糖尿病的代谢组学研究进展

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摘要: 糖尿病是一种发病率极高的代谢紊乱性疾病。随着糖尿病发病人数的逐年增加, 其发病人群也呈现出年轻化趋势。因此, 深入开展糖尿病研究工作迫在眉睫。近年来, 代谢组学在糖尿病的生物标记物发现、发病机制探索、早期诊断及预后、药物疗效评价等方面的研究中取得了可喜的进展。但限于代谢组学技术的发展局限及糖尿病研究的复杂性, 糖尿病的代谢组学研究仍然面临诸多的挑战。本文主要针对代谢组学在糖尿病中的研究进展及其发展方向进行合理的总结和展望。

关键词: 代谢组学; 糖尿病; 生物标记物; 研究进展

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Progress in metabolomics research of diabetes

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Abstract: Diabetes is a metabolic disease with an extremely high incidence in China. In parallel with an increased incidence yearly, the population of diabetes is showing a trend towards younger age. Therefore, it is urgent to carry out research on diabetes in order to develop strategy for prevention. In recent years, metabolomics has made significant progress in the study of biomarkers, pathogenesis, early diagnosis and prognosis, and evaluation of drug efficacy in diabetes. However, limited by metabolomics technology and the complexity of diabetes research, metabolomics in the diabetes research remains challenging. We summarize the progress and prospect the future development of metabolomics in the diabetes research.

Key words: metabolomics; diabetes; biomarker; research progress

糖尿病是由环境及遗传因素共同引起的代谢紊乱性疾病[1]。目前, 其较为公认的致病机制为: 胰岛素抵抗、胰岛功能受损等因素导致胰岛素分泌的相对或绝对不足, 引发机体血糖代谢异常进而引发糖尿病[2]。通常, 糖尿病患者血糖长期处于较高水平, 并伴有不同程度的代谢紊乱[1,3]; 严重者易出现各种并发症, 如心血管疾病、肾病、眼病、足病等[4,5]。糖尿病不仅对患者造成了身心上的双重伤害, 而且对社会发展带来了不可避免的影响。因此, 积极开展糖尿病的防治及研究尤为重要。

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“代谢组学”起源于 20 世纪末, 由 Nicholson[6]和 Fiehn[7]教授相继提出并定义为内源性代谢产物在机体受到外界刺激或扰动后变化情况及变化规律的新兴学科[6,7]。因其独特优势, 代谢组学在提出后迅速应用于生命科学研究的各个领域[8-12]。

目前, 代谢组学在糖尿病研究中的应用主要包括致病机制的探索[13]、生物标记物的筛选[14]、疾病早期诊断[15,16]、药物疗效评价[15]以及疾病预后[17-19]等方面。尽管以上研究均已取得良好进展, 但糖尿病代谢组学的研究仍然面临着诸多挑战, 如缺乏标准化的操作流程、检测通量有待提高、易受外源性代谢物干扰等。因此, 本文对糖尿病代谢组学研究的主要进展及发展方向做出了合理的总结和展望, 希望为后续研究提供参考与

借鉴。

1　糖尿病代谢组学研究简介

近年来, 糖尿病的发病率逐年升高, 发病人数逐年增加, 发病群体年轻化趋势显著[20-22]。研究报道[23], 截止2017年世界范围内约有4.5亿的糖尿病患者, 预计2045年患者总人数将达到6.93亿。糖尿病一旦发病, 机体代谢便易处于紊乱状态[3]。患者表现出血糖升高、身体消瘦、多饮多尿等症状, 而发病后期更易遭受各种并发症的困扰。

代谢组学作为考察机体代谢变化的新兴组学技术, 具有通量高、速度快、侵入性低等优点[24,25], 因而在临床疾病研究中广泛应用。代谢产物处于机体反应的下游, 体内基因的转录及翻译、蛋白的合成及调控等上游活动均会在此层面得到体现。同时, 外界环境的影响也会直接作用于机体代谢。因此, 代谢组学必然为从表征角度考察和研究机体变化的首选技术。反映到疾病的研究中, 则体现为对疾病患者代谢差异的考察、比较与分析。

