic lobectomy	5	3	1	1	1	4 (80.0%)	–
Gastrectomy	7	–	–	–	–	0 (0%)	–
Colectomy	5	–	–	–	–	0 (0%)	–
Healthy control	10	–	–	–	–	0 (0%)	–

– = Negative; BG = primer for genomic DNA encoding β -galactosidase to detect *E. coli*; BFR = primer for genomic DNA encoding glutamine synthase to detect *Bacteroides* spp.; 16S rRNA = primer for a highly conserved region of bacterial DNA (encoding 16S ribosomal RNA); Candida = primer for genomic DNA encoding 5.8S ribosomal RNA to detect *Candida albicans*. Adapted from Tsujimoto et al. [60].

Table 3. Expression of microbial DNA detected by PCR in the blood of patients with clinical circumstances under bacterial translocation

Patients	Diagnosis	PCR results with primers for				Blood culture
		BG	BFR	16S rRNA	Candida	
1	small bowel obstruction	–	–	–	+	–
2	small bowel obstruction	–	–	–	–	–
3	small bowel obstruction	+	–	+	–	–
4	small bowel obstruction	–	–	–	–	–
5	small bowel obstruction	–	–	–	–	–
6	SMAO	+	–	+	+	–
7	SMAO	–	–	+	–	–
8	ulcerative colitis	–	–	–	+	–
9	ulcerative colitis	–	–	–	+	–
10	colitis due to radiation	–	–	–	+	–
11	chemotherapy for colon cancer	+	–	–	+	–
12	chemotherapy for colon cancer	–	+	–	+	–
13	chemotherapy for colon cancer	–	–	–	–	–

– = Negative; + = positive; SMAO = superior mesenteric arterial occlusion; BG = primer for genomic DNA encoding β -galactosidase to detect *E. coli*; BFR = primer for genomic DNA encoding glutamine synthase to detect *Bacteroides* spp.; 16S rRNA = primer for a highly conserved region of bacterial DNA (encoding 16S ribosomal RNA); Candida = primer for genomic DNA encoding 5.8S ribosomal RNA to detect *Candida albicans*. Adapted from Tsujimoto et al. [60].

tients without a definite focus of infection [60]. We previously demonstrated that patients who underwent esophagectomy or hepatic lobectomy had positive microbial DNA in their peripheral blood on the morning of post-operative day 1, but this was not found in patients who underwent gastrectomy or colectomy, which are both considered to be relatively less invasive surgical procedures (table 2) [60]. In addition, we showed that enteric

bacterial DNA or *Candida* DNA was present in septic patients with small bowel obstruction, ulcerative colitis, or superior mesenteric artery occlusion, and in patients who underwent chemotherapy for advanced colon cancer (table 3). It is notable that all patients in tables 2 and 3 lacked a definite focus of infection, and had no positive culture in their peripheral blood.

Fig. 3. Flow cytometric analysis of translocated CpG DNA from the gut in peritonitis mice. FITC-labeled CpG DNA was injected into the terminal ileum of mice after laparotomy, and cecum ligation and puncture (peritonitis) or a sham operation was performed. The mice were sacrificed 48 h after surgery, and FITC-positive cells on the hepatic and splenic macrophages (F4/80-positive cells) were analyzed using flow cytometry.

A representative flow cytometry histogram from one of four independent experiments is depicted. CLP = Mouse with peritonitis that underwent cecum ligation and puncture; Sham = sham-operated mouse; FITC = fluorescein isothiocyanate. Adapted from Tsujimoto et al. [47].

We also investigated whether bacterial DNA in the gut translocates to other organs; fluorescein isothiocyanate (FITC)-labeled CpG DNA (ODN1826; InvivoGen) was injected into the end of the ileum of mice after laparotomy, and cecal ligation and puncture to establish peritonitis or a sham operation [61]. The mice were sacrificed 48 h after surgery, and FITC-positive cells on the hepatic and splenic macrophages (F4/80-positive cells) were analyzed using flow cytometry (fig. 3). CLP mice had abundant FITC-positive cells in hepatic macrophages. No FITC-positive cells were observed on the splenic macrophages in CLP mice. In sham-operated mice, neither hepatic nor splenic macrophages had FITC-positive cells. These data suggest that CpG DNA in the gut translocates to the liver during peritonitis, but this is not observed in simple laparotomy without peritonitis.

Taking these findings together, translocation of pathogen-associated molecular patterns from the gut occurs in a manner similar to live bacteria. Polymerase chain reaction is a more sensitive and specific modality for detecting microbial DNA in experimental and clinical samples compared to conventional culture methods.

