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Gut microbiota and its metabolites in pathogenesis of NAFLD

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Aim: to provide information on the results of recent scientific research in the field of non-alcoholic fatty liver disease (NAFLD) metabolomic profiling.
Key points. Metabolites of microbial origin are important biological molecules involved in many specific reactions of the human body. This literature review presents the results of recent studies in the field of metabolomics in patients with NAFLD. A more detailed understanding of the role of individual metabolites or their combinations in the NAFLD pathogenesis will allow us to determine the vector of further diagnostic and therapeutic approaches for this nosology. The research results of the probiotics effect on the levels of certain metabolites are currently being discussed.
Conclusion. New research data in the field of studying the human metabolomic profile are presented. The results allow us to summarize the effects of microbial agents and their metabolites in the formation of changes in the liver parenchyma in the context of NAFLD. Changes in the level of endogenous ethanol, secondary bile acids, aromatic amino acids, branched chain amino acids, etc. have been described. Correlation between metabolites and certain bacterial strains has been established. A correlation between the ratio of bacteria types and clinical/laboratory parameters was noted in patients taking prebiotics.
Keywords: metabolites, metabolomic profiling, biomarkers, mass spectrometry, liquid chromatography, non-alcoholic fatty liver disease
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Роль кишечной микробиоты и ее метаболитов в патогенезе неалкогольной жировой болезни печени

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Цель обзора: представить информацию о результатах последних научных исследований в области метаболомного профилирования при неалкогольной жировой болезни печени (НАЖБП)
Основные положения. Метаболиты микробного происхождения являются важными биологическими молекулами, участвующими во многих специфических реакциях организма человека. В данном обзоре литературы представлены результаты последних исследований в области метаболомики у пациентов с НАЖБП. Более детальное понимание роли отдельно взятых метаболитов или же их совокупности в патогенезе НАЖБП позволит определить вектор дальнейших диагностических и терапевтических подходов для этой нозологии. Обсуждаются результаты исследований влияния пробиотиков на уровень тех или иных метаболитов.
Заключение. Представлены новые данные исследований в области изучения метаболомного профиля человека. Результаты позволяют суммировать эффекты микробных агентов и их метаболитов в процессе формирования изменений паренхимы печени в рамках НАЖБП. Описаны изменения уровня эндогенного этанола, вторичных желчных кислот, ароматических аминокислот, аминокислот с разветвленной цепью и пр. Выявлена корреляция метаболитов с определенными штаммами бактерий. На фоне приема пробиотиков отмечена корреляция соотношения типов бактерий и клинико-лабораторных показателей у пациентов.
Ключевые слова: метаболиты, метаболомное профилирование, биомаркеры, масс-спектрометрия, жидкостная хроматография, неалкогольная жировая болезнь печени
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Introduction

The interactions between the microbiota and the human organism are highly dynamic and complex. The microbiota has an extensive metabolic activity that includes unique reactions which are not catalyzed by human cells but necessary for human life [1–7]. Microbial-derived metabolites are potentially important compounds that mediate a cross-talk between the microbiota and the host, both in relation to maintaining health, and in various diseases [2–6]. These molecular "profiles" carry unique information that can act as prognostic and diagnostic markers, as well as be a guide to the effectiveness of therapy. The major known classes of metabolites produced and transformed by the gut microbiota with known effects on human physiology include organic acids, short chain fatty acids, lipids, BCFAs (Branched chain fatty acids), BCAAs (Branched-chain amino acids), vitamins, bile acids, neurotransmitters [2, 8, 9]. The subtle interaction between microbiota metabolites, the microbiota itself and the host is mediated through a wide range of signaling pathways. They extend beyond the gut and form so-called functional axes (namely gut-brain axis, the gut-lung axis, the gut-heart axis, gut-liver axis).

Changes in the gut microbiota composition

There is a strong correlation between the diversity of the gut microbiota and the development of certain diseases, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The gut microbiota and its metabolites are involved in host metabolism through a range of cellular receptors and signaling pathways, remodeling liver cell metabolism through the gut-liver axis. Bacterial metabolites (short-chain fatty acids, secondary bile acids, protein fermentation products, choline, and ethanol), as well as bacterial components (lipopolysaccharides, peptidoglycans, bacterial DNA) are important factors in the pathogenesis of NAFLD [10].