定义具有临床意义的生物标记物及与致病相关的代谢通路是当前糖尿病代谢组学研究的主要思路[26]。针对这一思路展开的研究又可分为以下三个方向: ① 通过生物标记物的富集实现差异代谢通路的定义进而深化糖尿病发病机制理解; ② 通过生物标记物的对比及模型的建立实现糖尿病的早期诊断和预测进而开展糖尿病早期干预; ③ 通过生物标记物的变化趋势实现对糖尿病临床治疗的疗效评价, 进而推进个体化医疗的发展。

综上, 下文将从生物标记物定义、发病机制探索、早期诊断及预测、疗效评价、疾病预后五个方面讨论代谢组学在糖尿病研究中的主要进展。

2　糖尿病代谢组学研究进展

2.1　糖尿病生物标记物研究　生物标记物研究是代谢组学在疾病中的重要应用。本文通过在Scifinder数据库中输入关键词“metabolomics”、“diabetes”、“biomarkers”, 共检索到217篇糖尿病代谢组学研究文献(已排除非研究性论文及综述性文献)。经归纳汇总, 将所有文献中涉及的生物标记物按类别列于表1[27-58](不明确物质归入其他类)。

由表1可知: ① 目前与糖尿病相关的生物标记物主要集中在氨基酸 (其中包括支链氨基酸、芳香氨基酸等)、脂肪酸 (游离脂肪酸、长链脂肪酸)、脂质 (磷脂等)、有机酸、糖类等代谢产物, 少部分涉及核苷酸、酰基肉碱等 (图1); 其涉及的代谢通路主要包括氨基酸代谢、能量代谢、脂肪酸代谢等, 均与糖尿病发病高度相关。② 生物样品采集及预处理以及代谢组学检测手段对生物标记物的鉴别均有显著影响。相同样品在不

Table 1　Metabolic biomarkers of diabetes (2005−2018). "−" No relevant information was reported in literatures. PC ae: Phosphatidylcholines-acyl-alkyl; PC aa: Diacyl-phosphatidylcholines; Lyso PC: Lyso-phosphatidylcholine; Lyso PI: Lyso-phosphatidylinositol; SM: Sphingomyelin; MG: Mono acyl glyceride; PG: Phosphatidylglycerol; TG: Triglyceride; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus

Metabolites type	Biomarker	Regulation	Technique	Specimen	Reference	Diabetes type
Amino acids	Alanine	↑	NMR; GC-MS	Blood	[27,28]	T2DM; T1DM
	Valine	–	LC-MS	Urine	[29]	T2DM
	Valine	↑	NMR	Blood	[30]	T2DM
	Lysine	↑	NMR	Blood	[30]	T2DM
	Lysine	–	GC-MS	Faeces	[31]	T2DM
	Tyrosine	↑	NMR	Blood	[32]	T2DM
	Tyrosine	↓	LC-MS	Urine	[33]	T2DM
	Isoleucine	↑	NMR; GC-MS	Blood	[28,32]	T2DM; T1DM
	Methionine	↑	NMR; LC-MS; GC-MS	Blood; Faeces	[31,32,34]	T2DM; T1DM
	Tryptophan	↓	GC-MS	Blood	[35]	T2DM
	Tryptophan	↓	LC-MS	Urine	[33]	T2DM
	Phenylalanine	↑	NMR	Blood	[27]	T2DM
	Phenylalanine	–	GC-MS	Faeces	[31]	T2DM
	L-Aspartic acid	–	GC-MS	Faeces	[31]	T2DM
	Aspartic acid	↑	LC-MS	Urine	[33]	T2DM
	Leucine	↑	NMR	Blood	[30]	T2DM
	Glycine	↓	LC-MS	Blood	[36]	T2DM
	Proline	↑	NMR	Blood	[30]	T2DM
	Threonine	↑	NMR	Blood	[30]	T2DM
	Histidine	↑	NMR	Blood	[30]	T2DM
Organic acids	Dimethyl glycine	↑	NMR	Blood	[27]	T2DM
	Butane dioic acid	–	GC-MS	Faeces	[31]	T2DM

