Mechanisms of nonalcoholic fatty liver disease induced by antibiotic resistance and evaluation of bacteriophage-efficacy

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. With the deepening understanding of NAFLD, more and more evidence has shown that NAFLD is a group of highly heterogeneous diseases, which is closely related to metabolic dysfunction. Recent studies have shown that the occurrence of nonalcoholic fatty liver disease is closely related to the dysbiosis of intestinal flora. However, due to the abuse of antibiotics, long-term use of broad-spectrum antibiotics is the most common cause of intestinal flora disorders. Endocrine and metabolic disorders caused by intestinal microbiota imbalance promote the occurrence of obesity, and on this basis induce the emergence of NAFLD. In response to the current situation of antibiotic resistance pandemic, phage therapy has emerged as a potential solution to solve the problem of bacterial resistance. Relevant clinical studies have shown that fecal bacterial transplantation (FMT) can improve the clinical symptoms of patients with chronic liver disease, in which phage participate in the regulating effect. This suggests that phages may play a role in the treatment of non-alcoholic fatty liver disease caused by antibiotic resistance, but there is insufficient clinical evidence to support this therapy. Therefore, this review will discuss the mechanism of non-alcoholic fatty liver disease caused by antibiotics resistance and evaluate the therapeutic effect of bacteriophages.
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**Keywords:**
antibiotic tolerance; obesity; intestinal microbiota; nonalcoholic fatty liver disease; bacteriophage therapy

**Abbreviation list:**
1. nonalcoholic fatty liver disease: NAFLD
2. fecal bacterial transplantation: FMT
3. fatty acid β-oxidation: FAO
4. non-alcoholic fatty liver: NAFL
5. nonalcoholic steatohepatitis: NASH
6. sterol regulatory binding protein-1C: SREBP1c
7. carbohydrate response element binding protein: chREBP
8. peroxisome proliferator activated receptor γ: PPAR-γ
9. nuclear factor-kappa B: NF-kB
10. N-trimethyl-5-aminopentanoic acid: TMAVA
11. receptor-binding proteins: RBPs
12. lipopolysaccharide: LPS
13. gut vascular barrier: GVB

**1. Introduction:**
Antibacterial drugs are one of the most widely used drugs in clinical practice. They are mainly used to inhibit and kill bacteria and treat diseases by eliminating pathogenic bacteria. However, in recent decades, due to the overuse of antibiotics and the spread of drug-resistant bacteria, the phenomenon of bacterial drug resistance has become more and more common. Bacterial resistance refers to the tolerance and resistance of pathogenic microorganisms to the effects of antibacterial drugs. It is the result of a combination of antibacterial drugs, the bacteria themselves and the environment [1]. The emergence of bacterial resistance leads to the inactivity of antibiotics to play their due efficacy, which increases the difficulty in the treatment of clinical infections. In order to achieve the therapeutic effect, increasing the dosage of antibiotics will undoubtedly increase the adverse reactions of drugs to the human body, such as the increase of drug-induced infections. In addition, bacterial resistance is also prone to lead to microbiome abnormalities, namely, dysbiosis. Dysbiosis can lead to autoimmune diseases, gastrointestinal diseases, allergies, infections, obesity and other metabolic diseases. Studies have shown that bacterial resistance is linked to metabolic diseases, and that exposure to antibiotics during critical periods of early development may affect the development of weight gain and obesity, with the
gut microbiome playing a key role in this process [2,3]. Dysregulation of intestinal flora can lead to obesity and NAFLD by regulating fat metabolism, reducing the activity of lipolysis genes, increasing the activity of lipid-raising genes, and activating inflammatory reactions [4].

