بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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MONA MAGHRABY

INTRODUCTION

Liver is one of the major organs which has metabolic activities, nutrient storage, detoxification functions and is a complex immunological organ ***(Robinson et al., 2016).***

During the past 30 years and after the major progress in the liver disease management, millions of people are still suffering from an acute or chronic liver conditions worldwide ***(Farzaei et al., 2018).***

At present, there are few evidences of the role of the gut microbiota in the course of liver disease ***(Nicoletti et al., 2019).***

Liver is assumed to be major target for gut microbes due to anatomical and function connection between gut and liver ***(Elshaer et al., 2019).*** Healthy gut by balanced interactions among bacteria, epithelium and gut immune system can limit the access of pathogen and bacteria to the portal circulation and the liver ***(Peterson and Artis, 2014).***

The commensal bacteria of the intestine constitute a reservoir of foreign antigens that can interact with mucosal immune cells and influence systemic immune responses ***(Wu and Wu, 2012).***

Dysbiosis has been defined as qualitative and quantitative changes in the intestinal flora, their metabolic activity and their local distribution ***(Yan et al., 2011).***

The dysregulation of intestinal immunity, food antigens and bacterial antigens with strong immune-activating

properties can cross the intestinal epithelium ***(Wiest et al., 2017),*** this leads to chronic immune-mediated inflammatory liver disease ***(Czaja et al., 2016).***

Still the cause of autoimmune hepatitis (AIH) is uncertain. The principal target antigen in adults with AIH is unknown, and yet unrecognized self-antigens or foreign antigens that resemble self-antigens may trigger the disease or increase susceptibility to it, this is possibly by deviation components of the innate and adaptive immune responses toward a pro-inflammatory, autoreactive profile ***(Czaja, 2015).***

Any change occurs to the composition of resident commensal communities relative to the community found in healthy individuals lead to dysbiosis ***(Haque and Haque, 2017).***

Indomethacin, is a non-steroidal anti-inflammatory drug (NSAID) which is one of the most widely prescribed group of drugs for the treatment of inflammation and pain. It acts by inhibiting cyclooxygenase (COX) enzymatic activity, which prevents the generation of prostaglandins (PGs) ***(Maseda et al., 2019).***

Prostaglandins (PGs) are known to be involved in the mechanisms of NSAID-induced small-intestinal injury by alterations in the structure of the intestinal microbiota and disturb the intestinal permeability ***(Ishii et al., 2019).***

AIM OF THE WORK

The present study will be carried on to investigate whether the chronic use of indomethacin could disturb the intestinal barrier, the significance of bacterial translocation on the liver health and if there is an age preference.

Research questions:

- Does indomethacin disturb intestinal permeability?
- Is there any age preference?
- Do translocated bacteria affect the liver immunity?
- What is the molecular mechanism that may be involved in this pathological condition?

REVIEW OF LITERATURE

The liver is the central organ involved in metabolism, nutrient storage, detoxification, and is also an immune organ, having an important regulatory role in innate and adaptive immunity ***(Hoffmanová et al., 2018).*** It produces acute phase proteins, complement components, cytokines, chemokines, and contain large diverse populations of resident immune cells ***(Robinson et al., 2016).***

The liver is a highly immunotolerant organ ***(Robinson et al., 2016).*** But the hepatic immune system must be capable of activating immune responses to "dangerous" antigens or to liver tissue damage (of any origin) so if this immune tolerance to self-antigens in the liver is impaired, persistent activation of innate immune pathways, which are usually associated with cytopathic effects on liver parenchymal cells and autoimmune liver diseases could be occurred ***(Robinson et al., 2016).***

In hepatic injury, the hepatic immune system plays an important role in initiation and progression of liver diseases. Thus, chronic liver diseases of infectious, toxic, metabolic, cholestatic, and autoimmune hepatitis (AIH) are characterized by persistent activation of innate immune pathways ***(Carambia et al., 2018).***

The liver has a unique characteristic morphologic organization, cell composition, and functions. Kupffer cells (KCs), the liver-resident macrophages, and dendritic cells (DCs) which express a range of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), nucleotide-binding

oligomerization domain-like receptors (NLRs) and scavenger receptors ***(Yanan and Cai, 2019).***

