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Research on the Etiology of Type 2 Diabetes Using Gene Chips

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Abstract. Up to now the causes of type 2 diabetes have not been clarified. Gene chip technology is crucial for identifying key genes and pathways involved in type 2 diabetes, significantly advancing our understanding of its molecular mechanisms. This paper will mainly explore the assistance of gene chip technology in exploring the causes of type 2 diabetes. The results prove that the onset of type 2 diabetes mellitus (T2DM) is the result of the interaction of three core factors: obesity, genetic factors, and pancreatic β -cell dysfunction .Gene chips have considerable value in precisely analyzing the mechanism of T2DM, but current research still has problems such as insufficient sample representativeness and limited multi-omics integration. This research has enabled individuals to have a deeper understanding of type 2 diabetes and provided more ideas for its treatment.

Keywords: gene chips, type two diabetes, insulin resistance

1. Introduction

1.1. Research background

The global prevalence of type two diabetes is projected to rise from the current 150 million to 225 million by the end of the decade, potentially reaching as high as 300 million by 2025 [1]. As a metabolic disease with the highest worldwide incidence rate, type two diabetes seriously affects public health. Complications of type 2 diabetes,such as diabetic foot, cognitive dysfunction, severely harms the physical and mental health of patients, and increases the medical financial burden on ordinary families. It is proved that the vast majority of the genetic variance is attributed to numerous common variants, potentially numbering in the thousands [2]. Thus, genetic factors plays a decisive role in the occurrence of type II genetic diseases. Genetic factors may induce insulin resistance through genetic variations that regulate fat differentiation and inflammatory responses, or by causing variations in key genes in the insulin signaling pathway.

1.2. Current research status in China and other country

In bioinformatics, gene chip technology serves as a robust tool for examining gene expression levels. Utilizing a high- density nucleotide probe array, it can concurrently assess the expression of tens of thousands of genes. The current progress in China suggests that differences in the expression

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of underlying factors related to adipocyte differentiation and lipid metabolism may be associated with insulin resistance in type 2 diabetes [3].

This is one of the important directions of current metabolic research in China,and some scientific progress has already been made. For example, targeted knockout of PPA1 in adipose tissue can result in adipose atrophy, hepatic steatosis, and insulin resistance, indicating that disorders in adipose differentiation are closely linked to type 2 diabetes [4]. According to The Harvard Medical School team, RNA methylase METTL14 plays different roles in brown fat (BAT) and white fat (WAT). The absence of METTL14 in WAT promotes adipocyte apoptosis and insulin resistance, while in BAT it may improve metabolism 10 [5].

1.3. Research motivation and framework

Although majorities of studies have shown that adipocyte differentiation disorders and abnormal lipid metabolism are closely related to insulin resistance in type 2 diabetes mellitus, the molecular mechanism involved has not yet been fully studied and proven. This essay will conduct a case on the screening of differentially expressed genes in type 2 diabetes using gene chips and provide some advice on curing type 2 diabetes.

2. The pathogenesis of type 2 diabetes and the application of gene chip technology

2.1. Key pathogenic factors of type 2 diabetes

The pathogenesis of type 2 diabetes (T2DM) involves complex interaction of multiple factors, among which obesity, genetic factors and pancreatic β cell dysfunction are three core and interrelated risk factors, which promote disease progress through unique and overlapping molecular mechanisms.

Obesity is the main driving factor Unlike subcutaneous fat, visceral fat releases excessive free fatty acids (FFAs) and pro-inflammatory cytokines such as TNF - α and IL-6 of systemic insulin resistance, particularly associated with metabolically active visceral adipose tissue [6]. Free fatty acids can activate serine kinases such as JNK and IKK β, phosphorylate serine residues of insulin receptor substrate (IRS) proteins, inhibit their function, and disrupt the IRS-1/PI3K/AKT insulin signaling pathway; The pro-inflammatory cytokines further intensify their inhibitory effects, triggering chronic low-grade inflammation throughout the body. The high calorie environment in modern society can easily lead to "overnutrition", causing metabolic overload in liver cells, muscle cells, etc., forcing the tricarboxylic acid cycle and mitochondrial electron transfer chain (ETC) to overload, causing mitochondrial dysfunction, increased production of reactive oxygen species (ROS), exacerbating oxidative stress and inflammation [7]. In addition, overnutrition can induce mitochondrial dynamics abnormalities, promote excessive mitochondrial division, ETC uncoupling, and reduced ATP production, further exacerbating insulin resistance and creating conditions for the occurrence of T2DM.

