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Role of the Intestinal Microbiome in Cholestatic Liver Disease

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Abstract

Hepatobiliary health and disease is influenced by multiple factors including genetics, epigenetics, and the environment. Recently, multiple lines of evidence suggest that the microbiome also plays a central role in the initiation and/or progression of several liver diseases. Our current understanding of the dynamic interplay between microbes, microbial products and liver health and pathophysiology is incomplete. However, exciting insights are continually being made that support both a central role of the microbiome and a need for further interrogation of the microbes or microbe-associated molecules involved in the initiation and progression Of Select liver diseases.

Keywords

Microbiota; Liver diseases; Senescence; Sclerosing cholangitis

Introduction

Harboring roughly $2-5 \times 10^{11}$ bacteria per gram of feces in humans, the intestinal tract embodies an incredibly complex biological ecosystem. This 'microbiome' includes microbes, their metabolites and degradative products, and their genomes. Receiving approximately 75% of its blood supply from the intestine via the portal circulation, the liver is thus continuously exposed to a wide repertoire of molecules, be they beneficial or noxious, from the intestinal microbiome. An increasing body of literature has begun to shed light on this 'gut liver axis' in the maintenance of health as well as in the pathogenesis of liver disease [1]. In this review, I will focus primarily on the relationship of the intestinal microbiome with primary sclerosing cholangitis (PSC), a fibroinflammatory cholangiopathy of unknown etiology with no established pharmacologic therapy [2].

Discussion

There are several lines of evidence supporting an important role for the microbiome in PSC [3–6]. First, inflammatory bowel disease, a condition itself associated with intestinal dysbiosis, occurs in 75% of patients with PSC. Second, portal bacteremia, bacterobilia, and 16s ribosomal ribonucleic acid in bile have all been described in PSC. Third, cholangiocytes

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in patients and animal models of PSC, accumulate lipopolysaccharide (LPS) in vivo and are hyper responsive to LPS treatment in vitro. Fourth, several genomic associations have been established with loci implicated in host-microbiome interactions. Fifth, recent studies in germ-free (GF) MDR2 deficient mice, an animal model of PSC, have suggested a protective influence of the microbiome on disease development [7]. Finally, treatment with select oral antibiotics may offer therapeutic benefits in select patients with PSC. Nevertheless, it has become apparent that host-microbiome interactions are incredibly complex in spite of advances in high-throughput technologies, increased team science approaches and knowledge of the human microbiome, and GF animal models. What does seem increasingly clear is that the intestinal microbiome and the ‘gut liver axis’ are important in the maintenance of hepatobiliary health and in the pathogenesis of hepatobiliary diseases (fig. 1). More specifically, perturbations in the intestinal microbiome may lead to the initiation of selected liver diseases and/or impact the features and progression of existing hepatic disease.

PSC is characterized by a cholestatic biochemical profile and multiple alternating strictures and dilatations classically involving the entire biliary tree. While the generally accepted etiopathogenesis paradigm invokes unclear host genetic and immunological factors associated with an undefined environmental insult, we recently proposed a new conceptual model for the pathogenesis of PSC, namely, the concept of cellular senescence, a replicative arrested but metabolically active state associated with progression to the senescence-associated secretory phenotype (SASP), the latter characterized by hypersecretion of fibro-inflammatory molecules leading to chronic inflammation, tissue dysfunction and fibrosis [8]. Briefly, the data supporting the importance of cholangiocyte senescence in the pathogenesis of PSC include: (1) increased expression of cholangiocyte p16 mRNA (a molecular marker of senescence); and increased expression of cholangiocyte SASP markers in PSC livers; and, (2) similar evidence of cholangiocyte senescence in the MDR2^{-/-} mouse model of PSC. Given the fact that we’ve also demonstrated in an in vitro model of cholangiocyte senescence that the microbial-derived molecule, LPS, can induce cholangiocyte senescence, we speculated that alterations in the intestinal microbiome might be associated with and relevant to the development of cholangiocyte senescence. Indeed, several lines of data suggesting the importance of the intestinal microbiota in PSC were already published and addressed as mentioned above.

With this in mind, we began a series of experiments to directly test the hypothesis that the intestinal microbiome could influence disease progression in an animal model of PSC, the MDR2^{-/-} mouse [7]. Our approach involved assessing the MDR2^{-/-} phenotype in two subgroups of mice; that is, conventionally housed (CH) MDR2^{-/-} mice and GF MDR2^{-/-} mice. The data that we recently reported demonstrated the following major results: (1) the GF MDR2^{-/-} mice demonstrated significantly more severe serum biochemical abnormalities than the CH mice; (2) the GF MDR2^{-/-} mice exhibited significantly more hepatic fibrosis, ductular reaction and ductopenia compared to the CH MDR2^{-/-} mice; (3) the cholangiocyte microenvironment in the GF MDR2^{-/-} mouse was characterized by increased numbers of neutrophils and macrophages compared to the CH MDR2^{-/-} mouse; and (4) cholangiocyte senescence was increased in the GF MDR2^{-/-} mice relative to the CH mice. This work was accompanied by an editorial that stated ‘This article is likely to set a flurry of studies to

further address the role of microbiota in PSC, which may eventually lead to novel therapeutic avenues for treating this disease' [9].

All of these data are consistent with the hypothesis that the intestinal microbiome and cholangiocyte senescence are both likely important in the pathogenesis of PSC. We propose that the balance of hepatobiliary health and disease is directly influenced by microbe-derived cytoprotective and cytotoxic molecules including exogenous (e.g., short chain fatty acids) and endogenous (e.g., bile acids) metabolic products as well as microbe-associated molecules (e.g. LPS). The molecules and signaling pathways that may link cholangiocyte senescence and the intestinal microbiome are under active investigation (fig. 2).

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Fig. 1.

The gut liver axis is influenced by multiple factors. Broadly, liver and intestinal homeostasis is influenced by the genome, the environment, and the microbiome. While our current understanding of this dynamic is incomplete, exciting insights continue to support this complex network in the initiation and/or progression of liver disease.

Fig. 2.

Hepatobiliary health and disease is influenced by the balance of microbe-derived cytoprotective and cytotoxic molecules. In this model, an individual's genetic signature, environment, and microbiota are central to the maintenance of hepatobiliary health. Liver homeostasis may be associated with an increase in cytoprotective molecules, or a decrease in cytotoxic molecules derived in the gut. In contrast, liver injury may be the result of increased production of cytotoxic molecules or loss of cytoprotective molecules.