A change has been established in patients with NAFLD and obese individuals at the level of phylum, namely there is a decrease in the content of *Firmicutes* (mainly due to a decrease in *Lachnospiraceae* and *Ruminococcacea*) and an increase in *Bacteroidetes* and *Proteobacteria*, the latter have a pronounced pro-inflammatory potential [11]. Thus, in a study by L. Zhu in patients with NASH and obese persons without NASH, in comparison with a healthy group, a higher content of *Bacteroidetes* (mainly *Prevotellaceae*) and *Proteobacteria* (*Enterobacteriaceae*) and a significant decrease in the content of *Firmicutes* (*Lachnospiraceae*, *Blautia, Ruminococcaceae, Faecalibacterium*) and *Actinobacteria* (*Bifidobacteriaceae*). The *Proteobacteria* (*Enterobacteriaceae*) content differed significantly between patients with NASH and obese patients without NASH. At the same time, only in patients with NASH, the ethanol concentration in the blood was higher [12]. In children with NAFLD, in the intestinal microbiota composition, along with an increase in the proportion of *Gammaproteobacteria* (*Proteobacteria*) and *Prevotella* (*Bacteroidetes*) in the feces, the bacterial metabolites content changed. And the ethanol concentration increased. The concentration of acetate, formate, and valerate decreased, while the content of butyrate and propionate practically did not change [13]. It is assumed that with the progression of NAFLD to NASH, the proportion of *Bacteroidetes*, *Firmicutes* and *Proteobacteria* types does not change significantly. But changes are observed within the *Bacteroidetes* type: the *Prevotellaceae* proportion decreases, while the *Bacteroidaceae* proportion increases [14].

In patients with NAFLD, altered microbiota composition mediates the development of increased intestinal permeability. Levels of calprotectin, bacterial lipopolysaccharide (LPS) and zonulin-1 are higher in patients with NAFLD than in healthy volunteers. The gut microbiota profile (significant reduction in *Akkermansia* and *Bifidobacterium*) correlated with the level of systemic inflammatory response, increasing in patients with NAFLD and cirrhosis; elevated LPS concentration correlated with the insulin resistance severity in these patients. It has been established that bacterial endotoxemia, which develops during dysbiosis, increases the risk of developing NAFLD due to the activation of inflammatory liver cells. Bacterial endotoxins have high affinity for toll-like receptors (TLRs), located on hepatocytes, and Kupffer cells and liver stellate cells. LPS, by activating TLR4, initiates a cascade of reactions involving the nuclear transcription factor (NF-κB) and subsequent activation of inflammasomes with the secretion of pro-inflammatory cytokines such as Interleukin-1β (IL-1β) and interleukin-18 (IL-18) [16]. In addition, endotoxins can directly damage hepatocytes and activate Kupffer cells, promoting the release of inflammatory cytokines and the development of oxidative stress [17–19].

Separate studies have shown that a significant role in the transformation of steatosis into

steatohepatitis belongs to excessive bacterial growth in the small intestine, which is detected in 50–75 % of patients [20–24]. Small intestine bacterial overgrowth (SIBO) is accompanied by an increase in the production of the pro-inflammatory cytokine (TNF-α) by adipose tissue, an increase in the concentration of free fatty acids (FFA). FFA have a directly damaging effect on hepatocyte membranes and activate cytochrome P450 with an increase in lipid peroxidation and reactive oxygen species accumulation [25–28].

Changes in fatty acid metabolism

Study of germ-free mice showed that the microbiota can promote enhanced triglyceride synthesis and increased fatty acid accumulation in liver cells [29]. There is an increase in the content of saturated and monounsaturated fatty acids. Changes in the content of omega-3 (n-3) and omega-6 (n-6) long-chain polyunsaturated fatty acids (PUFAs) were found, which are key lipid components necessary for the growth and organism development. Omega-3 and omega-6 are recognized as bioactive molecules of membrane phospholipids, substrates for the eicosanoids synthesis and gene expression modulators. They also play a key role in inflammatory processes. It is known that omega-6 PUFAs induce inflammation, while omega-3 PUFAs have the ability to modulate inflammatory activity [30]. The ratio of these PUFAs (omega-6/omega-3) is important for the anti-inflammatory activity implementation of omega-3 PUFAs [31]. Levels of omega-3 PUFAs (eicosapentaenoic, docosahexaenoic and arachidonic acids) are reduced more in patients with steatohepatitis than in those with NAFLD [32]. Several studies have demonstrated omega-3 PUFAs deficiency, as well as an altered omega-6/omega-3 ratio [33, 34]. With such changes in the omega-6 and omega-3 PUFAs metabolism, the synthesis of pro-inflammatory lipid mediators is activated, namely eicosanoids (prostaglandins, cyclopentenones, thromboxane A2, leukotrienes) and the process of switching the synthesis of eicosanoids to the formation of mediators involved in the inflammation resolution (resolvins, protectins, maresins, lipoxins) [35].