Continued

Metabolites type	Biomarker	Regulation	Technique	Specimen	Reference	Diabetes type
	Glutaric acid	↑	LC-MS	Urine	[33]	T2DM
	Nicotinyl glycine	↑	LC-MS	Urine	[33]	T2DM
	N-beta-Alanyl-histidine	↓	LC-MS	Urine	[33]	T2DM
	Ornithine	–	LC-MS	Urine	[37]	T2DM
	Bradykinin hydroxyproline	–	GC-MS	Blood	[38]	T2DM
	N-Acetyl threonine	–	LC-MS; GC-MS	Blood	[39]	T2DM
	C-Glycosyl tryptophan	–	LC-MS; GC-MS	Blood	[39]	T2DM
	Maleic acid	↓	GC-MS	Urine	[40]	T2DM
	Oxylacetic acid	↓	GC-MS	Urine	[40]	T2DM
	Tartaric acid	–	GC-MS	Urine	[41]	T2DM
	Cholic acid	–	LC-MS	Urine	[42]	T2DM
	Chenodeoxycholic acid	–	LC-MS	Urine	[42]	T2DM
	Deoxycholic acid	–	LC-MS	Urine	[42]	T2DM
	Deoxycholic acid	↑	LC-MS	Blood	[43]	T2DM
	Hippuric acid	–	LC-MS	Urine	[37]	T2DM
	Hippuric acid	↑	GC-MS	Urine	[44]	T2DM
	Kynurenic acid	↓	LC-MS	Urine	[45]	T2DM
	Kynurenine	↓	GC-MS	Blood	[35]	T2DM
	Lactic acid	↑	NMR	Blood	[30]	T2DM
	Corosolic acid	–	LC-MS	Blood	[46]	T2DM
	3,7-Dimethyluric acid	↑	NMR	Blood	[30]	T2DM
	4-Aminobenzoic acid	↑	GC-MS	Urine	[40]	T2DM
	2,5-Bisoxy-benzeneacetic acid	↓	GC-MS	Urine	[40]	T2DM
	2-Oxoglutaric acid	↑	NMR	Blood	[32]	T2DM
	2-Aminoadipic acid	↓	LC-MS	Faeces	[47]	T2DM
	Pantothenic acid	↑	NMR	Blood	[30]	T2DM
	α-Amino-adipic acid	–	GC-MS	Blood	[28]	T1DM
	β-Muricholic acid	↑	LC-MS	Blood	[48]	GDM
	Glycine-hyodeoxycholic acid	↓	LC-MS	Blood	[48]	GDM
	Mono-4s bile acid	↑	LC-MS	Blood	[48]	GDM
	Mono-5s bile acid	↑	LC-MS	Blood	[48]	GDM
	Dehydro-s bile acid	↑	LC-MS	Blood	[48]	GDM
	Taurine-hydrocholic acid	↑	LC-MS	Blood	[48]	GDM
Lipids	Lyso PI	↑	LC-MS	Blood	[34]	T1DM
	Lyso PC	↓	LC-MS	Blood	[34]	T1DM
	Lyso PC 17:0	↓	LC-MS	Blood	[49]	T2DM
	Lyso PC 18:1	↓	LC-MS	Blood	[49]	T2DM
	Lyso PC 18:2	↓	LC-MS	Blood	[49,50]	T2DM
	PG	↓	LC-MS	Blood	[34]	T1DM
	PC(O-34:2)	↓	LC-MS	Blood	[32]	T2DM
	PC aa C32:1	↑	LC-MS	Blood	[50]	T2DM
	PC ae C34:3	–	LC-MS	Blood	[50,51]	T2DM
	PC ae C36:0	↑	LC-MS	Blood	[36]	T2DM
	PC aa C36:1	↑	LC-MS	Blood	[50]	T2DM
	PC ae C36:3	–	LC-MS	Blood	[51]	T2DM
	PC aa C38:3	↑	LC-MS	Blood	[50]	T2DM
	PC ae C40:6	↓	LC-MS	Blood	[50]	T2DM
	PC aa C40:5	↑	LC-MS	Blood	[50]	T2DM
	PC ae C42:5	↓	LC-MS	Blood	[50]	T2DM
	PC ae C44:4	↓	LC-MS	Blood	[50]	T2DM
	PC ae C44:5	↓	LC-MS	Blood	[50]	T2DM
	MG 18:2	↑	LC-MS	Blood	[43]	T2DM
	SM 16:1	↓	LC-MS	Blood	[50]	T2DM
	SM(OH) 26:0	–	LC-MS	Blood	[52]	T2DM
	SM(OH) 28:0	–	LC-MS	Blood	[52]	T2DM
	TG (48:0)	↑	LC-MS	Blood	[32]	T2DM
	TG (48:1)	↑	LC-MS	Blood	[32]	T2DM
	TG (50:5)	↑	LC-MS	Blood	[32]	T2DM