In order to effectively deal with the adverse reactions caused by bacterial drug resistance, a series of alternative or auxiliary antibiotic treatment methods have emerged, such as antibiotic adjuvant, vaccine, metal ion antibacterial agent, phage therapy and so on. Bacteriophage therapy is a treatment method to treat pathogen infection by bacteriophage lysis. Phages that invade bacteria play an anti-infection role by cracking bacterial cells, disrupting their metabolism and causing the bacteria to self-destruct [5]. Phage therapy is characterized by specificity and strong efficacy. There have been successful cases of using phage to treat pulmonary infection caused by Mycobacterium abscess and clear the obstacles for lung transplantation in patients with pulmonary cystic fibrosis [6, 7]. Studies have shown that phages are involved in the regulation of intestinal microbiota disorders, which may play a role in the treatment of NAFLD. Therefore, phage therapy as a response to the emergence of antibiotic resistance may be a therapeutic target for metabolic diseases such as NAFLD. Here we briefly review the mechanisms of bacterial resistance to nonalcoholic fatty liver disease and the efficacy of phage therapy.

2. Pathophysiological mechanism of nonalcoholic fatty liver disease:

2.1 Pathogenesis:

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and global prevalence is increasing rapidly, currently estimated at 25.24% [8]. NAFLD is a disease characterized by hepatic lipid accumulation and insulin resistance, which is induced by the disorder of glucose and lipid metabolism. It is a heterogeneous and multifactorial disease with a variety of pathogenic mechanisms, including neo-hepatic adipogenesis, oxidative stress, insulin resistance, inflammasome activation and fibrosis, and is closely related to obesity, dyslipidemia, type 2 diabetes and metabolic syndrome [9-12]. Studies have shown that insulin resistance (IR) is the initiator of NAFLD, and the prevalence of NAFLD is five times higher in diabetic patients than in non-diabetic patients. IR can be involved in the progression of NAFLD through regulation of lipolysis and de novo adipogenesis rates, impaired mitochondrial fatty acid β-oxidation (FAO), changes in fat distribution, and changes in gut microbiome and gut microbiota. The pathologic progression of NAFLD follows a "three-strike" process (i.e., steatosis, lipotoxicity, and inflammation [13,14]). The process includes non-alcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), Nash-related cirrhosis and hepatocellular carcinoma [15,16].

2.2 The role of obesity in nonalcoholic fatty liver disease:

Obesity is evaluated as the most common and well-documented risk factor for NAFLD [17,18], which contributes to the development of non-alcoholic fatty liver disease through inflammation, abnormal release of adipokines, increased free fatty acids, and ectopic storage of triglycerides.

The definition of hepatic steatosis is the presence of fat accumulation in > 5% of liver cells [19]. Hepatic steatosis is caused by the interplay of diet, gut microbiota, genetic factors, and promotion of de novo fat synthesis by upregulation of adipogenic transcription factors such as sterol regulatory binding protein-1C (SREBP1c), carbohydrate response element binding protein (chREBP), and peroxisome proliferator activated receptor γ (PPAR-γ) [20-22]. Obesity produces excess circulating free fatty acids by accelerating fat decomposition and reducing the uptake of fatty acids in subcutaneous adipose tissue, which often results in ectopic fat accumulation (e.g., in liver, skeletal muscle) due to the reduced capacity of adipose tissue to store excess lipids. When additional lipids, mainly in the form of triglycerides, are stored in liver cells, this results in hepatic simple steatosis.

NASH occurs when the liver is not controlled in the stage of simple steatopathy, where histopathologic examination reveals steatosis of more than 5% with hepatocellular balloon degeneration and lobular inflammation. During this process, immune cells in the liver release cytokines that alter lipid and glucose metabolism and create a pro-inflammatory environment that triggers the development of nonalcoholic steatohepatitis. At the
same time, the accumulation of visceral fat further promotes inflammation by evoking nuclear factor-kappa B (NF-kB) activation and proinflammatory cytokine production [14]. In addition, the level of intestinal endotoxin in obese patients is often higher than that in normal people. When the integrity of the intestinal barrier is impaired by the dysbiosis caused by antibiotics, lipopolysaccharide is heterotopically transmitted into the blood and triggers an inflammatory response, contributing to NAFLD.