A number of studies have found that a high-fat diet alters the gut microbiota and causes gut bacteria to convert dietary choline into the hepatotoxic methylamine, reducing choline bioavailability. This contributes to a change in the synthesis of very low-density lipoproteins (VLDL), which transport fat to adipocytes, thereby increasing the risk of developing steatosis [36, 37].

During fermentation in the colon, bacteria (primarily *Bacteroides* and *Firmicutes*) break down dietary fiber into short-chain fatty acids (SCFAs), branched-chain fatty acids and gases (hydrogen, carbon dioxide, and methane). SCFAs formed as a result of microbial fermentation are monocarboxylic acids with a chain length of up to 8 carbon atoms, including acetic, propionic, butyric acids and their isoforms. During the day, more than 300 mmol/L SCFAs are synthesized. The maximum concentration of SCFAs is formed in the caecum and ascending colon, reaching 70–140 mmol/L. In these sections of the intestine, there are more substrates for bacterial metabolism, despite the lower number of bacteria themselves compared to the descending and sigmoid colon, where the SCFAs content decreases to 20–70 mmol/L. Systemic SCFAs concentrations depend on both production and absorption rates in the gut, which in turn are related to dietary patterns and microbiota composition. SCFAs ratio (acetate:propionate:butyrate) of 60:20:18 is characterized as optimal [38, 39].

SCFAs exist in the colon lumen in the form of a non-ionized acids or as a fatty acid anions, due to this fact they are highly soluble in water and easily penetrate through the mucus layer and glycocalyx to the apical membrane of colonocytes. SCFAs — acetate, propionate and butyrate act as quorum-molecules of various vital physiological responses of the body, being the most important systemic regulators. Currently, three G-protein receptors are known to interact with SCFAs: GPR41 (FFAR3), GPR43 (FFAR2), GPR109A [40, 41].

Butyrate interacts mostly with the GPR41 and GPR109A receptors, while acetate and propionate have affinity for GPR43 [42]. Interaction with these receptors determines a number of physiological functions that are most important for the human body, including the reactive oxygen species production, neutrophil chemotaxis, and T-regulatory cells modulation [43]. It is noteworthy that GPR41 and GPR43 are also expressed in human white adipose tissue, skeletal muscle, and liver, which indicates the possibility of SCFAs influence on substrate and energy metabolism directly in peripheral tissues [44–46].

Each SCFA, including their isomers, is produced by a specific type of anaerobic bacteria. They are then distributed systemically and used either to provide energy to colonocytes or as signaling molecules, facilitating the activation and maturation of immune cells [47]. Therefore, a change in the composition and/or functional activity of the microbiota, which leads to a change in the ratio and amount of SCFAs, can have negative consequences for human health. This can contribute both to impaired intestinal permeability and the development of immunological intolerance. SCFAs affect the proliferation of enterocytes, lower the pH in the intestinal lumen, participate in the renewal of the intestinal epithelium (butyrate), stimulate the development

of hepatocytes (propionate) and peripheral tissues (acetate), and affect the absorption of calcium and magnesium in the colon. By lowering the pH in the intestinal lumen, SCFAs thereby limit the growth of pathogenic microorganisms. *Bifidobacterium* acetate production was found to inhibit the growth of enteropathogens in mice [48]. Moreover, in vitro and in vivo studies have shown that high levels of butyrate are associated with increased mucin production and decreased bacterial adhesion, as well as improved epithelial integrity [49,50]. Experimental studies have established the role of butyrate in the regulation of the transcription factor FOXP3, which acts as a regulator of the development and immune response cells (Treg) activity [51].

