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Research Progress of Intestinal Flora and High Fat Diet Obesity

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1. Abstract

Obesity is a chronic metabolic disorder caused by an energy imbalance, which is becoming an increasingly prevalent and ubiquitous problem worldwide. Its cause is complex, including genetic factors, high fat diet, intestinal tract bacterium group. The effect of intestinal flora on obesity has been widely recognized in the past few years. This article reviews the possible mechanism of intestinal flora in the occurrence of obesity, then proposes a new idea for using intestinal flora to intervene obesity.

Obesity is a chronic, relapsing progressive disease caused by abnormal or excessive fat accumulation [1, 2]. The age-standardized prevalence of obesity in adults worldwide has increased 1.5-fold since 2000, and in 2016, more than 1.9 billion adults were overweight. Crude prevalence increased from 2.9% to 6.8% in 5-19 year olds [3]. In 2018, WHO estimated that more than 650 million adults were obese. Obesity affects most physiological processes in the body, increases the risk of type 2 diabetes, cardiovascular disease and etc., and greatly increases mortality. The causes of obesity are complex, including genetics, High-Fat Diet (HFD), and intestinal flora. The intestinal flora is a complex and dynamic ecosystem that co-evolves with its host [4], It plays an important role in maintaining host health, including synthesizing vitamins, participating in food digestion and nutrient absorption, secreting small molecular substances involved in immune regulation, angiogenesis, nerve function and etc. [5, 6].There are approximately 1014 microorganisms in the human gastrointestinal tract [7], Mainly composed of anaerobic bacteria, facultative anaerobic bacteria and aerobic bacteria, it is divided into seven phylum Firmicutes, Bacteroidetes, Actinomycetes, Fusobacterium, Proteobacteria, Verrucobacterium and Cyanobacteria Category [8], Among them, Gram-positive Firmicutes and Gram-negative Bacteroidetes dominate [9]. The location of different bacteria in the intestinal tract is also different. For example, the top of the intestinal cryptovillous unit is usually dominated by Firmicutes, while the bottom is mainly dominated by Proteus [10]. The intestinal flora can be subdivided into different enterotypes, each enriched in specific bacterial genera, each with a high degree of functional consistency [11], and this consistency is not affected by the age, sex, body mass index and nationality of the host [12].

2. Intestinal Flora and Obesity

2.1. Animal Experiments Show that Intestinal Flora is Associated with Obesity

Experiments found that germ-free mice did not develop obesity and its metabolic complications, and related symptoms occurred after transplanting the cecum or fecal microbiota of obese mice into germ-free mice, indicating that intestinal flora is involved in the pathogenesis of obesity [13], obesity phenotype can be transmitted by intestinal flora [14, 15].

2.2. Population Study Finds Differences in the Distribution of Intestinal Flora in Obese People

The mother's womb is traditionally considered sterile [16], the intestinal flora is colonized after birth, and its diversity is influenced by a variety of factors, including mode of delivery, type of feeding, and administration of drugs (including antibiotics) [17], establish a complex and stable intestinal flora similar to adults at the age of three [18], remain relatively stable in adulthood. Demographic survey

found significant differences in intestinal flora composition between obese and general populations [19]. Some studies suggest that a high proportion of Firmicutes/Bacteroidetes can be regarded as a feature of "obesogenic enterotypes" [20]. However, due to differences in sample size, individual clinical and anthropometric characteristics (age, gender, microbiota distribution and obesity severity), and microbiota analysis methods used (qPCR, 16S rRNA gene sequencing and fluorescence in situ hybridization) ,the distribution of sexual flora is still controversial [21, 22].

3. High-fat diet alters gut permeability and causes obesity-related changes in intestinal flora

The human gut flora changes with the physiological state of the digestive system and diet structure [23, 24], even respond quickly to dietary changes within 24 hours [25].

HFD results in significant changes in the number of different gut bacteria, accompanied by a reduction in the diversity of intestinal flora [26], decreased bacteria that protect the intestinal mucosal barrier [27], bacteria that disrupt gut barrier integrity increase [28]. If the abundance of Firmicutes is relatively increased, the abundance of Bacteroidetes is relatively decreased [29], decreased numbers of Bifidobacterium in Actinobacteria and elevated numbers of Desulfovibrio, increased plasma bacterial Lipopolysaccharide (LPS) concentrations, excess sulfate reduction to hydrogen sulfide, disruption of the intestinal barrier, and promotion of inflammation happened [30, 31]. Akkermansia muciniphila (A. muciniphila) in the phylum Myxobacteria can degrade mucin, protect the intestinal mucosal barrier and have anti-inflammatory properties, and its relative abundance is reduced under HFD and the intestinal barrier system is disrupted [32].