These receptors bind to microbial-associated molecular patterns (MAMPs) and damage-associated molecular patterns (DAMPs) and act as a hepatic immune guard to remove or warn the immune system about the presence of damaging pathogens which are specific pathogenic "molecular signature" (figure 1) ***(Yanan and Cai, 2019).***

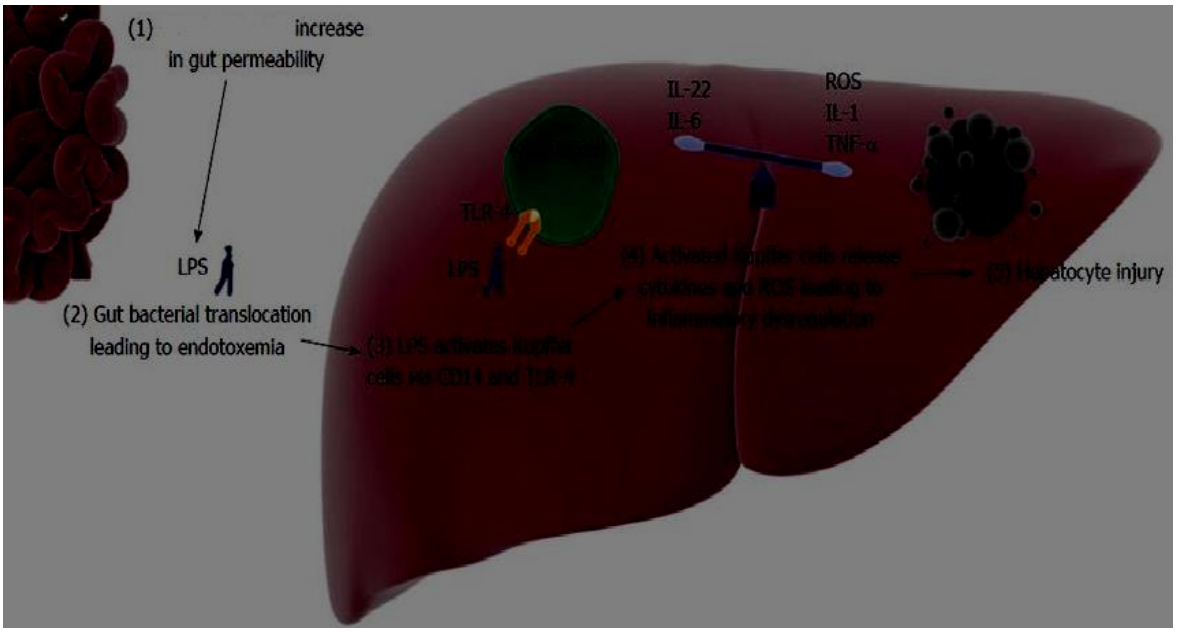

Figure 1: Shows role of kupffer cells in hepatic injury by dysregulation between the pro-inflammatory and anti inflammatory cytokines, LPS: Lipopolysaccharides; TLR-4: Toll-like receptor 4; IL: Interleukin; TNF: Tumor necrosis factor; ROS: Reactive oxygen species ***(Suraweera et al., 2015).***

Autoimmune hepatitis (AIH)

Autoimmune hepatitis (AIH) is a chronic hepatocellular disease caused by a loss of tolerance to hepatocyte-specific autoantigens. It is characterized by elevated levels of aminotransferases, specific autoantibodies and interface hepatitis on liver biopsy ***(Sahebjam and Vierling, 2015).*** AIH is a rare cause of acute liver failure (ALF) but more often presents as chronic liver disease. In untreated patients, AIH progresses at variable rates to cirrhosis with subsequent risks of complications as portal hypertension, liver failure or hepatocellular carcinoma (HCC) ***(Dalekos et al., 2019).*** According to other autoimmune diseases, AIH is a global disease that affects children and adults of all ethnicities and races ***(Gatselis et al., 2015).***