The effect of SCFAs on energy homeostasis is controversial and requires thorough study. On the one hand, it is hypothesized that the gut microbiota allows the host to obtain additional energy, mainly through the SCFAs production from indigestible carbohydrates. Obesity studies have shown an increased *Firmicutes* to *Bacteroidetes* ratio, which has been associated with high caecal concentrations of acetate and butyrate or acetate and propionate compared with controls [52–57]. At the same time, there are a large number of studies indicating that SCFAs therapy can reduce or reverse the development of the dominant risk factors for NAFLD (weight gain and obesity) [58–65]. For example, in obese mice, oral administration of sodium butyrate leads to weight loss by increasing energy expenditure and fat

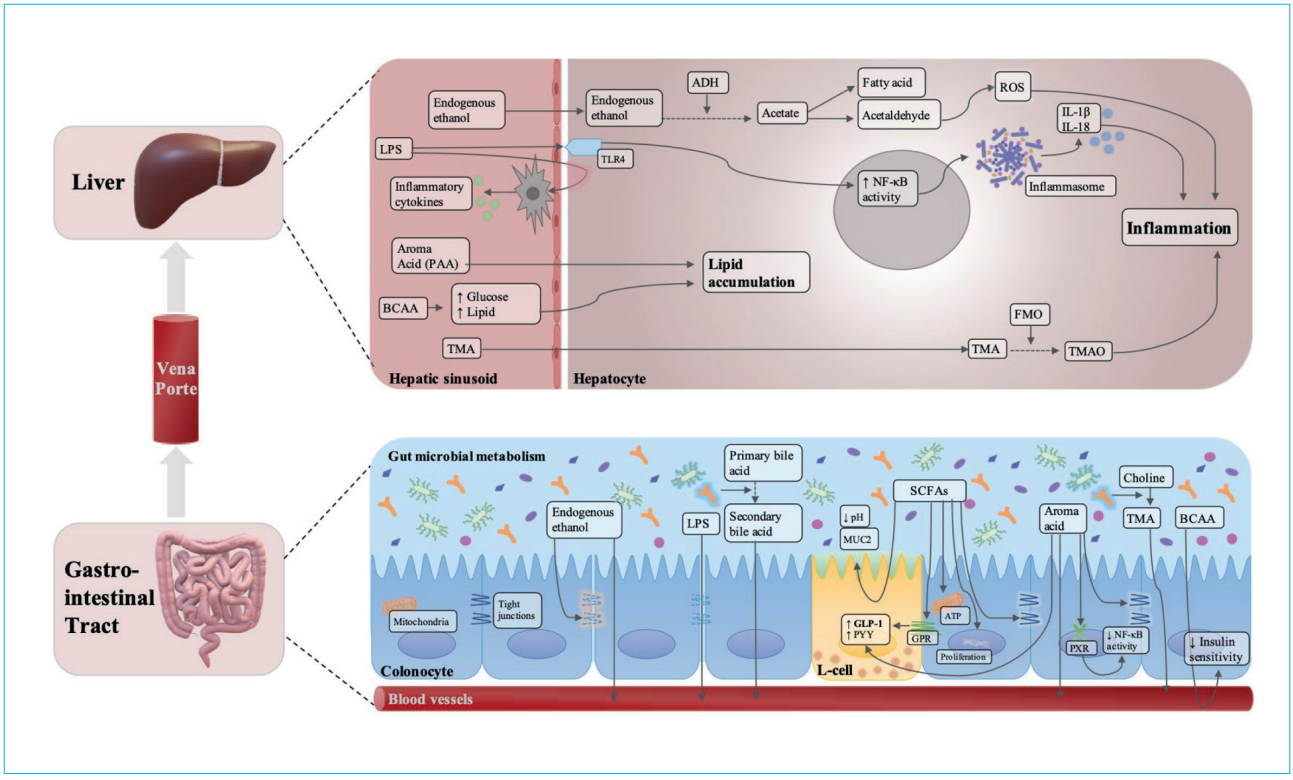

Fig. Microbial metobolites in NAFLD pathogenesis. *Endogenous ethanol damages tight junctions; increases the permeability of the intestinal mucosa, and exacerbates endotoxemia. In the liver, ethanol is oxidized to acetate and promotes the reactive oxygen species synthesis. Bacterial endotoxins directly or through TLR4 activation of hepatocytes and Kupffer cells activate IL-1β and IL-18. The microbiota affects the amount and ratio of primary and secondary bile acids. SCFAs affect pH, mucin production, epithelial integrity, and others. SCFAs are involved in the activation of GLP-1 and PYY. Aromatic (Indolepropionic) acid interacts with PXR and NF-κB to reduce the production of pro-inflammatory cytokines in the gut. Aromatic (Phenylacetic) acid increases BCAA utilization and leads to lipid accumulation in the liver. TMA, formed by the gut microbiota, is converted to TMAO in the liver and indirectly leads to the activation of inflammation.*