Continued

Metabolites type	Biomarker	Regulation	Technique	Specimen	Reference	Diabetes type
	Glycerol	↑	NMR	Blood	[32]	T2DM
	Stearic acid	↑	GC-MS	Blood	[53]	GDM
	Palmitic acid	–	GC-MS	Blood	[54]	T2DM
	Linoleic acid	–	GC-MS	Blood	[54]	T2DM
	7-Methyluric acid	–	LC-MS	Urine	[29]	T2DM
	D-Gluconic acid	↑	GC-MS	Urine	[44]	T2DM
	2-Aminobutyric acid	–	GC-MS	Urine	[55]	GDM
	2-Hydroxybutyric acid	–	GC-MS	Blood	[54]	T2DM
	3-Hydroxybutyric acid	↑	NMR	Blood	[30]	T2DM
	3-Hydroxybutyric acid	↑	LC-MS	Blood	[56]	T1DM
	5,8,11,14,17-Eicosapentaenoic acid	–	GC-MS	Blood	[57]	T2DM
Carbohydrate	*D*-Tagatose	–	GC-MS	Faeces	[31]	T2DM
	D-Lyxose	–	GC-MS	Faeces	[31]	T2DM
	D-Erythrose	–	GC-MS	Faeces	[31]	T2DM
	Xylo-hexos-5-ulose	–	GC-MS	Faeces	[31]	T2DM
	2-Deoxy-galactose	–	GC-MS	Faeces	[31]	T2DM
	D-Glucose	↑	GC-MS	Urine	[44]	T2DM
	D-Glucose	–	GC-MS	Urine	[41]	T2DM
	D-Galactose	–	GC-MS	Urine	[41]	T2DM
	Maltose	↑	LC-MS	Blood	[56]	T1DM
	Lactate	↑	NMR	Blood	[32]	T2DM
Nucleotides	N_1-Methylguanosine	–	LC-MS	Urine	[29]	T2DM
	Xanthosine	–	LC-MS	Urine	[29]	T2DM
	7*H*-Purine	–	GC-MS	Faeces	[31]	T2DM
	2'-Deoxyinosine	–	GC-MS	Faeces	[31]	T2DM
	Pseudo uridine	–	LC-MS; GC-MS	Blood	[39]	T2DM
Carnitine	*L*-Carnitine	–	LC-MS	Urine	[37]	T2DM
	C16	↑	LC-MS	Blood	[36]	T2DM
Others	Cortisol	↓	LC-MS	Blood	[43]	T2DM
	p-Cresol	↑	NMR	Blood	[27]	T2DM
	Acetoacetate	↑	NMR	Blood	[27]	T2DM
	Methyl succinate	↑	NMR	Blood	[27]	T2DM
	Methyl guanidine	↓	NMR	Blood	[27]	T2DM
	3-Hydroxymandelate	↓	NMR	Blood	[27]	T2DM
	Phenylacetylglutamine	↑	NMR	Blood	[27]	T2DM
	Choline	↑	NMR	Blood	[30]	T2DM
	Sorbitol	↑	NMR	Blood	[30]	T2DM
	Myoinositol	↑	NMR	Blood	[30]	T2DM
	Inositol	↑	GC-MS	Urine	[44]	T2DM
	Hex decanoate	–	GC-MS	Blood	[57]	T2DM
	Glycine betaine	↑	NMR	Blood	[32]	T2DM
	α-Tocopherol	–	GC-MS	Blood	[38]	T2DM
	2-Hydroxybutyrate	↑	GC-MS	Blood	[53]	GDM
	2-Hydroxybutyrate	↑	NMR	Blood	[32]	T2DM
	3-Hydroxybutyrate	↑	GC-MS	Blood	[53]	GDM
	Pyruvate	↑	NMR	Blood	[32]	T2DM
	Pantothenate	–	LC-MS	Urine	[37]	T2DM
	Guanidoacetate	↑	NMR	Blood	[27]	T2DM
	8,11,14-Eicosatrienoate	–	GC-MS	Blood	[57]	T2DM
	Ceramides	↑	LC-MS	Blood	[34]	T1DM
	Isopropanol	–	GC-MS	Exhaled breath	[58]	T2DM
	2,3,4-Trimethylhexane	–	GC-MS	Exhaled breath	[58]	T2DM
	2,6,8-Trimethyldecane	–	GC-MS	Exhaled breath	[58]	T2DM
	Tridecane	–	GC-MS	Exhaled breath	[58]	T2DM
	Undecane	–	GC-MS	Exhaled breath	[58]	T2DM
	1,5-Anhydroglucitol (1,5-AG)	–	GC-MS	Urine	[41]	T2DM
	1,5-Anhydroglucitol (1,5-AG)	↓	LC-MS; NMR	Blood	[32,56]	T1DM; T2DM