When liver cells fail to inhibit inflammatory damage, such as oxidative stress, dysregulation of the unfolded protein response leading to endoplasmic reticulum stress, lipid toxicity, and apoptotic pathways, further liver damage and fibrosis will eventually lead to cirrhosis and even hepatocellular carcinoma. During fiber formation, immune cells interact with wound-healing cells in the liver, including activated endothelial cells, myofibroblasts, and progenitor cells, to successfully repair damaged liver tissue under normal conditions. But when this mechanism is out of work (for example, persistent obesity), fibrosis occurs. HSC is a key cell involved in liver fibrosis by being activated and differentiating into myofibroblasts. Activated HSC can promote liver fibrosis through the following pathways: leading to extracellular matrix deposition and fibrosis through actin and collagen expressed by myofibroblasts; inducing granulocyte-macrophage colony stimulating factor and interleukin-15 to further lead to liver injury and fibrosis; specifically upregulating genes associated with fibrosis [23].

Obesity also promotes liver fibrosis through adipokines (e.g., leptin, adiponectin), hormones derived from adipose tissue, such as adiponectin (an anti-fat, anti-inflammatory, and anti-fibrotic adipokine), which reduces in response to hepatic adipose degeneration [24]. During the enlargement of adipose tissue, the secreted adipokines change into more adipogenic, inflammatory, and fibrous traits and interact with immune cells to promote fibrosis [25].

3. Imbalance of intestinal flora caused by bacterial resistance promotes NAFLD

In the occurrence and development of non-alcoholic fatty liver disease, the imbalance of intestinal flora and the destruction of the integrity of the intestinal barrier can often be observed [26, 27], which will promote the generation of chronic liver inflammation and induce insulin resistance. Consequently, these metabolic disorders ultimately further promote the occurrence and development of alcoholic fatty liver disease. Long-term use of broad-spectrum antibiotics can inhibit the intestinal sensitive bacteria and promote proliferation of drug-resistant bacteria, which is the most common cause of intestinal microbiome disorders.

The mechanisms of intestinal flora and nonalcoholic fatty liver disease mainly include: intestinal endothelial barrier dysfunction promoting systemic bacterial translocation; producing bacteria-derived toxins to activate liver macrophages to release pro-inflammatory cytokines and stimulate inflammatory responses; influencing the development of the disease by producing SCFAs, LPS and endogenous ethanol; stimulating the synthesis of triglycerides in the liver to regulate the endocannabinoid system and choline metabolism and the balance of bile acids.

3.1 Intestinal endothelial barrier dysfunction:

Studies have shown that disruption of the intestinal epithelial barrier and the gut vascular barrier (GVB) are early events in the pathogenesis of NASH, and GVB damage leads to translocation of bacteria or bacterial products into the bloodstream [28, 29]. The use of antibiotics not only leads to the imbalance of intestinal flora and the damage of intestinal barrier, but also impairs the gut-liver axis. The liver is overloaded with intestinal antigens, resulting in inflammatory changes [15]. High-fat diets cause intestinal dysbiosis, which in turn leads to GVB impairment and promotes the translocation of bacteria or their products into the liver [30]. The typical characteristics of intestinal flora in the progressive stages of NAFLD include decreased microbiome diversity, increased abundance of Gram-negative bacteria, mainly proteobacteria [31], and decreased abundance of Gram-positive bacteria, mainly firmicutes can produce butyrate [4, 32]. The proliferation of proteobacteria is often considered as a potential diagnostic marker of ecological disorders and disease risk [33]. Several studies have found reduced fecal fecal abundance in both obese and non-obese NASH patients [34], and reduced ruminococcus in obese NAFLD patients [32]. Klebsiella pneumoniae was present in 60% of the Chinese cohort of NAFLD patients [35] and injection of the strain into mice induced...
steatohepatitis. NAFLD patients also had a decrease in enterovirus diversity and a corresponding decrease in phages [36].

Studies have shown that Imbalance of intestinal flora not only increases intestinal permeability to intestinal microorganisms, but also leads to liver exposure to harmful substances and promotes liver adipogenesis and fibrosis. Advanced liver fibrosis secondary to NASH is associated with an overall decline in gut bacterial diversity and an increase in the relative abundance of Gram-negative bacteria such as Bacteroides and Escherichia coli [26,37].

