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REVIEW

What does irritable bowel syndrome share with non-alcoholic fatty liver disease?

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Abstract

Non-alcoholic fatty liver disease (NAFLD) and irritable bowel syndrome (IBS) are two very common diseases in the general population. To date, there are no studies that highlight a direct link between NAFLD and IBS, but some recent reports have found an interesting correlation between obesity and IBS. A systematic PubMed database search was conducted highlighting that common mechanisms are involved in many of the local and systemic manifestations of NAFLD, leading to an increased cardiovascular risk, and IBS, leading to microbial dysbiosis, impaired intestinal barrier and altered intestinal motility. It is not known when considering local and systemic inflammation/immune system activation, which one has greater importance in NAFLD and IBS pathogenesis. Also, the nervous system is implicated. In fact, inflammation participates in the development of mood disorders, such as anxiety and depression, characteristics of obesity and consequently of NAFLD and, on the other hand, in intestinal hypersensitivity and dysmotility.

Key words: Non-alcoholic fatty liver disease; Irritable bowel syndrome; Low grade chronic inflammation; Cytokines

Core tip: The link between non-alcoholic fatty liver disease (NAFLD) and irritable bowel syndrome (IBS) should be carefully evaluated in future research, representing an intriguing field of investigation. A better understanding of the role of systemic inflammation and activation of the immune system may be necessary to clarify obscure points of NAFLD and IBS pathogenesis, and therefore it can be helpful in the development of new therapies.

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INTRODUCTION

Fat accumulation in the liver in the absence of specific causes of hepatic steatosis, such as alcohol consumption, with or without liver inflammation and its consequences, is described as non-alcoholic fatty liver disease (NAFLD)[1]. To date, there are no studies that highlight the link between NAFLD and irritable bowel syndrome (IBS), but some recent reports have found an interesting correlation between obesity and IBS. A relationship between body mass index (BMI) and IBS-like symptoms seems to exist[2,3]. Moreover, in IBS subjects a high BMI is associated with significantly faster colonic and recto-sigmoid transit and high stool frequency[4]. Cremonini *et al*[5] have compared obese binge eaters and non binge eaters to healthy controls and have evidenced that obese subjects more frequently have constipation, diarrhea, straining and flatus regardless of the eating disorder, and that obese binge eaters are characterized by more recurrent upper

and lower gastrointestinal symptoms. Clements *et al*[6] have highlighted that obese patients experience more severe gastrointestinal symptoms than healthy controls, and that after laparoscopic Roux-en-Y gastric bypass they have increased abdominal pain, gastroesophageal reflux disease, sleep disturbance and IBS symptoms. The development of small intestinal bacterial overgrowth (SIBO) may explicate, perhaps partially, the incidence of IBS symptoms in obese subjects with previous abdominal surgery, and in this case the bacterial overgrowth may be the consequence of changes in the function and in the morphological structure of the gut[7].

NAFLD pathogenesis is strictly allied to metabolic syndrome, insulin resistance and obesity[8,9] but inflammation plays an equally important role. Day *et al*[10] have developed in 1998 the classical "two-hit" theory: liver fat accumulation is the "first-hit", linked to obesity, insulin resistance and metabolic syndrome, while the "second-hit" is activated by hepatic inflammation, together with oxidative stress and endotoxemia, which have a key role in the progression to non-alcoholic steatohepatitis (NASH) and, over time, to fibrosis, until the development of cirrhosis[11].

Actually, this classic view has been revised, because a frank distinction between "first-hit" and "second-hit" is not easy to make, leading to the "multiple-hit theory"[12]. Recent studies have shown that, independently from fat accumulation in the liver, obesity systemically leads to activation of the immune system and low-chronic inflammation from the first stage of the disease[13].

Obesity and hepatic fat accumulation are hypothetically implicated in IBS genesis or development. Moreover, an initial correlation between IBS and NAFLD can be suggested by some interesting data. In the pathogenesis of NAFLD and NASH, there is a strong involvement of the gastrointestinal system, as evidenced by many studies on the so-called "gut-liver axis", aiming to comprehend the role of gut microbiota, SIBO and intestinal permeability dysfunction[14]. On the other hand, hepatic fat accumulation and hepatic inflammation in NAFLD subjects[15] and gastrointestinal symptoms in IBS subjects[16] both improve after therapy with probiotics.

IBS, one of the most common gastrointestinal disorders with an estimated prevalence of 7%-10% worldwide[17], is characterized by abdominal pain/discomfort, changes in bowel habits and no association with organic cause. Despite the fact that in IBS subjects macroscopically evident pathological lesions at colonoscopy have not been found, molecular biology and in-depth histological investigations have revealed the activation of the immune system. A key piece of evidence is that the exposure of rodent[18-20] or human[21] tissues or cell cultures[22] to mucosal or luminal mediators from IBS subjects leads to impaired nervous stimulation or intestinal barrier damage. A proportion of patients develop IBS symptoms after infectious gastroenteritis, or in a remission state from microscopic colitis, Crohn's disease and ulcerative colitis, or on a gluten-free diet for celiac disease[23].

Inflammation and immune system activation may be the mechanisms linking two apparently very different diseases, and the purpose of our review is to collect key evidence supporting their relationship and therefore to explain the pathophysiological link between the intestine and the liver, which is exquisitely firstly anatomical and consequently also functional.

IMMUNITY IN NAFLD

A low-grade chronic inflammation underlies all NAFLD entities/stages and can develop and promote the liver damage[13].

Innate and adaptive immune pathways are activated in obesity and many findings show that adipose tissue inflammation exacerbates hepatic steatosis and promotes non-alcoholic steatohepatitis (NASH). Obese individuals more frequently develop infectious diseases[24-26] as complications after surgery[27,28], and an increased BMI is associated with enhanced risk of infections in institutionalized geriatric patients[29].

The adipose tissue has an important role in regulating energy utilization, vascular functions and immune system homeostasis[30]. C-reactive protein (CRP)[8], interleukin (IL)-6[31], fibrinogen and plasminogen activator inhibitor-1[32] levels are higher in obese patients compared to healthy subjects. Stanton *et al*[33] have recently found that obese mice, after high fat and high cholesterol diets, express abnormal levels of macrophages and inflammation-associated genes in adipose tissue and in liver.

