Review

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Pathological bacterial translocation in liver cirrhosis

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Introduction

Humans harbor nearly 100 trillion intestinal bacteria, which in terms of numbers, represents around ten times more microbial cells than eukaryotic cells. The gastrointestinal (GI) tract, the largest surface area of the body with an epithelial surface of approximately 400 m^2, is in constant exposure to these live microorganisms. Their peaceful coexistence demonstrated by the lack of pro-inflammatory responses against commensal bacteria implicates the presence of clearly defined lines of communication. In fact, bacterial translocation (BT), being defined as translocation of bacteria and/or bacterial products (lipopolysaccharides, peptidoglycans, muramyl-dipeptides, bacterial DNA, etc.) from the gut to mesenteric lymph nodes (MLN) [1], is a physiological process in healthy conditions and crucial for host immunity. In contrast, in cirrhosis "pathological" BT develops with a sustained increase in quantity (rate and/or degree) of BT. However, at least in humans, lack of access to MLN and/or upstream compartments towards the mucosal barrier until now hamper establishment of "cut-off" levels for physiological levels of BT in individual patients. Nonetheless, there appears to exist a hierarchy of three barriers against pathological BT, each of which encompasses a distinct set of mechanisms (Fig. 1). First, there are mediators that limit direct contact between the intestinal bacteria and the epithelial cell surface. Secondly, a layer of immune protection involves the rapid detection and killing of bacteria that manage to penetrate. Finally, a set of immune responses minimizes exposure of bacteria to the systemic immune system. In advanced liver cirrhosis, at each of these levels marked alterations have been developed throughout the course of the disease.

Background and potential relevance of pathological bacterial translocation

Pathological BT has been termed the "Achilles heel" in liver disease [2] playing an important role in the pathogenesis and complications of cirrhosis. The most evidenced clinical expression of pathological BT is spontaneous bacterial peritonitis (SBP). SBP often originates from bacteria in the gut that belong to the normal intestinal microbiota. It has been shown that green fluorescent protein (GFP) labelled *Escherichia coli* administered orally to cirrhotic rats reveal the presence of these bacteria not only in the intestinal lumen but also in the mesenteric lymph nodes (MLN) and ascites [3] (Fig. 2). However, not only culture-positive SBP and/or bacteremia impact on the cirrhotic host, but also increased inflow of translocating bacterial products into the hepato-splanchnic as well as systemic circulation. Augmented pro-inflammatory response to gut-derived products and failure to control invading bacteria and -products in concert with host susceptibility determine remote organ injury. This may include acute-on-chronic liver failure, hepato-renal-syndrome and hepatic encephalopathy [4]. Therefore, understanding the physiology of gut-bacteria interactions and the pathogenesis of BT can lead to new therapeutic targets in the prevention of infections and other complications of cirrhosis.

Compartments involved in pathological bacterial translocation

Gut associated lymphoid tissue (GALT)

The GALT represents the largest immunological organ in the human body. Despite the vast improvements made in understanding how the microbiota influence host immunity, very little is still known of the intestinal immune system in cirrhosis.

The innate immune system is considered the "first line of defence" against invading bacteria or their associated products. Invading bacteria are detected by the innate immune system through the recognition of highly conserved bacterial motifs that are present in all bacteria (microbial-associated molecular patterns, MAMPs) by germline-coded pattern-recognition receptors (PRR) on intestinal cells [5]. PRR are located on both the cell

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Abbreviations: AMP, antimicrobial peptides; APC, antigen-presenting cell; BDL, bile duct ligation; BT, bacterial translocation; CCl_4, carbon-tetrachloride; DC, dendritic cell; FxR, Farnesoid X receptor; GALT, gut-associated lymphoid tissue; GI, gastrointestinal; GNB, gram-negative bacteria; HE, hepatic encephalopathy; IEL, interepithelial lymphocyte; IFN, Interferon; IgA, Immunoglobulin A; IL, interleukin; LPS, lipopolysaccharide; MCP-1, monocyte chemotatic protein-1; MDP, Muramyl-Dipeptide; MLCK, myosin light chain kinase; MLN, mesenteric lmyph nodes; NO, nitric oxide; NOD, nucleotide binding oligomerisation domain 2; NFkB, nuclear factor kB; PGN, Peptidoglycans; ROS, reactive oxygen species; SBP, spontaneous bacterial peritonitis; SDD, selective gut decontamination; SIBO, small intestinal bacterial overgrowth; TJ, tight junction; TLR, toll-like-receptor; TNF, tumor necrosis factor; ZO, zonula occludens.

