Research progress on the role of intestinal flora in obesity and diabetes intervention

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ABSTRACT

Objective: In recent years, obesity has become an important threat to human health, which can produce many health problems, obesity is an important environmental factor of diabetes, obesity and diabetes at present, has been a popular trend. The relationship between intestinal microflora and obesity are closely, intestinal flora may lead to increased body weight, insulin is low, chronic inflammation, metabolic toxicity blood, intestinal flora imbalance, may be caused by chronic inflammation, obesity and other ways to participate in the development of diabetes, therefore, study on the intestinal microflora contribute to obesity and diabetes treatment.

1. Introduction

There are about 1,000 kinds of microorganisms in the human gut, the number of microbial cells is about 10 times than the number of human cells, the number of genes is 100 times than that of the human genes, which play an important role in the material metabolism, energy transformation, immune system development, neural circuit construction, and to prevent pathogens invasion and other aspects. These microorganisms are also associated with diabetes, cardiovascular disease, IBD/IBS, colorectal cancer, cirrhosis, rheumatism, autism, Parkinson, Alzheimer's disease and so on[1-4]. Intestinal microflora is also known as the second set of genomes, which is closely related to human health.

Due to the rapid development of genomics, the upgrading of sequencing technology, and the leap in bioinformatics analysis technology, it is possible to study microbiological systems including unknown/untrained microorganisms. As a result of the discovery of new enzymes, signaling molecules and new species, and as a biomarker associated with disease, microbial macro genome research has high hopes for precision medicine.

2. Intestinal microbes and obesity

In 2004, American microbiologist Gordon found mice obesity has something to do with intestinal flora in the world for the first time[5]. Through the research of four pairs of “fat sister” and “thin sister” twin sister intestinal microbial, American and French scientists found that human fat and thin is related with the ratio of intestinal thick bacteria and Bacteroides (F/B), the fat people ratio are higher, thin people lower[6]. Another large sample population of Danish intestinal flora studies found that there were significant differences in the types and numbers of intestinal flora between obese and non-obese people, people with low genetic abundance of intestinal flora are more likely to develop systemic obesity, insulin resistance, lipid metabolism disorders, and more pronounced chronic inflammatory phenotypes than those with high genetic abundance[7]. Intestinal bacteria can be divided into "thin bacteria" and "fat bacteria": thin bacteria can increase the intestinal short-chain fatty acids (acetic acid, propionic acid, butyric acid, etc.) synthesis, inhibit fat accumulation, increase energy consumption, promote leptin (Satiety hormone) secretion, so that mice become thinner, and fat bacteria increase the mouse intestinal amino acid synthesis, so that mice become obese, and produce insulin resistance[8]. Chinese scientist
Professor Zhao Liping for the first time identify the world's first obese bacteria in the level of bacteria, this enterobacter cloacae come from obese patients can produce endotoxin, the bacteria transplanted to sterile mice, the mouse fat consumption gene closure, fat synthesis gene activation, causing severe obesity and insulin resistance in mice[9].

Scientists at the University of Geneva, Switzerland, have used another way to confirm the effect of intestinal flora on obesity, they found that removal of intestinal flora can block obesity. In the high fat diet, mice treated with intestinal flora showed better glucose tolerance and insulin sensitivity, low fat low body mass index, producing beige adipose tissue that could burning more energy for the body[10]. Belgian Everard et al. found that A.muciniphila in the intestinal tract reduced obese mice by nearly half of their excess weight without changing their diet, accompanied by a reduction in the level of insulin antibodies. Another study found that the abundance of A. muciniphila in the diet induced obese mice was 100 times lower than that of the control mice, and Akkermansia muciniphila was found and isolated, which was important for fat and lean[11]. A. muciniphila can reduce insulin tolerance, control fat storage, fat metabolism, glycerol and glucose homeostasis. In 2016, Nature Medicine reported a membrane protein Amuc-1100 isolated from the outer membrane of A. muciniphila, interacting with Toll-like receptor II to improve the metabolism and intestinal barrier function of obese and diabetic mice, to achieve probiotic function independently[12]. From the above studies we can see that the correlation between obesity and intestinal flora has gone through three stages: first found flora activity and structural composition in the intestinal between obese and non-obese people were significantly different. Further discovery of intestinal flora abundance, structural changes can affect the outcome of obesity. At present, it is the focus of research to identify the partial structure of independent bacteria or bacteria that can directly participate in and affect the development of obesity.

At the same time, the researchers have focused on exploring the metabolic pathways of intestinal flora or related relationship between synthetic pathway genes and obesity complications, so as to provide a reliable basis for prevention and clinical treatment can be obese intervention.