Obesity can influence liver metabolism directly, *via* circulating free fatty acids (FFA), and indirectly, *via* pro-inflammatory cytokine production. FFA and other lipids in hepatocytes are involved in production of reactive oxygen species, mitochondrial dysfunction and endoplasmatic reticulum stress. They have proapoptotic capacity and can stimulate proinflammatory signaling pathways[30]. FFA from adipose tissue, food and intestinal bacteria can bind toll like receptors (TLR) expressed on immune cells systemically and also in the liver, and enhance the hepatic expression of TLR-4 and TLR-2[34], these being receptors fundamental to the activity of immune system.

The presence of a dysregulation of the immune system in NAFLD has been firstly evidenced by the modification in immune cell populations in the liver. Natural killer (NK) cell circulating levels are reduced in obese rats[35]; meanwhile in the liver of NASH subjects their concentration is increased[36]. These cells have anti-fibrotic effects and produce apoptosis directly[37] and *via* interferon gamma (IFNγ) production[38] from hepatic stellate cells (HSC), which have a major role in liver fibrosis[39]. In the light of the strict resemblance between NASH and alcoholic hepatitis, Jeong *et al*[40] have detected that alcohol contributes to the anti-fibrotic effect of IFNγ and NK cells in animals.

Another immune cell population, natural killer T (NKT) cells, which express NK cell markers and α/β T cell receptors, are reduced in steatotic, obese mice[41,42]

and in humans[43]. NKT cells are able to produce both T helper (Th) 1 and Th2 cytokines but their depletion in NAFLD has been associated with Th1 polarization of hepatic T cells in mice[44,45].

Two T helper cell subsets were recently discovered and are strictly related to the innate immune response. Th17 cells on one side and Treg cells on the other balance tolerance and elicitation of immune responses[46]. Th17 cells produce IL-17, IL-21 and IL-22, and require transforming growth factor-β (TGF-β) and IL-6 for their differentiation[47], the same cytokines that inhibit Treg cells. A Chinese study group has recently discovered that oxidative stress induces Treg cell apoptosis in mice with fatty livers[48] and subsequently has found also that Th17 cells are increased in the liver of animal and human NASH models[49].

Kupffer cells (KC) are liver macrophages involved in the response to such stressors as infections, ischemia and toxins[50] and they are also implicated in liver inflammation and NASH progression[51].

Tumor necrosis factor (TNF) -α, a cytokine produced by KCs, hepatocytes, and abdominal fat, is associated with the development in rodents[52,53] and in humans[54-57] of insulin resistance, NAFLD and NASH. The role of TNF-α in NAFLD may be due to its capacity to induce hepatocyte apoptosis, insulin resistance and to regulate KC activation locally[58,59]. Moreover, TNF-α regulates hepatic lipid metabolism[60].

In a NASH animal model involving choline-deficient diet fed rats it was found that there was an increase in serum and portal alanine aminotransferase levels and hepatic TNF-α, IFNγ and TLR4. Higher TNF-α levels were detected in KCs and, most importantly, increased TNF-α, TLR4 expression, and macrophage/dendritic cell populations were found in ileal tissue specimens, demonstrating also the involvement of the gut in steatotic liver damage[61].

To date, it is debatable whether circulating levels of TNF-α may discriminate the presence of NAFLD in obese subjects or in subjects with metabolic syndrome[62,63], but they seem to be useful in the non-invasive diagnosis of hepatic fibrosis in NASH[64].

IL-6 is a polyvalent cytokine with proinflammatory and prooncogenic activity, and it supports hematopoiesis[65] and is a predictive marker of insulin resistance and cardiovascular diseases[66]. In animal[67] and human[68,69] models respectively, hepatic and serum IL-6 levels are higher in NAFLD. Initially this cytokine was considered hepatoprotective because it reduces oxidative stress and prevents mitochondrial dysfunction in animal models[70,71]. Moreover, there are contrasting data on IL-6 production in the liver of NAFLD subjects[57,72]. IL-6, with TNF-α, suppresses adiponectin levels; meanwhile, TNF-α stimulates the production of leptin[73,74]. Adiponectin is an adipocytokine with anti-inflammatory properties and it decreases in subjects with increased liver fat concentration[75]. Leptin has opposite effects; it activates neutrophils and innate immune system[76], is associated with obesity and may contribute to NAFLD progression[77]. IL-6 production is also enhanced by TNF-α and IL-1 and can act with paracrine and endocrine mechanisms to activate IL-6 signaling systemically and peripherally in other organs such as liver and muscle[13]. FFA and IL-17 synergistically induce IL-6 production; on the other hand IL-6, with TGF-β1, enhances Th17 response in *in vitro* HepG2 cell models[49]. Tarantino *et al*[78] have also observed that, surprisingly, NAFLD subjects have increased TGF-β1 blood levels compared with those with chronic hepatitis C.

An anti-inflammatory cytokine, IL-10, is protective for hepatic steatosis, as seen in IL-10 deficient mice[79] as well as in NAFLD humans[80], and the inhibition of IL-10 promotes hepatic steatosis, enhances the expression of proinflammatory cytokines and impairs insulin signal transduction[81]. Main data on the pathophysiological role of inflammatory cytokines in NAFLD are summarized in Table 1.

Brun *et al*[82] have observed that HSCs isolated from genetically obese and diabetic mice show more pronounced fibrogenic responses induced by lipopolysaccharide (LPS) than HSCs from lean animals. Thus, HSCs are more sensitive to bacterial endotoxins, because genetically obese mice have an impaired intestinal permeability leading to increased portal endotoxemia. To expand on the evidence that systemic inflammation is also related to intestinal inflammation, a recent study undertaken by Kant *et al*[83] has found that weight loss in obese subjects reduces fecal calprotectin levels. Precedent studies have pointed out that circulating calprotectin levels are related to increased BMI[84,85]. As detailed later, the intestine, and especially intestinal inflammation, is closely related to NAFLD pathogenesis.

IMMUNITY IN IBS

In IBS subjects a low chronic inflammation is present and many other immune phenomena are also points of contact with hepatic steatosis.

The intestinal mucosa physiologically contains immune cells much more than other organs and tissues, and this is mainly due to its anatomical configuration and function as the first barrier of the organism[86]. In the "irritated" gut there is an increased population of immune cells in the small and large intestine, as reported in many studies[87,88]. Moreover, the inflammatory infiltrate is lower than in ulcerative colitis (UC) but is similar to that revealed in microscopic colitis[89]. These findings, with others discussed later, lead to the theory that IBS could be considered as an inflammatory disease.

