Advances in Clinical Medicine 临床医学进展, 2025, 15(2), 229-237
Published Online February 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.152338

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NAFLD与T2DM的相关研究

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收稿日期：2025年1月11日；录用日期：2025年2月4日；发布日期：2025年2月11日

摘　要

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)主要表现在肝脏脂肪堆积和脂肪变性，其发生与肥胖、血脂异常等因素紧密相关。与此同时，2型糖尿病(T2DM)作为一种以慢性高血糖为特征的代谢性疾病，亦与胰岛素分泌及抵抗问题有关。二者互相促进，互为因果，共享相似的病理基础——糖脂代谢紊乱。胆汁酸(bile acid, BA)作为胆汁的成分之一，在肠道中扮演着脂质和脂溶性分子乳化与吸收的角色，通过FXR、TGR5、FGF19、GLP-1等途径调节糖脂代谢和能量平衡。研究发现，NAFLD和T2DM患者的胆汁酸谱发生显著变化，胆汁酸可能与NAFLD和T2DM的发病机制和发展过程密切相关。这些发现为胆汁酸成为NAFLD和T2DM的诊断、预防和治疗中的新型生物标志物提供了科学依据。此外，胆汁酸代谢的调控机制，包括胆固醇合成途径、肠道菌群的影响以及胆汁酸的肠肝循环。深入研究胆汁酸代谢与NAFLD和T2DM之间的关系，将有助于开发基于BA代谢调控的治疗策略，从而改善患者的生活质量。因此，本文就BA代谢在NAFLD合并T2DM中的作用及临床应用前景进行综述，为该合并症的诊治提供创新的理论支持和科学依据。

关键词

胆汁酸，非酒精性脂肪性肝病，2型糖尿病，法尼醇X受体，G蛋白偶联胆汁酸受体

The Correlation between NAFLD and T2DM

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Received: Jan. 11th, 2025; accepted: Feb. 4th, 2025; published: Feb. 11th, 2025

Abstract

Nonalcoholic Fatty Liver Disease (NAFLD), characterized by hepatic lipid accumulation and

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文章引用: 雷笑, 福泉. NAFLD 与 T2DM 的相关研究[J]. 临床医学进展, 2025, 15(2): 229-237.
DOI: 10.12677/acm.2025.152338

steatosis, is closely associated with factors such as obesity and dyslipidemia. Concurrently, Type 2 Diabetes Mellitus (T2DM), a metabolic disorder marked by chronic hyperglycemia, is related to issues of insulin secretion and resistance. These two conditions mutually exacerbate each other, forming a causal relationship and sharing a similar pathological basis—disorders of glucose and lipid metabolism. Bile acids (BA), as a component of bile, play a crucial role in the emulsification and absorption of lipids and lipid-soluble molecules in the intestines. They regulate glucose and lipid metabolism and energy balance through pathways involving FXR, TGR5, FGF19, and GLP-1. Studies have shown that the bile acid profile in patients with NAFLD and T2DM undergoes significant changes, suggesting that bile acids may be closely related to the pathogenesis and progression of NAFLD and T2DM. These findings provide a scientific basis for bile acids to serve as novel biomarkers in the diagnosis, prevention, and treatment of NAFLD and T2DM. Moreover, the regulatory mechanisms of bile acid metabolism, including cholesterol synthesis pathways, the influence of gut microbiota, and the enterohepatic circulation of bile acids, are of great interest. In-depth research into the relationship between bile acid metabolism and NAFLD and T2DM may facilitate the development of therapeutic strategies based on the regulation of bile acid metabolism, thereby improving the quality of life for patients. Therefore, this article reviews the role of bile acid metabolism in the coexistence of nonalcoholic fatty liver disease and Type 2 diabetes mellitus, as well as its clinical application prospects, providing innovative theoretical support and a scientific for the diagnosis and treatment of this comorbidity.