3.1. HFD Promotes Increased Intestinal Permeability

Previous studies have established that HFD can increase intestinal epithelial cell permeability, induce inflammation and promote obesity [33]. The main mechanisms by which HFD promotes increased intestinal permeability have been observed:

Intestinal epithelial cells under HFD consume a large amount of fat, and the energy metabolism is vigorous. The mitochondrial respiratory chain produces ATP and generates a large amount of Reactive Oxygen Species (ROS), iron, copper, aldehydes, lipid peroxides and etc. [34], Under the action of ROS, the lipid peroxidation of the phospholipid layer of the intestinal epithelial cell membrane, the cell structure is destroyed, and the permeability of the intestinal epithelial cell is enhanced [35], the intestinal barrier function is destroyed, and pathogenic bacteria such as Salmonella and Escherichia coli multiply in the intestinal cavity, and the hydrogen sulfide produced inhibits the mitochondrial respiratory chain, which is conducive to further infection by pathogens [36].At the same time, the digestion and absorption of high dietary fat will also produce iron, copper, aldehydes lipid peroxides and etc., which will increase the level of oxidative stress in the intestinal tissue, destroy the living environment of the flora and lead to the imbalance of the intestinal flora.

HFD is rich in polyunsaturated fatty acids, in which the double bonds are prone to oxidation [37], derived free fatty acids act directly on the gut immune system [38], induces the increase of barrier-destructive cytokines such as TNF-α, IL-1B, IL-6, IFN-γ, and the decrease of barrier-protective cytokines such as IL-10, IL-17, and IL-22, and enhances intestinal permeability [39], pathological changes such as low-grade inflammation, decreased expression of antimicrobial peptides, decreased mucus secretion, and decreased expression of tight junction proteins [40], This in turn affects the functioning of multiple systems in the body, leading to obesity and its metabolic complications (insulin resistance, hyperglycemia, systemic inflammation and dyslipidemia) [41-43].

The intestinal barrier system is composed of mucus layer, Intestinal Epithelial Cells (IECs), Tight Junctions (TJs), immune cells and intestinal flora [39].TJs and Adhesive Junctions (AJs) exist in the form of membrane proteins and form the Apical Junctional Complex (AJC) [44]. AJCs connect with adjacent IECs to form a closed lumen that selectively allows the passage of nutrients and inhibits isotonicity of toxins and antigens, thus leading to hyperpermeability of the gut when the integrity of AJCs is reduced. Dietary fat can act directly on AJC, affecting its integrity [45-47]. Intestinal TJ protein expression is reduced under chronic HFD [48], Intestinal occlusive zone-1 (ZO-1) and occlusive protein gene expression decreased and intestinal permeability increased [49].

HFD contains a large amount of gamma-linolenic acid and docosahexaenoic acid, which can stimulate protein kinases, mediate actin and TJ protein redistribution, and enhance intestinal permeability [50], In addition, some eicosapentaenoic acids in HFD can be converted into bioactive metabolites to enhance intestinal permeability [51].

There is a direct positive correlation between dietary fat intake and bile acid secretion [52], Under normal physiological conditions, IECs can resist the dissolution of bile acids, HFD stimulates long-term high-level secretion of bile acids, and a large number of hydrophobic bile acids, such as lithocholic acid and deoxycholic acid [53], causes AJC dissociation by activating occlusin dephosphorylation [54], enhance intestinal permeability [55], damage the intestinal mucosal barrier [56], even induce a series of reactions such as IEC oxidative stress and apoptosis intensified [57]. The peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway is inhibited in mice under HFD [58], disruption of the intestinal mucus layer with reduced electrolyte secretion and reduced mucosal immune defense.

3.2 Increased Gut Permeability Promotes Gut Dysbiosis and Mediates Obesity and Related Metabolic Disorders

Under HFD, the permeability of intestinal epithelial cells is enhanced, the balance between intestinal mucosal immunity and intestinal flora is broken, and the structure of the flora changes, which eventually leads to dysbiosis [47]. Among them, the proportion of Gram-negative bacteria increases, and the LPS produced binds to the CD14/Toll-like receptor 4 (Toll-like Receptor 4, TLR4) complex

of intestinal epithelial cells, triggering innate immunity and causing persistent local and systemic low levels. Horizontal inflammation aggravates the destruction of the mucus layer and the increase in the permeability of IECs, making it easier for the metabolites of the intestinal flora to enter the blood from the intestinal lumen, resulting in a vicious cycle of dysbiosis—continuous activation of the LPS/TLR4 signaling pathway—inflammation. Key links leading to obesity and related metabolic disorders [59-61].

