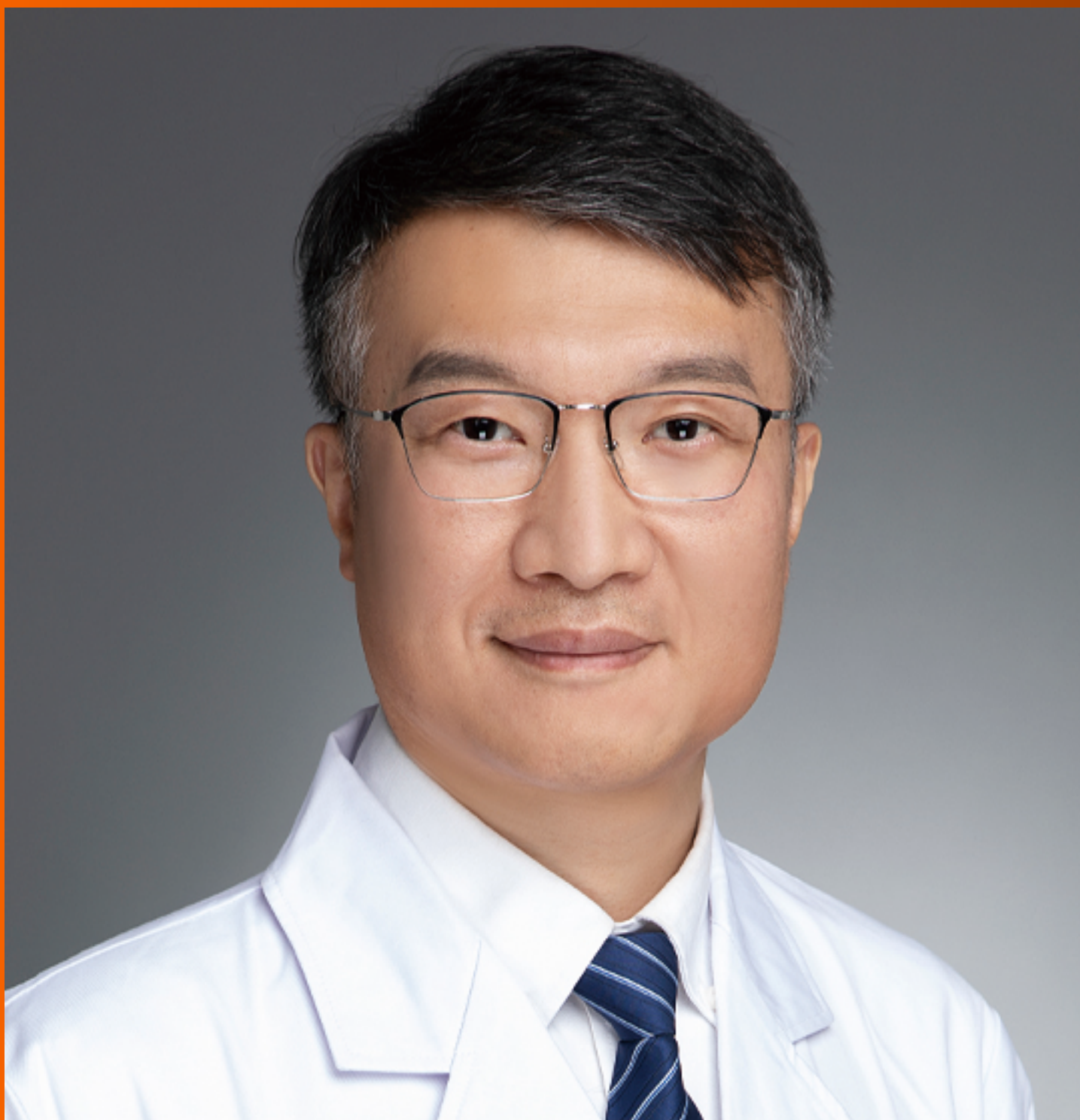


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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Multi-omics: Opportunities for research on mechanism of type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a burdensome global disease. In-depth understanding of its mechanism will help to optimize diagnosis and treatment, which reduces the burden. Multi-omics research has unparalleled advantages in contributing to the overall understanding of the mechanism of this chronic metabolic disease. In the past two decades, the study of multi-omics on T2DM-related intestinal flora perturbation and plasma dyslipidemia has shown tremendous potential and is expected to achieve major breakthroughs. The regulation of intestinal flora in diabetic patients has been confirmed by multiple studies. The use of metagenomics, 16S RNA sequencing, and metabolomics has comprehensively identified the overall changes in the intestinal flora and the metabolic disturbances that could directly or indirectly participate in the intestinal flora-host interactions. Lipidomics combined with other “omics” has characterized lipid metabolism disorders in T2DM. The combined application and cross-validation of multi-omics can screen for dysregulation in T2DM, which will provide immense opportunities to understand the mechanisms behind T2DM.

Key Words: Type 2 diabetes mellitus; Gastrointestinal microbiome; Intestinal flora; Lipid metabolism disorders; Dyslipidemias; Metabolomics

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Core Tip: The prospects of multi-omics in the study of the mechanisms of type 2 diabetes mellitus (T2DM)-related intestinal flora perturbation and plasma dyslipidemia are tremendous. The use of multi-omics has identified variations in T2DM intestinal

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flora composition and human-microbiota interactions. However, further sequencing is required, and the clinical application needs to be clarified and simplified. Multi-omics is also identifying T2DM lipid profiles, which will provide immense opportunities to understand the mechanisms of T2DM-related dyslipidemia.