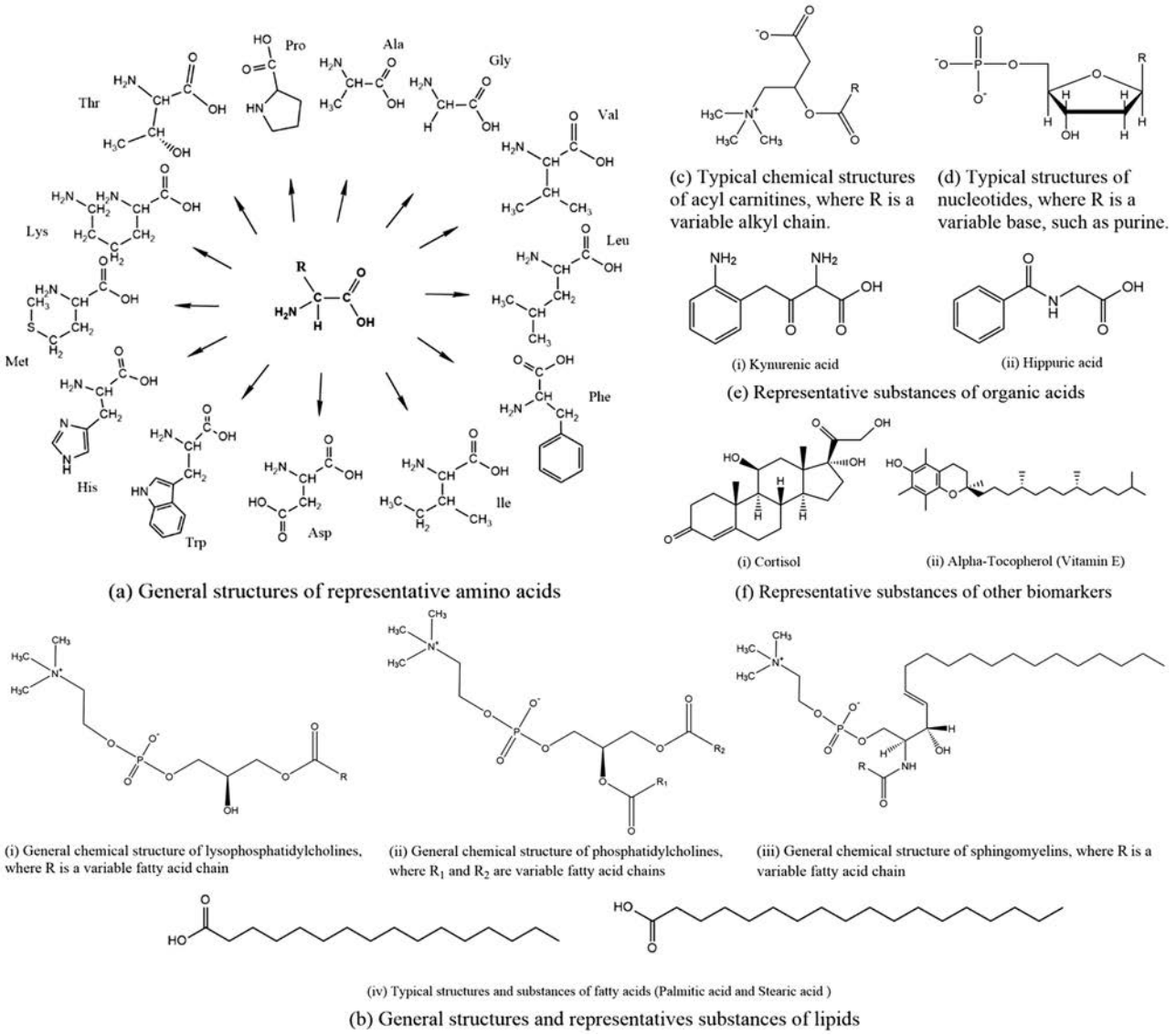

Figure 1 General structures and representative substances of typical diabetic biomarkers