Keywords

Bile Acids, NAFLD, T2DM, FXR, TGR5

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1. 引言

随着经济社会发展和大众生活水平不断提高，代谢性疾病发生率居高不下。NAFLD 和糖尿病是最常见的 2 种慢性代谢性疾病。NAFLD 是在无酒精中毒的情况下以肝脏脂质过度累积和肝脂肪变性为特征的疾病，严重则发展为脂肪性肝炎(NASH)、肝硬化甚至肝细胞癌(HCC) [1]。Estes 等[2]建立 NAFLD 人群动态模型，指出了 2016~2030 年 NAFLD 全球患病人数将进一步增加，预计到 2030 年，中国增长率最高将达到 22.2%，患病人数也最多，从 2016 年的 24633 万例增加到 2030 年的 31458 万例，增幅为 29.1%。T2DM 是糖尿病的主要临床表型，是由于胰岛 B 细胞功能失调导致胰岛素分泌相对不足或者靶器官发生胰岛素抵抗(IR)，而引起的糖、脂肪和蛋白质代谢紊乱[3]。

NAFLD 与 T2DM 经常并发，二者相互促进、互为因果。高血糖不仅属于 NAFLD 发病的危险因素，同时还会明显加重 NAFLD 患者病情。T2DM 患者肝脏长期处于糖脂代谢紊乱的状态，其产生的“糖毒性”和“脂毒性”易导致肝细胞脂肪变性，使肝糖原转化为脂质而沉积，从而促进 NAFLD 的发生发展[4]。T2DM 促进 NAFLD 进展为肝硬化，并将肝脏相关和全因死亡的风险提高 2~3 倍[5]。NAFLD 使 T2DM 发病率增加了 5 倍，并且在男性、吸烟者、久坐不动和体重指数 $\geq 25\ kg/m^2$ 的肥胖人群中，这种相关性更强[6]。几项队列研究表明 T2DM 患者中 NAFLD 的发病率增加，患病率在 42.6%至 76.1%之间[7]。约 80%的 T2DM 患者合并脂肪肝，同时约 45% NAFLD 患者患有糖尿病。

NAFLD 合并 T2DM 是亟待解决的公共卫生问题，但是二者之间相互作用关系及复杂机制尚不明确。有研究表明，BA 代谢紊乱是 NAFLD/T2DM 合并症的重要因素[8]。BA 是胆汁中主要成分，除了能促进

膳食脂肪和脂溶性分子的吸收，还可以作为肠–肝轴的化学信号结合细胞膜和核受体发挥调节代谢的作用。NAFLD、T2DM 都被报道与患者血液和粪便代谢物中 BAs 的异常水平密切相关[9]。本文就 NAFLD 与 T2DM 之间的联系以及 NAFLD/T2DM 合并症与 BA 代谢相关的可能分子机制进行综述，探讨此类疾病新的视角。

2. BA 合成及代谢

BA 的合成和排泄是哺乳动物胆固醇分解代谢的主要途径。成人肝脏每天大约有 500 mg 的胆固醇转化为 BA。这个过程将胆固醇转化为水溶性强且易于排泄的分子，有利于维持体内胆固醇稳态[10]。BA 由几种形状、结构和功能相似的化合物组成。按结构可分为游离胆汁酸和结合胆汁酸。游离胆汁酸主要包括胆酸(CA)、鹅去氧胆酸(CDCA)、去氧胆酸(DCA)和少量石胆酸(LCA)。上述游离胆汁酸的 24 位羧基可与甘氨酸或牛磺酸结合形成各种结合胆汁酸，包括甘氨胆酸、牛磺胆酸、甘氨鹅脱氧胆酸和牛磺脱氧胆酸等[8]。按来源可将 BA 分为两类，一类为初级胆汁酸，在肝内由胆固醇直接合成，作为胆汁的重要成分储存在胆囊中。它们主要包括 CA、CDCA 及其与甘氨酸和牛磺酸的结合产物。几种常见的胆汁酸见表 1。初级胆汁酸主要靠两种形式合成，首先是经典途径，也是体内 BA 合成的主要途径，在三种胆固醇羟化酶(CYP7A1、CYP8B1 和 CYP27A1)的酶促作用下，产生初级胆汁酸 CA 和 CDCA；另一种是替代途径，通过 CYP27A1、CYP7B7 对胆固醇侧链的羟基化产生 CDCA。初级胆汁酸在肝脏中产生，并通过肠道菌群转化为次级胆汁酸；次级胆汁酸，是初级胆汁酸进入肠道在肠道菌群作用下生成的 BA，如 DCA 和 LCA 以及它们与甘氨酸和牛磺酸的结合物[11]。次级胆汁酸 95%会被肠道重吸收，其中结合型胆汁酸主要在回肠远端通过主动吸收被重吸收，游离型胆汁酸在小肠、结肠段通过被动运输的形式被重吸收，这些重吸收的 BA 随门静脉再次进入肝脏，肝脏再将游离型胆汁酸转化为结合型胆汁酸并与新合成的 BA 一起进入肠道，即 BA 的“肝肠循环”。剩余 5%随粪便排出体外。这一循环维持了体内胆汁酸池的稳态。