The adaptive immune system is involved in the low grade inflammation of the gut, specifically, $CD3^+$, $CD4^+$ and $CD8^+$ T cell count is increased[89-91] in the gut and in the peripheral blood of IBS subjects.

The innate immune response is also implicated in IBS pathogenesis. An increased number of mast cells are found in the small[92] and large[93] intestine. These cells are in close contact with enteric nerve endings[94] and this is an important factor in the neuronal stimulation that underlies the establishment of typical IBS symptoms[95]. Braak *et al*[96] are discordant on this point because they

Table 1 Principal findings on inflammatory cytokines in non-alcoholic fatty liver disease in humans, and in *in vitro* and animal models

Principal findings
TNF-α
In vitro: FFA induce *TNF-α* gene expression[60]. KC and hepatocytes from NAFLD produce ↑ TNF-α and ↑ lipid peroxidation and accumulation[59,61]. TNF-α induces hepatocyte apoptosis[59]
Animal: TNF-α regulates KC apoptosis[58]. Hepatic, portal blood and intestinal TNF-α is ↑[52,53,61]
Human: Circulating levels are ↑ in NAFLD and NASH[57,68]. Contrasting data on simple FL[55,62]. They correlate with activity and progression of NAFLD[64] But do not differentiate mild to severe NASH[60]. NASH subjects have also ↑PBMCs TNF-α, IL-6 and IL-8 production[68]. TNF-α mRNA expression is ↑ in liver and fat of NASH compared with NAFLD[57], but there are contrasting data[55,238] TNF-α polymorphism is most frequent in NAFLD and correlates also with IR[56]
IL-6
In vitro: FFA induces IL-6 expression in hepatic cell cultures[72] and enhances Th17 response[49]
Animal: IL-6, TNF-α, IL-8 production is ↑ in liver and muscle of NAFLD mice[64]. Possible hepatoprotective role[70,71]
Human: ↑ IL-6 blood levels and other inflammatory and cytonecrosis indexes in NAFLD and NASH subjects compared to controls and obese[57,68,69]. IL-6 is an index of NASH activity and progression[72]. Normal levels of IL-6 and normal spleen longitudinal diameter may be useful in excluding NASH from NAFLD[34]. IL-6 tissue expression is controversial in liver of NAFLD[57,72]
IL-8
In vitro: IL-8 with TNF-α are ↑ in NAFLD and in NASH compared to FL[64]. FFA induces IL-8 expression[60]
Human: Blood levels of IL-8, IL-6 and TNF-α are ↑ in NASH[68,69]
IL-1β
Animal: NAFLD rats express similar IL-1β, TNF-α and IL-6 levels in liver and in muscle[64]
Human: TNF-α, IL-6 and IL-1β blood levels are ↑ in NAFLD and NASH[68,69]
TGF-β1
In vitro: IL-17 and FFA induce IL-6 in hepatocytes and IL-6, with TGF-β1, enhance Th17 response[49]
Human: TGF-β1 blood levels in NAFLD are ↑ than CHC[78]
IL-10
Animal: After IL-10 inhibition, TNF-α, IL-6 and IL-1β levels increase in liver of HFD mice[81]. IL-10 knock-out mice have ↑ FFA plasma levels and hepatic TG[79]
Human: In NAFLD and obese children, lower IL-10 blood levels correlate with markers of visceral and subcutaneous fat, insulin, HOMA-IR, ALT, AST and GGT[77]
IL-17
In vitro: IL-17 and FFA induce IL-6 production[49]
Animal: LPS-induced liver injury ameliorated after IL-17 blockade in HFD rats[49]
Th2 cytokines (IL-4, IL-5, IL-13)
Animal: Rats genetically oriented to a Th1 response develop steatosis and lobular inflammation more than others oriented toTh2 response[44,45]

TNF-α: Tumor necrosis factor-α; FFA: Free fatty acids; KC: Kupffer cells; NAFLD: Non-alcoholic fatty liver disease; NASH: Non alcoholic steatohepatitis; FL: Fatty liver; PBMCs: Peripheral blood mononuclear cells; IL: Interleukin; IR: Insulin resistance; TGF-1β: Tumor growth factor 1 β; Th17: T helper 17; CHC: Chronic hepatitis C; HFD: High fat diet; TG: Triglycerides; HOMA-IR: Homeostasis model of assessment-insulin resistance; ALT: Alanine-aminotransferase; AST: Aspartate-aminotransferase; GGT: γ-Glutamyltransferase; LPS: Lipopolysaccharide; Th2: T helper 2; Th1: T helper 1.

have observed a decreased number of mast cells, macrophages and T cells in IBS subjects. Moreover, they do not find visceral hypersensitivity or abnormal stress response.

Few reports have examined other immune cells involved in the innate immune system in IBS. NK cells[97] and neutrophils[98] may be hyper-activated but, to determine their role in intestinal inflammation, more studies are needed.

Contrasting data are reported on the monocyte/macrophage population. These cells were reduced[99] or normal[90] in number in the gut of IBS patients compared to controls but they may be hyper-activated, as seen by increased calprotectin expression[90]. Calprotectin is a calcium-binding protein produced by phagocytes with pro-inflammatory activity, such as leukocyte recruitment[100]. Fecal calprotectin may be useful in the differential diagnosis between inflammatory bowel diseases (IBD) and IBS[101]. Moreover, other authors have observed that patients with IBD and IBS-like symptoms have significantly higher fecal calprotectin levels than those with IBD but without IBS symptoms[102]. Shulman *et al*[103] have shown that fecal calprotectin concentration is greater in children with IBS and functional abdominal pain compared to controls, and also in the same population there is an impaired permeability in the proximal and distal gut.

There are contrasting data on the role of Treg cells, a T cell subpopulation with regulatory functions in IBS: these cells seem to be normally or under-expressed in intestinal tissues and blood of IBS subjects[104,105], even though previously Chadwick *et al*[88] have observed increased $CD25^+$ T cell population in the lamina propria of IBS subjects. The role of Th17 cells in the pathophysiology of IBS is still unexplored but, recently, Andoh *et al*[106] have summarized the main evidence on the role of this subpopulation in intestinal inflammation. It would be interesting to see if IBS might be involved in the dysregulation between Th17 and Treg cells as shown in NAFLD.