同检测手段下, 可检出的代谢产物不尽相同; 同一代谢产物在不同的检测条件下体现出的变化趋势也不尽相同 (表 1 中部分标记物列出多个条目, 可体现以上结论)。这些差异对糖尿病生物标记物的确定造成了一定的困难。

以上趋势主要由当前代谢组学检测中普遍存在的两个差异所造成。首先, 不同检测样本在代谢组成、样品采集及预处理过程上的差异造成检测结果的不同[59]。如采自不同部位的样品存在代谢差异: 血液与全身的代谢状态密切相关, 而尿液则能更好地反映与肾脏相关的局部代谢[60]; 又如样品采集时间不同导致的样品代谢差异: 晨尿样本与随机尿样本的代谢轮廓差异较大[61]; 再如体液样本与组织样本预处理造成的代谢差异: 血液样品需加入肝素或 EDTA, 组织样品需置入液氮均匀化等[62]。其次, 代谢组学检测平台由于分离技术偏好及检测原理差异造成检测结果的不同[63]。例如, 质谱与核磁由于检测原理不同导致检测通量及检测结果存在明显差异; 气相色谱、液相色谱、毛细管电泳法等由于分离原理及使用范围的不同而导致最终检测结果出现差异[63,64]。

综上, 目前糖尿病的生物标记研究需从样品采集预处理及代谢组学检测手段两个方面做出相关的改进和提升。积极地制定用于规范化代谢组学操作的标准流程并努力提升当前设备检测水平将是改变现状的有效途径。

2.2 糖尿病发病机制研究 长期以来, 发病机制的揭示都是糖尿病研究的热点问题。由于糖尿病发病涉及环境及遗传因素的共同作用, 其发病基因的寻找尤为重要。然而仅从基因层面得到的分析难以阐释复杂的环境作用及机体代谢对糖尿病发病的作用与影响[65,66]。

代谢组学作为研究机体下游代谢的技术学科, 为糖尿病发病代谢机制的研究提供了更加全面、可靠的补充手段。通过关键生物标记物的富集可以实现对致病相关代谢通路或代谢网络的构建, 从代谢层面对糖尿病的发病机制做出深入解析[13]。

例如, Thomas[67]发现支链氨基酸的代谢与机体胰岛素的敏感性密切相关。支链氨基酸积累可以激活哺乳动物雷帕霉素靶向基因复合物Ⅰ(mTORC1), 进而影响下游靶核糖体蛋白S6激酶Ⅰ(S6K1), 从而影响机体对胰岛素敏感性。这一调节有效证实了糖尿病发病与机体氨基酸代谢失常存在密切联系。此外, Sas等[68]发现支链氨基酸代谢也会通过影响三羧酸循环 (TCA cycle) 进而影响机体供能这一与疾病密切相关的代谢过程。Law等[69]通过妊娠期糖尿病患者的代谢谱研究发现: 肥胖可促进炎性因子分泌而激活色氨酸–犬尿氨酸代谢途径及黄嘌呤酸合成, 高血糖可刺激核苷酸分解而导致尿酸合成及超氧阴离子产生。这些过程都会促进糖尿病的发生和发展。

2.3　糖尿病预警及早期诊断　研究表明[70,71], 60%～80%的糖尿病可以通过早期诊断和及时干预而变为可防可治。通过饮食和运动调节, 糖尿病患者可以很大程度上将血糖控制在正常水平[71]。传统的糖尿病风险评价常常基于患者的临床特征指标进行, 如性别年龄、家族病史、空腹血糖、体质指数 (BMI) 及动脉血压等[72,73]。这些指标往往容易受到饮食及生活习惯的影响而产生较大波动。然而, 随着生物标志物 (如氨基酸、脂质、酰基肉碱等) 的加入, 糖尿病风险评估水平明显提高[74], 有效地保证了预测的准确可靠。