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INTRODUCTION

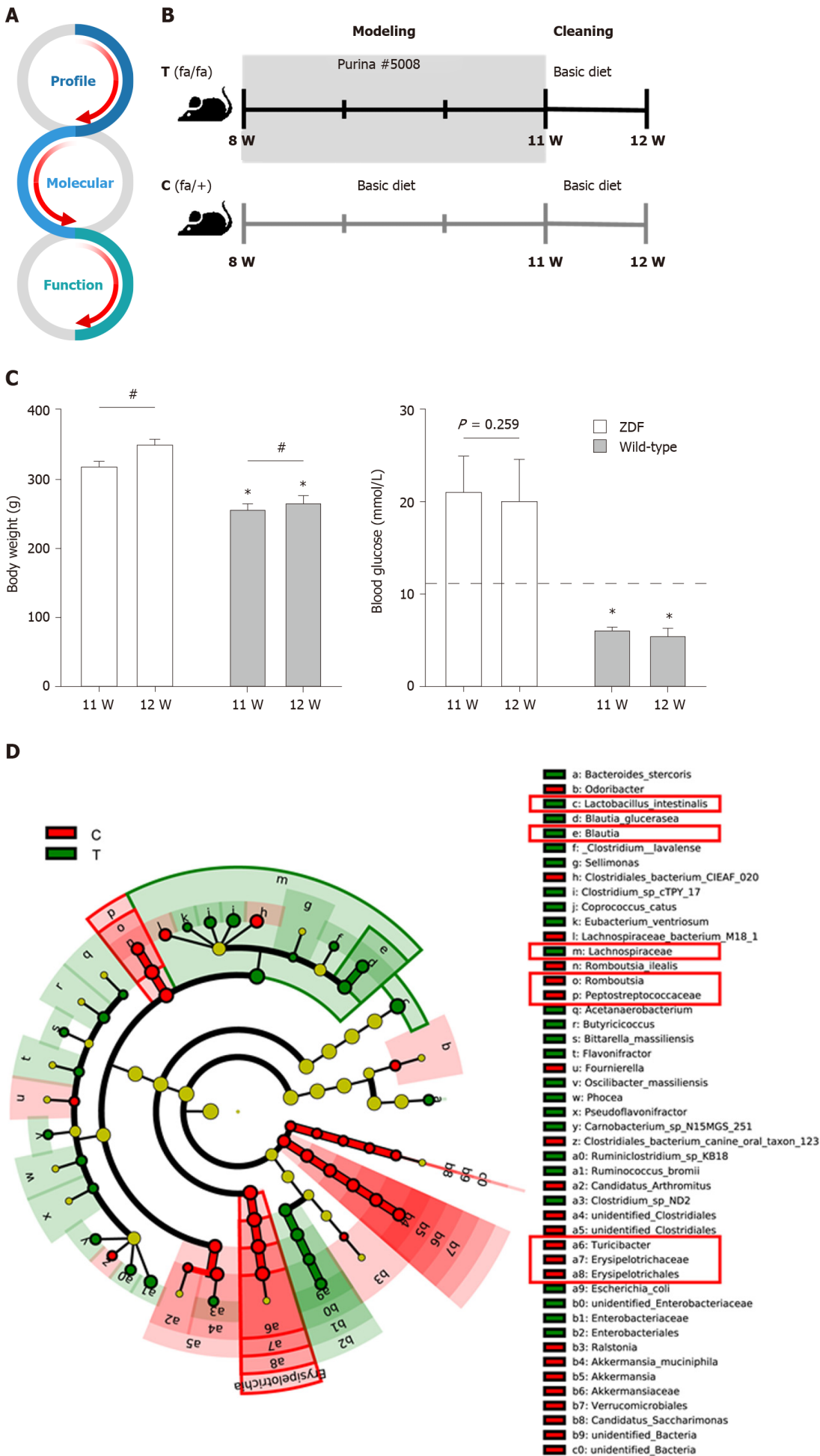
According to the World Health Organization, about 422 million people worldwide have diabetes and 1.6 million deaths are directly attributed to diabetes each year. Diabetes is a chronic, metabolic disease characterized by elevated blood glucose (or blood sugar) levels, which increases morbidity and mortality. When the body does not produce enough insulin or does not use it efficiently, diabetes manifests. The number of patients with diabetes is increasing, which expands the magnitude of the disease burden[1]. The most common type of diabetes is type 2 diabetes mellitus (T2DM)[2]. When genetics, age, and family history are fixed, reducing exposure to other known risk factors for T2DM using a variety of interventions and improving access to and quality of care decrease the incidence of T2DM and benefit patients with T2DM[3]. The effectiveness of these interventions depends largely on the understanding of the mechanism of T2DM. Due to the complexity of the mechanisms and causes of T2DM, traditional bench science has limitations. Multi-omics, including genomics, transcriptomics, proteomics, glycomics, metabolomics, epigenomics, ncRNomics, lipidomics, and interactomics, offers a fresh and exciting conceptual lens that will aid scientists to comprehensively and systematically understand the physiological processes and regulatory mechanisms of T2DM[4].

ADVANTAGES OF MULTI-OMICS ON STUDY OF MECHANISM OF T2DM

Since the concept of genomes and genomics was introduced, “omics” research has profoundly affected systems biology discoveries. Multi-omics research enables researchers to identify the differences in genes, proteins, and metabolites that lead to understanding overall functional disturbances in diseases, including T2DM.