4. Intestinal Flora Interferes with Host Metabolic Regulation and Participates in Obesity

4.1. Intestinal Flora is Directly Involved in the Expression Regulation of Host Metabolism-Related Genes

A study found that a intestinal flora dominated by Firmicutes can alter host methylation of gene promoters associated with lipid metabolism, obesity and inflammation [19, 62]. However, existing intestinal flora research cohorts are often too small and underrepresented at the individual level, posing significant challenges to understanding population-level patterns in the intestinal flora-obesity relationship [63], this is also the focus of future research.

4.2. Intestinal Flora Intervene in Host Glucose Metabolism through Metabolic Intermediates

The intestinal flora can influence the host's ability to obtain and store energy from the diet through short-chain fatty acids (SCFAs) [64]. Intestinal flora ferment soluble dietary fiber and resistant starch to produce SCFAs [65]. Includes acet ate, butyrate, and propionate. SCFAs bind to G protein-coupled receptors GPR41 and GPR43 合 [66-68]. Modulate molecular signaling pathways that indirectly affect gene expression, such as increased expression of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) in the gut [38], both peptides suppress appetite [69, 70], reduces body weight, improves insulin resistance in obese mice [71, 72], but PYY also reduces intestinal transit and may increase the absorption of nutrients including SCFAs leading to weight gain [73, 74]. Decreased levels of PYY in plasma in the absence of GPR41 signaling lead to increased intestinal motility and reduced energy gain from meals [75]. Acetate can act on the parasympathetic nervous system, positively upregulate insulin and ghrelin secretion and appetite, and promote obesity and related complications [76]; propionate activates the sympathetic nervous system, increases glucagon and fatty acid-binding protein secretion, leads to insulin resistance and hyperinsulinemia, and promotes obesity and metabolic abnormalities [77]. Therefore, SCFAs appear as mediators linking food, intestinal flora, and body physiology, and the changes in their number and types and obesity need to be further studied.

4.3. Intestinal Flora Interferes with Host Lipid Metabolism by Affecting Enzyme Activity

Bäckhed et al. suggest that changes in specific intestinal flora lead to obesity through several mechanisms: intestinal flora promotes the absorption of monosaccharides in the gut, leading to increased hepatic triglyceride synthesis; intestinal flora induces inhibition of lipids Fasting-Induced Adipocyte Factor (FIAF), a central regulator of metabolism, leads to enhanced Lipoprotein Lipase (LPL) activity in adipocytes and increased fatty acid storage in adipocytes [8].

FIAF, also known as PPAR-gamma angiopoietin-associated protein, is a cell signaling glycoprotein hormone, an adipokine produced by White Adipose Tissue (WAT), gut, liver, heart, skeletal muscle [78, 79]. Studies have found that intestinal flora fermentation products such as SCFAs promote the increase of FIAF expression in intestinal cells through PPAR-γ. [80], inhibits LPL, stimulates WAT lipolysis [81]; intestinal flora stimulates adipogenesis by inhibiting FIAF expression [82], therefore, FIAF may be a regulatory factor for the intestinal flora to interfere with lipid metabolism and participate in the occurrence of obesity.

The Endocannabinoid system (EC) system is involved in the regulation of blood lipid and blood sugar metabolism, and its overactivation is an important risk factor for obesity. EC system activity can be modulated by specific intestinal flora [83], such as A.muciniphila. LPS can interfere with body fat metabolism by blocking EC-driven lipogenesis [84], promotes adipocyte proliferation and fat accumulation in adipocytes [85].

5. Summary and Outlook

It is now clear that the distribution of intestinal bacteria in obese individuals is different from that of normal-weight individuals, and the results of animal microbiota transplantation experiments suggest that the intestinal microbiota may play a key role in the development of obesity and related metabolic disorders. The intestinal flora participates in energy metabolism by obtaining energy from the diet, regulating fat storage, regulating lipogenesis, or regulating fatty acid oxidation. It is currently considered to be a new method for improving high-fat diet-induced obesity, reducing systemic inflammation, and participating in weight management. the point of intervention. Researchers have tried to intervene in intestinal bacteria to treat obesity and have achieved preliminary results. Some specific flora have been shown to restore the balance of intestinal flora by increasing the number of bacteria, improving intestinal epithelial barrier function and regulating the production of cytokines. But the human intestinal flora is a research field full of great challenges and potential, many factors affect the composition of intestinal flora, such as season, diet, exercise, drugs, country and gender. Some of these factors are beyond control, and the complex relationships between millions of different bacterial groups, thousands of host cell types, and molecular mediators make it difficult to grasp their mechanisms. The metagenomics relationship between changes in intestinal flora composition and specific populations under HFD conditions needs to be further investigated by establishing well-designed and appropriate experimental models (in vivo or in vitro). Advances in microbiome science and analytical techniques are driving this field forward, providing insights into the link between specific intestinal flora composition and host health, and by targeting the intestinal flora to provide potential therapeutic options, are important ways to promote human health in the future.

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