Feng等[75]通过对2014～2016年内发现的糖尿病预测标记物进行了汇总, 结果表明支链氨基酸、芳香氨基酸及三酰甘油等内源性代谢产物均可有效评估糖尿病发病风险。Würtz等[76]的研究也充分表明, 支链氨基酸、芳香氨基酸对青年人的胰岛素抵抗患病风险具有极好的预测能力。此外, 组合生物标记物对于糖尿病的预测具有更加明显的优势。Carter等[77]在对61名Ⅱ型糖尿病患者及78名对照组成员的血浆代谢物进行检测后得到一组由糖类、酮体、有机酸、脂质和胆汁酸等代谢指标构成的诊断模型。验证集 (56名糖尿病患者及445名正常人) 检验表明, 组合生物标记的糖尿病鉴别能力相比单一标记有明显提高, 能够有效实现糖尿病预测。由其建立的诊断模型能够将糖尿病的预测关口提前至发病前18个月, 可充分实现糖尿病预警。

2.4　糖尿病临床疗效评价　在糖尿病的治疗过程中, 对患者的治疗效果进行及时的评价是十分必要的。传统的疗效评价指标是患者治疗前后的血糖水平, 然而血糖检测存在诸多缺陷[78], 如空腹血糖易受时间限制、餐后血糖不稳定且难重现、OGTT/IGTT因需要多次采血增加患者痛苦、糖化血红蛋白仅能反映一段时间内患者血糖水平等, 因此采用患者血糖进行疗效评价难免存在一定局限。

通过代谢组学方法监测患者体内生物标记物或代谢通路的变化则可以更加全面了解患者的治疗情况。Yu等[79]采用基于超高效液相色谱–飞行时间质谱技术的代谢组学方法对采用糖肾方治疗的糖尿病肾病患者的血浆代谢谱进行研究, 用于糖尿病肾病发病机制的探索及糖肾方治疗效果的评价。研究结果表明, 经糖肾方治疗后, 患者的血浆代谢产物发生明显变化; 磷脂代谢、脂肪酸代谢、氨基酸代谢、嘌呤嘧啶代谢、固醇类代谢等多条代谢途径得到纠正。事实表明, 基于代谢组学的疗效研究能够从整体水平反映疾病治疗过程中代谢网络的变化趋势, 并有助于临床治疗中的疗效评价。

2.5　糖尿病预后及病程监控　糖尿病预后也是糖尿病治疗中的一个重要方面[80], 如何最大程度对发病后患者的疾病发展做出预判以及如何避免并发症的发生是糖尿病预后工作的重中之重。根据代谢组学方法, 精准定义并监测糖尿病并发症的预警生物标记物可有效实现对糖尿病病情发展的预测[80,81], 达到及时跟踪病程、积极预测疾病发展的目的。例如, Sang等[82]通过观测有/无视网膜病变的糖尿病患者以及正常对照组的血浆代谢谱差异得出了可用于有效预测糖尿病视网膜病变的生物标记物。实验结果表明, 血浆谷氨酰胺和谷氨酸的比值为预测糖尿病视网膜病变的显著生物标记物。此研究为代谢组学用于糖尿病的并发症的预测提供了宝贵的思路。

3　糖尿病代谢组学研究发展趋势

3.1　深化代谢组学在糖尿病生物标志物发现中的研究　首先, 从表1可见, 由生物样品及检测手段不同造成的结果差异是目前糖尿病生物标记物发现过程中的主要问题。生物样品、采集方法、预处理手段的差异给代谢组学生物标记物的研究带来了巨大的影响。同时, 操作标准的缺乏也会导致不同机构的研究结果缺乏可比性, 数据交流层面困难频出, 以及生物标记物鉴定难度的提升[58]。因此, 操作流程的标准化是建立糖尿病生物标记物系统研究必然趋势。

其次, 检测通量的限制是当前代谢组学研究面临的普遍问题。对于已知的约三千种人体代谢产物[83], NMR仅能覆盖几十至近百种[84,85], 而通量较高的质谱检测也仅能够覆盖近千种[83,86]。因此, 努力提升检测通量将是突破目前糖尿病生物标记物研究局限的先决条件。首先, 分离技术的改善对于提升检测通量作用