Note: alcohol dehydrogenases (ADH), reactive oxygen species (ROS), lipopolysaccharides (LPS), mucin 2 (MUC2), Toll-like receptor (TLRs), transcription nuclear factor kappa B (NF-κB), short-chain fatty acids (SCFAs), G protein-coupled receptor (GPR), glucagon-like peptide-1 (GLP-1), peptide YY (PYY), pregnane X receptor (PXR), phenylacetic acid (PAA), branched-chain amino acids (BCAA), flavin-containing monooxygenase (FMO)

oxidation [58]. In addition, administration of acetate, propionate, and butyrate to mice fed a high-fat diet reduced the animals' body weight and improved insulin sensitivity without altering food intake or physical activity levels [59]. It has been shown that a diet high in dietary fiber, which promotes SCFAs production, reduced the effects of hepatic steatosis by limiting the accumulation of intrahepatic lipids and restored insulin resistance in obese mice [60–63].

It is known that SCFAs can increase energy expenditure, stimulate the production of satiety hormones and influence the central regulation of appetite, preventing the development of obesity. One of the mechanisms underlying the effect of SCFAs on food intake is associated with the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) [64]. These proteins are secreted by intestinal enteroendocrine L-cells, which are found most densely in the epithelium of the ileum and colon. PYY and GLP-1 influence appetite and satiety by downregulating neuropeptide Y (NPY) and activating proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC) and/or delaying gastric emptying [65, 66]. A study in mice has shown that acetate can cross the blood-brain barrier and be metabolized in the brain [66], affecting the central regulation of appetite.

It has been established that SCFAs control energy consumption by leptin stimulation [67]. Therefore, in addition to PYY and GLP-1 and the direct effects of acetate on the central nervous system, leptin secretion may partly explain the possible satiety-inducing effects of SCFAs. However, obesity is usually characterized not only by changes in leptin concentration, but also by the development of leptin resistance [67, 68]. Whether SCFA-induced increases in leptin secretion can overcome leptin resistance and thereby affect satiety remains to be explored (Fig.).

Propionate administration has been confirmed in clinical studies to modulate gut hormone release and reduce food intake in healthy individuals. Thus, the administration of inulin and propionate reduced the amount of food consumed by 8.7 % (73 kcal), which corresponded to the action of the signal of physiological satiety, without suppressing the appetite subjective reactions. With the simultaneous administration of inulin and propionate, a greater postprandial release of PYY and GLP-1 was observed, as well as stimulation of leptin release due to the activation of adipocyte FFAR2 [69].

SCFAs may also positively influence body weight control by influencing energy expenditure. In obese mice, oral administration of sodium butyrate results in weight loss by increasing energy expenditure and fat oxidation [70, 71]. Thus, oral administration of acetate to mice fed a high-fat diet can reduce total body fat and liver fat accumulation without altering food intake, which has been associated with increased expression of thermogenesis-associated proteins (peroxisomal acyl-CoA oxidase (ACOs), carnitine palmitoyltransferase, mitochondrial uncoupling protein 2) [72–74].

It is known that SCFAs can regulate low-grade chronic inflammation caused by obesity by activating anti-inflammatory Treg cells and suppressing pathways involved in the production of pro-inflammatory cytokines and chemokines, including those derived from adipose tissue [79–81]. SCFAs may also enhance gut barrier function, providing additional support for their anti-inflammatory potential. In several studies using gut cell lines, SCFAs (especially butyrate) improved epithelial barrier function and intestinal permeability by modulating tight junction protein and mucin expression [82–85]. In vitro, acetate and butyrate can reduce the lipopolysaccharide-induced release of tumor necrosis factor (TNF-α) and inhibit nuclear factor κB (NF-κB) [86, 87].

Alterations in bile acid metabolism

Recent evidence has shown that dysbiosis contributes to the development of NAFLD by altering bile acid metabolism.