Incidence of AIH patients was classified according to age at presentation, as in patients aged ≤30 years (9.6%), 31-39 years (10.8%), 40-49 years (16.9%), 50-59 years (31.3%) and ≥60 years (31.3%) ***(Milin et al., 2014).***

In comparison with the age- and gender-matched general population, the mortality of AIH is two-fold higher than that of the general population ***(Ngu et al., 2012).***

AIH is a clinical condition characterized by considerable demographic, clinical, laboratory and histological heterogeneity. Therefore, extended differential diagnosis should be performed, considering the possibility of AIH in any acute or chronic liver disease, as the diagnosis of AIH is based on detection of characteristic autoantibodies as well as a typical pattern on liver histology ***(Sebode et al., 2018).***

Insidious onset with unspecific symptoms is commonly the clinical phenotype of the disease. It is characterized by fatigue, right upper quadrant pain, lethargy, malaise, anorexia, nausea, pruritus, fluctuating jaundice and polyarthralgia without arthritis, sometimes dating back years. Acute onset of AIH exists and contains two different clinical patterns (the acute exacerbation of chronic AIH and the true acute AIH without histological findings of chronic liver disease) ***(Gatselis et al., 2015).***

Diagnosis depends on elevated serum IgG. Other serum biochemical abnormalities show mainly hepatitic pattern, but bilirubin concentrations and aminotransferase activities may range from just above the upper normal limits to more than 50 times these levels,. In keeping with the fluctuating nature of the condition, these biochemical indices may even spontaneously normalise despite histological evidence of continuing activity ***(Gordon, 1998).***

In typical cases of AIH, ANA (anti nuclear antibody) and ASMA (anti smooth muscle antibody) autoantibodies are detected in significant titers (≥1;80 in adults and ≥1:40 in children) in almost half of Caucasians patients with AIH-1, while ANA alone are detected in 15% and SMA alone in 35% ***(Obermayer-Straub, 2000).***

AIH classified into three types AIH-1 which is the more frequent type (90% of cases) mostly present in young females and AIH-2 approximately 10% of cases, which usually occurred in childhood, young adulthood and mediterranean population ***(Dalekos et al., 2019).***

Type I AIH is the classic syndrome which associated with marked hypergammaglobulinemia, lupoid features, and

positive ANAs. Type II AIH is associated with anti-liver and kidney microsomal antibodies and a negative ANA ***(Dienstag and Isselbacher, 2001).***

Type III autoimmune hepatitis is associated with positive ANA, SMA, and antibodies to soluble liver antigen/liver pancreas (anti-SLA/LP). Autoimmune hepatitis is diagnosed when typical immunological (serum autoantibodies), histological (interface hepatitis), clinical (associated autoimmune disorders), and biochemical (hypergammaglobulinemia with high IgG) features are present, and all other causes of liver disease are ruled out ***(Czaja, 2002).***

The etiology of AIH is undefined but it could be caused by immunogenetic susceptibility and environmental triggers that produce an unregulated immunological attack against hepatocytes ***(Dalekos et al., 2019).***

The unrecognized self-antigens or foreign antigens that resemble self-antigens may trigger the disease or increase susceptibility to it, possibly by deviation components of the innate and adaptive immune responses toward a pro-inflammatory, autoreactive profile ***(Czaja, 2015).***

Autoimmune hepatitis could be induced by the intestinal microbiota (i.e., bacterial components and products) ***(Czaja, 2015)*** as they act as a reservoir of foreign antigens that can interact with mucosal immune cells and influence systemic immune responses ***(Wu and Wu, 2012).***

A large numbers of foreign molecules are received by the liver coming from the gastrointestinal tract via the portal vein. These non-self-antigens are derived from food such as (antigens including peptides derived from gluten and related cereals), and

from the microbiota that have breached and overcome the intestinal barrier, these gut–derived molecules must be tolerated by the liver, while still providing immune surveillance for pathogenic infections and malignant cells. The variety of immune interplay determines the balance between tolerance, protective immunity against infection, tissue damage, metastases, and autoimmunity in the liver ***(Sturgeon et al., 2016).***