明显。事实证明联合二维色谱或超高效液相色谱分离的质谱检测相比于简单的气相或液相质谱检测范围明显提升[64]。其次，检测器性能的提高对于实现检测范围的提升意义显著。通过提升NMR场强可以有效提升核磁检测的灵敏度，提升检测通量[87]。

综上，从标准化操作流程及提升仪器检测水平两个方面积极提升代谢组学研究质量是促进糖尿病生物标记物研究向着纵深发展的必要过程，其将从根本上决定糖尿病生物标记物研究的深度和广度[64]。

3.2 深化代谢组学在糖尿病的分型及预后中的研究 目前，糖尿病主要可分为1型、2型、妊娠期糖尿病以及其他类型[88]。其中，部分分型还包含更为细化的亚型划分，如1型糖尿病可按照发病机制继续划分为自身免疫型和特发型。由于不同分型的糖尿病治疗手段不同，因而积极探索糖尿病分型对其治疗具有重要意义。然而目前的分型手段主要依据患者的临床症状及胰岛素自身抗体等进行判断，涉及主观因素，故存在一定的缺陷。

同时，基于代谢组学的糖尿病预后体系的建立也并不完善，部分并发症的预警标记物并不完整。尽管并发症预警标记物对于患者的病程监控、干预治疗十分必要，但目前的研究状态依然缺陷明显。因此，在今后的研究中积极探索糖尿病的分型及预后生物标记物，对于辅助糖尿病分型判断、监控患者的病程发展不可忽视[89]。

3.3 实现代谢组学在糖尿病精准医疗中的应用 精准医疗是当前疾病治疗领域的新兴理念。对于复杂的代谢紊乱性疾病，精准医疗可有效适应个体差异，实现个体化给药或治疗[90]。目前，无论是常规的血糖监控还是临床的疾病诊断，糖尿病均基于机体的血糖浓度或血糖耐受水平进行判断[78]。然而，随着糖尿病的进展以及饮食、环境的改变，机体代谢水平也在不断变化。此时，仅依靠对机体的血糖检测固然不能充分反映机体的整体变化进而实现有效的监测。

代谢组学技术通过代谢物检测可反映机体代谢的整体变化，在疾病的精准医疗中具有重要意义。然而，目前基于代谢组学的精准医疗在糖尿病监测中的应用鲜有报道[89]。因此，加快实现代谢组学在糖尿病精准医疗中的临床应用也将是未来糖尿病代谢组学研究的重要发展方向之一。

3.4 促进代谢组学整合化在糖尿病致病机制研究中的应用 多组学整合化技术的应用始终是各种疾病研究中的重要方向之一[91,92]。通过代谢组学与其他组学的联合分析可以实现技术间的优劣互补[92]，进而有效实现对糖尿病的发病机制的深入探索。具体而言，将代谢组学与蛋白质组学结合，则有可能实现对调控糖尿病差异代谢通路的关键蛋白的发现；将代谢组学与转录组学结合，则有可能实现糖尿病在RNA水平上发病机制的理解；将代谢组学与基因组学结合，则有可能实现对糖尿病发病基因的定位，进而在基因层面上理解糖尿病发病机制，寻找新的治疗方案。

在糖尿病的研究中，代谢组学数据与其他组学数据结合分析的研究屡见不鲜。例如，Connor等[93]通过结合代谢组学与转录组学数据，联合展示了多组学数据整合在2型糖尿病研究中对于生物标记发现的促进作用。相比于单一组学，多组学联合分析通过对差异代谢通路在基因、蛋白质层面的研究提供了更多的可能与糖尿病发病相关的潜在标志物，如调控胰岛素抵抗的重要基因、控制胰岛素反应的限速酶等。因此，积极促进代谢组学与其他组学的联合分析在糖尿病研究中的应用对深入了解糖尿病的致病机制尤为重要。

4 小结

代谢组学在糖尿病研究中具有显著地位，其在糖尿病领域已经取得了令人瞩目的进展。但当前研究中仍存在较多局限，仍需在未来进一步突破，诸如代谢组学检测技术的标准化、代谢物检测平台通量的提升、动态检测手段的探索、多组学整合化发展等方面。因此，糖尿病研究中的代谢组学应积极总结自身优势，突破自身局限，有效结合疾病特点，适应未来发展方向，从而实现更加全面、高效的临床应用转化，促进糖尿病研究的纵深发展。

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