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## Nutrition, inflammation and liver-spleen axis

Luigi Barrea <sup>a</sup>, Carolina Di Somma <sup>b</sup>, Giovanna Muscogiuri <sup>a</sup>, Giovanni Tarantino <sup>c</sup>, Gian Carlo Tenore <sup>d</sup>,  
Francesco Orio <sup>e,f</sup>, Annamaria Colao <sup>g</sup>, and Silvia Savastano <sup>g</sup>

<sup>a</sup>I.O.S. & COLEMAN Srl, Medicina Futura Medical Center, Acerra, Naples, Italy; <sup>b</sup>IRCCS, SDN, Via Gianturco 113, Naples, Italy; <sup>c</sup>Dipartimento di Medicina Clinica e Chirurgia, Federico II University Medical School of Naples, Via Sergio Pansini 5, Naples, Italy; <sup>d</sup>Department of Pharmacy, University of Naples “Federico II”, Via D. Montesano 49, Naples, Italy; <sup>e</sup>Department of Sports Science and Wellness, Unit of Endocrinology, “Parthenope” University of Naples, Via Ammiraglio Ferdinando Acton 38, Naples, Italy; <sup>f</sup>Via Ammiraglio Ferdinando Acton 38, Naples, Italy; <sup>g</sup>Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, Naples, Italy

### ABSTRACT

Chronic low-grade systemic inflammation represents a mechanism common to many diseases linked to atherosclerosis-related pathways. There is a growing body of evidence indicating that the combination of food quantity and quality along with genetic susceptibility are able to induce the aberrant activation of innate immune signalling, which initially contributes to chronic low-grade inflammation. Liver represents the central player to inflammatory response. Dietary/metabolic factors contribute to the pathogenesis of Non-alcoholic Fatty Liver Disease (NAFLD), the main causes of liver disease in the Western world. Enlargement of the spleen, central organ in regulating the inflammation-related immune response, is commonly seen in patients with of NAFLD, depicting the so called “liver-spleen axis.” The aim of this review was to provide an at-a-glance overview of the possible bi-directional mechanisms linking nutrition and inflammation, particularly pinpointing the inflammatory effects stemmed by nutrition on “liver-spleen axis.” In particular, the role of unhealthy diet, healthy dietary patterns, such as the Mediterranean diet style, dietary vitamins and micronutrients, such as vitamin D or Magnesium, and Glucagon-Like Peptide-1, a well-known incretin released in response to meal intake, will be discussed. The highly variability of the inflammatory response highlights the role of expert nutritionists in refining methodologies apt to assess nutritional epidemiology and to apply appropriate dietary intervention to counteract diet-induced inflammation mechanisms.

**Abbreviations:** T2DM: Type-2 Diabetes Mellitus; NEFA: Nonesterified Fatty Acids; LPS: Bacterial Lipopolysaccharide; NAFLD: Non-Alcoholic Fatty Liver Disease; HS: Hepatic Steatosis; IR: Insulin Resistance; GI: Glycemic Index; HF: High-Fat; ROS: Reactive Oxygen Species; NADPH: Nicotinamide Adenine Dinucleotide Phosphate Oxidase; SFA: Saturated Fatty Acids; TLRs: Toll-like Receptors; NF-κB: Nuclear Factor-kappa B; IL: Interleukins; TNF-α: Tumour Necrosis Factor-α; MCP-1: Monocyte Chemoattractant Protein-1; PAI-1: Plasminogen Activator Inhibitor-1; AP-1: Activator Protein; FOXO3: Forkhead Box P3; IRF: Interferon Regulatory Factor; STAT: Signal Transducer and Activator of Transcription; CRP: C-Reactive Protein; FA: Fatty Acids; MUFA: Monounsaturated Fatty Acids; PUFA: Polyunsaturated Fatty Acids; TG: Triacylglycerol; IFN: Interferon; KCs: Kupffer Cells; Tregs: Regulatory T Cells; n-6 PUFA: Omega-6 Polyunsaturated Fatty Acids; n-3 PUFA: Omega-3 Polyunsaturated Fatty Acids; PGE<sub>2</sub>: Prostaglandin E<sub>2</sub>; LTB<sub>4</sub>: Leukotriene B<sub>4</sub>; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; PPAR-γ: Peroxisome Proliferator-Activated Receptor γ; NASH: Non-Alcoholic Steatohepatitis; Mg: Magnesium; EDC: Endocrine-Disruptors Chemicals; MD: Mediterranean Diet; GLP-1: Glucagon-Like Peptide-1; GLP-1R: GLP-1 Receptor

### KEYWORDS

Diet; Inflammation;  
Liver-spleen Axis;  
Nutrition; Nutritionist

## 1. Introduction

Extensive research over the last several decades has focused on the role of chronic low-grade systemic inflammation as a mechanism common to various chronic non-transmissible diseases linked to atherosclerosis-related diseases, including obesity, Type-2 Diabetes Mellitus (T2DM) and cardiovascular disease (Wong et al. 2012). Of interest, chronic low-grade systemic inflammation can be also caused and modified by diet as well (Minihane et al. 2015; Shivappa et al. 2017). There is a growing body of evidence indicating that the combination of food quantity and quality, mainly dietary patterns with high calorie intake or low in micronutrients, and genetic

susceptibility are able to influence the chronic inflammatory state (Neustadt 2006). Consequently, the recognition of the emerging role of diet-induced inflammatory process in disease development has been accompanied by efforts to identify dietary factors and dietary patterns that may promote or inhibit the inflammatory process, thereby affecting disease risk and severity.

Previous studies evidenced that among environmental factors, specific nutrients have consistently been associated with both increased or reduced levels of inflammation (Nasef, Mehta, and Ferguson 2017). However, diet is a complex combination of foods from various groups and nutrients, and some

nutrients are highly correlated (Minihane et al. 2015; Jacobs and Tapsell 2013). Additionally, nutrients that may regulate inflammation are also strictly associated with obesity and obesity *per se* is associated to chronic low-grade systemic inflammation (Minihane et al. 2015; Neale, Batterham, and Tapsell 2016). Thus, the inflammatory response is highly variable, and it might be challenging to separate the effect of single nutrients or food groups from that of others in free-living populations and those obesity-related ones.

Liver is a pivotal player for immunologic and inflammatory responses (Baeck and Tacke 2014). Metabolic factors, innate immune alterations, including inflammation caused by Non-esterified Fatty Acids (NEFA), Bacterial Lipopolysaccharide (LPS), chemokines, cytokines, and adipokines, contribute to the pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD), the main causes of liver disease in the Western world (Cobbina and Akhlaghi 2017). Spleen is central organ in regulating the inflammation-related immune response (Bronte and Pittet 2013). More recently, spleen enlargement is commonly seen in patients with NAFLD or, generally speaking, Hepatic Steatosis (HS), depicting the so called “liver-spleen axis” (Tsushima and Endo 2000). In light of the highly variability of the diet-induced inflammatory response, and besides the great body of evidence linking diet, inflammation and NAFLD, the aim of this review was to provide an at-a-glance overview of the possible bi-directional mechanisms linking nutrition and inflammation, particularly highlighting the inflammatory effects stemmed by nutrition on “liver-spleen axis.”

## 2. Nutrition and inflammation

The innate immune system is the first-line defense mechanism against invading pathogens. However, the same system also serves as the first-line initiator of chronic low-grade inflammation in the absence of any systemic or local infection, also called sterile inflammation, metabolic inflammation or meta-inflammation (Hotamisligil 2006; Chawla, Nguyen, and Goh 2011). There is a considerable agreement in the current literature that unhealthy nutritional patterns are associated with the aberrant activation of innate immune signalling, which triggers the chronic low-grade systemic inflammation (Galland 2010). Chronic low-grade systemic inflammation directly drives atherogenesis by playing a critical role in the initiation, progression, and rupture of atherosclerotic plaque (Aravindhan and Madhumitha 2016). Thus, chronic low-grade systemic inflammation has been proposed as the link between Insulin Resistance (IR), T2DM, obesity, and cardiovascular disease (Shah and Brownlee 2016).

Excess calorie intake (overnutrition) or undernutrition (diet that is poor in micronutrients) *per se* stimulate inflammatory cytokines, leading to IR and associated disorders. Healthy and unhealthy dietary patterns and food components have been shown to induce chronic low-grade systemic inflammation, through both direct and indirect effects, the latter mediated by accrual of dysfunctional adipocyte (Neale, Batterham, and Tapsell 2016; Galland 2010; Paniagua 2016). Among pro-inflammatory dietary factors, high complex carbohydrates intake, or foods with a high Glycemic Index (GI) scale, as such as foods low in fiber and rich in refined carbohydrate, and High-Fat

(HF) diets, common to nutritional patterns collectively termed the “Western diet” (Cordain et al. 2005), have been extensively evaluated (Esposito et al. 2002; Steckhan et al. 2016; Feliciano Pereira, das Graças de Almeida, and Alfenas Rde 2014). Fructose, which is often consumed in diets also rich in glucose and lipids, is more harmful than glucose and its effects are amplified when it is associated with glucose and lipids (Jegatheesan and De Bandt 2017). High calorie diets have been reported to be associated with exaggerated postprandial spikes in glucose and lipids that stimulate chronic low-grade systemic inflammation (Galland 2010; Esposito and Giugliano 2006; Diamanti-Kandarakis et al. 2017).