Bile acids (BAs) modulate glucose and lipid metabolism by binding and activating the membrane G-protein bile acid receptor (TGR5) and the farnesoid X receptor (FXR). FXR is a nuclear receptor expressed in the liver, intestine, and kidney. FXR acts as an elevated levels indicator of bile acids and initiates homeostatic responses to control their level, and also modulates gluconeogenesis and lipogenesis [88]. Activation of FXR results in decreased formation and increased catabolism of triglycerides and free fatty acids (Fig 1). Elevated levels of triglycerides and glucose have been noted in mice lacking this receptor [89]. Activation of the TGR5 receptor prevents the development of insulin resistance and obesity by increasing energy use [90–93]. In an experimental study performed on laboratory animals (mice), it was found that TGR5 activation increases energy expenditure and oxygen consumption, thereby reducing insulin resistance and preventing the development of obesity [93]. In brown adipose tissue adipocytes and skeletal muscle myocytes, interacting with TGR5, bile acids initiate a cascade of reactions with the activation of type 2 iodothyronine deiodinase, which is involved in the metabolism of thyroxine (regulator of cellular basal metabolism) [94]. It has been shown that stimulation of TGR5 induces the glucagon-like peptide 1 (GLP-1) secretion by intestinal enterochromaffin cells, with an increase in insulin production by pancreatic beta cells [95].

It is discussed that changes in BAs metabolism are directly related to the composition of the intestinal microbiota, namely, with a decrease in the activity of bacteria that dehydroxylate BAs (*Lachnospiraceae, Ruminococcaceae,* etc.), and an increase in bacteria that deconjugate BAs (*Lactobacillales,* etc.) [96]. L.A. Adams et al. published a study investigating the correlation between bile acid levels, microbiota composition, and fibrosis development in patients with NAFLD. The study involved 122 adult patients with an established diagnosis of NAFLD. All subjects underwent a liver biopsy, the determination of bile acids levels was performed using high-performance liquid chromatography and mass spectrometry. Gut microbiota was analyzed by 16S rRNA sequencing. The results of the study demonstrated a positive correlation between the stage of liver fibrosis progression and an increase in the level of bile acids, both primary and secondary, in serum and stool samples of patients. A correlation was also observed with microbial taxa. The level of secondary non-conjugated bile acids and total secondary bile acids correlated with representatives of *Bacteroidaceae, Bacteroidales, Lachnospiraceae*. A positive correlation was also observed between these microorganisms and the F3/4 fibrosis stage [97].

In another study involving patients with NAFLD and NASH, the authors investigated metabolomic markers that can differentiate these two nosological forms. The study included 35 non-diabetic patients with a histologically confirmed diagnosis of NASH (n = 24) and NAFLD (n = 11). The control group included 25 clinically healthy volunteers. Using liquid chromatography and mass spectrometry, 437 metabolites were identified, of which 228 were described in reference materials. When analyzing the results obtained, some differences were observed in the metabolomic profile of patients with NAFLD and NASH from the metabolomic profile of the control group. At the same time, the authors did not reveal significant differences in metabolites among patients with NAFLD and NASH. In the NASH group, there was a 4-fold increase in the concentration of glycocholate and taurocholate in plasma and a 2-fold increase in the concentration of glycochenodeoxycholate compared with the control group [98].

Change in endogenous ethanol metabolism

Ethanol, produced by the gut microbiota, may be another reason for the formation of adipose tissue in the liver. Endogenous ethanol is a metabolite of many bacterial species [99–101]. Ethanol is absorbed and then reaches the liver, where, under the action of alcohol dehydrogenase, it is oxidized to acetate. Acetate is a substrate for the synthesis of fatty acids and acetaldehyde, which promotes synthesis of reactive oxygen species. It was shown that more ethanol was present in the exhaled air of ob/ob mice than in normal-weight rodents. However, ob/ob mice exhaled 50 % less ethanol after antibiotic treatment [102]. Elevated ethanol levels have been found in obese patients [103] as well as in children with NASH [104]. 5-day antibiotic therapy in patients with NASH contributed to a significant decrease in ethanol levels [105].

It is also known that ethanol increases the permeability of the intestinal mucosa, which exacerbates the effects of endotoxemia and contributes to the progression of NAFLD (Fig.).

Changes in BCAAs Metabolism

Branched-chain amino acids (BCAAs) (leucine, isoleucine and valine) are a group of proteinogenic essential amino acids characterized by a branched aliphatic side chain structure. BCAAs are currently being discussed as potential biomarkers of insulin resistance and predictors of type 2 diabetes (T2D) [106]. Clinical studies have shown that elevated plasma levels of BCAAs correlate with insulin resistance and an increased risk of T2D [107].

It is discussed that the gut microbiota is involved in BCAA metabolism. *Prevotella copri* and *Bacteroides vulgatus* have been found to be main species associated with elevated levels of circulating BCAAs and insulin resistance [108]. In an experimental study, the antibiotics treatment (vancomycin, ciprofloxacin, metronidazole) to mice significantly reduced the levels of BCAAs (leucine, isoleucine and valine), as well as aromatic amino acids (phenylalanine and tyrosine) [109].