3.2 Activation of liver macrophages by endogenous toxins:

Endogenous toxins activate liver macrophages: a hallmark of NAFLD is increased macrophage activity. Macrophages in the liver are Kupffer cells and can be activated by endotoxins, fatty acids, cholesterol and its metabolites, and molecules associated with liver cell damage. Macrophages amplify the inflammatory response by secreting inflammatory cytokines and recruiting monocytes. Studies have shown that both NAFLD patients and animals have elevated serum LPS levels, and chronic low-grade inflammation induced by LPS is considered to be a key factor in the progression of NAFLD [38,39]. Toll-like receptor 4 (TLR4) is a pattern recognition receptor for LPS and a variety of free fatty acids [40]. Lps-induced activation of TLR4 causes Kupffer cells to secrete inflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α) and chemokines, leading to liver injury and NASH. Mice lacking TLR-4 were resistant not only to LPS-induced obesity and NAFLD, but also to HFD-induced obesity and NAFLD. Although macrophages can participate in liver remodeling after liver cell injury by promoting tissue repair, they also promote liver fibrosis.

3.3 Bacterial metabolites affect disease progression:

Bacterial metabolites affect disease progression: Bacterial metabolites such as short-chain fatty acids, ethanol, N-trimethyl-5-aminopentanoic acid, indole and its derivatives, mediate the regulation of intestinal microbiota and host inflammatory responses. For example, butyrate in short-chain fatty acids is an effective anti-inflammatory mediator, which can reduce local inflammation in the intestine and prevent the progression of inflammatory responses to systemic circulation [41]. Reduced levels of butyrate production in NAFLD may lead to increased intestinal permeability and an increased risk of bacterial and LPS translocations into the systemic circulation [41,42]. Indoles, produced by bacteria acting on tryptophan, enhance the intestinal barrier and reduce inflammatory responses [43], and were significantly reduced in high-fat diet mice and NAFLD patients. The metabolites TMAVA produced by intestinal flora inhibit mitochondrial fatty acid oxidation by increasing lipolysis and decreasing carnitine levels, which plays an important role in liver steatosis, exacerbating fatty liver induced by high fat diet, increasing free fatty acids, and changing microbial diversity [44]. In addition, microbial fermentation in the gut can also lead to endogenous alcohol production. In the absence of exogenous alcohol intake, increased endogenous ethanol production by the microbiota can also lead to the development and progression of NAFLD [27, 45, 46].

Among the microbial flora, Clostridium butyricum plays an important role in fat production, which can be reduced by bacterial wall components and butyrate [47]. Clostridium butyricum can inhibit adipose deposition and reduce adipose gene expression by increasing the frequency of adipose tissue-resident regulatory T cells [48]. Studies also have shown that a high fat diet can reduce clostridium butyricum levels, and the total bacteria and clostridium butyricum levels in obesity-prone rats are reduced compared with those in obesity-resistant rats. Clostridium butyricum also has protective effects on the liver. It can improve inflammatory tension by increasing the activity of antioxidant enzymes (superoxide dismutase and catalase) and oxidative stress sensors, and protect the liver by antioxidant and anti-inflammatory effects, thereby reducing acute liver injury [49].

3.4 Disorder of bile acid metabolism:

The relationship between gut microbiota and NAFLD also depends on changes in bile acid metabolism. Bile acids not only promote the absorption of lipid in the intestinal tract, but are increasingly being appreciated as complex metabolic integrators and signalling factors [50], especially secondary bile acids [51, 52]. Intestinal
microbiome can convert primary bile acids into secondary bile acids. Disturbed bile acid metabolism has been observed in NAFLD. The number of bacteria converting primary bile acids into secondary bile acids is reduced [52], resulting in insufficient activation of bile acid receptors FXR and TGR5 [53,54], which further disrupts the gut microbiome and energy balance. It has been shown that reduced taurine levels promote the occurrence of NAFLD in mice. It is also reported that Obeticholic acid treatment led to improved insulin sensitivity, suppressed hepatic inflammation and reduced fibrosis in patients with NAFLD [55].

Therefore, the imbalance of intestinal flora caused by antibiotic resistance may lead to obesity and liver inflammation, and obesity will further lead to non-alcoholic fatty liver disease. Bacteriophage therapy is expected to be an important therapeutic target for the prevention and treatment of obesity and non-alcoholic fatty liver disease by solving the problem of antibiotic resistance and reducing the impact of antibiotic therapy on the intestinal micro-ecosystem.