Table 1. Classification of several common bile acids
表 1. 几种常见胆汁酸分类表

序号	英文名称	缩写	中文名称	游离/结合胆汁酸	初级/次级胆汁酸
1	Cholic acid	CA	胆酸	游离胆汁酸	初级胆汁酸
2	Chenodeoxycholic acid	CDCA	鹅去氧胆酸	游离胆汁酸	初级胆汁酸
3	Taurocholic acid	TCA	牛磺胆酸	结合胆汁酸	初级胆汁酸
4	Glycocholic acid	GCA	甘氨胆酸	结合胆汁酸	初级胆汁酸
5	Taurochenodeoxycholic acid	TCDCA	牛磺鹅去氧胆酸	结合胆汁酸	初级胆汁酸
6	Glycochenodeoxycholic acid	GCDCA	甘氨鹅脱氧胆酸	结合胆汁酸	初级胆汁酸
7	Deoxycholic acid	DCA	去氧胆酸	游离胆汁酸	次级胆汁酸
8	Hyodeoxycholic acid	HDCA	猪脱氧胆酸	游离胆汁酸	次级胆汁酸
9	Glycodeoxycholic acid	GDCA	甘氨脱氧胆酸	结合胆汁酸	次级胆汁酸
10	Taurodeoxycholic acid	TDCA	牛磺脱氧胆酸	结合胆汁酸	次级胆汁酸
11	Taurohyodeoxycholic acid	THDCA	牛磺猪脱氧胆酸	结合胆汁酸	次级胆汁酸
12	Tauroursodeoxycholic acid	TUDCA	牛磺熊脱氧胆酸	结合胆汁酸	次级胆汁酸
13	lithocholic acid	LCA	石胆酸	游离胆汁酸	次级胆汁酸
14	hyocholic acid	HCA	猪胆酸	游离胆汁酸	初级胆汁酸
15	Taurolithocholic acid	TLCA	牛磺石胆酸	结合胆汁酸	次级胆汁酸
16	alpha-muricholic acid	α-MCA	α-鼠胆酸	游离胆汁酸	初级胆汁酸
17	beta-muricholic acid	β-MCA	β-鼠胆酸	游离胆汁酸	初级胆汁酸

3. NAFLD 和 T2DM 中 BA 的变化

由于 BA 与机体代谢关系密切，BA 作为一种信号分子，其水平的改变可能是 T2DM 和 NAFLD 病理生理学中的一个重要指标，可能与胰岛素抵抗、脂肪代谢紊乱、肝脏炎症和氧化应激有关。Wang 等[12]研究显示，T2DM 患者总胆汁酸水平与甘油三酯、胰岛素抵抗指数、血压、BMI 呈正相关，T2DM 患者血浆中熊去氧胆酸降低，石胆酸和牛磺胆酸升高。在动物实验中，T2DM 模型鼠总胆汁酸浓度明显高于正常鼠[13]，在 T2DM 患者中，CDCA、DCA 和 CA 显著升高，且 CDCA、CA 和 DCA 与胰岛素抵抗呈正相关，DCA 在较小程度上与胰岛素抵抗呈正相关[14]。BA 代谢紊乱同样存在于 NAFLD 患者中[15]。多个临床试验对比了 NAFLD 患者与正常人 BA 水平的变化，结论各不相同。NAFLD 患者总胆汁酸有中度升高[16]。例如，代谢组学分析显示，与作为对照组的健康人群相比，NASH 患者血清中甘氨鹅脱氧胆酸、甘氨胆酸、牛磺胆酸水平升高。并且甘氨胆酸、牛磺胆酸随着疾病从脂肪变性到脂肪性肝炎、脂肪性肝硬化的严重程度的增加而增加[17] [18]。而 Jahnel 等[19]报道与正常儿童相比，处于 NAFLD 疾病早期的儿童血清总胆汁酸水平显著降低，这可能因为 UDCA 更亲水并且毒性更小，本研究中 NAFLD 早期患者血清中 UDCA 水平明显升高，UDCA 具有抗炎和抗凋亡作用，可以清除活性氧并促进抗氧化物质的产生。在儿童 NAFLD 第一阶段产生了炎症级联反应，导致 BA 代谢出现短暂不平衡，总胆汁酸水平显著降低[20]。不同疾病中胆汁酸池大小、组成有明显差异，可能背后存在复杂的作用机制。了解胆汁酸池和组成的变化对 NAFLD 合并 T2DM 的发病机制的探究具有重要意义，临床上不同 NAFLD 和 T2DM 患者 BA 变化情况见表 2。