Gut Microbiota

Gut microbiota refers to the community of the microorganisms colonized in the gastrointestinal tract (GIT), around 100 trillion microorganisms (mostly bacteria) inhabit the human GIT ***(Valdes et al., 2018),*** also other microbes such as fungi, archaea, viruses, and protozoans are present ***(Sekirov et al., 2010).***

The term microbiome is the name given to all components of the microbes, their genes and their metabolites ***(Adamovsky et al., 2018).***

The microflora as commensals in the GIT represents a complex ecosystem of the gastrointestinal tract. Many roles are done by commensals in the body; thus, there are a lot of areas of host health that can be compromised when the microflora is severely distorted ***(Yan et al., 2011).***

Microbiota is useful for both themselves and their hosts, as long as the body is in a healthy state ***(Leulier et al., 2017).***

It is also involved in normal host physiology, ranging from nutrition to behavior, it protects against exogenous pathogen microorganisms via active and/or competition mechanisms, in normal conditions, commensal microbes and the host share many mutual advantages ***(Vajro et al., 2013).***

Gut microbiota is vital for maintenance of the integrity of the barrier function of the mucosa, it is necessary for the maturation of gut-associated lymphoid tissue (GALT), (i.e. Peyer's patches, intraepithelial & lamina propria lymphocytes and mesenteric lymph nodes), the secretion of Immunoglobulin A (IgA), and the production of antimicrobial peptides ***(Vajro et al., 2013).***

In addition, they have a major metabolic function as they ferment the undigested carbohydrates and proteins leading to organic acids formation like butyrate, acetate, and other short chain fatty acids (SCFAs). SCFA have important intestinal trophic effects and represent an additional energy source for the host ***(Zheng et al., 2019).***

They also are involved in synthesis of vitamins (B group and K) ***(Chen et al., 2015),*** enhancement of GIT motility and function, digestion and nutrient absorption, inhibition of pathogens (colonization resistance), metabolism of plant compounds/drugs, and production of short-chain fatty acids (SCFAs) and polyamines and stimulation of the immune system ***(Wang et al., 2011).***

It is progressively more clear from epidemiologic, clinical, and basic studies that an appropriate colonization of the gastrointestinal tract is essential for short- and long-term immunologic and metabolic health, as the gut microbiome acts as an additional organ to the body providing more cells and genes that exist in the human body and functions as an active metabolic structure contributing to nutrient digestion and absorption, immune function, and metabolic activity necessary for health ***(Levy et al., 2017).***

From an immunological point of view, microorganisms are viewed as pathogens by the host immune system that recognizes and eliminates them. However, majority of the gut bacteria are non-pathogenic and, co-habit with the enterocytes in a symbiotic relationship ***(Jandhyala et al., 2015).***

Many factors are influencing human microflora like antibiotic use, psychological and physical stress, radiation, altered GIT peristalsis, dietary changes and lifestyle alterations,

all these factors that limit microbial exposure which predispose populations of people in developed countries to autoimmune disease ***(Wu and Wu, 2012).***

The adaptations of the microbiome to altered environmental conditions or changes in the state of the host, which result in abnormal community composition and function, may generally have beneficial, neutral or harmful consequences for the host ***(Levy et al., 2017).***

These conditions affect microbiotal structure and subsequently, the co evolutionary relationship between our immune system and the symbionts we host ***(Joseph et al., 2017).***

Any change occurs to the composition of resident commensal communities relative to the community found in healthy individuals leading to many diseases is called dysbiosis ***(Haque and Haque, 2017).***

Dysbiosis

Dysbiosis is a state in which the microbiota produces harmful effects through qualitative and quantitative changes in the intestinal flora itself ***(Grivennikov et al., 2012).***

Three factors can cause dysbiosis; loss of beneficial microbial organisms, expansion of pathobionts and loss of overall microbial diversity ***(Chow & Mazmanian, 2010).*** These three types of dysbiosis are not mutually exclusively and may all occur concurrently ***(Sonnenburg et al., 2016).***

Expansion of pathobionts potentially harmful microorganisms which are members of the commensal microbiota that causes pathology ***(Chow & Mazmanian, 2010).***