Studies on proinflammatory cytokine production in IBS have evidenced the activation of both the innate and adaptive immune systems. Indeed, different study methods were used to explore the systemic cytokine production and results were not always concordant[107].

IL-6 and TNFα are the most studied inflammatory cytokines in IBS. In many reports blood levels of TNFα and IL-6 are increased[108-112]. Similar results are reported in cultured peripheral blood mononuclear

Table 2 Principal findings on inflammatory cytokines in irritable bowel syndrome in humans, and in *in vitro* and animal models

Principal findings
TNF-α
Animal: D-IBS supernatants have ↑ levels of proinflammatory cytokines and they cause hypersensitivity in mouse colonic afferent endings[122]
Human: IBS has ↑ circulating TNF-α levels[109,112], especially D-IBS[112] or in patients with comorbidities such as fibromyalgia, premenstrual dysmorphic disorder and chronic fatigue syndrome[109]. Baseline and LPS-stimulated levels in PBMCs of proinflammatory cytokines as TNF-α, in IBD and D-IBS, are ↑ and are related to symptom intensity[108]. TLR-2, TLR-4 and TLR-5 antagonists induce TNF-α production[128]. No difference in TNF-α and other proinflammatory cytokine production (IL-6 and IL-1β) in the gut of IBS subjects compared to controls[116]
IL-6
In vitro: No differences in colonic production between IBS and controls 116. IL-6 have excitatory action on colonic cells from IBS rats producing neuronal activation and absorption/secretory responses[115]
Animal: IL-6 colonic secretion is ↑ in IBS rats and activate submucosal neurons[127]
Human: IL-6 blood levels are ↑ in all IBS subtypes[109-111]. IL-6 levels are related to ACTH response and ΔACTH/ΔCortisol ratio[110]. Baseline and LPS or TLR agonist-stimulated PBMC levels are ↑ in IBS[108]
IL-8
In vitro: Reduced expression of mRNA of IL-8 in *ex vivo* biopsy cultures[116]
Human: Circulating levels of IL-8 are ↑ in IBS[109-111,119]. TLR-3 and TLR-7 agonists induce IL-8 production in PBMCs[128]
IL-1β
Animal: In stressed rats with previous acute colitis IL-1β mRNA expression is ↓[117]
Human: ↑ IL-1β levels in IBS[108,128], in C-IBS and in D-IBS[108]. With TNF-α, IL-1β ↑ levels are found in IBS subjects with fibromyalgia, premenstrual dysmorphic disorder and chronic fatigue syndrome[109]. IL-1β ↑ production in PBMCs stimulated by antiCD3/CD28 antibody[91] and by TLR-4 and TLR-5 agonists[128]. Increased IL-1β expression in rectum of PI-IBS[121]
TGF-1β
Animal: No different expression of TGF-β1 protein in colon of IBS rats[11]
Human: TGF-1β intermediate producers may be at risk of developing IBS[114]
IL-10
Human: IBS subjects have ↓ circulating levels of IL-10[112]. Altered IL-10/IL-12 ratio in PBMCs with Th1 proinflammatory state[113]. IL-10 levels are ↓ and IFNγ levels are ↑ in colon of PI-IBS compared to non PI-IBS and controls[119]. IL-10 high producer genotype is protective against IBS[114]
Th2 cytokines (IL-4, IL-5, IL-13)
Animal: Th2 cytokines may have a role in intestinal hypercontractility[123]
Human: Stimulated PBMCs IL-5 and IL-13 levels are ↑ in IBS[124]

TNF-α: Tumor necrosis factor α; D-IBS: Diarrhoea-predominant irritable bowel disease (IBS); IBD: Inflammatory bowel disease; LPS: Lipopolysaccharide; PBMCs: Peripheral blood mononuclear cells; TLR: Toll like receptor; IL: Interleukin; ACTH: Adrenocorticotropic hormone; C-IBS: Constipation-predominant IBS; PI-IBS: Post-infectious IBS; TGF-1β: Tumor growth factor 1 β; IFNγ: Interferon γ; Th2: T-cell mediated helper response.

cells[108,111]. Studies on Peripheral blood mononuclear cells (PBMCs) have also noticed decreased levels of the anti-inflammatory IL-10[112,113], in agreement with the systemic inflammatory state in IBS. Moreover, the IL-10 high producer genotype seems to be protective against IBS, whereas IL-10 low producer, and maybe even TGF-1β intermediate producer genotypes, are a risk factor for IBS development[114]. In IBS mice, IL-6 may enhance colonic cells neuronal activation and their absorption/secretory responses[115]. The intestinal cytokine production is poorly understood[116-119], and, as described in a recent review by Ortiz-Lucas *et al*[120], only IL-1β expression is clearly increased in post-infectious IBS (PI-IBS)[121]. On the contrary, Hughes *et al*[122] have observed increased cytokine expression in supernatants of mice with IBS and that visceral neurons express receptors for IL-6, TNF-β, IL-1β and IL-10, confirming the role of these pro-inflammatory cytokines in gut homeostasis.

Th 2 cytokines were also considered in recent reports: in animals Th 2 cytokines enhance intestinal motility[123] and in IBS subjects stimulated PBMCs produce more IL-5 and IL-13 than controls[124].

Cytokines have several roles in the development of IBS symptoms. For example, TNF-α can act on the peripheral nervous system as well as on the central nervous system (CNS) to develop a symptom burden of hypersensitivity, nausea, emesis, gastric hypomotility, anorexia and fever[125,126]. IL-6 is able to stimulate submucosal neurons in IBS animal models[127], most probably *via* a TLR-mediated mechanism[128]. TNF-α and IL-6 are also implicated in intestinal barrier integrity[129] (Table 2).

NAFLD AND IBS MAY BE RELATED

The above-mentioned evidence suggests that innate immunity is a main pathogenetic component of both NAFLD and IBS. But, how does the immune system work in patients with both NAFLD and IBS? In other words, is the similar action of pro-inflammatory cytokines, such as IL-6 and TNF-α, the only one that can be found on the immune system side?