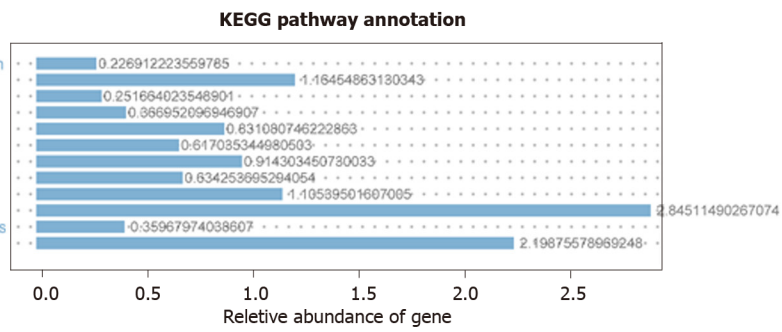
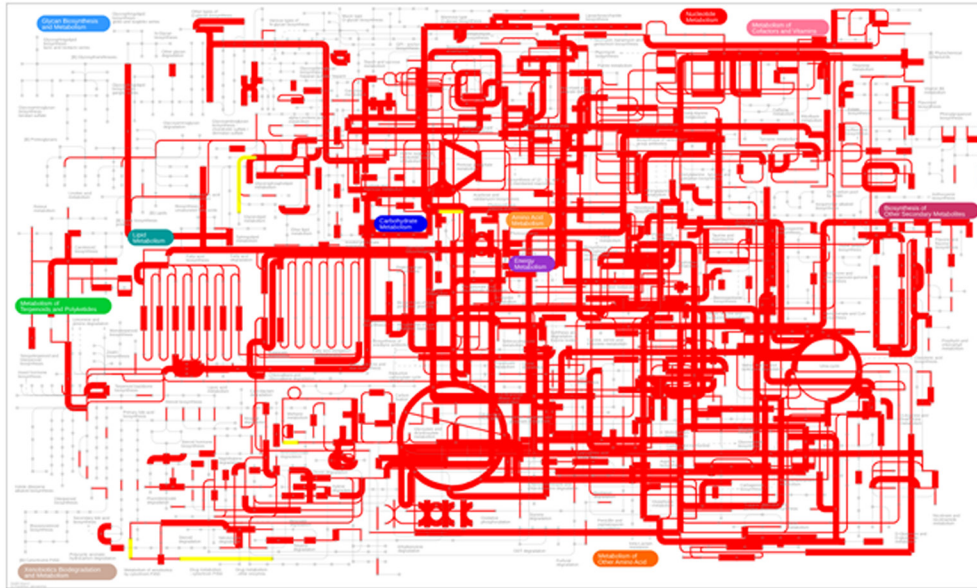
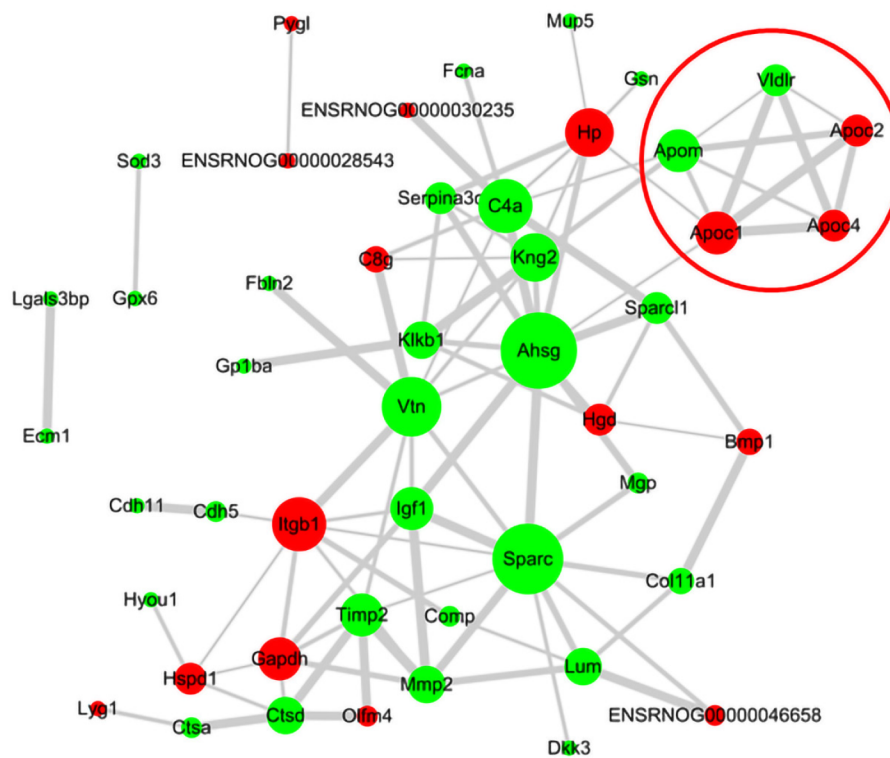
Using multi-omics, our previous research[5,6] described the intestinal flora alterations and the plasma protein metabolic profile perturbations in the Zucker diabetic fatty rat, which is a spontaneous T2DM animal model commonly used to develop drugs for treating diabetes[7-10]. The altered intestinal microbiota and differentially expressed proteins and metabolites clearly distinguished the treatment group [T: Zucker leptin receptor gene-deficient rats (fa/fa) treated by Purina #5008] from the control group [C: basic diet-fed litter mate wild-type controls (fa/+)]. This provided an important reference for screening and verifying T2DM by utilizing intestinal flora and plasma biomarkers. Using “omics” techniques, the increased levels of glycated hemoglobin, ceruloplasmin, triacylglycerols, diacylglycerols, phosphatidylethanolamines, *etc.* in plasma/urine have been verified in the human population. They are gradually being introduced in the early diagnosis of diabetes and the prediction of serious adverse complications[11-13].