3. Intestinal microbiology and diabetes

More and more studies have shown that type 2 diabetes is associated with intestinal flora imbalance. A study from the European MGWAS analysis in female patients with type 2 diabetes, the study found that the abundance of 4 kinds of lactic acid bacteria of the genus Lactobacillus and some Clostridium bacteria increased, accompanied by at least 5 Clostridium decreased. Researchers have developed a new mathematical model of metagenomics gene caller (MGC), using the model through the analysis of metagenomic to distinguish between type 2 diabetic patients and healthy people, and can predict which patients are at risk for diabetes. This model has better predictive value than the currently used classical predictive markers, such as body mass index and waist to hip ratio[13]. In the role of intestinal flora on the incidence of diabetes, the study found that copri and Bacteroides in the intestinal tract commonly involved in the promotion of branched-chain amino acid biosynthesis, and cause insulin resistance[14], intestinal bacteria metabolites acetic acid can also enhance rat insulin resistance[15]. The main symptoms of type II diabetes in vivo - insulin levels are also reduced by the addition of A.muciniphila bacteria to the diabetic mice without altering their diet[11]; Fasting diets (FMD) has recently been shown to promote Ngn3-driven beta-cell regeneration to reverse diabetes[16]. Further studies have found that intestinal microbial can regulate insulin-secreting cell differentiation: In the early development of zebrafish, bacteria encoding BefA (β-cell proliferating factor A) genes can induce beta cell proliferation and promote insulin secretion[17]. The A variety of drugs for the treatment of diabetes has also been shown to significantly regulate the intestinal flora, metformin can enhance the intestinal bacteria production of butyrate and propionate capacity, and increase the patients’ catabolism of glycine, tryptophan and other amino acids[18]. In addition, the intestinal-brain axis is also an important way to regulate metabolism, intestinal flora and its metabolites can regulate the hormone secretion function of intestinal endocrine cells (EEC), to regulate glucose and lipid metabolism, transmission satiety, Thereby regulating appetite and insulin secretion[19].

Therefore, the misregistered intestinal flora can be used as an important biomarker of type 2 diabetes, precise medication in metabolic pathways, cell differentiation and regeneration, neurotransmitter signaling has unprecedented potential in preventing obesity and type 2 diabetes epidemic. Modern lifestyle and high calorie foods have led to a high incidence of metabolic syndrome. Targeted regulators of intestinal microbes can be used as a new tool for the prevention and treatment of diabetes, Disease risk. Modern lifestyle and high calorie foods leads to metabolic syndrome incidence, relative to the living habits of inertia is difficult to change, targeted regulation of intestinal microbes can be used as a good tool for the prevention and treatment of diabetes mellitus in new, used to reduce the risk of metabolic diseases.

4. Intestinal microbes and cardiovascular diseases such as hypertension and hyperlipidemia

There is a close relationship between the changes in intestinal flora and the occurrence of hypertension and hyperlipidemia. In the spontaneously hypertensive mouse model (SHR), the ratio (F/B) of the thick-walled bacteria to the bacillus was increased, and the diversity, abundance and uniformity of the flora were lower than those of the normal mice. Among which Streptococccaceae abundance increased, while the abundance of certain genera of Bifidobacteriaceae and Bacteroides was reduced[20,21]. Intestinal bacteria can affect levels of neurotransmitters such as 5-serotonin, dopamine, which affect the synthesis of blood pressure related hormones. Metabolites of intestinal bacteria, such as trimethylamine (TMAO) and various types of short chain fatty acids (SCFAs), can also significantly affect the health of the human cardiovascular system[22]: the intake of phosphatidylcholine and L-carnitine through the body diet, which produce trimethylamine (TMA) after metabolism of intestinal bacteria. TMA is absorbed into human liver, oxidized trimethylamine (TMAO) at the liver, and TMAO has the side effect of promoting atherosclerosis[23], can lead to...
coronary heart disease. 2017, the domestic Cai Jun and Zha Baoli, who in the intestinal microflora professional authority Microbiome published an important discovery: intestinal flora imbalance to promote the progress of hypertension. Comparisons of macrogeome and metabolic groups in 41 healthy people, 56 hypertensive patients, and 99 primary hypertensive patients were found in patients with prehypertension and hypertension the flora imbalance is very similar, the microbial abundance and diversity decreased significantly, Probiotics significantly reduced while Prevotella and Klebsiella overgrowth. Based on the flora analysis, the researchers established a classifier that could accurately distinguish between prehypertensive and hypertensive individuals, and suggested that hypertensive characteristic flora could be used as a new biomarker to alert the risk of hypertension. From the human to the mouse fecal transplantation experiment, the first time in the international community to confirm the flora imbalance in the causal relationship induced hypertension[24].

