Leaky Gut and Fatty Liver

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Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and the leading cause of chronic liver disease in pediatric and adult populations living in industrialized countries. NAFLD encompasses steatosis and nonalcoholic steatohepatitis (NASH), and it is characterized by perivenular and lobular inflammation. Progression to fibrosis and cirrhosis are the primary complications of NAFLD. Based on a recent meta-analysis, one in four people in Europe, the United States, and Asia have NAFLD.

Keywords: leaky gut ; gut permeability ; nonalcoholic fatty liver disease ; nonalcoholic steatohepatitis ; endotoxin

1. Overview

The liver directly accepts blood from the gut and is, therefore, exposed to intestinal bacteria. Recent studies have demonstrated a relationship between gut bacteria and nonalcoholic fatty liver disease (NAFLD). Approximately 10–20% of NAFLD patients develop nonalcoholic steatohepatitis (NASH), and endotoxins produced by Gram-negative bacilli may be involved in NAFLD pathogenesis. NAFLD hyperendotoxicemia has intestinal and hepatic factors. The intestinal factors include impaired intestinal barrier function (leaky gut syndrome) and dysbiosis due to increased abundance of ethanol-producing bacteria, which can change endogenous alcohol concentrations. The hepatic factors include hyperleptinemia, which is associated with an excessive response to endotoxins, leading to intrahepatic inflammation and fibrosis. Clinically, the relationship between gut bacteria and NAFLD has been targeted in some randomized controlled trials of probiotics and other agents, but the results have been inconsistent. A recent randomized, placebo-controlled study explored the utility of lubiprostone, a treatment for constipation, in restoring intestinal barrier function and improving the outcomes of NAFLD patients, marking a new phase in the development of novel therapies targeting the intestinal barrier. This review summarizes recent data from studies in animal models and randomized clinical trials on the role of the gut–liver axis in NAFLD pathogenesis and progression.

2. Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and the leading cause of chronic liver disease in pediatric and adult populations living in industrialized countries. NAFLD encompasses steatosis and nonalcoholic steatohepatitis (NASH), and it is characterized by perivenular and lobular inflammation. Progression to fibrosis and cirrhosis are the primary complications of NAFLD [1]. Based on a recent meta-analysis, one in four people in Europe, the United States, and Asia have NAFLD [2]. The “multiple parallel hit” hypothesis may explain the pathogenesis and progression of NAFLD. Especially in recent years, there has been increasing interest in gut–liver axis dysfunction (dysbiosis, bacterial overgrowth, and changes in intestinal permeability) associated with the progression of NAFLD; therefore, gut–liver axis dysfunction is considered important as a possible alternative therapeutic target for patients who are unable to benefit from lifestyle changes, healthy eating, and promotion of physical activity [3][4]. In NASH, chronic inflammation is triggered by hepatocyte fat accumulation, followed by exposure to inflammatory cytokines, insulin resistance, oxidative stress, lipotoxicity mainly from free fatty acids (FFAs), and gut-derived endotoxins. Here, we focused on gut-derived endotoxins and reviewed the most recent data regarding the gut–liver axis and its role in the pathogenesis and progression of NAFLD. We also reviewed experimental studies in animal models and preliminary results from several randomized clinical trials (RCTs). The objectives of our review were to (1) appraise the pathophysiology of the gut–liver axis focusing on endotoxins and (2) delineate novel therapeutic perspectives via intestinal permeability.

3. The Inflammatory State

The inflammatory state associated with the metabolic syndrome is unique because it is not accompanied by signs of infection or autoimmunity. Furthermore, there is no major tissue damage. In addition, the dimension of inflammatory activation is not large and is often referred to as low-grade chronic inflammation. Other researchers have named this

inflammatory condition metainflammation, which corresponds to metabolically induced inflammation [5], or parainflammation, which is defined as an intermediate state between basal and inflammatory states [6]. Whatever the terminology, the inflammatory processes that characterize metabolic syndrome have unique features and mechanisms that are not fully understood [7]. Metabolic syndrome, especially NASH, is caused by metainflammation. Indeed, chronic mild inflammation is an important factor in the pathogenesis of NASH [8][9].