Table 2. Changes in bile acids across different patient groups
表 2. 不同患者胆汁酸变化

疾病	胆汁酸变化	样本类型	参考文献
T2DM	熊去氧胆酸降低，石胆酸和牛磺胆酸升高	血浆	[12]
T2DM 和糖耐量受损	牛磺酸结合胆汁酸升高	血清	[21]
T2DM	去氧胆酸升高	血浆	[22]
NASH	总胆汁酸升高	血清	[23]
NASH	甘氨鹅脱氧胆酸、甘氨胆酸、牛磺胆酸水平升高	血浆	[17] [18]
NAFLD	总胆汁酸降低	血清	[19]
NASH	TDCA 和 GDCA，12α 羟基化胆汁酸升高(纤维化患者) 非 12α-羟基化胆汁酸降低(无纤维化患者)	血清	[24]-[26]
T2DM	12α-OH Bas 升高，非 12α-oh BAs、HCA 降低	血清	[27] [28]

4. BA 调节糖脂代谢的机制

4.1. BA 的自身反馈调节

BA 通过负反馈调节自身合成，在进入小肠后，与小肠细胞核受体法尼酯衍生物 X 受体(farnesol X receptor, FXR)结合可激活成纤维细胞生长因子 19 (FGF19)，该因子可以抑制胆固醇 7α-羟化酶(CYP7A1)基因的表达，而 CYP7A1 基因编码的胆固醇 7α-羟化酶为 BA 合成的限速酶[29]。除了 FGF19 信号转导途径，BA 的合成也受另一 FXR——小分子异源二聚体伴侣(small heterodimer partner，SHP；非典型的孤儿核受体)信号通路的调节，FXR 诱导 SHP 的表达，而 SHP 介导 CYP7A1 基因的下调，从而反馈性抑制胆汁酸的合成[30]。

4.2. BA 调节糖脂代谢机制

糖脂代谢紊乱是 T2DM、NAFLD 和肥胖等疾病的主要临床表现，越来越多证据表明 BA 在糖脂代谢调节中有着关键作用[31]。BA 受体有核受体 FXR、Takeda G 蛋白偶联受体 5 (Takeda G protein-coupled receptor 5, TGR5)等，初级胆汁酸主要激活 FXR 受体，次级胆汁酸主要激活 TGR5 受体，FXR，TGR5 作为关键代谢过程的转录调节因子被胆汁酸激活后，调节机体的胆汁酸代谢、脂质和糖代谢和能量消耗等。有利于维持糖脂代谢稳态、改善胰岛素抵抗，在 NAFLD 合并 T2DM 的发生发展中发挥重要作用。