The metabolic syndrome, which often anticipates or is detected in conjunction with NAFLD, leads to a state of chronic inflammation, systemic or local (hepatic)[12], but to date it is still unclear which one of the two types has a greater impact on these patients, even if a lot of evidence favors the former[13]. A very similar scenario, but with partly different participants, is possible in IBS. Although the disease has not been overtly related to an inflammatory systemic disease, as happens for the metabolic syndrome, nevertheless, IBS is characterized by hyper-activation of the immune system and general inflammation. Indeed, many

researchers have struggled to find a similar component at local level, studying the intestinal cytokine production, but they have not always had a favorable outcome[107,120]. In some subsets of IBS patients, such as diarrhoea-predominant IBS (D-IBS) and IBS developing following infective gastroenteritis (PI-IBS), there is often a frank intestinal inflammation[108,119]. On the contrary, in C-IBS a systemic inflammation is not always associated with a local counterpart or is less apparent than in D-IBS[122].

NAFLD and IBS are classically defined as different diseases. NAFLD is related to the metabolic syndrome, obesity, diabetes and insulin resistance and IBS is a functional intestinal disease closest to psychological disorders such as depression and anxiety, certainly not to liver diseases. But, surprisingly, there are many points of contact, such as the dysfunction of the intestinal microbiota, the impaired intestinal barrier, intestinal dysmotility and brain-gut axis dysfunction, which are fundamental to their pathogenesis, being related to the immune activation and inflammation.

Thus, principal questions are: Can metabolic liver disease affect the functions of the gastrointestinal tract leading to syndromic manifestations typical of IBS? and may the bowel dysfunction lead or otherwise support the development of a chronic hepatic inflammatory state?

GUT MICROBIOTA

The gut microbiota is a composite member of our body. Intestinal bacteria interact with the intestinal epithelial barrier and subsequently with extraintestinal organs performing physiological and pathological actions.

This close contact makes the microbiota important for the metabolism of nutrients and energy delivery[130], the intestinal barrier function[131], the natural tropism of the intestinal wall[132] and ensures the maturation of intestinal immune tolerance and the immune response[133].

The dysregulation of the intestinal bacterial milieu is a component of NAFLD and IBS. Recent reports have also shown both in NAFLD and in IBS an important role for TLR. These are receptors that characterize the innate immunity and link specific molecules such as pathogen-associated molecular patterns, LPS, and danger-associated molecular patterns[134]. These receptors are able to elicit the innate immune response once activated (they induce the expression of proinflammatory chemokines, cytokines and adhesion molecules on immune cells)[135]. In NAFLD and in IBS this role is consistently related to the alteration of gut microbiota, impaired intestinal permeability and impaired intestinal motility[136,137].

Changes in microbiota composition and simultaneous or subsequent dysregulation of intestinal permeability let PAMPs and TLRs be in strict contact in the deeper layers of the intestinal wall and thus lead to stimulation of the innate immune response[138].

Despite the fact that the roles of TLRs in the liver of NAFLD and NASH are well established[137], only recently have the activity of TLRs in IBS been studied. Ohman *et al*[139] have observed increased expression of TLR2 on circulating monocytes in IBS. A study from McKernan *et al*[128] demonstrated that the TLR-induced cytokine release (IL-1β, IL-6, IL-8 and TNF-α) was enhanced in blood from IBS subjects. The TLR mRNA production in the gut mucosa of mice with colonic visceral hypersensitivity was studied and significant increases were seen[140]. Similar results were found in humans[141].

TLRs are fundamental in T-cell differentiation and activation, particularly for Th17 and Treg cells[142]. In the gut, bacterial products[143], acute phase proteins[144] and proinflammatory cytokines such as IL-6 and TGF-β[145] promote Th17 response, meanwhile IL-25 and IL-23[146] produced by epithelial cells inhibit it.

Obesity and NAFLD

In the literature there are few reports on the intestinal microbiota composition in NAFLD. The role of intestinal dysbiosis in these patients may be assumed by reports on microbiota present in obese subjects or by indirect data on the action of bacterial products from the gut delivered to the liver in NAFLD.

Obese patients are characterized by low intestinal bacterial diversity. They have a reduced *Bacteroides* and increased *Firmicutes* population compared to controls, and this proportion improves with weight loss[147]. Studying the microbiome, the same group has found that obese patients exhibit impaired bacterial gene expression[148].

Animal models have shown that the intestinal microbiota may have an important role in energy harvesting and fat storage. Germ-free mice seem to be protected from diet-induced weight gain[149] most probably because intestinal bacteria are involved in the fermentation of polysaccharides to monosaccharide and in the metabolism of short chain fatty acids[150]. The microbiota can also enhance the lipoprotein lipase activity because it reduces the expression of the fasting-induced adipocyte factor in the intestinal epithelium resulting in enhanced FFA storage in adipocytes[149].

LPS produced by intestinal bacteria constitutes the outer membrane of Gram-negative bacteria and can elicit an immune response acting as an endotoxin. LPS may also have a role in the development of obesity, low-grade inflammation and insulin resistance[151]. An elegant study by Cani *et al*[152] noticed that high-fat diet induces LPS production in mice and probably its abnormal absorption through the intestinal epithelium may be fat-dependent. The same study has evidenced that endotoxemia induces weight gain, intrahepatic triglyceride accumulation and hepatic insulin resistance, leading to increased expression of TLR4 and proinflammatory cytokines (TNF-α, IL-6, IL-1 and PAI1) in muscle, adipose tissue and liver.

The correlation between intestinal dysbiosis and lipid accumulation in the liver is evidenced by recent research by de Wit *et al*[153]: in mice, a diet with high concentration of palm oil induces higher weight gain and liver triglyceride concentration, reduces microbial diversity and increases *Firmicutes*/*Bacteroidetes* ratio compared to one high in poly-

unsaturated fatty acids. The fecal microbiota of women following a choline-deficient diet, which induces steatosis, varies during choline depletion and correlates with changes in liver fat concentration, showing modifications in *Gammaproteobacteria* and *Erysipelotrichi* populations[154].

IBS

Intestinal dysbiosis is also involved in the development of IBS symptoms. The intestinal microbiota modulates intestinal motility and sensitivity[155]. An animal study has observed that oral antibiotic therapy perturbs the intestinal microbiota, reduces *lactobacilli* and decreases *bacteroides* and *enterococci* populations, and affects pain perception and viscero-motor responses in the gut. The myoelectrical activity in the gut is also altered in germ-free animals and it reversed after colonization[156]. The supernatant made from *Escherichia coli Nissle 1917* stimulates smooth muscle cells and enhances colonic contractility[157], and also *Lactobacillus rhamnosus GG* has a dose- and time-dependent effect on the acetylcholine-stimulated contraction of human colonic muscle cells[158]. *Lactobacillus rhamnosus* also has a protective role in pain prevention in animal models[159].