### 2.1. Carbohydrates and inflammation

Postprandial hyperglycemia is responsible for oxidative stress, an accumulation of several transition metals as well as increased generation of Reactive Oxygen Species (ROS) by polymorphonuclear and mononuclear leukocytes, accompanied by enhanced expression of Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH) and reduced expression of anti-oxidative enzymes (Mohanty et al. 2000). Of interest, chronic consumption of fructose promotes generates 100 times more ROS than glucose through different mechanisms, such as hepatic phosphate deficiency, leading to AMP accumulation and increased uric acid synthesis, *via* the activation of transforming growth factor and NADPH oxidase 4, which in turn stimulates the production of ROS (Jegatheesan and De Bandt 2017). In addition, fructose has been shown to promote the synthesis of Saturated Fatty Acids (SFA), such as palmitate (Sun and Empie 2012). ROS act as a potential activator of a class of proteins involved in innate immunity, known as Toll-like Receptors (TLRs), thereby mediating the activation and expression of Nuclear Factor Kappa B (NF- $\kappa$ B), a family of transcription factors controlling apoptosis and pro-inflammatory cytokine expression, with increased release of pro-inflammatory cytokines into the bloodstream, such as Interleukins (IL)-1 $\beta$  and IL-6, Tumour Necrosis Factor (TNF)- $\alpha$ , Monocyte Chemoattractant Protein-1 (MCP-1) and Plasminogen Activator Inhibitor-1 (PAI-1) (Buyken et al. 2014). In addition, other pro-inflammatory transcription factors are activated, including Activator Protein (AP)-1, Forkhead Box P3 (FOXP3), Interferon Regulatory Factor (IRF), and Signal Transducer and Activator of Transcription (STAT) families (Pahwa and Jialal 2016).

Pro-inflammatory cytokines signal the liver to produce a variety of proteins known as acute phase reactants, including C-Reactive Protein (CRP). CRP is involved in endothelial dysfunction and atherosclerotic process and serves not only as the most promising indicator for vascular inflammation, but also as major predictor of cardiovascular diseases risk (Soeki and Sata 2016). IL-6 plays a key role in the synthesis of CRP by the liver and the regulation of TNF- $\alpha$ . Increased levels of IL-6 are correlated to greater occurrence of cardiac events (Teeman et al. 2016). TNF- $\alpha$  induces the expression of adhesion molecules, such as vascular cell adhesion protein 1 and intercellular adhesion molecule-1 (Güray et al. 2004), shown to have implications in the development of atherosclerosis, and to enhance the production of other inflammatory cytokines (Teeman et al. 2016). Esposito et al. reported that hyperglycemic spikes more

than continuous hyperglycemia were able to affect the cytokine concentrations, at least in the short term, suggesting that an oxidative mechanism could mediate the effect of hyperglycemia (Esposito et al. 2002). In the Harvard Women's Health Study, blood levels of CRP increased progressively in across quintiles of dietary GI (Levitan et al. 2008). In addition, levels of NF- $\kappa$ B were three times higher among lean subjects consuming high-GI meals (Buyken et al. 2010). On the other hand, fiber consumption was associated with significantly greater reductions in CRP levels (North, Venter, and Jerling 2009), likely related to its beneficial effect on glycemia (Bo et al. 2008). Contrarily, in the Women's Health Initiative Observational Study, IL-6 and TNF- $\alpha$  were inversely associated with a relatively high consumption of both soluble and insoluble fiber (24 g/day), but there was no significant association between intake of dietary fiber and CRP (Ma et al. 2008). The complex anti-oxidant/anti-inflammatory effects of several bioactive compounds contained in cereals have been extensively investigated by Fardet A. (Fardet 2010); additionally, a recent exhaustive meta-analysis including 14 RCTs showed that intervention with dietary fiber or fiber-rich food, compared with control, produced a slight, but significant reduction of 0.37 mg/L (95% CI 0.74, 0) in circulating CRP levels in overweight/obese adults, but only when the total fiber intake was 8 g/d higher in the intervention group than in the control group (Jiao et al. 2015).

## 2.2. Lipids and inflammation

Fatty acids (FA) are a heterogeneous group of macronutrients that can be divided into SFA, Monounsaturated Fatty Acids (MUFA) and Polyunsaturated Fatty Acids (PUFA). In fasting state, NEFA, compartmentalized in lipid droplets, are the vehicle by which Triacylglycerol (TG) stored in adipose tissue is transported to its sites of utilization (Karpe, Dickmann, and Frayn 2011). In fed state, circulating dietary TG represents an additional source of NEFA and reflects the composition of the meal fat. Dietary FA intake influences in relative FA composition of the cell membranes, thus influencing membrane fluidity and membrane functions, especially at the mitochondrial membrane level (Halliwell and Gutteridge 1999). Dietary fat are mostly accommodated in the constitutively secreted chylomicrons that entry into the circulation leading to the generation of NEFA, subsequently taken up by the liver. NEFA generated from fat digestion and metabolism either are esterified into TG or enter mitochondria for  $\beta$ -oxidation (Redgrave 2004). NEFA derived also from adipose tissue depots, but mobilization of NEFA from adipose tissue is normally suppressed by insulin. Thus, IR further increasing lipolysis, potentially leads to a vicious cycle. HF diet increases mitochondrial  $\beta$ -oxidation of NEFA, with activation of NADPH oxidase system, lipid peroxidation of the unsaturated lipids of fat deposits. Lipid peroxidation triggers pro-inflammatory signalling pathways and endoplasmic reticulum stress (lipotoxicity), either alone or in combination with other lipid metabolites, with the expression of NF- $\kappa$ B-dependent pro-inflammatory agents namely, inducible nitric oxide synthase, TNF- $\alpha$ , and Interferon (IFN)- $\gamma$  (Hauck and Bernlohr 2016; Petta et al. 2016; Kennedy et al. 2009). In particular the activation of the TLR4/inducible nitric oxide synthase/NF- $\kappa$ B pathway induces

oxidative stress in hepatocytes via the production of pro-inflammatory cytokines, such as TNF- $\alpha$  by Kupffer cells (KCs). Additionally, regulatory T cell (Tregs) populations, specialized lineage of suppressive CD4-T+ cells that act as critical negative regulators of inflammation in various biological contexts (van der Veecken et al. 2016). Non-lymphoid Tregs, such as adipose tissue derived Tregs, are distinct from their counterparts in lymphoid organs based on immune functions (Cipolletta 2014). Normal mouse adipose tissue, mainly Visceral Adipose Tissue (VAT), is particularly enriched with Tregs, and a protective role for adipose tissue-resident Tregs "Fat Tregs" against obesity-associated inflammation and obesity-driven insulin resistance has been described (Cipolletta 2014). Of interest, VAT-associated Tregs are significantly reduced in insulin-resistant animal models of obesity (Zeng and Chi 2015). This protective role of adipose tissue-resident Tregs on metabolic syndromes is also confirmed by studies on human subjects, thereby highlighting a potential therapeutic value of modulating Tregs to improve obesity-associated metabolic disorders (Cipolletta 2014). Metabolic status and multiple nutrient metabolites influence Treg homeostasis, and changes in Tregs may in turn trigger metabolic disorders and associated inflammation as well as impairment in immune regulatory parameters, as reported in experimental models of diet-induced obesity (Maioli et al. 2016). Thus, also the consumption of a fatty meal results in the secretion of pro-inflammatory cytokines into the circulation (de Vries et al. 2014). The controversial, relation of SFA to chronic low-grade inflammation and cardiovascular disease has been extensively discussed by a recent review, indicating that dietary SFA is only one of unfavorable lifestyle factors, not necessarily the most important, influencing dyslipidemia in Western societies (Ruiz-Núñez, Dijck-Brouwer, and Muskiet 2016). The current pathophysiological hypothesis is that the prolonged elevation of TG and TG-rich lipoproteins in the blood stream up to fourfold, known as postprandial lipemia, promotes the formation of small, dense low-density lipoproteins, inflammatory cell recruitment, proliferation and migration of smooth muscle cells of vessel walls, as well as oxidative stress, inflammation, and endothelial dysfunction (Chan et al. 2013). Although not consistently, it has been reported that even a single HF meal is associated to a transient increase in the concentrations of pro-inflammatory cytokines, soluble adhesion molecules and in pro-oxidant activity (Burdge and Calder 2005). The plasma TG response to the test meal induced significantly increased in IL-6 (Lundman et al. 2007). An updated study by Heriaka et al. indicated that CRP increased in the immediate hours following a HF meal after acute increases in IL-6 and TNF- $\alpha$  have already occurred in the inflammatory cascade (Heriaka and Erridge 2014). High dietary intake of SFA may contribute to greater serum levels of inflammatory mediators either *via* TLRs or cyclooxygenase-2, the rate-limiting enzyme of prostaglandin and thromboxane biosynthesis (Lee et al. 2001). Additionally, SFA palmitate and stearate acids can trigger IL-1 $\beta$  secretion through mechanisms involving inflammasome sensor NLRP3 (L'homme et al. 2013). Consumption of trans isomers of unsaturated fatty acids, so-called trans-fatty acids, mainly present in solid fats produced by part hydrogenation of oils and high-fat diet, are commonly found in Western diet. The

intake of trans-fatty acids has been consistently associated with chronic low-grade systemic inflammation (Harvey et al. 2008) and autoimmune diseases (Manzel et al. 2014). In particular, dietary trans-fatty acids incorporated in the phospholipids of endothelial cells enhance the cell surface expression of adhesion molecules and MCP-1 cytokine production (Harvey et al. 2008).