4.2.1. BA-FXR-FGF19 途径

FXR，又称为胆汁酸核受体，是配体依赖性的核转录因子，广泛分布于体内肝脏、肠道、脾脏等多个组织器官[32]；BA 是其内源性天然配体。虽然不同部位的 FXR 可能发挥的作用不尽相同，但 FXR 在维持体内 BA 动态平衡，脂质、葡萄糖、氨基酸等代谢方面都具有重要作用[33]。近年来随着对 FXR 研究的逐渐深入，研究人员发现特异性激动或拮抗肠道 FXR 可通过多条不同的代谢通路调控糖脂代谢。FXR 基因敲除小鼠出现胰岛素抵抗和脂肪肝，血浆游离脂肪酸和血清葡萄糖水平升高，血清甘油三酯和高密度脂蛋白胆固醇水平升高[34]。相反，BA 或非甾体合成 FXR 激动剂激活 FXR 可降低血浆甘油三酯。Sarah 等[35]发现 GW4064 (一种 FXR 激动剂)、牛磺胆酸、脱氧胆酸治疗可以显著降低小鼠餐后血脂，并且 GW4064 还降低了肠道 TG 含量。但牛磺胆酸在 FXR 基因敲除小鼠中不能发挥降脂作用。奥贝胆酸(OCA)是胆汁酸中鹅去氧胆酸的类似物，是一种 FXR 激动剂[36]。多中心、随机、安慰剂对照的 FLINT 试验纳入了 283 名非肝硬化 NASH 患者(其中约 50%为 T2DM 患者)，结果显示 OCA 改善了包括纤维化在内的 NASH 的组织学特征[37]。FXR 除了有改善胰岛素抵抗，调节糖脂代谢的作用，并在动物 NASH 模型中表现出直接的抗炎和抗纤维化作用[36] [38]。这些研究都证明 FXR 通过调控 BA 代谢参与糖脂代谢。

FGF19 是成纤维细胞生长因子蛋白质家族中的一员，在 BA 合成和分泌，糖脂代谢调节及调节维生素 D 代谢和磷酸盐平衡等多种生物活性过程中起作用[39] [40]。FGF19 在回肠高表达，与成纤维细胞因子受体和跨膜糖蛋白 β-Klotho 组成的共受体结合发挥其生物学功能，是胆汁酸盐稳态的生理调节剂。分泌增多的 BA 进入肠道激活 FXR，引起 FGF-19 的分泌，并通过肠肝循环激活肝脏 FGFR4-β-Klotho 复合体导致邻近细胞中 CYP7A1 的抑制来减少胆汁酸合成和脂质合成[29]。FGF19 还具有类似于胰岛素的作用，能促进糖原合成，降低糖尿病小鼠血糖。研究发现，经侧脑室注射 FGF19 可降低糖尿病小鼠的血糖水平，而不影响胰岛素分泌或全身胰岛素敏感性，表明 FGF19 在中枢神经系统中以非胰岛素依赖性方式降低血糖水平[41] [42]。在一项临床研究中，FGF-19 类似物(即 ngm282)对于 166 例活检证实的 NASH 患者(平均年龄 52 岁；约 60%确诊为 T2DM)病情有改善作用，治疗 12 周后 NAS 和纤维化评分显著降低，并伴有无创成像和血清标志物的改善[43]。

4.2.2. 胆汁酸-TGR5-GLP-1 途径

TGR5 广泛分布于肝脏、胆囊、肠道、肌肉等组织中，BA 激活的 TGR5 在调节胰岛素敏感性和葡萄糖代谢方面有重要作用[44]。Ashley 等[45]发现在给小鼠急性脑室内注射合成的 TGR5 特异性激动剂 CCDC 的 24 h 后，小鼠食物摄入量和体重增加量明显减少，并改善了胰岛素抵抗情况。BA 与 TGR5 结合后激活刺激肠 L 内分泌细胞分泌胰高血糖素样肽 1 (glucagon-like peptide1, GLP1)，促进胰岛素分泌，减弱胰岛素抵抗[46]。另外 BA 亦可直接刺激胰岛细胞中的 TGR5 受体促进胰岛素释放[47]考来维仑是二代胆汁酸螯合剂，它可通过 TGR5 抑制糖代谢和减少胆固醇合成，从而减轻脂肪肝的形成[31]。

GLP-1 是回肠 L 细胞分泌的一种肠肽类激素，以胞吐方式释放到细胞外，与 GLP-1 受体特异性结

合，强化胰腺 β 细胞的功能。肝脏分泌 BA，BA 与 TGR5 结合，刺激回肠和结肠的 L 细胞分泌 GLP-1，NAFLD 胆汁酸代谢异常，影响 GLP-1 的分泌从而影响糖代谢，诱导 T2DM 的产生[48]。抑制肠道 FXR，可促进 GLP-1 的分泌，增加胰腺 β 细胞餐后分泌胰岛素，缓解胰岛素抵抗，从而改善葡萄糖代谢[49]。胰高血糖素样肽 1 受体激动剂(Glucagon-like peptide 1 receptor agonists, GLP-1 RAs)是一类降血糖药物，能够显著减轻体重(平均 3~5 kg)并改善胰岛素抵抗[50] [51]。GLP-1 受体已在小鼠和人肝细胞中被证实，这种受体的激活可能通过改善胰岛素信号通路、肝细胞脂毒性和线粒体功能来促进肝脂肪变性的减少[52] [53]。