Genetic factors play an important role in T2DM, making it a typical polygenic disease. Individual genetic risk is determined by the cumulative effects of multiple common variants, with each variant having a relatively small independent impact. A meta-analysis of genome-wide association studies (GWAS) on over 650000 individuals and identified 243 independent genomic loci significantly associated with T2DM risk, of which approximately half were located in non coding regions, suggesting that they may affect the disease by regulating gene expression rather than altering protein structure [8]. Key genes such as TCF7L2, PPARG, KCNJ11 mainly exert their effects by affecting

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beta cell function (insulin synthesis and secretion), and have a weaker impact on insulin sensitivity in surrounding tissues.

The combination of insulin resistance and genetic susceptibility can create unsustainable functional demands on pancreatic beta cells. Long term hyperglycemia (glucose toxicity) and insulin resistance force beta cells to excessively secrete insulin to maintain blood glucose stability, ultimately leading to cell exhaustion and functional failure. This process is related to epigenetic reprogramming, such as the high methylation of the key regulatory gene PDX-1 promoter for beta cell maturation and insulin production, which can lead to its silencing, and other histone modifications can also have similar harmful effects. A single-cell study found that there are subpopulations of cells with unique clustering patterns in the pancreas, and most of the 64 marker genes characterized by them are related to exocrine function, indicating potential interactions between various parts of the pancreas. Among them, 38 new candidate marker genes provide new targets for understanding beta cell failure [9].

In fact, these three factors do not act in isolation: obesity induced insulin resistance increases the functional load on beta cells, and genetically susceptible beta cells are more difficult to withstand this load, accelerating functional decline; The failure of beta cells can exacerbate hyperglycemia, further worsen insulin resistance and obesity, form a vicious cycle, and ultimately lead to the manifestation of clinical symptoms of T2DM.

2.2. Principles and applications of gene chip technology

Gene chips (also known as DNA microarray) is a high-throughput technology that can simultaneously analyze the expression profiles of thousands of genes in a single experiment, and promote the development of functional genomics by parallel detection of whole genome transcriptional activity. The core principle is based on the Watson Crick base pairing rule: adenine (A) and thymine (T) pair through two hydrogen bonds, and guanine (G) and cytosine (C) pair through three hydrogen bonds. This specific "hybridization" effect allows the DNA probe on the chip to capture complementary cDNA target sequences in the sample. The hybridization intensity and specificity are regulated by experimental conditions such as temperature and ion concentration, and strict control is required to ensure reliable results.

The operation of gene chips requires multiple detailed steps: firstly, the design and synthesis of DNA probes, ensuring that the probes are complementary to the target gene sequence to achieve specific binding. The preparation of high-density oligonucleotide probes (over 100000 per square centimeter) on glass surfaces through photolithography technology, laying the foundation for technological applications [10]; Next is sample preparation, which involves isolating high-quality RNA from target cells or tissues, converting it into cDNA through reverse transcription, and labeling it with fluorescent markers such as Cy3 (control sample) or Cy5 (experimental sample) to achieve subsequent detection and quantification of expression levels; Next is the hybridization stage, where the labeled cDNA is incubated with the chip probe under strictly controlled temperature and salinity conditions to promote complementary sequence binding. After hybridization, unbound or weakly bound fragments are removed by strict washing to reduce non-specific background signals; Finally, the fluorescence signal intensity at the probe position was detected by a laser scanner (proportional to the amount of target cDNA bound), and the raw data was processed using bioinformatics techniques to generate an interpretable gene expression profile.

Gene chip technology is widely used in various fields: in medical diagnosis, genetic diseases can be screened by decoding specific gene sequences (such as alpha/beta globin gene mutation analysis, which is the gold standard for diagnosing thalassemia), or pathogens and gene typing can be quickly

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identified (such as tracking the evolution of SARS-CoV-2 mutant strains in the COVID-19 epidemic); In drug development, it can be used to identify disease-related target genes, analyze individual genomic variations to guide personalized treatment, and evaluate drug efficacy and toxicity by monitoring changes in whole genome expression after drug treatment; In agricultural biotechnology, it can assist in crop molecular breeding (identifying genes related to disease resistance, high yield, and other traits) and safety assessment of genetically modified crops (verifying gene insertion sites and copy numbers).

2.3. Application of gene chip technology in the study of molecular mechanism of type 2 diabetes

Gene chip technology, especially GWAS, provides a key tool for analyzing the genetic structure of T2DM. Through systematic gene localization, it can identify susceptibility sites on a large scale across the entire genome, promoting the understanding of the molecular mechanisms of the disease.

In early research, the Weikang Trust Case Control Consortium (WTCCC) published a milestone study in Nature in 2007, which for the first time validated the genetic association of T2DM through GWAS. Strong and reproducible risk variants were detected in three key genes, TCF7L2, PPARG, and KCNJ11, with TCF7L2 having the strongest association signal and confirmed in different populations. This study suggests that TCF7L2 may affect disease risk through the WNT signaling pathway, primarily through β - cell dysfunction (rather than insulin resistance), shifting the focus of genetic research towards insulin secretion defects.