Since the portal vein is the direct venous outflow of the intestine, the liver is continuously exposed to factors that have an intestinal origin, including bacteria and bacterial components. The liver is an important site for bacterial phagocytosis and clearance because it contains the largest population of tissue macrophages. Experimental data demonstrate that exposure of membrane components of Gram-negative bacteria and bacterial products to proinflammatory mediators such as LPS results in the activation of Kupffer cells. Kupffer cells, the resident macrophages of the liver, are the nitrogenous species that contribute to liver damage in the presence of proinflammatory cytokines and are a major source of inflammatory mediators such as ROS [10]. Through pattern recognition receptors, including Toll-like receptors (TLRs), the innate immune system recognizes conserved pathogen-associated molecular patterns (PAMPs) [11]. Although healthy livers have a low TLR mRNA level and a high resistance to TLR ligands from the constant exposure of the microflora, TLR-mediated signaling plays a major role in liver physiology and pathophysiology [12]. LPS is a potent activator of innate immune responses as it can bind to the TLR4 complex. TLR4 is expressed by Kupffer cells, hepatic stellate cells, hepatocytes, biliary epithelial cells, sinusoidal endothelial cells, and hepatic dendritic cells, which are consequently responsive to LPS [13]. There is a positive correlation among hepatic dysfunction, increased bacterial transfer, and LPS. Furthermore, in conditions with hepatic dysfunction such as cirrhosis, the clearance of LPS from circulation is reduced [13]. Cytoplasmic screening and selective recruitment of signaling adapter proteins target downstream of TLR4 signals through interactions between Toll/IL-1 receptor (TIR) domains [14][15][16]. Therefore, TLR4 activation involves the bone marrow differentiation factor 88 (MyD88), an adapter protein containing the TIR domain, or the MyD88 adapter-like factor, which is associated with the nuclear factor kappa B (NF-κB) and AP-1 transcription factor. There is substantial evidence that TLR4-mediated intracellular events exacerbate liver damage in fatty liver [17][18].

Kupffer cells produce tumor necrosis factor-α (TNF-α) and interleukin (IL)-10 in response to physiological concentrations of LPS [19][20][21]. TNF-α is an inflammatory cytokine that activates various signaling cascades, including many pathways that are described below, as important inhibitors of insulin action. TNF-α is overexpressed in obese rodents and in human adipose tissue and liver. Furthermore, it has a decreased concentration when the body is undergoing weight loss. Geoffrey et al. [22] explored the administration of a methionine–choline-deficient (MCD) diet to TNF-α and NF-κB knockout animals. Activation of TNF-α and NF-κB is essential for hepatic inflammatory recruitment in steatohepatitis. Furthermore, NF-κB activation occurs independently of TNF-α. Other studies using the MCD dietary model have reported that curcumin, which blocks oxidative stress-mediated NF-κB activation, provides protection [23], but TNF-α antiserum reduces liver injury in rats administered the MCD diet [24]. Tomita, et al. [25] demonstrated that TNF-receptor knockout mice were protected against liver fibrosis in their MCD experiments.

Alternatively, activated macrophages, including Kupffer cells, which are also referred to as M2, as opposed to the classical M1 or pro-inflammatory phenotype, represent another important pathway in resolving the inflammatory response. The coordinated program of alternative activation is primarily stimulated by the Th2 cytokines, IL-4 and IL-13, and is characterized by cell-surface expression of M2 signature genes, such as mannose receptor, arginase-1, and dectin-1 [26]. There is evidence that adiposity promotes Th1 polarization of cytokine balance, favoring congenital or classical activation of macrophages in NAFLD. Thus, in experimental and human NAFLD, the pool of hepatic natural killer T cells (NKT) is reduced, while the pool of hepatic tissue Th1 cytokines such as TNF-α, IL-12, IL-18, and interferon-γ is elevated [27][28][29][30].

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