Omega-6 (n-6 PUFA) and omega-3 PUFA (n-3 PUFA) are essential unsaturated fatty acids that must be derived from the diet. Western diet contain excessive levels of n-6 PUFA but very low levels of n-3 PUFA, leading to an unhealthy n-6/n-3 ratio of 20:1, instead of the ideal ratio 1:1 that existed for millions of years during the long evolutionary history of the genus *Homo* (Simopoulos 2016; Kromhout and de Goede 2014). A significant role for both n-3 and n-6 PUFA has been previously reported, especially in the pathological inflammatory responses associated with metabolic diseases (Calder 2015), or with systemic immune-inflammatory disease, such as arthritis (Oliviero et al. 2015) and psoriasis (Barrea et al. 2015a; Barrea et al. 2016a).

Eicosanoid products derived from n-6 PUFA, such as Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and thromboxane A<sub>2</sub> synthesized from arachidonic acid by lipid-oxidizing enzyme lipoxygenase-5 and cyclooxygenase-2, are potent mediators of thrombosis and inflammation, while n-3 PUFA have well documented anti-inflammatory properties by increasing the production of PGE<sub>3</sub> and LTB<sub>5</sub> and by affecting lymphocyte and monocyte functions, crucially involved in adaptive and innate immunity *via* the TLR4-induced signalling pathways (Lee et al. 2001; Yates et al. 2014; Siriwardhana et al. 2013). In addition, unsaturated fatty acids prevented activation of NLRP3 inflammasome in human monocytes/macrophages (L'homme et al. 2013). In particular, Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), the main n-3 PUFAs in marine oil, are associated with reduction of inflammation, increase in anti-inflammatory adipokines, and decrease in pro-inflammatory cytokines (Lee et al. 2001). Oleic acid is the main MUFA found in human diet, which naturally occurs in vegetal oils, such as extra-virgin olive oil and sunflower oil. Oleic acid also exerts beneficial anti-inflammatory effects through different mechanisms, including the activation of AMP-activated protein kinase and Peroxisome Proliferator-Activated Receptor  $\gamma$  (PPAR- $\gamma$ ), as well as suppression of TLRs and NF- $\kappa$ B pathways (Siriwardhana et al. 2013). Of interest, postprandial lipemia after the SFA intake was more pronounced than the lipemia due to MUFA and PUFA, which can lead to a higher pro-inflammatory state associated with SFA consumption (Rocha, Bressan, and Hermsdorff 2017). Animal studies, human trials and epidemiological studies have shown the potential preventive effects of replacing SFA with n-3 PUFA in reducing inflammation (Saremi and Arora 2009; Yashodhara et al. 2009; Nagakura et al. 2000).

### 2.3. Vitamin D and inflammation

Among nutrients, the importance of vitamin D beyond its traditional role in bone metabolism has gathered increasing consensus (Trummer et al. 2016). Currently, although a causative association between vitamin D, obesity and inflammation

appears to be complex (Savastano et al. 2017), it is now recognized that vitamin D represents a key modulator of immune and inflammation mechanisms and that vitamin D deficiency can result in chronic inflammatory diseases (Savastano et al. 2017; Gonçalves de Carvalho and Ribeiro 2016). There are a large number of studies indicating that vitamin D suppresses the production of cytokines in a seasonal manner, with a higher suppression in the summer, and modulates the expression of TLR2 and TLR4 (Khoo et al., 2011a; Khoo et al., 2011b), NF- $\kappa$ B inflammatory signalling pathway, T and B lymphocytes homeostasis, and immunoglobulin production (Savastano et al. 2017).

### 2.4. Diet, microbiota, and inflammation

There is a consolidated evidence that there are elevated concentration of adipose tissue-derived cytokines in obese humans, suggesting the concept that inflammation may be derived from the accumulation of activated macrophages surrounding enlarged adipocytes in obese subjects (Greenberg and Obin 2006; Margioris 2009). Moreover, gastrointestinal tract might represent a potential source of inflammation associated with excess calorie intake (Cani et al. 2007; Cani et al. 2008). In particular, high calorie diet is associated with changes in gut microbiota, with reduction in gram-positive bifidobacteria and increase in gram-negative bacteria. These changes are associated with the impairment of the intestinal membrane integrity, followed by increasing plasma LPS, which triggers systemic inflammation *via* the stimulation of TLR4 on immune cells (de Jong, González-Navajas, and Jansen 2016). As an alternative mechanism, gut microbiota on a high-fat diet may reduce the dietary choline bioavailability, an essential nutrient that is necessary for the secretion of very-low-density lipoprotein, thus promoting HS, IR and lipid peroxidation and inflammation (Dumas et al. 2006). In details, specific microbes contribute to the split of the nutrient choline into trimethylamine and acetaldehyde in the human gut, thereby reducing the bioavailability of dietary choline (Romano et al. 2015). Taken together, these studies suggest that inflammation can possibly occur after every high calorie meal, also independently of obesity-induced inflammation (Laugerette et al. 2011). On the other side, the use of dietary fibers has been reported to favourable modulate the intestinal microbiota population (Cuervo et al. 2014).

### 2.5. Nutrition, epigenetic change, and inflammation

Currently, the possible impact of nutrients on epigenetic signature and induced susceptibility to disease has drawn significant interest. Most studies done in environmental epigenetic demonstrates that nutrients exert profound effects on the regulation of genes by DNA methylation and covalent histone modifications (Park et al. 2017). According to the developmental programming of health and disease hypothesis, unfavourable environmental conditions can affect physiology and structure of the developing foetus, which can also predispose to different pathological conditions later in life (Eriksson 2016). Exposure to unhealthy diet, particularly during sensitive developmental

periods, such as pregnancy can induce detrimental effects in key organs responsible for nutrient regulation, including liver, adipose tissue, muscle and pancreas, to provide short-term survival benefit aimed to maintain the energy-dependent basal metabolic functions in vital organs, primarily the heart and brain (Kim 2016). The persistence of these adaptive mechanisms might result in permanent adjustments in different homeostatic systems, which influence energy uptake and utilization beyond metabolic capability, unhealthy feeding behaviour, adipocyte and  $\beta$ -cell dysfunction, imbalance between inflammatory and anti-inflammatory networks, thereby promoting phenotypes more susceptible to metabolic syndrome-like characteristics in adult life and reproductive dysregulation in the offspring (Szarc vel Szc et al. 2015; Vaiserman 2017).

Nutrition-driven epigenetic changes might be triggered across the entire life span of organisms, from the periconceptional period until old age, with a relevant role for the epigenetic transgenerational inheritance in the obesity epidemic (Niculescu and Lupu 2011; Kanherkar, Bhatia-Dey, and Csoka 2014).

Experimental data indicates that genotoxic effects of oxidative stress might be proposed among the potential mediators of the nutrition-driven epigenetic change leading to increased risk for obesity, IR, cardiovascular disease (Diamanti-Kandarakis et al. 2017).