The intestinal bacterial population inhabits a complex environment and its composition varies throughout the gut. It is necessary to distinguish at least three different types of microbiota evaluated in different studies: the luminal microbiota, within the intestinal lumen; the mucosal microbiota that adheres to the intestinal wall; and the fecal microbiota, excreted in feces. In IBS subjects, studies on fecal microbiota have found increased facultative and anaerobic bacteria (as *Escherichia coli* and *Clostridium*) and decreased *lactobacilli* and *bifidobacteria*[160,161]. Later studies used molecular techniques because most bacterial species in the gut are not cultivable; a recent report of the Rome foundation reviewed principal results[162]. The majority of reports have studied fecal microbiota while only a few are focused on the mucosal flora. Furthermore, different molecular techniques are carried out and other limitations may explain that data shown are often contradictory or inconsistent. Moreover, the evidence that SIBO is frequently found in IBS subjects[163], especially in diarrhoea-predominant IBS (D-IBS)[164], and that IBS can develop following infective gastroenteritis (PI-IBS)[165] confirms the role of gut dysbiosis in the IBS pathogenesis.

INTESTINAL PERMEABILITY

A single layer of cells composes the intestinal epithelium, a selective filter and barrier for exogenous substances and water[129]. The ways to pass the epithelial layer are mainly two: transcellular and paracellular[166].

The regulation of the paracellular pathway is mainly due to complex structures localized at the apical-lateral and along the lateral membrane between the cells of the intestinal epithelium: desmosomes, adherent junctions and tight junctions (TJs)[167].

TJs regulate selective paracellular ionic solute transport, prevent the passage of luminal antigens, microorganisms and toxins, but also regulate the tropism of enterocytes[168]. TJs are so called "kissing points", fusion points where there is no space between two enterocytes[166], and are formed by different transmembrane proteins: tricerullin, occludin, claudins and junctional adhesion molecules, which seal together adjacent cells and cytoskeleton[169].

Several stimuli can modulate the intestinal permeability, but bacterial toxins *inter alia* are able to modify the localization of TJ proteins directly[170] or *via* the release of proinflammatory cytokines such as TNF-α, IFN-γ[171] and IL-6[172] that *per se* can reduce the expression of zonula occludens-1 (ZO-1), occludin and claudin.

NAFLD and NASH

In a recent review, Ilan[151] have focused on the role of bacterial translocation in NASH. The bacterial translocation is intimately connected with liver damage from the first step of lipid accumulation in the liver to the development of steatohepatitis, passing through the activation of the innate immune system and mitochondrial dysfunction.

Many animal and human studies have focused on the microbial dysbiosis in NAFLD and to date the endotoxemia, subsequent to bacterial translocation from the gut to the liver through the venous portal system, is an important factor in the development of NASH[173]. The mechanisms that lead up to endotoxemia are bacterial overgrowth and impaired intestinal barrier. Sabaté *et al*[174], and previously Wigg *et al*[175], have pointed out that obese subjects have an increased prevalence of SIBO and this condition correlates with severe hepatic steatosis.

Obese mice have a modified distribution of occludin and ZO-1 in the intestinal mucosa in combination with a lower intestinal resistance and higher circulating levels of inflammatory cytokines and portal endotoxemia[82]. Similar results are found in mice with fructose-induced steatosis: treatment with metformin leads to a decrease in hepatic triglyceride accumulation and plasma alanine-aminotransferase levels and protection against the loss of the TJ proteins occludin and ZO-1 in the duodenum[176].

In humans, an immunohistochemical analysis of duodenal expression of ZO-1 performed by Miele *et al*[177] has highlighted that subjects with biopsy-proven NAFLD have increased gut permeability and high prevalence of SIBO, and that both correlate with the severity of steatosis. Also, NASH subjects have a higher prevalence of SIBO, related to enhanced expression of TLR-4 and release of IL-8[178]. The presence of endotoxins in portal blood is found also in cirrhotic patients and is related to an impaired intestinal barrier function[179]. Non-cirrhotic NAFLD subjects have increased LPS[180] and LPS-binding protein serum levels[181]. Probiotic treatment of obese mice leads to a lower intestinal permeability and improved TJ function, a lower plasma LPS and cytokine concentration and a decreased hepatic expression of inflammatory and oxidative stress markers[182]. Recently, the association between metabolic syndrome, gut micro-

biota dysregulation and impaired intestinal barrier has been further confirmed in an animal model where dietary obese rats show reduced expression of ZO-1 in the gut and higher TNF-α levels in combination with reduced *Lactobacillus* and increased *Oscillibacter* fecal population. Moreover, TNF-α and IL-6 mRNA levels were higher in mesenteric fat[183].

IBS

The impaired intestinal permeability is not only a key factor in the development of NAFLD and NASH. Other inflammatory gastrointestinal diseases such as Crohn's disease, UC, bacterial infections caused by *Escherichia coli*, *Clostridium difficile* and *Vibrio cholera*, anti-inflammatory agents associated enteritis and IBS are involved. *In vivo* studies have observed that IBS patients have an impaired intestinal barrier function[87,90]. Nevertheless, it is likely that these findings are specific only to D-IBS and PI-IBS subjects and in other IBS subtypes similar results are not found[87,184].

In IBS, intestinal dysbiosis is an important factor participating in damaging the intestinal barrier through the activation of the immune system[185] even though another possible cause of impaired intestinal barrier is the exposure to chronic stress. In healthy animals and humans, acute or chronic stress enhances the intestinal permeability to water and also to macromolecules, and IBS subjects are more sensitive to physical and mental stressors compared to healthy subjects[110].

It has been explicated that in IBS subjects there is a low grade inflammation in the gut. Mast cells and T lymphocytes represent the majority of intestinal inflammatory infiltrate and mast cells are also involved in the regulation of motor and visceral responses in the intestine[19,21,88].