Clinical Consequence of Pathogen-Associated Molecular Patterns Translocation

When pathogen-associated molecular patterns in the gut translocate into the systemic circulation or another organ, this will cause a systemic inflammatory response and organ injury through TLRs expressed on immunocompetent cells. Patient 3 in table 3 had simple intestinal obstruction and developed a systemic inflammatory response syndrome [62] with a high-grade fever up to 40°C and leukocytosis without an apparent focus of infection. At that time, bacterial DNAs, including *E. coli*-specific DNA, were found in the blood, although culture of peripheral blood was negative (fig. 4). Thus, bacterial translocation was highly suspected as the pathogenesis of sepsis, and treatment with selective digestive decontamination was started. The septic condition improved 1 day after selective digestive decontamination treatment, and bacterial DNA was no longer detected in the blood. This case suggests that the presence of bacterial DNA in the blood was a harbinger for the presence of sepsis caused by bacterial translocation from the intestine.

Fig. 4. Agarose gel electrophoresis of samples run after PCR with specific primers for microbial DNA in patients with small bowel obstruction. Patient 3 in table 3 with simple intestinal obstruction developed SIRS without an apparent focus of infection. Bacterial DNAs were present in the patient's blood (SIRS). However, bacterial DNAs were not detected when the patient recovered from SIRS (Recovery). SIRS = Systemic inflammatory response syn-

drome; BG = primer for genomic DNA encoding β -galactosidase to detect *E. coli*; BFR = primer for genomic DNA encoding glutamine synthase to detect *Bacteroides* spp.; 16S rRNA = primer for a highly conserved region of bacterial DNA (encoding 16S ribosomal RNA); M = marker; GAPDH = glyceraldehyde phosphodehydrogenase. Adapted from Tsujimoto et al. [61].

In order to investigate the effect of pathogen-associated molecular patterns translocated from the gut on the inflammatory response, we administered deoxy-cystidylate-phosphate-deoxy-guanylate (CpG) DNA to sublethal peritonitis by cecal ligation and puncture using a 21-gauge needle, which had a mortality rate of approximately 10% 120 h after surgery [63]. CpG DNA challenge following sublethal peritonitis induced a significant production of both pro- and anti-inflammatory cytokines, increased liver injury, and had a significantly higher mortality than a control DNA challenge (fig. 5). These results suggest that bacterial DNA that has translocated into the portal and/or systemic circulation may contribute to organ injury and death associated with sepsis. Thus, pathogen-associated molecular patterns from the gut may have clinical importance in continuing and overwhelming sepsis, causing many cases of severe systemic inflammatory response syndrome and sepsis, ultimately leading to death in humans and animals.

Fig. 5. Kaplan-Meier survival curves for CpG DNA or control DNA challenge in sublethal CLP in mice. To investigate the toxic effects of pathogen-associated molecular patterns in the bloodstream during sepsis, mice with sublethal CLP (whose cecum was perforated with a 21-gauge needle) were randomly divided into two groups: CpG DNA (n = 14; solid line) or control DNA (n = 14; dashed line) administered intravenously 12 h after CLP induction. The survival rate of CpG DNA-treated CLP mice was significantly lower than that of control DNA-treated CLP mice as determined by the log-rank test ($p < 0.05$). CLP = Cecum ligation and puncture. * $p < 0.05$ vs. control DNA-treated CLP mice. Adapted from Tsujimoto et al. [63].

Conclusions and Suggestions for Future Investigations

Since Carrico et al. [64] suggested that the gut is a 'motor' of multiple organ failure, there has been an emerging consensus to incriminate the gut in the pathogenesis of sepsis. The data supporting the occurrence of bacterial translocation in humans are substantial. However, the lack of strong data correlating bacterial translocation with clinically significant problems in humans has lessened the interest of many investigators. However, a molecular-based methodology, polymerase chain reaction, is now available as a highly specific and prompt indirect marker for the occurrence of bacterial translocation, and we believe that this technique will reveal important clinical consequences of bacterial translocation in the future.

In addition, TLRs are known to be expressed on immunocompetent cells, which reside in almost all organs, including the brain, heart, kidneys, liver, lungs, placenta, spinal cord, etc. [65], and translocated pathogen-associated molecular patterns may induce the perpetuated and exacerbated systemic inflammatory responses that result in organ injury through toll-like receptor binding. In 1990, bacterial translocation as defined by Berg was extended by Alexander et al. [50] to include the passage of viable and nonviable microbes and their toxic products across the intact intestinal barrier. Recently, the role of the pathogen-associated molecular pattern, toll-like re-

ceptor interaction in the innate immunity and in the pathogenesis of sepsis has been shown, and we propose a new concept to redefine bacterial translocation by including translocation of pathogen-associated molecular patterns in the gut (PAMP translocation).

In conclusion, convincing evidence has been provided that translocation may occur in humans during various disease processes. However, whether bacterial translocation has major clinical consequences in humans continues to be questioned. Even if bacteria fail to grow in conventional culture, most organisms are nonculturable, and other components of killed bacteria, i.e. pathogen-associated molecular patterns, may remain in blood and tissue. Therefore, pathogen-associated molecular pattern translocation may be, at least partly, responsible for the systemic inflammatory response under conditions in which bacterial translocation could occur, even if cultures are negative. Detection of bacterial DNA in the blood and tissues/organs should be useful as a specific marker of translocation of pathogen-associated molecular patterns and/or bacteria, and has the potential to have predictive values of the development and clinical course of sepsis in surgical patients.

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