Further functional analysis of the differential molecules using multi-omics revealed the pathophysiological mechanism of T2DM (Figure 1). The intestinal flora and the host exhibit similar features that focus on oxidative stress, insulin resistance, and metabolic disorders. This data confirmed previous T2DM mechanism research[14-16] and provided insight into the overall levels of molecules.



E**Metabolism**

Xenobiotics biodegradation and metabolism
 Nucleotide metabolism
 Metabolism of terpenoids and polyketides
 Metabolism of other amino acids
 Metabolism of cofactors and vitamins
 Lipid metabolism
 Glycan biosynthesis and metabolism
 Enzyme families
 Energy metabolism
 Carbohydrate metabolism
 Biosynthesis of other secondary metabolites
 Amino acid metabolism

**F****G**

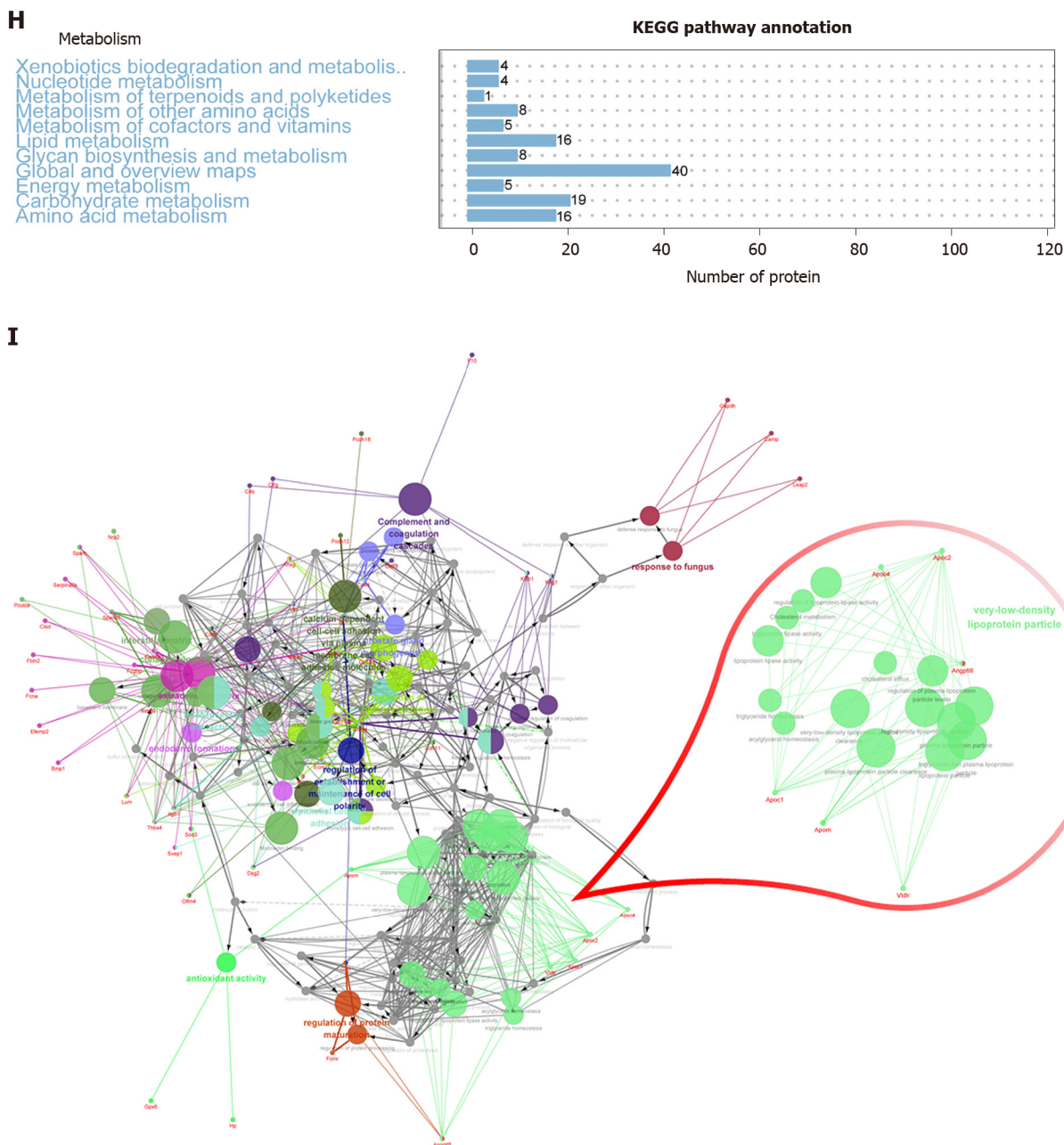


Figure 1 Multi-omics verification of the mechanism of type 2 diabetes mellitus. A: Schematic diagram of multi-omics verification; B: Conceptual diagram of the Zucker diabetic fatty rat modeling process; C: Body weight (left) and blood sugar (right) before and after basic diet feeding in B; D: Fecal 16S rRNA sequencing biomarkers; E: Genomic functions of the disturbed intestinal flora; F: Overview of the complete metabolism in the two biological system; G: Protein-protein interaction network of plasma differentially expressed proteins (DEPs); H: Functional enrichment of DEPs; I: Visualization of G and H. The cross-validation of intestinal flora and the plasma proteome further emphasizes that oxidative stress, insulin resistance, energy intake and consumption imbalances, and lipid metabolism disorders play an important part in the occurrence of type 2 diabetes mellitus (T2DM). Dyslipidemia may be a major hub for the *in vivo* and *in vitro* changes in T2DM (unpublished data). The data used in the figure are our published and public data in open access journals, which are displayed after further analysis. C and G: Citation: Wang S, Lu Z, Wang Y, Zhang T, He X. Metalloproteins and apolipoprotein C: candidate plasma biomarkers of T2DM screened by comparative proteomics and lipidomics in ZDF rats. *Nutr Metab (Lond)* 2020; 17: 66. Copyright ©The Author(s) 2020. Published by Springer Nature[6]. T: Zucker leptin receptor gene-deficient rats (fa/fa) treated by Purina #5008 for 3 wk; C: Basic diet-fed litter mate wild-type controls (fa/+); DEPs: Differentially expressed proteins; T2DM: Type 2 diabetes mellitus.