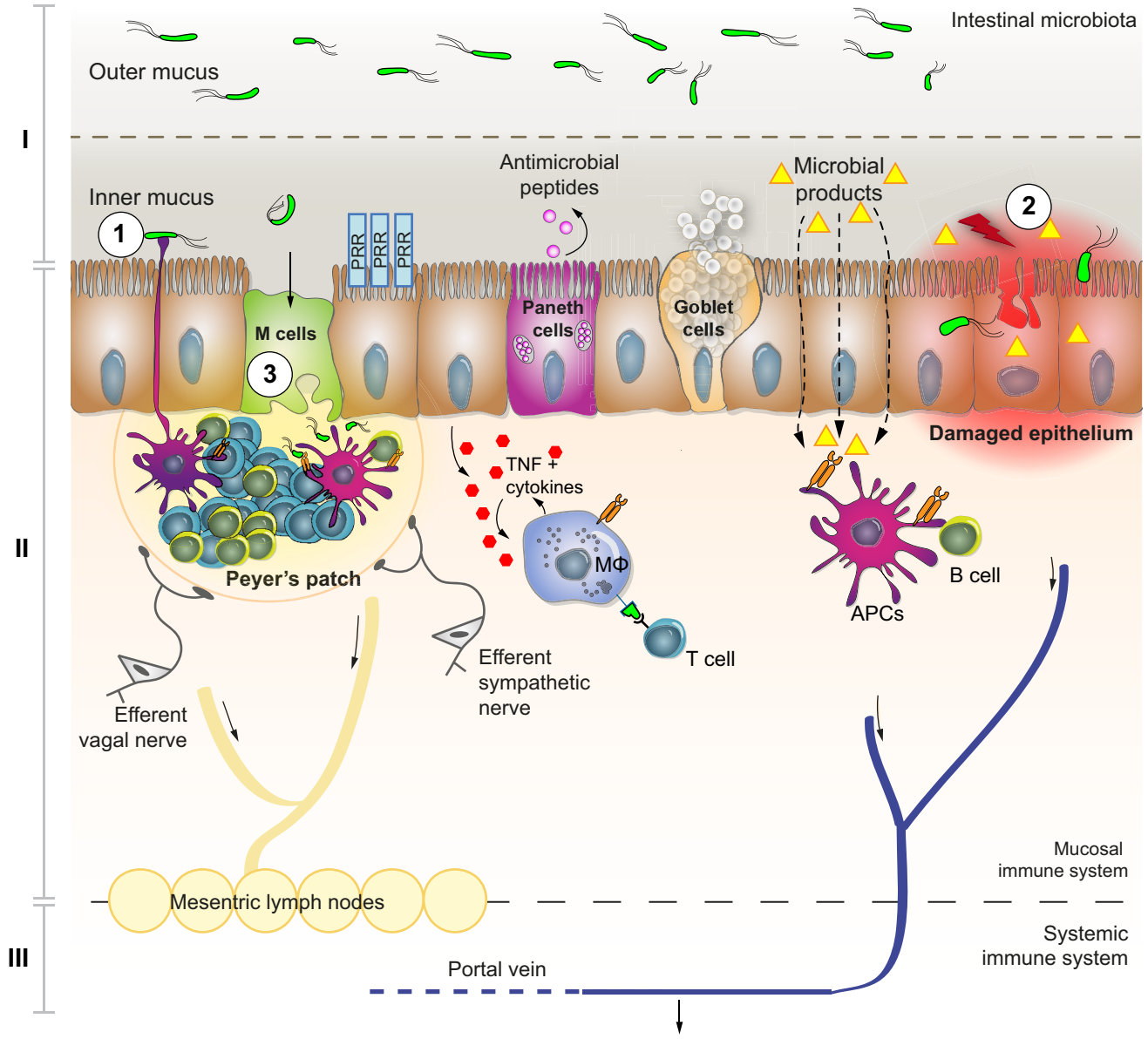

Fig. 1. Compartments and key players involved in mediating pathological BT and the associated host response. Three different routes (1–3) of bacterial translocation can be separated: (1) direct sampling of luminal bacteria (l products) by dendritic cells via processes between epithelial cells, not affecting tight junction function; (2) injured/inflamed epithelium with dysfunctional epithelial barrier and (3) M-cells overlying Peyer Patches as specialized cells providing access of microbial products to antigen-presenting cells. Moreover, three different levels of barriers (I–III) against bacterial translocation are shown: (I) lumen and secretory component (e.g., inner and outer mucus layer, antimicrobial peptides) of gut barrier; (II) mechanical epithelial barrier and the gut-associated lymphatic tissue (GALT) beneath with response elements to BT (e.g., TNF and other pro-inflammatory cytokines) and autonomic nervous system; (III) systemic immune system as third barrier in case of spreading of bacteria(l products) beyond MLN including hematogenous (portal venous) and lymphatic (ductus thoracicus) route of delivery. APC, antigen presenting cell; PRR, pattern recognition receptors; TNF, tumour necrosis factor.

surface and within endosomal compartments and these receptors can be further divided into two subgroups: Toll-like receptors (TLRs) and cytoplasmic NLR (nucleotide binding domain, leucine-rich repeats) proteins.

The mucosal immune system is not ignorant to the commensal bacteria, rather microbial antigens are continuously sampled via various routes (Fig. 1): (1) Dendritic cells (DCs) that underlie the epithelium may open tight junctions (TJ) between epithelial cells, sending processes into the lumen that directly sample microbes [6]; lamina propria DCs compromise two different subsets: *CD103*$^{+}$*CX3CR1*$^{-}$ DCs (inducing development of regulatory T cells) and *CD103*$^{-}$*CX3CR1*$^{+}$ DCs (with features of macrophages, promoting TNF-production and development of *Th1/Th17* T cells) (2) through interaction with antigenic material in underlying tissue that occurs particularly when epithelial integrity is compromised; or (3) through sampling by specialized M cells within villous epithelium or the follicle-associated epithelium overlying Peyer patches [7]. Alterations in these sampling mechanisms in