Subsequent research has further expanded our understanding of the genetic mechanisms underlying T2DM. GWAS research has identified more than 100 common genetic variant loci associated with T2DM risk, with odds ratios (ORs) of only 1.05-1.30 for each variant [11].However, the accumulation of risk alleles at multiple loci can form a significant polygenic risk score (PRS). These findings confirm that T2DM is a polygenic disease, and genetic susceptibility is mainly due to genetic defects in pancreatic beta cell function (most risk genes are involved in beta cell development, insulin secretion, and cell survival), rather than direct genetic drivers of insulin resistance.

Gene chip technology has also been used to screen differential genes related to insulin resistance and fat metabolism in T2DM. For example, A study compared the gene expression of insulin resistance group and normal group through gene chip technology, focusing on fat metabolism related genes and verifying the expression changes of FOXC2 gene, providing new clues for analyzing the mechanism of insulin resistance in T2DM and reflecting the value of this technology in accurately locating disease-related genes [12]..

2.4. Further exploration of genetic mechanism of type 2 diabetes

The interaction between genetics and environment further enriches the pathogenesis model of T2DM. Obesity, as a key environmental factor, can expose genetic susceptibility. For example, variations in the FTO gene (the first body mass index related locus discovered through GWAS) increase the risk of obesity, while obesity, as a physiological stressor, can significantly amplify the risk of T2DM in genetically susceptible individuals, reflecting the impact of gene environment dynamics on the disease.

In recent years, research on protective genetic variations has provided new directions for the treatment of T2DM. The protein truncation and loss of function (LoF) mutation of SLC30A8 gene has been found to significantly reduce the risk of T2DM. This conclusion is based on a meta-

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analysis of exome and genome sequencing data from hundreds of thousands of people in different populations, and its core mechanism is related to zinc transporter function. A β - cell specific knockout mouse model showed that partial or complete loss of SLC30A8 function can regulate intracellular zinc homeostasis, enhance glucose stimulated insulin secretion, promote β - cell proliferation and survival, and reduce apoptosis under metabolic stress; Functional omics analysis of human pancreatic islets further reveals that changes in zinc flux can affect insulin crystallization, granule packaging, and proinsulin insulin conversion rate. Based on this, current translational research focuses on developing inhibitors targeting zinc transporters (such as fragment based drug discovery, high affinity monoclonal antibodies), which simulate protective heterozygous LoF states through precise partial inhibition, while ensuring efficacy and avoiding off target effects of complete functional loss.

3. Conclusion

This paper set out to review the key pathogenic factors of type 2 diabetes (T2DM) and to assess the application and impact of gene chip technology in exploring its molecular mechanisms. ype 2 diabetes mellitus (T2DM) develops through a triad of obesity-triggered insulin resistance, β-cell damaging genetic variants (including TCF7L2 and PPARG), and epigenetically-mediated β-cell decline. Gene chip analyses have revealed crucial targets such as FOXC2 and SLC30A8, offering mechanistic and therapeutic insights. Subsequent research must emphasize functional validation in human tissues and multi-omics data integration to enable precise clinical translation. The utilization of high-density gene chips not only accelerates the discovery of previously overlooked pathogenic pathways but also enables more precise prognostic stratification and targeted drug development.

While gene chip studies have significantly advanced our understanding of T2DM genetics, their clinical translation remains constrained by critical methodological gaps. Most analyses continue to rely on bulk sequencing approaches, which obscure functionally distinct β-cell subpopulations recently identified through single-cell transcriptomics. More fundamentally, the overwhelming Eurocentric bias in existing genomic databases—exemplified by the underrepresentation of African and Asian haplotypes in GWAS catalogs—severely limits the generalizability of established risk variants like TCF7L2 and PPARG. Perhaps most notably, the functional characterization of proposed genes such as FOXC2 and SLC30A8 remains dependent on heterologous expression systems rather than human pancreatic models, creating uncertainty regarding their pathophysiological roles.

Future efforts must prioritize three dimensions: First, implementing single-nucleus RNA sequencing in preserved human islet samples could resolve transcriptional heterogeneity while overcoming technical limitations of fresh tissue analyses. Second, large-scale international collaborations—modeled on initiatives like the DIAMANTE Consortium—are urgently needed to expand ethnic representation in genomic databases. Finally, CRISPR-based functional screening in stem-cell-derived human islet organoids presents the most physiologically relevant platform for validating genetic targets and evaluating therapeutic interventions. Such approaches may ultimately enable stratified treatment strategies based on individual genetic signatures rather than generalized glycemic management.

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