Changes in the metabolism of aromatic amino acids (indole, indole propionic acid, phenylacetic acid) and trimethylamine N-oxide (TMAO)

The role of other microbiota metabolites in the pathogenesis of NAFLD is currently being studied. Indole and indolepropionic acid, which are aromatic amino acids (AAA), are the most common metabolites of tryptophan. It has been determined that representatives of the intestinal microbiota such as *Bacteroides, Clostridium, Lactobacillus, Bifidobacterium, Peptostreptococcus, Ruminococcus gnavus* and *Escherichia coli* are involved in tryptophan metabolism [110]. After absorption through the intestinal epithelium, indole enters the liver, where it is hydroxylated to 3-hydroxyindole and then converted (sulfation by sulfotransferase enzymes) to indoxyl sulfate. It has been established that indole increases the secretion of glucagon-like

peptide-1 (GLP-1) by enteroendocrine cells. That determines the severity of hepatic steatosis by interfering with the insulin signaling pathway. Studies have found an inverse correlation between indole content and hepatic fat accumulation [111]. L. Ma et al. showed that the concentration of circulating indole in the blood is significantly lower in obese patients compared with patients with a normal body mass index [111].

Indolepropionic acid, through activation of the nuclear pregnane X receptor (PXR) and inhibition of the transcription nuclear factor NF-κB, suppresses the pro-inflammatory cytokines production in the intestine, it also protects the liver from damage caused by oxidative stress [112]. In addition, indole propionic acid prevents the development of NAFLD by lowering glucose and insulin levels [24]. In the intestine, indole propionic acid induces the expression of tight junction proteins (zonulin and occludin). That maintains the integrity of the intestinal epithelium and thereby reduces the level of LPS in the blood [113, 114].

Phenylacetic acid (PAA) is produced by several species of *Bacteroides, Eubacterium hallii, Clostridium barlettii*. It is one of the bacterial metabolism products of phenylalanine [115]. It has been established that, through PAA, the intestinal microbiota can contribute to the development of hepatic steatosis [116].

PAA significantly reduces protein kinase phosphorylation, resulting in increased insulin resistance. PAA increases the utilization of branched chain amino acids, leading to the hepatic lipid accumulation [117].

It was shown that PAA promotes lipid accumulation and changes in the gene expression involved in glucose and lipid metabolism on hepatocyte cell culture [117]. In vivo experiments, mice were given PAA for two weeks, which led to a significant increase in hepatic triglycerides accumulation [118].

Trimethylamine (TMA), a metabolite of choline, is produced by the gut microbiota. In the liver, under the enzyme flavin monooxygenase influence, TMA is converted to trimethylamine N-oxide (TMAO). TMAO may affect bile acid metabolism and can be also associated with NAFLD [119]. In a mouse model, 18 weeks of TMAO administration was found to impair liver function and increase hepatic triglyceride accumulation and lipogenesis in mice fed a high-fat diet. TMAO increases the synthesis of fatty acids and changes the composition of fatty acids in the liver towards FXR-antagonistic activity [120].

Probiotics

Changes in the intestinal microbiota, as one of the pathogenetic factors in the development of NAFLD. They determine the growing interest in the use of probiotics as an effective treatment for NAFLD. Administration of probiotics to a patient with NAFLD is aimed at restoring the normal gut microbiota and thereby reducing liver inflammation. A large number of experimental studies in animal models have been published, showing the therapeutic potential of probiotics in the treatment of NAFLD.