MULTI-OMICS AND T2DM-RELATED INTESTINAL FLORA DISTURBANCE

Multi-omics aided the dramatic discovery that diabetes was associated with the intestinal flora. The altered microbiota observed in genetically obese mice[17] or people[18–20] is sufficient to promote increased adiposity in lean mice that receive a microbiota transplant. Germ-free mice, which lack a microbiota, have reduced adiposity and improved tolerance to glucose and insulin when compared to their counterparts[21]. They are also free from diet-induced obesity when fed a Western-

style diet[22-24]. Taken together, the correlation between intestinal flora, obesity, and diabetes demonstrates that the microbiota contributes to the regulation of adiposity and T2DM[25]. However, the precise mechanism is still not clear.

Increased metagenomics data (usually 16S RNA sequencing) suggest that the extent of biodiversity within an ecosystem can be an important mechanism and serve as a measure of stability and robustness. In other words, a reduction in gut microbiome diversity and richness is linked to susceptibility to T2DM[26,27]. The complex composition of the intestinal flora can quickly change in response to a diverse diet, while simpler flora composition can only interact with specific diets and increase the vulnerability of the intestinal tract[28]. In T2DM rats and patients, the proportion of *Firmicutes* decreased and that of *Bacteroidetes* increased[29]. This ratio can be used as a simple indicator of intestinal flora diversity in T2DM. Although metagenomics has an irreplaceable advantage in T2DM-related intestinal flora studies, sequencing depth and defects in methods still need to be paid more attention. 16S RNA sequencing enables taxonomic identification to at least the family level but is rarely able to make a distinction between different strains of the same species or related species[30]. *Salmonella*, *Escherichia coli*, and *Shigella* would be identified by the same sequence, yet their significance in T2DM may vary.

Although the intestinal flora ratios may be important, the metabolic function of the intestinal flora on nutrients and food likely plays a more significant role[31,32]. Metabolites of the intestinal flora are involved in numerous functions. They can affect the absorption of nutrients (bile acid metabolism is closely related to lipid absorption [33,34]), and they can be absorbed to provide nutrients for the host (carbohydrates are fermented to form short-chain fatty acids to provide energy for the host[35-37]). Metabolites can be signaling molecules to regulate inflammation and immunity inter- or intra-intestinally. Bacterial L-tryptophan metabolites enhance the secretion of glucagon-like peptide-1[38-40]. Endotoxins (lipopolysaccharides) induce inflammation [41] and limit the autoimmune response[42,43]. Many metabolites produced due to the interaction of numerous species, the allocation of resources, and the dynamic response to perturbation within the gut may serve as potential T2DM biomarkers[44]. Table 1 briefly summarizes related gut microbiota metabolites and their interactions with the host in diabetes. The complementation of intestinal metabolomics and metagenomics will enhance the research on T2DM-related intestinal flora disturbance[45].

Discovering the interactions of the intestinal microbiota under complex conditions, such as diet[46], drugs[47], genetic background of the host[48] and colonizing flora [49], modification of the intestinal flora through antibiotics[50-54], probiotics, prebiotics[55-57], and fecal microbiota transplantation, and causal relationships in people and precision treatment[58] will become more accessible using multi-omics. The potential of understanding the mechanisms of diabetes using multi-omics is tremendous. However, the systematic examination of T2DM-related colonic flora studies in therapeutic and clinical application must still be completed.

An interesting example of fully understanding the mechanism of intestinal bacteria is *Akkermansia muciniphila* (*A. muciniphila*). *A. muciniphila* is a mucosal-dwelling anaerobe and the only known member of its genus. Animal and human data have indicated an inverse correlation between the intestinal abundance of *A. muciniphila* and obesity, dyslipidemia, and T2DM[59-61]. *A. muciniphila* supplementation restores epithelial mucosal integrity, reduces weight gain and fat accumulation, improves glucose tolerance, and reduces inflammation and metabolic endotoxemia in animal models. It may be a potential treatment for T2DM. However, *A. muciniphila* levels are increased in patients with Parkinson's disease, multiple sclerosis, or Alzheimer's disease[62-64], suggesting that this bacterium may have unforeseen harmful effects on the nervous system. Pure culture, sterilization, and component extraction can reduce this risk[65], which is consistent with the recently proposed concept of culturomics [66]. In short, through multi-omics it is likely that major breakthroughs in the study of the mechanism of T2DM-related intestinal flora perturbation will be made and that these breakthroughs will be gradually applied in the clinic.