Dietary components, such as those containing folate, selenium, vitamin B6, vitamin B12, betaine, choline, methionine, and serine, are linked to epigenetic regulation by altering the transfer of methyl groups from S-adenosyl methionine to DNA and histone (Niculescu and Lupu 2011; Wang et al. 2012). Animal studies have shown that a diet with too little methyl-donating folate or choline before or just after birth causes certain regions of the genome to be under-methylated for life. The effects of intrauterine inflammation due to high calorie diet during pregnancy on the offspring predisposition to adult chronic non-communicable diseases has been analyzed by Hemalatha (2013). In particular, inflammation due to over-nutrition during pregnancy, coupled with undernutrition and micronutrient malnutrition, has been shown to impair fetal skeletal muscle development (Wang et al. 2015), while promoting adipogenesis (Berg et al. 2004), thereby contributing to start the cascade of low grade systemic inflammation, IR, and chronic diseases linked to atherosclerosis-related pathways later in life. For adults too, a methyl-deficient diet leads to a decrease in DNA methylation, but the changes are reversible when methyl is added back to diet (Niculescu and Lupu 2011). Methyl-deficient diet, as those with low methionine and without choline and folic acid, have been proven to induce epigenetic alterations and pathomorphological changes in an animal model of NAFLD (Pogribny et al. 2009). Importantly, a number of pro-inflammatory transcription factors, along with the inflammatory genes, are regulated by epigenetic mechanisms, including DNA methylation, histone methylation or acetylation, and RNA associated silencing by small non-coding RNAs (Samanta et al. 2017). In particular, epigenetic modifications have been reported to play an important role in the regulation of TNF- $\alpha$  and thereby in TNF- $\alpha$ -associated inflammation pathways (Sullivan et al. 2007). On the other side, a number of dietary antioxidants, including catechins, curcumin, quercetin and

resveratrol, modulate the Tregs functions and decrease cytokine production and NF- $\kappa$ B expression (Park et al. 2017).

### 3. Non-alcoholic fatty liver disease (NAFLD)

Besides its multiple role in intermediary metabolism, bile secretion, serum homeostasis, and xenobiotic detoxification, the liver may be also viewed as a further immunological organ (Baeck and Tacke 2014). The liver is enriched in various resident innate immune cells, including natural killer T cells and KCs, inflammatory macrophages resident in the liver and accounting for 80–90% of the total population of fixed tissue macrophages in the body (Samanta et al. 2017). By receiving blood coming from the gastrointestinal tract through the portal vein, immune cells in the liver have the potential to initiate innate and adaptive immune responses in the case of infections, e.g. in response to antigens and microbiological components coming from the intestine. The aberrant activation of innate immune signalling, such as that due to diet/metabolic factors, may trigger the rapid recruitment to the liver of other innate immune cells (Sullivan et al. 2007). NAFLD is now the most common chronic liver disease (Gao, Jeong, and Tian 2008). NAFLD is histologically categorized into simple HS also known as ‘fatty liver’, and Non-Alcoholic Steatohepatitis (NASH). The latter represents the stage when the fatty liver starts to show inflammatory change associated with KCs dysfunction, which contributes to its pathogenesis (Ganz and Szabo 2013). The progression of NASH to cirrhosis or hepatocellular carcinoma is responsible for the liver-specific morbidity and mortality of NAFLD. By definition, to have NAFLD, >5% of the liver weight must be due to accumulation of fat in the form of triglycerides in the absence of significant alcohol intake [ $<10$  g and  $<20$  g of alcohol *per* day for women and men, respectively (Ratziu 2017)]. It is well-known that the liver is directly exposed to various types of lipids (NEFA, cholesterol and TG) from both diet and visceral adipose tissue depots, and that an excessive NEFA flux into the liver *via* the hepatic portal vein contributes to HS (Rinella et al. 2015). NAFLD is strongly associated with obesity, IR and metabolic diseases, such as T2DM (Singh et al. 2015; Juárez-Hernández et al. 2016). IR is well known to play a key role in increasing levels of NEFA, but, in turn, HS can contribute to worsen IR leading to a vicious cycle, with progression to more severe forms of liver damage by one side, and T2DM by the other side. NAFLD has also been linked to increased cardiovascular risk, largely mediated through IR and components of the metabolic syndrome (Buzzetti, Pinzani, and Tsochatzis 2016; Valenti et al. 2016). IR results in increased hepatic *de novo* lipogenesis and impaired inhibition of adipose tissue lipolysis, with consequent increased flux of NEFA to the liver, followed by the enhancement of NEFA for the triglycerides synthesis, intrahepatic fat accumulation, and decreases in very-low-density lipoprotein secretion (Mikolasevic et al. 2016). IR also promotes adipose tissue dysfunction and macrophage accumulation, with consequent altered production and secretion of adipokines and inflammatory cytokines that are associated with marked hepatic inflammation in obese humans (Bellentani 2017). IR and obesity, accompanied by HF feeding, lead to hepatic inflammation, *via* activation of the NF- $\kappa$ B pathway and downstream cytokine production, including IL-1 $\beta$ , IL-

6 and TNF- $\alpha$  in the liver (Koo 2013). Pro-inflammatory cytokines and NEFA, produced by hepatocytes in response to HS and released from visceral adipose tissue, activate the production of pro-inflammatory cytokines by liver KCs, which further activate KCs in a positive-feedback mechanism (Canello et al. 2006).

In the past years, the “two-hit theory” in the development of NASH has gained sufficient support from both clinical and experimental evidence, where the first “hit” refers to the accumulation of intrahepatic fat favoured to sedentary lifestyle, high fat diet, obesity and IR, and the second “hit” to the activation of the inflammatory cascades and fibrogenesis (Cai et al. 2005). Nevertheless, according to the “Multiple Hit Hypothesis”, NAFLD stemmed from the synergistic effects of multiple parallel factors, including dietary habits and environmental factors in genetically predisposed individuals (Huang et al. 2010).

The accumulation of intrahepatic fat happens contemporarily with increased lipotoxicity from high levels of NEFA, free cholesterol and other lipid metabolites causing increased lipid peroxidation, activation of endoplasmic reticulum and mitochondrial dysfunction, with oxidative stress and production of ROS. In addition, changes in the intestinal microbiota leads to further production of FA in the bowel, increased small bowel permeability and thus increased fatty acid absorption and contribute to the pro-inflammatory state (Buzzetti, Pinzani, and Tsochatzis 2016). However, the “one-hit theory” suggests that NASH might occur by liver fat directly causing chronic inflammation (Seydel et al. 2011), with the activation of the TLR4 and NF- $\kappa$ B inflammatory pathway (Pahwa and Jialal 2016). In animal models it has been shown that increased NF- $\kappa$ B signalling in the liver is induced by high-fat diets, with resultant as chronic low-grade inflammation, IR and HS (Ratziu 2017). Additionally, NF- $\kappa$ B signalling also leads to activation of KCs and macrophages within liver tissue, which cause further damage to liver tissue (Rinella 2015).

#### 4. Nutrition and liver-spleen axis

A further mechanism linking NAFLD to inflammation could be represented by the so called “liver-spleen-axis” (Tsushima and Endo 2000). Spleen, the largest peripheral lymphoid organ in the human body with a close anatomical relationship with the liver, is strictly involved in the modulation of both nonspecific and specific immune response, also known as innate and acquired immune response (Tarantino et al. 2011). The primary function of the spleen is mainly the maintenance of peripheral tolerance *via* the clearance of circulating apoptotic cells, which allows a fine tuning of the immune system (Bronte and Pittet 2013). In particular, the spleen contains in the white pulp high levels of specialized T-cells and B-cells, committed to the production of new immune cells and antibodies, respectively (Cobbina and Akhlaghi 2017; Mebius and Kraal 2005), and it serves as a reservoir to circulating monocytes for their rapid recruitment to various inflammatory sites (Swirski et al. 2009; Chen et al. 2014). By isolation of spleen lymph, Semaeva et al. (2010) demonstrated that the permeable microvasculature of the spleen ensured the local production of inflammatory as well as anti-inflammatory cytokines, including TNF- $\alpha$  and IL-6 from one side, and IL-10 from the other side, which provide a

determinant contribution to the systemic circulation and modulate the ensuing immune-inflammatory response. Of interest, pro-inflammatory cytokines released from the spleen flow directly into the liver, through the splenic and portal veins, thus enhancing natural killer cytotoxicity in the liver (Inoue et al. 2012). On the other side, a clinical study showed that obesity is associated with reduced levels of the anti-inflammatory cytokine IL-10 (Esposito et al. 2003). Experimental data confirmed the diet-induced obesity in mice impaired the spleen ability to synthesize this cytokine (Gotoh et al. 2012), thereby directly contributing to increase the levels of pro-inflammatory cytokines, which in turn play a role in the development of inflammation-driven ectopic fat accumulation. Of interest, in knockout mice for IL-10 spleen weight were heavier than those of wild-type controls, as manifestation of spleen lymphoproliferation (Gotoh et al. 2012). In addition, in an experimental model of double knockout mice for mast cell and IL10 showed splenomegaly and elevated serum cytokines levels, indicating exaggerated systemic inflammation (Zhang et al. 2013).