The intestinal permeability is controlled by mast cells, *via* histamine, serotonin 5-hydroxytryptamine (5-HT) and protease production[21]. Proteases are markedly increased in the mucosa of IBS subjects[18,186] and supernatants rich in proteases from D-IBS subjects are able to evoke epithelial dysfunction and allodynia in healthy mice[20]. In addition, colonic soluble mediators in supernatants from IBS subjects are able to reproduce permeability alterations in Caco-2 cells and decrease ZO-1 expression[22]. A recent study by Martínez *et al*[187] confirms this hypothesis because it has been demonstrated that activated mast cells induce the downregulation of ZO-1 in intestinal epithelium.

Another class of TJ proteins, claudins, is involved too; in fact, claudin-1 and claudin-4 levels are decreased in the small and large intestine of D-IBS patients, whereas claudin-1 and claudin-3 were elevated in constipation-predominant IBS (C-IBS) patients[188].

INTESTINAL MOTILITY

Intestinal motor and sensory functions are influenced by the immune system to activate a mechanism of defense from noxious agents in the intestinal lumen[189].

Mice infected with *Trichinella spiralis* develop muscle hyper-contractility in the gut[190] but these effects disappear in animal models of athymic and $CD4^+$ cell-deficient mice[191], encouraging the hypothesis of a role for the immune system and inflammation in intestinal motor functions. Th2 cytokine production was associated with enhanced motor functions and appropriate helminthic elimination. On the other hand, the response with a reduced intestinal motility of Th1, but interestingly also of Th17 cells, seems to be involved in small intestine motor functions. In this setting, specifically IL-17 induces smooth muscle cell contraction[192].

Among Th2 cytokines, IL-13 is secreted by $CD4^+$ cells and by many other immune cellular types of innate immunity, as the so called "innate helper cells", which can be found normally in the gut and in blood. IL-13 has, in low concentrations, regulatory effects, increasing IL-10 and decreasing IL-17 levels, but, when up-regulated, it leads to inflammatory modifications and hyper-contractility of smooth muscle in the gut[193].

In agreement with these findings, the production of 5-HT, one of the most important neurotransmitters of intestinal motility[194], is also influenced by immune response and cytokine production and its secretion seems to be enhanced by Th2 and reduced by Th1 response[195]. 5-HT is synthesized and secreted by enterochromaffin cells (EC) and acts on receptors located on the processes of intrinsic and extrinsic primary afferent neurons in the lamina propria of the gut to initiate peristaltic and secretory reflexes[196]. The 5-HT transporter (SERT) is the physiological inhibitor, it is expressed by enterocytes and removes 5-HT from the intestinal space by internalizing it[197].

Obesity and NAFLD

In high-fat diet fed mice a slower gastric emptying was found, as well as modified intestinal hormone production: higher plasma leptin and cholecystokinin (CCK) concentrations and lower plasma ghrelin levels were found[198]. Covasa *et al*[199] have shown that in high-fat diet fed mice there is a reduction in CCK-induced and oleate-induced inhibition of gastric motility.

In obese rats, after Roux-en-Y gastric bypass, an increase in peptide YY and a decrease in ghrelin concentrations occurred. These hormonal modifications may contribute to weight loss by decreasing the food intake and slowing the gastric emptying and transit time[200].

A recent study by Hyland *et al*[201] confirms the presence of an impaired intestinal motility, a modified submucosal nerve function and a decreased electrogenic glucose transport in obese rats. The author hypothesizes that the loss of motor control may lead to an altered host defense and intestinal dysbiosis, and the adapted glucose transport may be a control mechanism in the restriction of nutrient absorption.

Obese subjects have an accelerated esophageal and gastric motility and impaired gastrointestinal hormone secretion[202,203]. Vazquez Roque *et al*[204] have detected a lower postprandial gastric volume in obese subjects. A recent report disputes their data: in newborns, fasting

and postprandial gallbladder volumes and gastric emptying were similar between obese and lean subjects, but in obese pre-adolescents, and even more in adults, a larger fasting gallbladder volume with slower postprandial gastric emptying was found[205].

Small and large intestinal motility are also involved, as reported by Xing *et al*[206]. As we see above, SIBO is most frequently viewed in obese subjects and it has been associated with an altered pattern of migrating motor complexes (MMC) in the small intestine[207].

The role of intestinal dysmotility in liver cirrhosis is confirmed by numerous data[208]. *Vice versa*, in NAFLD, only a few studies have focused on impaired intestinal motility, although obesity, which is one of the most important etiological factors of NAFLD, is strictly related to impaired intestinal motility. Initial studies have found that NAFLD[209] and non-alcoholic cirrhosis[210] subjects have a prolonged orocecal transit time.

Interestingly, an up-to-date study correlates 5-HT$_3$ antagonists to reduced endotoxin levels in the portal system, attenuated liver fat content, inflammation, and cell necrosis, improved TNF-α levels and increased TJ expression in the duodenum of obese, leptin-deficient mice[211]. The same group has confirmed these data and has found that SERT deficiency causes hepatic steatosis and impaired intestinal permeability[212]. These findings suggest that obesity, and consequently NAFLD, are affected by impaired gut motility and most probably the impaired intestinal barrier, the gut inflammation and also neuronal signaling are key points in their maintenance.

IBS

IBS subjects frequently report upper gastrointestinal symptoms such as functional dyspepsia[213]. Impaired lower esophageal motility and delayed gastric emptying are frequently viewed[214] and should be related to small-bowel dysmotility[215].

Many studies have focused attention on the small intestine and large intestine gut dysmotility in IBS subjects. As reviewed elsewhere, studies on MMCs and clustered activity as well as intestinal transit for the small intestine and on myoelectrical activity, intraluminal pressure recordings and transit for the large intestine confirm this hypothesis[216].

In the small intestine of IBS subjects, alterations in the periodicity of MMCs are found[217]. Kellow *et al*[218,219] have demonstrated that MMCs have a shorter periodicity in D-IBS, whereas in C-IBS this is longer.

EC cell numbers in the intestinal wall are increased[220,221] and postprandial 5-HT levels are increased in platelet-poor plasma[222] of IBS subjects, especially in PI-IBS. 5-HT signaling is involved in the pathogenesis of intestinal dysmotility and hypersensitivity; indeed 5-HT modulators are used in IBS therapy[223]. 5-HT$_4$ agonists accelerate colonic transit and are useful in constipation unresponsive to laxative treatment, while 5-HT$_3$ antagonists inhibit colonic secretion and motility, and visceral sensation, and for this reason are used in D-IBS.

