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Editorial

Role of Toll-like Receptor 4 in the Development of Non-alcoholic Fatty Liver Disease

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The liver is known as a major organ in the body which fulfils multiple functions such as metabolic activities, detoxification, nutrient storage, and production of acute phase proteins and complement components. The structure and function of liver can be changed under the effect of various factors including nutrients, toxins, and fatty acids (1-4).

Non-alcoholic fatty liver disease (NAFLD) is recognized as the main common form of chronic liver disorder and is the known cause of liver disease worldwide (5-7). NAFLD is described by a pathologic spectrum that ranges from hepatic steatosis to non-alcoholic steatohepatitis (NASH) and generally happens along with insulin resistance, inflammation, and obesity. Moreover, NAFLD is histologically considered by a liver lipid that exceeds more than 5%, thereby resulting in hepatic inflammation and steatosis (8). Prevalence of NAFLD has significantly increased worldwide, to such a degree that the global prevalence of this disease has been reported 25.24% with the maximum prevalence in the South America and Middle East and the lowest prevalence in Africa (9). In the US, the prevalence of NAFLD has been estimated to range from 21% to 46% (7).

The increase of fat accumulation causes the liver damage, and stimulates an inflammation that worsens the progress of the hepatocyte injury. The inflammatory markers in the liver are generated by the action of immune cells including monocytes, dendritic cells, neutrophils, Kupffer cells, natural killer cells, and NK T cells, which begin and keep the liver inflammation by producing chemokines and cytokines, particularly interleukin (IL)-1β and TNF, as well as arising the oxidative stress (10).

Numerous experiments have confirmed the significant role of gut microbiota in the NAFLD pathogenesis via lipopolysaccharide (LPS)/toll like receptor 4 (TLR4) signaling cascade. LPS, as an endotoxin and lipoglycan, is the main constituent of the outer membrane of Gram-negative bacteria, and the exogenous ligand for TLR4, and causes potential inflammatory responses and is directly associated with NAFLD (11). The results of animal studies and human clinical trials have demonstrated that the change of gut microbiota is related with the development of insulin resistance, obesity, and NAFLD (7).

Furthermore, it has been reported that hepatocytes express TLRs and produce numerous inflammatory markers in response to TLR ligands. In this respect, sinusoidal endothelial cells and hepatic stellate cells produce cytokines and chemokines in response to a TLR9 ligand and a TLR4 ligand, respectively (5, 7). Among different types of liver cells, Kupffer cells are well recognized to respond to several TLR ligands including bacterial DNA, double-stranded RNA, peptidoglycan, LPS, and perhaps other TLR ligands (5). TLRs have a vital role in liver fibrogenesis and inflammation and are accompanied with liver disorders such as liver fibrosis, ischemia/reperfusion liver injury, alcoholic liver injury, and hepatocellular carcinoma (12). Among various TLRs recognized in animals, TLR9 and TLR4 play pivotal roles in the NAFLD development (10).

Numerous studies have established that TLR4 signaling aggravates NAFLD (5-7, 13), as it is known as the LPS receptor. Blood LPS levels are increased in rodent models of NAFLD which is induced by different types of diet such as high-fat, high fructose, methionine/choline, and deficient diets (14, 15). These diets alter the intestinal permeability and affect gut microbiota (13, 16). A high fat diet used on wild type mice revealed steatosis/steatohepatitis with elevated proinflammatory cytokines and TLR4 expression. Moreover, injection of LPS to NAFLD animal models augmented inflammatory markers and stimulated liver injury (6, 17). TLR4 is usually expressed in several liver cell types such as hepatocytes, Kupffer cells, stellate cells, and monocytes, and represents a relationship with gut bacteria, endotoxin, and liver injury (7).

Elevated levels of circulating LPS have been documented

in diet-induced obese animal models, and as such in diabetic patients (7). It has been highlighted that the exposure of these animals to LPS may lead to NASH (18). Likewise, alterations in gut microbiota have been seen in subjects with NAFLD and obesity. In addition to LPS, TLR4 senses various endogenous ligands such as free fatty acids (FFAs) (i.e., palmitic and stearic acids) (11). As is predictable, FFAs are present in obesity conditions, and elevated levels of it have been observed in NASH patients and been associated with the activation of cell death and inflammation in liver. TLR4 signaling can be divided into the myeloid differentiation factor 88 (MyD88)-independent and MyD88-dependent pathways. The stimulation of both MyD88-dependent and independent routes eventually triggers the activation of nuclear translocation of nuclear factor-κB (NF-κB) and inflammatory signaling cascades that in turn generate several inflammatory cytokines (7, 11). LPS motivates the dimerization of TLR4 to stimulate the activation of downstream signaling cascades (7, 11). The dimerization of this receptor triggers transcription factor NF-κB, causing the expression of inflammatory genes (e.g., COX-2 and iNOS) which consequently increase the NAFLD prevalence (19).

The critical role of LPS/TLR4 signaling pathway in the development of NAFLD was established in TLR4 mutant animals (18). These animals were resistant to NAFLD and the expression of proinflammatory markers were inhibited in these animals (5, 6). Furthermore, in humans, the association of fructose-induced high endotoxin with the stimulation of liver TLR4 expression was established (18).

Since 80% of intravenously injected LPS accumulate in the hepatocyte within 30 minutes, the liver is known as the target of LPS (6). Administration of LPS to laboratory animals acts like a high fat diet and augments fasting insulin and glucose levels, elevates weight gain, induces steatosis, and increases liver fat and inflammatory markers (18). In this regard, numerous studies have established the vital role of inflammatory markers in the development of NAFLD (10). Antibiotics therapy to kill Gram-negative bacteria reduced the level of circulating LPS and decreased the steatosis in the human subjects. Hence, it seems LPS closely contributes to the development of NAFLD, and TLR4 cascade could be attended as a key route in the progression of NAFLD (6).

Conflict of Interests

None.

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