Since the spleen is located in the upper left abdomen, between the diaphragm and the fundus of the stomach, it has narrow anatomical and functional relationships with the liver, through the splenic vein, which conflues with the superior mesenteric vein to form the hepatic portal vein. Consequently, spleen volume is increased in advanced cases of liver diseases, such as cirrhosis, in association with increased portal pressure gradient and portal hypertension (Berzigotti et al. 2013). A positive correlation between splenic iron levels with the severity of NASH manifestations in experimental models of mice spontaneously developing obesity and T2DM has recently reported, further confirming the relevance of the anatomical and functional relationships between spleen and liver (Murotomi et al. 2016). Besides the common presence of splenomegaly in patients with cirrhosis, a positive correlation between the spleen volume and the degree of fatty infiltration was demonstrated also in patients with NAFLD (Tsushima and Endo 2000), where the lack of the re-arrangement of hepatic tissue, at least in the early and intermediate stages, is not likely to support any role of portal hypertension in spleen modification in these patients. Therefore, different mechanisms could be proposed to account for the finding of spleen enlargement among NAFLD patients. The possible spleen involvement in obesity-driven low-grade chronic inflammation is evidenced in a recent study, in which using isolated spleen-derived immune cells together with cultured adipocytes, a crosstalk between adipocytes and immune cells, followed by an increase in the secretion of IL-6 over what was secreted by individual cultures has been found, clearly evidencing the reinforcing role of spleen (Nitta and Orlando 2013). In this context, the link between adipose tissue and spleen might lead to immunologic activation, with consequent expansion of the white pulp, which eventually is the cause of the spleen enlargement. Increased spleen longitudinal diameter along with increased serological inflammatory markers, such as IL-6, were found in patients with NASH compared with patients with HS (Tarantino et al., 2009b). Thus, large spleen longitudinal diameters coupled with high IL-6 levels were suggestive of severe HS (Tarantino et al., 2009b), and spleen enlargement evaluated by computed tomography images

has been proposed as a marker of early-stage NASH (Suzuki et al. 2010). Accordingly, increased spleen volume and elevated concentrations of CRP have been found in young adult obese subjects with HS (Tarantino et al., 2009a). Additionally, an association has been described between spleen enlargement, HS and low insulin-like growth factor-I axis, an endocrine axis frequently altered in patients with HS, as a consequence of the underlying chronic inflammation status (Savastano et al. 2011). In that, the common inflammatory milieu linking IR, obesity and NAFLD might provide a further explanation for spleen enlargements in obese individuals with HS. A hallmark of the low-grade chronic inflammation in obesity is the expansion of inflammatory macrophages in the visceral adipose tissue, along with the decrease in anti-inflammatory Tregs (Weisberg et al. 2003). In murine models of obesity, chronically inflamed visceral adipose tissue has proved to stimulate the bone marrow hematopoietic progenitor cells to proliferate, expand, and increase the production of myeloid cells (Nagareddy et al. 2014).

Similarly, the expansion of visceral adipose tissue macrophages is associated with a pro-inflammatory activation profile of macrophages in a wide variety of tissues that include the liver thereby contributing to the hepatic inflammation in obese humans (Bellentani 2017). Thus, it is tempting to speculate that inflamed the visceral adipose tissue could as well as stimulate myelopoiesis not only in the liver, but also in the spleen, the main sites of extramedullary myelopoiesis (Kim 2010). Taking in mind the close circulatory link of the spleen with the liver and its key role in modulating the immuno-inflammatory response, the spleen enlargement in obese individuals might represent an index of the aberrant activation of the immuno-inflammatory response associated to NAFLD and obesity, in the so-called “liver-spleen axis” (Tsushima and Endo 2000; Tarantino et al. 2013). On the other hand, Inoue et al. (2012) reported that in diet-induced obese rats the HS and inflammation were accelerated by the splenectomy, thus favouring the progression to NASH. Although, based on these interesting data the Authors suggested that in obese subjects preservation of the spleen function may be an important factor regulating the progression of HS, no mechanisms by which the asplenic state modulated immune cell function and the metabolic system in various compartments of the body have provided.

#### 4.1. Diet and liver-spleen axis

There is a clear imbalance between the great body of evidence linking diet, inflammation and NAFLD (de Vries et al. 2014; Ferolla et al. 2015) and the data exploring the effects of diet on spleen, despite its key role in immune function and signalling. The effects of nutrition on liver function has been dealt with more extensively elsewhere (Watts 2010; Haghghatdoost et al. 2016). Rusu et al. assembled a meta-analytic dataset on the role of nutritional interventions in NAFLD (Rusu et al. 2015) concluding that, although there was no univocal consensus on the best diet or lifestyle approach for NAFLD patients (Finelli and Tarantino 2012), these patients may benefit from a moderate-to low-carbohydrate (40%–45% of total calories) diet, coupled with increased dietary MUFA and n-3 PUFAs, reduced SFA. A recent meta-analysis on the effects of low carbohydrate diets in

subjects with NAFLD evidenced a significant reduction in intrahepatic lipid content also without significant changes in liver enzymes (Ferolla et al. 2015). However, the quality and combination of macronutrients have been found to be more important than their isolated amounts in nutritional and clinical treatment of patients with NAFLD (Juárez-Hernández et al. 2016). Currently, fructose is considered the most potent lipogenic carbohydrate contributing to the development of HS (Jegatheesan and De Bandt 2017). Both acute fructose load and chronic fructose consumption lead to the saturation of the glycolytic pathway, with an accumulation of glycolysis intermediates which can be converted to glycerol-3-phosphate used in triglyceride (TG) synthesis. In turn, the activation of the lipogenic pathway promotes oxidative stress, either *via* mitochondrial dysfunction and endoplasmic reticulum (ER) stress due to the fructosylation of the ER membrane proteins or the lipid accumulation into ER paving the way for inflammation, oxidative stress, and apoptosis and contributing to the progression of HS and of IR (Malhi H et al. 2011).

A low consumption of MUFA, a well-known mechanism contributing to the pathogenesis of NAFLD in the general population (Ryan et al. 2013), has been proposed as a possible adjunctive mechanism in increasing the inflammation milieu of psoriatic patients (Barrea et al. 2015b), a common chronic inflammatory skin disease associated with obesity (Barrea et al. 2015a; Barrea et al., 2016a) and HS (van der Voort et al. 2014). Besides diet and unhealthy lifestyles, the possible adjunctive effects of gut microbiota and genetic background are believed to be important in the development and progression of NAFLD (Buzzetti, Pinzani, and Tsochatzis 2016; Yu et al. 2016).

Going back to the spleen, Gotoh et al. (2012) evaluated the splenic and serum levels of pro- and anti-inflammatory cytokines in knockout mice for IL-10 and wild type mice fed with a HF diet (60% fat, 20% carbohydrate, 20% protein; HF). The Authors found that while the expression of the anti-inflammatory cytokine IL-10 was significantly lower in both spleen and serum in the HF group compared with the control group, the expression of the inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , MCP-1 was reduced only in spleen. This finding suggested that splenic cytokine expression was down-regulated by HF feeding, but this effect was more evident on the secretion of the anti-inflammatory IL-10, which is mainly derived from the spleen, whereas the secretion of the inflammatory cytokines was probably maintained by other organs, such as the adipose tissue and the liver. Similarly, Kim, Choi, and Han (2011) reported in diet-induced obese mice that, after LPS stimulation, splenocytes from the HF group produced significantly higher levels of IL-6 and IL-1 $\beta$  than in control, thus further supporting the involvement of diet-induced obesity in increased inflammatory response of immune cells. Recently, Soni NK et al. investigated the effects of EPA and DHA on spleen metabolism (Soni et al. 2017). In this study, the Authors reported that the supplementation with menhaden fish oil, a mix of fatty acids and other lipophilic compounds, including EPA and DHA, down-regulated the immune system in mouse spleen tissue by affecting the mechanisms involved in activation of NF- $\kappa$ B transcription factor. In addition, EPA and DHA down-regulated the arachidonic acid pathway, thus reducing the production of inflammatory mediators, such as prostaglandins and



leukotrienes, and the mitogen-activated protein kinase 2, a protein encoded by a gene member of the serine/threonine protein kinase family expressed in human lymphoid follicles tricky involved in immunity and inflammation (Svahn et al. 2016). Of interest, again the specific fatty acid diet composition, rather than the increase in fat amount, seems to be the main triggering factor for the changes in expression of spleen transcriptome, as dietary PUFA markedly suppressed the expression of immune stimulating genes in the spleen, while dietary SFA have only negligible effects (Svahn et al. 2016).