Loman BR examined 25 studies: 9 evaluated prebiotics, 11 evaluated probiotics, and 7 evaluated symbiotic therapies in a total of 1309 patients. Patients treated with probiotics made up the majority of the general patient population (43.3 % for probiotics versus 34.0 % and 16.5 % for synbiotics and prebiotics, respectively), and the majority were confirmed cases of NAFLD or NASH by ultrasound or biopsy liver (68.0 %). The average duration of the intervention was 2.9 ± 1.4 months. Dose and treatment characteristics were more variable within the prebiotic class. Treatments included cereal β-glucans, psyllium husk, fructooligosaccharides (FOS), xylooligosaccharides (XOS), chicory inulin, and fiber extracts (ex. Chlorella vulgaris). For the synbiotic group of studies, FOS was the main source of prebiotics (n=5 out of 7 studies); 2 other studies used inulin. As with prebiotics, research on probiotics varied widely in the microbial species that were added (*L. reuteri, L. bulgaricus, L. acidophilus, L. rhamnosus, L. lactis, L. casei, L. plantarum, L. sporogenes, L. delbrueckii, B. bifidum, B. longum, B. infantis, B. breve and St. thermophilus*), and most of the studies used multiple organisms. *L. acidophilus* were the most commonly used species in both probiotic and synbiotic treatments. A meta-analysis showed that such therapy reduced BMI (-0.37 kg/ m^2; 95 % confidence interval [CI], -0.46 to -0.28; $P < 0.001$), liver enzymes (ALT, -6 .9 U/L [95 % CI -9.4 to -4.3], AST, -4.6 U/L [95 % CI, -6.6 to -2.7], γ-GT, -7.9 U/L [95 % CI, -11.4 to -4.4]; $P < 0.001$), serum cholesterol (-10.1 mg/dL 95 % CI, -13.6 to -6.6; $P < 0.001$), LDL-c (-4.5 mg/dL, 95 % CI, -8.9 to -0.17; $P < 0.001$) and TAG (-10.1 mg/dL). dl; 95 % CI, -18.0 to -2.3; $P < 0.001$). But inflammation markers remained unchanged (TNF-α, -2.0 ng/mL [95 % CI, -4.7 to 0 .61)]; CRP, -0.74 mg/L [95 % CI, -1.9 to 0.37]). Subgroup analysis by treatment category showed similar effects of prebiotics and probiotics on BMI and liver enzymes, but not on total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol [121].

Another meta-analysis included 28 trials involving 1555 patients with NAFLD who received probiotics for 4–28 weeks. Overall, probiotic therapy had beneficial effects on body mass index (weighted mean difference [WMD]: -1.46, 95 % CI: [-2.44, -0.48]), alanine aminotransferase (WMD: -13.40,

95 % CI: [-17.03, -9.77]), aspartate aminotransferase (WMD: -13.54, 95 % CI: [-17.86, -9.22]), gamma-glutamyl transpeptidase (WMD: -9.88, 95 % CI: [-17.77, -1.99]), insulin (WMD: -1.32, 95 % CI: [-2.43, -0.21]), assessment of the homeostasis model — insulin resistance (WMD: -0.42, 95 % CI: [-0.73, -0.12]) and total cholesterol (WMD: -15.38, 95 % CI: [-26.50, -4.25]), but not fasting blood sugar, lipid profile, or tumor necrosis factor-alpha [122].

Meta-analysis in 2019 — 15 randomized controlled trials involving 782 patients with NAFLD has indicated that the addition of probiotics and synbiotics reduced the severity of hepatic steatosis according to the results of ultrasound diagnostics, reduced the serum levels of alanine aminotransferase, aspartate aminotransferase, triglycerides, total cholesterol, high density lipoprotein, low density lipoprotein and tumor necrosis factor-alpha (all indicators $p < 0.05$). The supplement did not improve body mass index ($p = 0.99$), waist circumference ($p = 0.57$) and fasting blood sugar ($p = 0.39$) [123]

Similar results are shown in meta-analyses published in 2021. H. Jin analyzed the results of 22 randomized controlled trials (RCTs) (1301 participants) comparing treatment with prebiotics, probiotics and synbiotics. Efficacy criteria were normalization of aspartate aminotransferase, alanine aminotransferase, total cholesterol, high-density lipoprotein and low-density lipoprotein, as well as body mass index. [124]. The study by R. Yang et al. included 9 RCTs involving 352 patients with NAFLD. The results of the meta-analysis showed that in the probiotic therapy group there was a significant decrease in the levels of serum indicators: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total cholesterol compared with the control group. Probiotic therapy was not associated with changes in body mass index (BMI) [125].

Currently, the questions remain open — which particular strain of probiotics have the maximum effectiveness against NAFLD, what should be the optimal duration of treatment and dosing regimens of probiotics. The identified problems are the subject of future research.

Conclusion

Improvements in methods for assessing the metabolome allow expanding the range of understanding of the pathogenesis of many diseases. Currently, studies are described that evaluate the role of microbial metabolites in the development of NAFLD.

However, a number of processes that affect the liver, leading to the development of inflammation, remain unclear. Of particular interest is a more targeted study of certain types of molecules with the subsequent development of the new methods of prevention and treatment.

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