It is due to obesity, diabetes often accompanied by high blood pressure and high blood lipids and, to understand the potential relationship of the intestinal microbial metabolic syndrome in different symptoms and various stages of progress can provide a scientific basis for preventing the progression of metabolic syndrome into high-risk complications and reduce the risk of developing simple symptoms into high-risk complications. "Treat before getting illness" ,which is the importance of health management.

5. Intestinal flora is the most important regulatory factor in metabolic syndrome

Over the past 50 years, humans have found a number of risk factors for obesity and diabetes, and over the past 10 years, scientific advances have found that intestinal flora is the most important predictor[25]. The human genome is immutable and the intestinal microbial population is variable. Flora can regulate carbohydrate metabolism, short-chain fatty acid production, insulin response and resistance, while playing a key role in the regulation of immune system, nervous and hormonal signaling, host gene expression and epigenetic processes, and is closely related to disease[26]. Genetic and environmental factors such as a-diversity reduction, inflammation, LPS, high endocannabinoid, unhealthy diet, lack of exercise, etc., can cause intestinal microbes and host balance disorders leading to host metabolic syndrome. This can be improved and repaired by regulation of intestinal flora[27]. Optimizing diet structure and improving the intestinal flora can improve the metabolic status of[28], and change rapidly through the diet induced intestinal flora[29]. The last two years, scientists have also found that metformin, berberine, and even Pueraria Decoction and other traditional Chinese medicine have an important regulatory role on intestinal microflora[30,31].

At present, the intestinal microbial population is the only adjustable factor relative to the human genome. To clarify the relationship between intestinal microbiota and human health, and find new biomarkers and therapeutic targets, which is the key to health management and disease treatment in the era of precision medical treatment. To this end, the international community have been carried out in HMP (the Human Microbiome Project, the United States, 2007-2012) and MetaHIT (EU, 2008-2010) and other large groups of microorganisms on the human body plan, symbiotic relationship between the microbiome and human health awareness has made great progress. Due to differences in genetic background and the way of life, compared with the west, Chinese metabolic syndrome has its specificity, to understand and solve the metabolic syndrome, the need for our scientists, clinicians and government cooperation and the common effort in epidemiology, diagnosis, prevention and disease treatment and other clinical research areas, and molecular mechanisms such as the incidence of basic research areas.

6. Individualized therapies of targeted flora, challenges and opportunities coexist.

Targeting flora is an exciting new therapy. The early clinical trials of targeting flora to treat Clostridium difficile infection have been successful[32]. Fecal bacteria transplantation have also brought the dawn to IBD patients. A. Muciniphila is known as the magical "thin" and weight loss effect is remarkable. Lactobacillus reuteri is expected to reverse the autism, antitumor bacteria, which play an important role in adjuvant anticancer drugs, have been discovered. Coli[33] carrying the quorum sensing factor (autoinducer-2) can restore the microecological balance between Bacteroides and Escherichia coli. All this opens the way for personalized medicine targeting intestinal microbes.

On the other hand, health management and disease treatment can be carried out accurately according to individual intestinal microbial markers. For example, Pseudomonas can prevent poor tolerance to glucose caused by Bacteroides, to promote the liver glycogen storage, intestinal Pseudomonas and Bacteroides (P/B) ratio responses with dietary fiber, for the people of Pseudomonas abundance, giving dietary fiber is more obvious to improve metabolic[34]. As a result of individual differences, even if eating the same food, different people may be have quite different postprandial blood glucose levels, recently, the Israeli scientists have developed a "machine learning" algorithm, combining intestinal flora, blood tests, health questionnaires, body measurements, and food diaries dates, the results accurately predict and alter the blood glucose levels of volunteers[35].

The human genome and the intestinal microflora group are precise medical wings, and the lack of intestine microbial group of precision medicine is incomplete. There are many kinds of intestinal microbes, large amount of sequencing data, macro-genome analysis of biological information analysis is of high technical requirements, the interaction between microbes and between microbes and human cells is complicated, and challenges and new knowledge coexist. For the study of metabolic syndrome in China, a genomic database containing a comprehensive medical information, authoritative, and open intestinal microbiology is urgently needed to be established. The understanding of the scientific problems of the occurrence and progression of metabolic syndrome needs to be more systematic and in-depth, Corresponding biomarkers and targeting bacteria/drug targets also make people look forward to it.

In summary, a better understanding of the relationship between intestinal flora and health, will be the implementation of individualized treatment of targeted bacteria, which can provide metabolic syndrome for the prevention, diagnosis and treatment to
provide scientific basis and technical means to block the occurrence of high-risk complications, it is of great significance for Chinese people to overcome metabolic syndrome.

References