#### 4.2. Vitamin D and liver-spleen axis

Vitamin D deficiency is closely associated with many hepatic diseases, including NAFLD (Roth et al. 2012). A bidirectional association between low vitamin D levels and NAFLD is increasingly recognized, with an inverse association with the histologic severity of NAFLD (Elangovan, Chahal, and Gunton 2017). In particular, a recent meta-analysis reported that low vitamin D status were 26% more common in NAFLD patients than in healthy individuals (Eliades et al. 2013). As above mentioned, the activation of the TLR4-mediated inflammatory pathways in hepatocytes plays an important role in the early stages of NAFLD (Seydel et al. 2011). Of interest, an increased expression of TLR4, NF- $\kappa$ B, and downstream inflammatory factors in association with low vitamin D levels has been reported in an *in vitro* animal model of primary hepatocytes, which is reversed by vitamin D supplementation through the down-regulation of components of the TLR4-mediated inflammation pathways (Wang et al. 2015). However, although a line of evidence indicates the existence of an independent association between the low vitamin D status and NAFLD, this association could be a consequence of shared risk factors for NAFLD and obesity, such as a sedentary lifestyle or unhealthy dietary pattern (Savastano et al. 2017). Studies included in a very comprehensive review exploring spleen functions have shown that vitamin D supplementation reduced CD4+ T lymphocyte and splenocyte counts and induced splenocyte apoptosis down-regulating the anti-apoptotic proteins Bcl-2 and Bcl-xL (Tarantino et al. 2011) also in the clinical setting of chronic inflammatory diseases, including psoriasis (Barrea et al., 2017b).

#### 4.3. Magnesium and liver-spleen axis

Magnesium (Mg) deficiency is commonly found in metabolic disorders, such as obesity, T2DM, and IR (Nielsen 2010). Mg is an essential mineral found abundantly in whole grains, leafy green vegetables, legumes and nuts, acting as cofactor of numerous enzymes involved in hundreds of body physiologies. Inadequate dietary Mg intake depletes extracellular Mg ion and consequently causes activation of macrophages and influx of calcium ions into cells with increased secretion of pro-inflammatory cytokines (Nielsen 2010). There is a close relation between Mg, the second-most abundant cation in cellular systems, and the immune-inflammatory response (Chacko et al. 2010; Gommers et al. 2016; Liu et al. 2016). In particular, a comprehensive meta-analysis including a large number of participants evidenced an inverse association between Mg intake and serum CRP levels (Dibaba, Xun, and He 2014). Mg

deficiencies, such as on gluten-free diets, have been proposed as risk factor of atherosclerosis (Vici et al. 2016). Different effects of Mg deprivation was reported by Tam et al. (2003), including an increased number of macrophages and reduced the proportion of CD8+ cytotoxic T lymphocytes in spleen homogenates, increased levels of pro-inflammatory cytokines and clinical signs of inflammation, splenomegaly and leukocytosis (Tam et al. 2003).

Mg antioxidant effect has been well documented through different mechanisms, including the increase of the rate of production of the free-radical quenching enzyme superoxide dismutase and the regulation of the mitochondrial formation of ROS (Golshani-Hebroni 2016). Observational studies have demonstrated that Mg deficiency is associated with a higher risk of several cardiovascular and metabolic diseases, including IR and diabetes (Veronese et al. 2016). In particular, Mg is significantly involved in the insulin secretion from pancreatic  $\beta$ -cells and in the insulin signal transduction (Chaudhary, Sharma, and Bansal 2010). Given the relationship between Mg deficiency and IR and between IR and NAFLD, a role for Mg deficiency as a potential risk factor for NAFLD has been postulated (Patrick 2002).

#### 4.4. Endocrine-disruptors chemicals and liver-spleen axis

Diet is also common source of a number of chemical compounds acting as Endocrine-Disruptors Chemicals (EDC) (Nappi et al. 2016; Barrea et al., 2016b). In particular, bisphenol A is the most common chemical used in polycarbonate plastics and epoxy resins used in food packaging (Polyzos et al. 2012; Deceuninck et al. 2015). EDC have been considered responsible for the alterations similar to those encountered in NAFLD, either directly through a hepatotoxic effect and/or indirectly by triggering IR (Polyzos et al. 2012). Of interest, an association has been described between serum bisphenol A levels, HS and markers of chronic low-grade inflammation, in particular with spleen size in patients with polycystic ovary syndrome (Tarantino et al. 2013), a condition in which the chronic low-grade inflammation can be part of the underlying mechanisms involved in the pathogenesis of this syndrome (Duleba and Dokras 2012).

### 5. Mediterranean diet and liver-spleen axis

The Mediterranean diet (MD) is the healthy dietary pattern prevailing in the Mediterranean basin before the mid-1960s, which is high in fruits, vegetables, olive oil, whole grains, and fish, and low in red meat and butter, with moderate red wine consumption and olive oil intake (Bach-Faig et al. 2011; Trichopoulou et al. 2014; Barrea et al., 2017a). Recently, the US Dietary Guidelines Advisory Committee identified healthy cuisine-based dietary patterns, such as the MD, to be associated with reduced risk of chronic disease. Specific nutrients commonly found in MD have consistently been associated with anti-inflammatory properties, including complex carbohydrates and fiber (Ma et al. 2006; Kitabchi et al. 2013), Mg (King et al. 2005), and polyphenols (Schwingshackl and Hoffmann 2014; Zhang 2015). In particular, polyphenols, natural compounds generally considered non-nutritive agents, which are

largely present in fruits, vegetables, cereals, virgin olive oil and red wine, are able to reduce the ROS generation by human leukocytes (Mena et al. 2009; Marzulli et al. 2014) and to shift the M1 macrophage response to the anti-inflammatory M2 type response with production of IL-10 (Casas et al. 2014; Aharoni et al. 2015). Very recently Magrone T et al. investigated the anti-inflammatory effect of polyphenols isolated from seeds of red grape on cytokines release on peripheral blood mononuclear cells, showing that an increased release of IL-10 by these cells contributed to a condition of immune homeostasis among the various T cell subsets in obese individuals (Magrone et al. 2017; Martínez-González et al. 2016). The anti-inflammatory and anti-oxidant effects of the MD has been investigated in a recent meta-analysis of randomized clinical trials, showing that CRP and other inflammatory biomarkers were significantly more decreased with MD than with different control diets (Schwingshackl and Hoffmann 2014). As there are many different “MD” among different countries and populations of the Mediterranean basin, a number of different dietary score have been built to evaluate the role of the MD in influencing the risk of developing cardiovascular disease (D’Alessandro and De Pergola 2015; Calder et al. 2002), including the PREDIMED score used in the PREvention with MEDiterranean Diet trial (Martínez-González et al. 2016; Jaudszus et al. 2013). Substudies from the PREvention with MEDiterranean Diet trial have reported a strong anti-inflammatory effect from MD supplemented with extra-virgin olive oil or nuts compared with the control group on a low-fat diet (Mena et al. 2009; Marzulli et al. 2014; Casas et al. 2014; Aharoni et al. 2015; Magrone et al. 2017; Martínez-González et al. 2016). Specific fatty acid diet composition of MD can modulate immune functions through the membrane composition and their interaction with membrane-bound enzymes and receptors of lymphocyte and monocyte (Calder et al. 2002; Jaudszus et al. 2013). A role for the MD in managing NAFLD is supported in attenuating the progression of the disease (Abenavoli et al. 2014; Velasco, Contreras, and Grassi 2014). In particular, observational studies showed that higher MD scores were inversely related to alanine aminotransferase levels, IR, and NAFLD severity (Kontogianni et al. 2014). The MD pattern has been also recommended as the diet of choice for the treatment of NAFLD by the EASL-EASD-EASO Clinical Practice Guidelines (Marchesini et al. 2016). The main clinical trials investigating the beneficial effects of the MD as a whole and each of its components on NAFLD are summarized in a recent review (Zelber-Sagi, Salomone, and Mlynarsky 2017), while the Table 1 details clinical interventional and observational studies carried out in humans over the last five years (Misciagna et al. 2017; Papamiltiadous et al. 2016; Trovato et al. 2016; Abenavoli et al. 2015; Aller et al. 2015; Georgoulis et al. 2015; Chan et al. 2015; Trovato et al. 2015; Ryan et al. 2013; Bozzetto et al. 2012).

Coming back to the “liver-spleen axis”, besides the great body of evidence linking MD and NAFLD or MD and immune system, up to now no studies have specifically addressed the effects of MD on spleen immune function. Very recently, the spleen longitudinal diameter has emerged as a further indicator of systemic inflammation in patients with psoriasis. In this study, a clear link between psoriasis, HS and the spleen was evidenced (Balato et al. 2015).

Therefore, considering the well-established beneficial effects of MD as adjuvant therapy of a number of systemic immune diseases associated with metabolic derangement and NAFLD, including psoriasis (Barrea et al. 2015a), a role of MD also in modulation of spleen immune function is highly conceivable.