Moses *et al*[224] have found that SERT was less expressed in C-IBS and UC colonic biopsy specimens. Camilleri *et al*[225] have shown that SERT polymorphisms may influence colonic motility in patients with D-IBS and may influence the response to a 5-HT$_3$ antagonist.

In the colon of IBS subjects activated mast cells in proximity to mucosal innervations may contribute to pain perception[93] and are correlated with 5-HT release by intestinal EC cells[226]. Interestingly, Mizutani *et al*[123] have observed that in an animal model of IBS, muscle hyper-contractility is related to an increased Th2 cytokine profile (IL-4 and IL-13). Even if these data confirm the role of immune activation in gut motility alteration, it is mandatory to observe that in IBS, and especially in D-IBS and PI-IBS, there is an enhanced gut motor activity even though these IBS subtypes are often related to a Th1 cytokine profile, at least in peripheral blood or in PBMCs. However, there are no reports on the possible role of IL-17 and Th17 in IBS; meanwhile, IL-13 production by PBMCs is higher compared to controls[124].

Recent studies have shown that bacterial products may regulate gastrointestinal motor functions[227,228], but intestinal motility may also influence the gut microbiota composition[229]. Pimentel *et al*[230] for the first time demonstrated that the impaired intestinal motility may be related to SIBO in IBS subjects, but subsequent contrasting data have questioned this theory[163]. Moreover, as has been described before, IBS and NAFLD are characterized by an intestinal dysbiosis and only a proportion of subjects meet diagnostic criteria for SIBO.

CNS INVOLVEMENT

A recent review by Capuron *et al*[231] has focused on how the immune system can affect the CNS and contribute to the development of neuropsychiatric disorders such as depression, with particular relevance to cytokine signaling. Cytokines are involved in production, function and reuptake of several neurotransmitters, such as 5-HT. They affect the hypothalamic-pituitary-adrenal (HPA) axis and can modify the neuronal architecture, neuronal plasticity and aging, and neuronal circuits in CNS.

As previously described, 5-HT is an important neurotransmitter of the enteric nervous system (ENS) but it is also fundamental to CNS functioning. 5-HT, produced from tryptophan, plays a major role in the modulation of brain-gut axis[232]. The brain-gut axis is constituted peripherally of ENS communicating with the gut wall and centrally with the CNS and HPA axis[233]. The gastrointestinal system and the brain communicate in bi-directional mode, both of them influencing each other (the so called top-down and bottom-up model developed in functional GI disorder studies)[234]. The HPA axis is composed of corticotropin-releasing hormone (CRH), produced in the hypothalamic para-ventricular nucleus, which stimulates adrenocorticotropin (ACTH) production in the anterior pituitary gland that in turn induces the adrenal cortex to produce cortisol in response to various stressors[235].

In animal and human models the turnover of 5-HT in the brain is altered by acute and chronic exposure to pro-inflammatory cytokines[236,237].

Cytokines stimulate CRH, ACTH and cortisol production and in chronic states influence the diurnal cortisol curve because they stimulate inflammatory signaling that reduces glucocorticoid receptor functions and expression leading to decreased responsiveness to glucocorticoids.

Obesity and NAFLD

Recently, animal studies have shown that in the hippocampus and cortex of high-fat fed mice there is increased production of inflammatory products[238,239] and systemic inflammation is also related to cognitive dysfunctions[240,241]. Depression and depressed serotoninergic state are strictly related to metabolic syndrome and obesity[242,243]. Tarantino *et al*[244] have studied urinary 5-hydroxy-3-indoleacetic acid, a 5-HT metabolite, in depressed and obese/overweight subjects and have found that it negatively correlates with dysthymia and depression status.

Alteration in the HPA axis is well established in obese patients and chronic stress with hyper-alimentation is an important factor in its development[245]. Although there are contrasting data on urinary free cortisol (UFC) in obese subjects, a recent study has evidenced in NAFLD subjects increased UFC and cortisol serum concentrations after dexamethasone suppression, both correlated with hepatic inflammation and fibrosis stage[246]. Moreover, in a human model, cortisol clearance is increased in NAFLD subjects and is correlated with insulin sensitivity[247]. Peripherally, cytokines such as TNF-α and leptin stimulate 11β-HSD1, an enzyme required for the activation of cortisone to cortisol[248]. Also leptin and ghrelin increased levels are related to HPA axis dysregulation in obese subjects[245].

Finally, early life stress predisposes to overweight and insulin resistance, at least in animal models[249].

IBS

Hypersensitivity and brain alterations, investigated with different study methods, have been found in the last 15 years in IBS subjects; and, despite often contradictory data, there is strong evidence of dysregulation in pain and other stimuli perception[250]. Moreover, mood disorders (depression, anxiety) and other psychiatric disorders (eating disorders, posttraumatic stress syndrome, panic attack, *etc.*) are frequent, evidencing the role of gut-brain dysfunction in these patients[107].

As has been mentioned above, the majority of reports on 5-HT in IBS have studied its intestinal production; meanwhile, few are focused on its systemic production. Clarke *et al*[251] have found that IBS subjects degrade tryptophan more *via* the kynurenine pathway, an alternative metabolic way producing neurotransmitters other than 5-HT. Subsequently, the same group has found that kinurein from blood of IBS subjects can influence TLR expression[252] in an *in vitro* model.

The main evidence on HPA dysregulation in IBS[250] is the following: CRH and ACTH stimulate colonic secretion, intestinal motility, visceral sensitivity and anxiety. Principal brain regions influenced by HPA axis are the amygdala and hippocampus. In IBS there are increased HPA axis responses to stressors such as meals, hormonal stimuli, and mental stress compared to controls. Fatigue and depression are associated with increased mast cell counts in the colonic mucosa of IBS subjects, confirming the role of gut-brain dysfunction in IBS[253]. Indeed, a key question still unresolved is whether the SNC dysfunction is the *primum movens* of the gut inflammation and consequently the visceral hypersensitivity and dysmotility in IBS or whether the gut inflammation represents the main cause of subsequent SNC and systemic disorder.

UNANSWERED QUESTIONS

Could weight loss ameliorate IBS symptoms by influencing intestinal microbiota? Is there a relationship between NAFLD severity and IBS symptoms? Could patients suffering from IBS be at major risk to develop NASH? Are circulating levels of inflammatory cytokines overlapping in IBS subjects and NAFLD? Could intestinal dysbiosis affect CVD risk *via* NAFLD[254]?

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