MULTI-OMICS AND T2DM-RELATED DYSLIPIDEMIA

While intestinal flora disorder is a diet-related *in vitro* regulatory mechanism of T2DM, glucose and lipid metabolism disorders and insulin resistance are *in vivo* mechanisms [67]. In addition to glycomics[68,69], we want to emphasize the role of lipidomics in T2DM-related dyslipidemia. Dyslipidemia in T2DM, characterized by a high concentration of triglycerides, low concentration of high-density lipoprotein cholesterol, and

Table 1 Intestinal flora-related metabolites and their host interaction mechanism

Metabolites	Potential interaction mechanism between intestinal flora-related metabolites and the host
Bile acids	Promotes fat absorption; serves as signaling molecule [acts with G-protein-coupled bile acid receptor 1 (Gpbar1, TGR5) and the bile acid receptor FXR]; limits the autoimmune response
SCFA	
Acetate and butyrate	Acts as histone deacetylase inhibitors; ameliorates inflammation
Propionate	Participates in carbohydrate esterification
Valeric	Provides calories; affects inflammation; enteroendocrine regulation through G-protein-coupled receptors (<i>e.g.</i> , GPR41, GPR43)
Indole	Promotes the function of the intestinal cell epithelial barrier; enhances the secretion of glucagon-like peptide-1 (GLP-1)
Endotoxins (LPS)	Induces inflammation; limits the autoimmune response
H ₂ S	Destroys the intestinal barrier function
TMA	Interferes with metabolism

Gpbar1 (TGR5): G-protein-coupled bile acid receptor 1; FXR: Farnesoid X receptor; SCFA: Short-chain fatty acid; GPR: G-protein-coupled receptors; GLP-1: Glucagon-like peptide-1; LPS: Lipopolysaccharide; H₂S: Hydrogen sulfide; TMA: Trimethylamine.

increased concentration of small, dense low-density lipoprotein cholesterol particles, is associated with insulin resistance. It is also one of the major risk factors for cardiovascular disease in patients with diabetes[70]. Although active control of triglycerides and low-density lipoprotein cholesterol can delay the progression of T2DM and reduce the risk of adverse cardiovascular outcomes in patients, interventions to increase high-density lipoprotein cholesterol have had little success. Niacin was thought to raise high-density lipoprotein cholesterol and was used to control diabetic dyslipidemia previously. However, it was proven to be ineffective and removed from the treatment guidelines[71-75]. Lipidomics, the systematic analysis of lipid composition and expression changes, can intensify the understanding of lipid metabolism alterations in T2DM. Recent population lipidomics data revealed that the T2DM-related lipid profile included decreased lysophospholipids, phosphatidylcholines, sphingomyelins, and cholesterol esters and increased triacylglycerols, diacylglycerols, and phosphatidylethanolamines[76-78]. Although these indicators can be used as potential biomarkers to predict the risk of T2DM, its prediction for a particular disease has not yet been verified. Balgoma *et al*[79] compared the lipid profiles from patients with non-alcoholic fatty liver disease, cardiovascular incidents, hepatocellular carcinoma, and T2DM. They noted that the upregulation of triacylglycerols, palmitic acid, palmitoleic acid, stearic acid and oleic acid is a fingerprint of liver X receptor-mediated lipogenesis in the liver. To thoroughly understand the mechanisms of T2DM-related lipid metabolism disorders, the utilization of lipidomics, and the integration of databases will undoubtedly achieve this goal.

CONCLUSION

Multi-omic studies have provided new breakthroughs and directions to guide traditional molecular biology research. The expansion of “omics” data and the continuous advancement of bioinformatics analysis technology will surely continue the advancement of our knowledge on the mechanisms of T2DM, especially on intestinal flora perturbation and dyslipidemia.

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