## 6. Glucagon-like peptide-1 and liver-spleen axis

Meal macronutrients are well-known physiologic stimulants of Glucagon-Like Peptide-1 (GLP-1), an incretin hormone involved in postprandial glucose homeostasis (Ripken et al. 2016). GLP-1 stimulates glucose-related insulin secretion, and stimulates  $\beta$ -cell proliferation and differentiation, while inhibiting  $\beta$ -cell apoptosis and glucagon secretion (Baggio and Drucker 2007). GLP-1 is produced by the cleavage of the proglucagon gene product and mainly secreted upon nutrient interaction with G-protein coupled receptors by from the enteroendocrine L cells in the distal intestine (Marathe et al. 2013). Consequently, GLP-1 has also been considered a satiety signal, possibly involved in meal termination and causing delay of gastric emptying, as part of the “ileal brake” mechanism (Holst 2007; D’Alessio 2008). Although GLP-1 action was primarily localized to pancreatic  $\beta$ -cells, the expression of the GLP-1 Receptor (GLP-1R) has been found in different cell types and organs, including human hepatocytes and spleen (Bullock, Heller, and Habener 1996). GLP-1R mRNA is widely expressed in several immune subpopulations and the activation of the GLP-1R signalling contributes to the regulation of both thymocyte and peripheral T cell proliferation, including Tregs cells from spleen and other lymphoid organs (Hadjiyanni et al. 2010).

In experimental models CD4+CD25+FOXP3+ Tregs can negatively regulate splenic extramedullary myelopoiesis (Lee, Wang, and Kim 2009), while Tregs ablation increases in the numbers of B cells, macrophages, granulocytes, and natural killer cells in both spleen and lymph nodes (Kim, Rasmussen, and Rudensky 2007). Of interest, GLP-1r transcripts are demonstrated in Tregs isolated from the spleen (Hadjiyanni et al. 2010); although GLP-1R activation do not increase proliferation of splenocytes, it increase cAMP accumulation, a mechanism by which Tregs induce immunosuppression (Hadjiyanni et al. 2010).

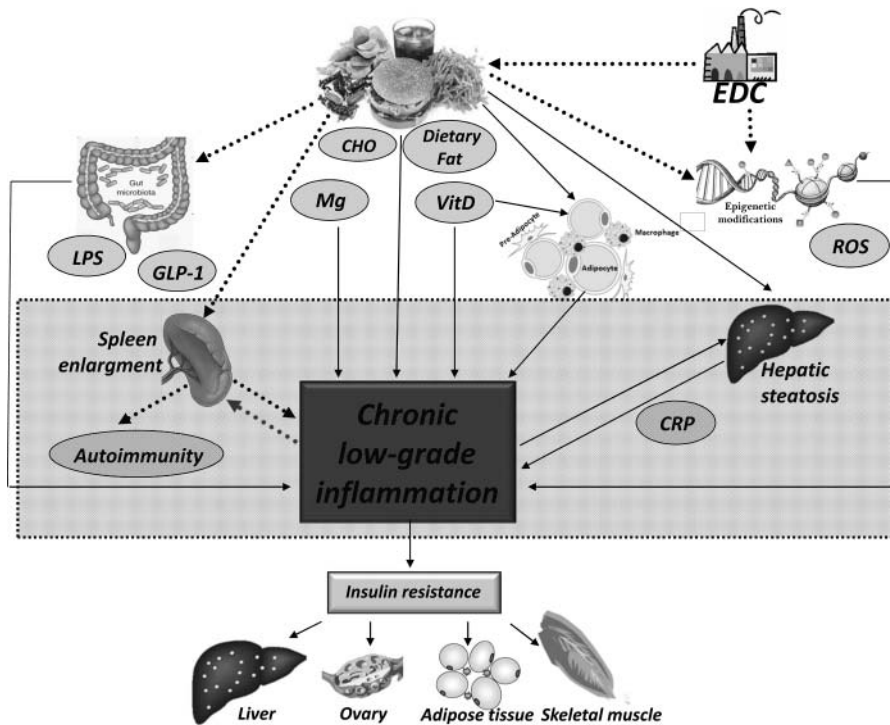
The expression of GLP-1R unravels the presence of additional beneficial effects of GLP-1 beyond its glucose-lowering properties, such as direct anti-inflammatory actions (Lee and Jun 2016). Consequently, the role of GLP-1R agonists implicating GLP-1R-dependent signalling pathways in immune-regulatory processes (Hadjiyanni et al. 2010) and in NAFLD pathogenesis (Lund, Knop, and Vilsbøll 2011) generated much interest. Recent studies have found that GLP-1R agonists have a direct role in the decrease of HS *in vitro* (Gupta et al. 2010). The possible proposed mechanisms by which GLP-1 reduced the intrahepatic lipids are the following: the activation of PPAR- $\alpha$  on the hepatic cell surface, a lipid sensor which modifies the gene expression of proteins regulating fatty acid metabolism in liver cells; delayed gastric emptying; enhanced insulin sensitivity and secretion, which reduces lipid metabolism indirectly (Wang

Table 1. Clinical interventional and observational studies carried out in humans evaluating the association between the MD pattern and NAFLD over the last five years.

Study	Study Design	Study location	Cases-Subjects	Intervention (duration, type)/ Diet evaluated	Adherence to MD score	Outcomes	Confounders controlled	Results
(Misciagna et al., 2017)	Parallel-group randomized controlled clinical trial	Putignano (Southern Italy)	98 moderate/severe NAFLD pts	6 months LGIMD vs control diet INRAN guidelines	MAI	NAFLD score (US)	Generalized Estimating Equation /	Negative correlation between LGIMD and NAFLD score ↓NAFLD ↑insulin sensitivity independent of weight loss
(Papamiliadous et al., 2016)	Multi-centre, parallel, randomized controlled trial	Hospital-based-control study	94 NAFLD pts with IR	12 months, MD vs low-fat diet	PREDIMED	HoMA-IR intrahepatic lipid content (by MR-S), ALT, lipid profile, liver stiffness (Fibroscan®), inflammatory cytokine markers, quality of life anthropometry and body composition, dietary intake and blood pressure	BMI HoMA-IR	BMI and MD score independent predictors of NAFLD severity
(Trovato et al., 2016)	Cross-sectional controlled study	Catania (Southern Italy)	532 NAFLD pts and 667 non-NAFLD subjects	MD vs Western diet	AMDS	NAFLD (US) BMI HoMA-IR Physical activity Sun exposure Sleep hours	BMI HoMA-IR	
(Abenavoli et al., 2015)	Controlled Randomized trial	Catanzaro (Southern Italy)	30 NAFLD pts	6 months MD vs MD+ silybin — phytosome complex and vitamin E vs control	—	NAFLD score (US) FLI HoMA-IR WC	/	MD alone, or additionated ↓NAFLD score ↓HoMA-IR ↓BMI ↓WC
(Aller et al., 2015)	Cross-sectional study	Valladolid (Spain)	82 NAFLD pts	MD	PREDIMED	Lipid profile Liver biopsy age, BMI, WC, blood pressure, fasting basal glucose, transaminases, HoMA-IR, lipid profile, adiponectin and leptin	/	MD was associated with lower likelihood of high grade of HS and NASH
(Georgoulis et al., 2015)	Cross-sectional study	Athens (Greece)	73 NAFLD pts	MD	MedDietScore	NAFLD (elevated liver enzyme levels, and US) Liver biopsies (34/73 pts) MetS	Age, sex, daily energy intake and sedentary activities	MD was associated with lower odds of MetS
(Chan et al., 2015)	Cross-sectional study	Hong Kong (China)	797 pts (NAFLD vs No-NAFLD)	MD	MDS DQH	NAFLD (H-MRS)		MDS and DQH were negatively correlated with intrahepatic lipid content ↓NAFLD ↓HOMA-IR No change in Liver enzymes
(Trovato et al., 2014)	Single arm clinical trial	Catania (Southern Italy)	90 NAFLD overweightnon-diabetic pts	6 months MD	MDS	NAFLD (US) HoMA-IR Physical activity		

(Kontogianni et al., 2014)	Case-control study	Athens (Greece)	73 NAFLD pts vs 58 controls	MD	MedDietScore	NAFLD liver stiffness Fibroscan® liver biopsies HoMA-IR Abdominal fat by BIA Plasma cytokines (TNF- $\alpha$ , IL-6, IL-8, VEGF, TGF- $\beta$ 1) adiponectin Dietary & physical activity assessment	Age, sex, smoking, abdominal fat level and serum adiponectin levels	MD was negatively associated with HOMA-IR and ALT, and positively with adiponectin
(Ryan et al., 2013)	Randomized, cross-over clinical trial	Melbourne, (Australia)	12 NAFLD non-diabetic pts	6-weeks MD vs standard low-fat-high-CHO Diet	MD	NAFLD (liver biopsy and MR-S) Hyperinsulinemic-euglycemic clamp	Alcohol intake	MD $\downarrow$ NAFLD and independent of weight loss. No differences in plasma GGT and ALT
(Bozzetto et al., 2012)	Parallel-group randomized controlled clinical trial	Naples (Southern Italy)	45 T2DM pts	8 weeks isocaloric high-CHO/ fiber diet vs isocaloric high MUFA diet +/- physical activity program	INRAN	NAFLD (MR-S) HOMA-IR	BMI, age, sex, and diabetes therapy	$\downarrow$ liver fat in the MUFA group independent of exercise and body weight