在调节胆汁酸稳态和物质代谢过程中，FXR 和 TGR5 可以发挥协同作用。FXR 通过诱导 TGR5 信号传导，并通过增加细胞内 cAMP 和 Ca^{2+}刺激葡萄糖诱导的胰高血糖素样肽-1 (GLP-1)分泌，刺激胰腺 β 细胞分泌胰岛素[54]。另外一项研究表明，FXR/TGR5 胆汁酸受体激动剂 INT-767 对治疗糖尿病小鼠和饮食诱导肥胖的小鼠的肾损伤显着减少[55]。综上所述，胆汁酸及其受体和其他信号分子在糖脂代谢的调节中发挥关键作用，其可能机制见图 1。

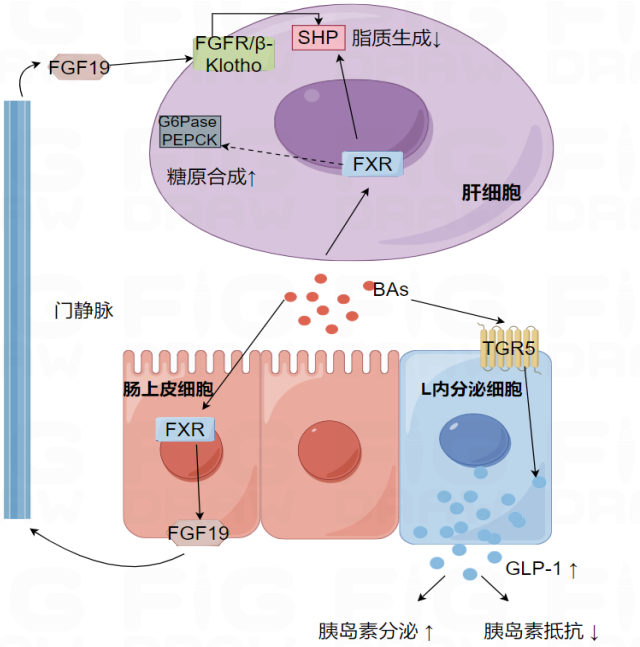

Figure 1. Mechanisms of bile acids regulation in lipid and glucose metabolism
图 1. 胆汁酸调节脂质和葡萄糖代谢的相关机制

5. 小结

NAFLD 合并 T2DM 使 NAFLD 向更严重的方向发展，NAFLD 增强 T2DM 的发病风险。目前临床上针对 NAFLD 合并 T2DM 的认识不足、重视程度也不够。本文以 BA 代谢为切入点，探究 NAFLD 合并 T2DM 发病机制，BA 作为一个重要的信号因子，主要通过 FXR、TGR5、FGF19、GLP-1 等在糖尿病、NAFLD 中发挥作用，调节糖脂及能量代谢。通过对 BA 及其介导的信号通路机制的探究，将为 NAFLD 合并糖尿病患者提供新的治疗策略。BA 未来也可以成为诊断或治疗 NAFLD 合并糖尿病一种新型非侵入性的生物标志物。BA 的变化可以反映 NAFLD 和糖尿病的病情活动性，从而在治疗过程中监测疾病进展。通过监测 BA 的变化，可以评估治疗的有效性。一些胆汁酸类似物可以作为 FXR、TGR5 等 BA 受体

激动剂调节糖脂代谢、影响胰岛素分泌，为 NAFLD 合并 T2DM 的治疗提供新的思路和靶点。随着疾病发生与 BA 变化关系的日益明确，未来 BA 的分离检测将发挥越来越重要的诊断价值和指导作用。分离各种 BA 并检测其在样品中的浓度变化，有利于科学研究、疾病诊断甚至疾病预测，对人类医疗卫生事业的发展具有十分重要的意义。

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