4. Phage therapy

4.1 Definition of bacteriophages and mechanisms for treating bacterial resistance:

Bacteriophage is a virus that can specifically attack bacteria. It is composed of nucleic acid (DNA or RNA) and protein, which can effectively destroy the defense system of bacteria [56, 57]. Therefore, the use of bacteriophage therapy instead of antibiotic therapy or the combination of bacteriophage and antibiotics in treatment has broad prospects in dealing with the problem of antibiotic resistance.

Phages can be classified as mild phages and lytic phages. Mild phage infects host bacteria and integrates its genes into bacterial chromosomes without proliferation. Lytic phages replicate and proliferate in host bacteria, producing numerous progeny and eventually lytic host bacteria [5, 58]. Phage therapy usually utilizes lytic phages [59, 60]. Lytic phage-infected bacteria first need to be specifically recognized by their tail proteins and adsorbed to host bacteria surface receptors. Tailed phages release their daughter phages by lysis peptidoglycan on the cell wall.

4.2 Mechanisms of phage therapy for NAFLD:

4.2.1 Targeting specific pathogenic bacteria:

Bacteriophage therapy is highly host-specific. Phage-encoded receptor-binding proteins (RBPs) allow phage to located on the outer surface of bacterial cells with high affinity LPS, lipoteichoic acid, capsular polysaccharides, flagella, and pili, selectively reducing pathogenic or inflammatory bacteria in the microbial environment [36, 61]. Swapping domains or changing the sequence of specific regions of the RBPs results in host-scope-specific changes that allow the phage to attach to different strains or different bacterial genera [36, 62].

Several experiments focusing on the therapeutic use of phages have demonstrated that the use of phage preparations can effectively eliminate pathogens in gastrointestinal diseases. Although the therapeutic effect of phages may be limited to reducing the number of pathogens to the point where the immune system can effectively control their reproduction, a small dose of phage administration allows the infected bacteria to replicate in situ and produce more phages, exerting a potent therapeutic effect.

4.2.2 Stabilize intestinal microecology

Phages offer a new and selective way to alter the gut microbiome, thereby affecting the gut environment without causing the overall disturbance that could lead to microbial dysregulation [63]. Evidence suggests that phage treatment, compared with antibiotic treatment, shows a reduction in E.coli, a lower proportion of potentially pro-inflammatory bacteria, and an increase in butyrate producing fermentative groups such as Clostridium butyricum, indicating a shift to a healthier environment in the gut [64]. Studies have shown that circulating IL-4 is reduced in phage treated rodents, which may play an anti-inflammatory role by lowering LPS levels. Lytic phages can not only knock out bacterial targets, but also affect non-susceptible species in the intestinal symbiotic bacterial community through a cascade effect, and ultimately regulate the intestinal microecological environment. In previous cases, probiotic bacteria were used to improve liver function and
were successfully used in the treatment of NAFLD [65]. Different probiotics may play a role in improving intestinal microecology by changing the composition of intestinal flora, producing antimicrobial peptides, reducing intestinal permeability, or preventing translocation of bacterial products [66, 67]. This suggests that if phage therapy can play a similar mechanism of action, its reliability in the treatment of NAFLD will be further enhanced.

4.2.3 Reduce the use of antibiotic:

Phages produce peptidoglycan hydrolases and polysaccharide depolymerases when they infect bacteria. Phage-derived depolymerases can target and remove bacterial capsular and biofilm structures by destroying the extracellular matrix, increasing the permeability of antibiotics into the inner layer of biofilm, and inhibiting its formation by stopping the quorum-sensing activity [68, 69], enabling better access of antibiotics into cells, which is of great significance in the treatment of bacterial drug resistance. And studies have shown that sublethal concentrations of antibiotics can greatly increase the ability of lytic phages to produce themselves. Bacteriophages in combination with antibiotics can cooperate to lyse host bacteria and better control or eradicate bacterial infections. Using the "order" effect of phage in combination with antibiotics can provide effective treatment for MDR. Therefore, if phage can be used reasonably to treat infectious diseases, it will reduce the use of antibiotics to a certain extent, and effectively control the intestinal flora disorder caused by antibiotic resistance, which has a broad prospect in the treatment of obesity and non-alcoholic fatty liver disease caused by bacterial resistance.