**MD**, Mediterranean Diet; **NAFLD**, Non-Alcoholic Fatty Liver Disease; **LGIMD**, Low Glycemic Index Mediterranean Diet; **INRAN**, National Institute of Research on Food and Nutrition; **MAI**, Mediterranean Adequacy Index; **US**, Ultrasound Score; **IR**, Insulin Resistance; **PREMIDED**, PREvention with MEDITerranean Diet; **HOMA-IR**, Homeostasis Model Assessment-insulin Resistance; **MR-S**, Magnetic Resonance-Spectroscopy; **ALT**, Alanine Aminotransferase; **AMDS**, Adherence to Mediterranean Diet Score; **BMI**, Body Mass Index; **FLI**, Fatty Liver Index; **WC**, Waist Circumference; **HS**, Hepatic Steatosis; **NASH**, Non-Alcoholic Steatohepatitis; **MedDietScore**, Mediterranean Diet Score; **MetS**, Metabolic Syndrome; **MDS**, Mediterranean Diet Score; **DQI-I**, Dietary Quality Index-International; **<sup>1</sup>H-MRS**, Proton Magnetic Resonance Spectroscopy; **BIA**, Bioelectrical Impedance Analysis; **TNF- $\alpha$** , Tumour Necrosis Factor- $\alpha$ ; **IL**, Interleukins; **VEGF**, Vascular Endothelial Growth Factor; **TGF- $\beta$** , Transforming Growth Factor Beta; **CHO**, Carbohydrate; **GGT**, Gamma-Glutamyl Transferase; **T2DM**, Type-2 Diabetes Mellitus; **MUFA**, Monounsaturated Fatty Acids.



**Figure 1.** Main mechanisms likely operating in diet-induced chronic low-grade inflammation and reported in the text. There is a clear line of evidence connecting unhealthy diet, adipose tissue dysfunction (Paniagua, 2016) and hepatic steatosis (Liu et al., 2016), known conditions associated with the development of chronic low-grade systemic inflammation arising from aberrant activation of the innate inflammatory response (Diamanti-Kandarakis et al., 2017). Pro-inflammatory cytokines signal the liver to produce a variety of proteins known as acute phase reactants, including CRP. Chronic low-grade systemic inflammation paves the way to insulin resistance and atherosclerosis-related diseases (Wong et al., 2012), in close linking with environmental EDC exposure (Nappi et al., 2016; Barrea et al., 2016a) and changes in epigenetic pathways linked to oxidative stress in the offspring (Diamanti-Kandarakis et al., 2017). Additionally, many high-carbohydrate and high fat foods common to Western diets promote postprandial spikes in glucose and lipids (Mohanty et al., 2000), resulting per se in the development of chronic low-grade systemic inflammation. Deficiencies in Mg, the second-most abundant cation in cellular systems, and vitamin D, a key modulator of immune and inflammation mechanisms, are associated to unhealthy diet, obesity and NAFLD and can participate to promote chronic low-grade systemic inflammation (Nielsen, 2010; Savastano et al., 2017; Gonçalves de Carvalho and Ribeiro, 2016). Diet-induced changes in microbiota phyla are associated with impairment of the intestinal membrane integrity, followed by increasing plasma LPS, which triggers systemic inflammation via the stimulation of TLR-4 on immune cells (de Jong, González-Navajas, and Jansen, 2016). GLP-1 secreted from intestinal L-cells in response to meal-ingestion contributes to the immune-inflammatory response with direct anti-inflammatory actions (Lee and Jun, 2016) and protection of hepatocytes from fatty acid-induced lipotoxicity (Wang et al., 2014). Despite its key role in immune function and signalling, up to now limited evidence is available on the relationships between diet, inflammation and spleen function. In this complex scenario, spleen enlargement in obesity and hepatic steatosis might represent an index of chronic inflammation and activation of the immune system, in the so-called “liver-spleen axis” (Tsushima and Endo, 2000; Tarantino et al., 2013). Black arrows indicate evidence-based mechanisms, while red arrows indicate hypothetical mechanisms. Modified figure from Nappi et al. (2016). *CRP*, C-Reactive Protein; *EDC*, Endocrine-Disruptors Chemicals; *Mg*, Magnesium; *NAFLD*, Non-Alcoholic Fatty Liver Disease; *LPS*, Bacterial Lipopolysaccharide; *TLR-4*, Toll-Like Receptor-4; *GLP-1*, Glucagon-like Peptide-1.

et al. 2014). In addition, GLP-1R agonists have been proven to protect hepatocytes from fatty acid-induced lipotoxicity, either by reducing the oxidative stress and by promoting both macro-autophagy and chaperone-mediated autophagy (Wang et al. 2014). In that, GLP-1R agonists might have a role in stopping the progression of HS to more aggressive lesions in patients with NAFLD. A meta-analysis included 12 trials that studied the effects of with liraglutide in patients with T2DM showed that alanine aminotransferase were reduced after at least 20 week of treatment thereby improving liver function in patients with NAFLD and T2DM (Ohki et al. 2012). Long-term exenatide treatment in patients with T2DM resulted in improvements in lipid profile with significant reduction in triglycerides (12%), total cholesterol (5%), low density lipoprotein-cholesterol (6%), and increase in high density lipoprotein-cholesterol (24%) (Klonoff et al. 2008). In addition, in line with the data previously reported, treatment with GLP-1R agonists increased the number of splenic Tregs (Xue et al. 2008). Of interest, very recently it has been demonstrated that mice fed with a HF diet, in spite of the early increase in basal GLP-1

secretion, exhibited an impaired production of many genes required for the normal function of enteroendocrine cells in response to their secretagogues, including the reduced amplification of GLP-1 secretion by nutrients (Richards et al. 2016). Thus, on the one side GPL-1 is likely to exert a critical for the molecular basis of the emergence of IR at the hepatocyte level up regulating key elements of the hepatocyte insulin signaling pathway on the other side it could finely tune Tregs-induced immunosuppression at the spleen level. In that, besides the vicious cycle of over-eating resulting from the reduced ability of GLP-1 to signal post-prandial satiety, it is tempting to speculated that reduced post-prandial elevation of GLP-1 associated with a diet rich in fat and sugar and low in fiber, such as those commonly consumed by humans in the Western world, might contribute to deeply affect the liver-spleen axis by promoting NAFLD progression and by enhancing spleen myelopoiesis through the reduction of Tregs activity. However, further investigations are warranted to establish the extent of the physiological involvement of GLP-1 and pharmacological stimulation in the wider landscape of the bidirectional

relationships between nutrition, inflammation and liver-spleen axis.

## 7. Conclusions

Animal experimental data, human epidemiological studies and large clinical trials have identified a number of potential diet derived anti- and pro-inflammatory components, some of which have been discussed in this review. A possible pathway involving the “liver-spleen axis” in diet-induced immuno-inflammatory process is depicted in Figure 1. However, it is evident that the inflammatory response is highly variable, and a full understanding of the source of heterogeneity is distinctly lacking. There is a need to adopt a more holistic approach and to consider the impact of combinations of foods components and dietary patterns, such as the MD, on diet-induced inflammation. NAFLD acts as both target and critical regulator of the inflammatory-related immune responses, and the “liver-spleen axis” might represent a common pathway for different diet-induced inflammatory mechanisms. The recognition of a robust diet–inflammation–health association makes the adoption of healthy nutritional approaches a key future preventive and therapeutic target thereby affecting disease risk and severity. Considering the substantial role of chronic low-grade inflammation in the pathogenesis of numerous chronic diseases, the need of implementing innovative technologies in nutritional epidemiology and appropriate anti-inflammatory dietary interventions depict a role of expert nutritionists in the prevention of diet-induced inflammation.









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## Author contributions

The authors' responsibilities were as follows: LB and SS: were responsible for the concept of this paper and drafted the manuscript; GM, GCT, FO, CDS and AC: provided a critical review of the paper. All authors contributed to and agreed on the final version of the manuscript.

## ORCID

Luigi Barrea  <http://orcid.org/0000-0001-9054-456X>  
 Carolina Di Somma  <http://orcid.org/0000-0002-5724-1951>  
 Giovanna Muscogiuri  <http://orcid.org/0000-0002-8809-4931>  
 Giovanni Tarantino  <http://orcid.org/0000-0002-4014-5824>  
 Gian Carlo Tenore  <http://orcid.org/0000-0002-0251-9936>  
 Francesco Orio  <http://orcid.org/0000-0002-9127-5987>  
 Annamaria Colao  <http://orcid.org/0000-0001-6986-266X>  
 Silvia Savastano  <http://orcid.org/0000-0002-3211-4307>

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