Conflict of interest

Vincent Wong, Grace Wong, and Henry Chan have served as speakers for Echosens. Henry Chan is a consultant of Furui Medical Science.

References

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Bacterial translocation in liver cirrhosis: Site and role in fibrogenesis

To the Editor:

I read with great interest the comprehensive review by Wiest and colleagues [1] on pathological bacterial translocation in liver cirrhosis. They remarkably analyzed the compartments involved and their influencing factors. My concern regards the possible site(s) of bacterial translocation (BT), and the role of BT in the progress of both precirrhotic chronic liver damage, particularly fibrosis, and installed liver cirrhotic lesions themselves.

Regarding the site of bacterial translocation in cirrhosis, the authors rightly outline that, whereas small intestinal bacterial overgrowth has the greatest potential for promoting BT and bacteria causing spontaneous infections are most frequently exactly those overgrowing in the small intestine [2,3], studies of experimental liver injury in mice revealed that the cecum and the colon might be the sites with largest rate of BT and increase in intestinal permeability [1]. Data in humans were lacking. A recent in vivo human study, not referenced in the Wiest’s review [1], has reported that colonic permeability was increased in patients with compensated liver cirrhosis, as compared to matched controls using a multisugar test, whereas gastroduodenal and small intestine permeability were not altered [4]. Whether or not these changes preceded alterations of the gut microbiome is not known.

A second point of increasing importance, not discussed in the review [1], regards the experimental role of inflammasomes at the colonic level in both local microbiota taxonomy and potential translocation associated with chronic precirrhotic liver disease, namely non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). There is suggestive evidence that a deficiency in components of two inflammasomes (NLRP6 and NLRP3) – which are large multiprotein complexes that sense intracellular danger signals via NOD-like receptors (NLRS), the sensor, NLR, forming a complex with the effector molecule, procaspase-1, with or without the contribution of an adapter molecule, such as the apoptosis-associated speck like CARD-domain containing protein (ASC) – normally acting as sensors of endogenous or exogenous pathogen-associated molecular patterns (PAMPs) and regulators of the colonic microbiota, leads to dysbiosis associated with aggravation of NAFLD and progression to NASH [5]. Thus, members of the altered colonic microbiota in inflammasome-deficient mice may promote a signalling cascade in the liver upon translocation, resulting in progression to NASH in susceptible animals. Toll-like receptors (TLRs) have a major role in NAFLD pathophysiology due to the liver’s exposure to relatively large amounts of PAMPs derived from the intestine and delivered via the portal circulation. Intact bacteria or bacterial products derived from the intestine trigger TLR4 and TLR9 activation, which results in an increased rate of chronic liver disease progression in mice that house a colitogenic gut microbiota associated with inflammasome deficiency [5]. Indeed bacterial overgrowth, including in colon [7], is particularly important in patients with a leaky gut because it increases the luminal amount of PAMPs. It is noteworthy that mice deficient in sensing PAMPs or downstream signaling are resistant to NASH [6].

Finally, the consequences of intestinal dysbiosis or bacterial overgrowth associated with gut leakage may not be limited to infectious complications, as spontaneous bacterial peritonitis, due to translocation. Animal studies have clearly pointed that
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intestinal microbiota may contribute to progression of chronic liver damage, especially liver fibrogenesis [8], which in turn may aggravate not only installed cirrhotic lesions through increased inflammation and fibrosis, but also accelerate or provoke progression of NASH and alcoholic steatohepatitis to cirrhosis. Thus, the role, in humans, of BT in the progression of chronic hepatic damage, both in installed cirrhosis and precirrhotic lesions, may appear of paramount importance, in conjunction with persistent alcohol consumption in cases of alcoholic chronic liver disease and cirrhosis. There is increasing suggestive evidence that bacterial translocation and intestinal flora dysfunction are associated with the development of liver fibrosis [9], and that bacteria and microbial products, including endotoxins – like lipopolysaccharides (LPS) macromolecules, the major molecular component of the outer membrane of Gram-negative bacteria –, bacterial DNA or microbial metabolites – like ethanol produced by the intestinal microbiome or choline – may contribute to the pathogenesis of NAFLD and NASH, and presumably to progression to overt cirrhosis due to increased fibrogenesis [6]. Finally, this clearly suggests the possible associated role of chronic, repetitive BT, not only in mesenteric lymph nodes but also in portal blood and the liver itself [10], as elicited by a chronically leaky intestine (which may precede and/or be the consequence of cirrhosis and be aggravated – in alcohol-induced chronic liver disease – by persistent chronic alcohol consumption), in cirrhosis pathogenesis itself.

Conflict of interest

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References


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Reply to: “Bacterial translocation in liver cirrhosis: Site and role in fibrogenesis”

To the Editor:
We greatly appreciate the comments raised by Dr Matuchansky regarding our recent review on pathological bacterial translocation (BT) in liver cirrhosis [1]. As for the site of BT in cirrhosis we acknowledge the investigation in compensated cirrhotic patients utilizing a multisugar test [2]. The study described by Dr Matuchansky reports in cirrhotic individuals an increased sucralose/erythritol ratio in 5–24 h urine (supposed to indicate colonic permeability) whereas the lactulose/rhamnose ratio in 0–5 h urine (supposed to represent small intestinal permeability) was not altered. This study has not been cited by us due to (i) the fact, that any information gained by using sugar tests most likely does not reflect permeability to macromolecules such as bacteria and/or bacterial cell wall components, (ii) criticisms related to methodological issues in performance of those sugar tests [3–5], and finally (iii) the limitation in references to be used.

Sugars utilized in those permeability tests are very small molecules (182–400 Da) whose passage across the mucosal barrier is not necessarily related to structural damage in the tight junction barrier that permits increased penetration of large molecules (e.g., lipopolysaccharide can reach up to 100,000 Da). Moreover, although not convincingly proven at least for living bacteria, likewise larger in size than mono-/disaccharides, BT occurs most likely via transcytosis (Fig. 1). Transcytosis of vital bacteria however is complex, includes active sampling by dendritic cells and transport across M cells as well as epithelial cells all of which is regulated different from transport of sugars in terms of initiation, kinetics and host response. Therefore, also others have proposed that measuring permeability to small sugar molecules does not correlate with gut dysbiosis, endotoxin release, microbial translocation and/or activation of the mucosal immune system [6,7]. Mucosal defense mechanisms (e.g., number and secretion of