5. Evaluation of phage therapy:

5.1 Advantages of phage therapy:

A growing number of studies suggest that phage therapy is superior to antibiotics. First, phages are so specific to their host that they can target specific disease-causing bacteria without affecting the normal flora in the body [6], thus minimizing the chance of secondary infections compared to antibiotics. Second, phages replicate at the site of infection where they are most needed to lyse pathogens, accumulating at the site of infection concentration, and can be administered in small doses with high potency. Moreover, phages are not toxic, they only attack bacteria but human cells, and the side effects of phages on humans are barely [70-72]. Finally, phages are environmentally friendly, based on natural selection, and the process of bacterial isolation and identification is very fast and relatively inexpensive compared to the development of new antibiotics [73].

Although the use of phage therapy has not been evaluated in NAFLD, preclinical data support its use in alcohol-related liver disease. Phage therapy has been tested in a mouse model of alcoholic hepatitis, and humanized mice treated with phages targeting Enterococcus faecalis hemolyticus resulted in a reduction in alcoholic liver disease without altering liver ethanol metabolism or the overall microbial community of intestinal components [35, 74], showing the potential therapeutic prospect of phage therapy.

5.2 Limitations of phage therapy

One of the major limitations of phages is that the host spectrum is too narrow, and the specificity of phages is the reason for this limitation. Because a phage typically targets only a limited number of bacterial strains and cannot kill all of the bacteria that agree, this means that many different phages are needed to treat a bacterial infection. There may not be enough phages to treat all bacterial infections, as opposed to broad-spectrum antibiotics. In addition, the pharmacokinetics of bacteriophages and the mechanism of bacterial resistance remain unknown, and bacteria may resist phage attack through spontaneous mutation, restrictive modification system, and adaptive immunity through CRISPR-CAS system [58].

6. Summary and Outlook:

Currently, management of NAFLD is mainly based on lifestyle interventions (including low-calorie diet, exercise, and weight loss) and early treatment of patients with cardiometabolic risk factors. There are many drug targets for NASH, one of the reasons is that the pathogenesis involves metabolism, inflammation, insulin resistance and liver fibrosis. Based on the complexity of the pathogenesis of NASH and the clinical efficacy
and side effects of existing drugs, in order to improve the efficacy and reduce side effects, the combination of drugs for different targets has become a new trend in clinical research and development. Drugs used in the treatment of NAFLD include lipid-lowering agents, antioxidants, insulin sensitizers, cytoprotective agents, bile acid metabolism regulators, probiotics, etc. Intervention of gut microbiota has become a new target for the treatment of NAFLD. Existing research results show that the possibility of using microbiotics in the theoretical treatment of NAFLD can be explained from the perspective of gut microbiota and "gut-liver axis". Restoring the balance of intestinal microbiota is expected to become an important part of the comprehensive prevention and treatment of NAFLD. Studying the mechanism of intestinal microbiota on the pathogenesis and progression of NAFLD can better guide clinical treatment, and intervention against intestinal microbiota may also become a therapeutic target for NAFLD in the future. This review examines the mechanisms of bacterial drug-resistant nonalcoholic fatty liver disease and evaluates the efficacy of phage therapy in a model of bacterial drug-resistant fatty liver disease. These results indicate that phage may have therapeutic effects on nonalcoholic fatty liver disease by targeting specific pathogenic bacteria, improving intestinal microecological mechanism and reducing antibiotic use, indicating the possibility of its clinical application. However, phage therapy has limitations, such as a narrow antimicrobial spectrum and how to combat the production of phage bacterial variants. Moreover, phage therapy targeting the intestinal microbiota of liver disease has not been studied outside of mouse models, and needs to be further evaluated not only for efficacy, but also for clinical safety in humans. More studies of phage therapy are needed in the future to verify its feasibility.

Reference:


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