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专论与综述

乳酸菌胆盐水解酶和共轭脂肪酸产生及对宿主脂代谢影响的研究进展

段亮亮[1]，张蒙[1]，冯洁[1]，张维敏[1]，商晋[1]，杨芳*[2]

1 陕西中医药大学公共卫生学院，陕西 咸阳 712046
2 湖北中医药大学检验学院，湖北 武汉 430065

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摘　要：乳酸菌是一类影响宿主脂代谢的人体肠道益生菌。乳酸菌对脂代谢的影响作用与其产生胆盐水解酶(bile salt hydrolase，EC3.5.1.24，BSH)及共轭转化多不饱和脂肪酸(polyunsaturated fatty acids，PUFAs)关系密切。菌株差异、菌群分布和饮食差异是影响 BSH 及共轭脂肪酸产生的重要因素。本文重点阐述了两类物质对宿主脂代谢的影响机制，以期为后续研究提供借鉴。BSH 能够降解肝脏分泌的胆汁酸(bile acids，BAs)，降低脂类物质的吸收。BAs 的降解产物胆汁酸脱氧胆酸(deoxycholic acid，DCA)和石胆酸(lithocholic acid，LCA)能够通过机体信号通路法尼类 X 受体(farnesoid X receptor，FXR)、小异二聚体伴侣(small heterodimer partner，SHP)及肝脏 X 受体(liver X receptor，LXR)等信号通路进行调控，促进胆固醇转运及向 BAs 转化。此外，BSH 还能够通过下调固醇调节元件结合蛋白 1c (sterol regulatory element binding protein 1c，SREBP-1c)、上调 5′-腺苷单磷酸激活蛋白激酶 α (5′-AMP activated protein kinase，AMPKα)和过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor α，PPARα)抑制脂质合成，促进脂质的分解。PUFAs 可被乳酸菌转化产生共轭脂肪酸，如共轭亚油酸(conjugated linoleic acid，CLA)和共轭亚麻酸(conjugated linolenic acid，CLNA)，CLA/CLNA 能够促进机体产生瘦素(leptin，LP)，抑制食欲、

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***Corresponding author:** E-mail: fangy521@hbtcm.edu.cn

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促进能量消耗; CLA/CLNA 还可以通过激活 PPARα 进行调控，促进人体脂质的氧化分解。乳酸菌通过以上多种途径共同作用调节宿主的脂代谢，对深入理解乳酸菌调控脂代谢机制及临床应用有着重要意义。

关键词：乳酸菌；胆盐水解酶；共轭脂肪酸；脂代谢；分子机制

Production of bile salt hydrolase and conjugated fatty acids by lactic acid bacteria and their effects on host lipid metabolism: a review

DUAN Liangliang[1], ZHANG Meng[1], FENG Jie[1], ZHANG Weimin[1], SHANG Jin[1], YANG Fang[*2]

1 School of Public Health, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
2 School of Laboratory Medicine, Hubei University of Chinese Medicine, Wuhan 430065, Hubei, China

Abstract: Lactic acid bacteria are a representative probiotic in human intestine that affect host lipid metabolism, which is closely related with the production of bile salt hydrolase (EC3.5.1.24, BSH) and the conjugate conversion of polyunsaturated fatty acids (PUFAs). The production of BSH and conjugated fatty acids is influenced by strain differences, flora distribution, and dietary differences. This paper focuses on the mechanism of BSH and conjugated fatty acids in regulating the host lipid metabolism, in order to provide reference for further research. BSH can degrade bile acids (BAs) secreted by liver and reduce the absorption of lipids. The degradation products of BAs, deoxycholic acid and lithocholic acid, can promote cholesterol transport and conversion to BAs through signaling pathways such as farnesoid X receptor, small heterodimer partner and liver X receptor. Additionally, BSH can also inhibit lipid synthesis and promote lipid decomposition by down-regulating sterol regulatory element binding protein 1c, up-regulating 5′-AMP activated protein kinase and peroxisome proliferator-activated receptor α (PPARα). PUFAs can be converted into conjugated fatty acids by lactic acid bacteria, such as conjugated linoleic acid (CLA) and conjugated linolenic acid (CLNA). CLA/CLNA boosts the production of leptin in the body, suppresses appetite and promotes energy consumption. Moreover, CLA/CLNA can promote the oxidative decomposition of human lipids by activating PPARα. Lactic acid bacteria modulate the host lipid metabolism through the above-mentioned multiple pathways, which is of great significance for the in-depth understanding of its regulatory mechanism and clinical application.

Keywords: lactic acid bacteria; bile salt hydrolase; conjugated fatty acids; lipid metabolism; molecular mechanism

脂类代谢紊乱是一种严重的慢性疾病，是引起氧化应激、胰岛素抵抗、诱发炎症的重要因素，与心脑血管疾病、糖尿病、高血压、癌症等重大疾病密切相关[1]。乳酸菌是人体肠道的一类益生菌，在人体消化系统数量庞大、相互辅助，作为肠道保护屏障来维护人体整个胃肠道的微生态平衡。大量研究表明，乳酸菌具有调控宿主脂代谢的作用，能够起到较好的降

脂减肥作用[2-4]。乳酸菌可以通过多种方式对宿主脂代谢产生影响，其中，通过胆盐水解酶(bile salt hydrolase，EC3.5.1.24，BSH)的产生[5-6]及对膳食中多不饱和脂肪酸(polyunsaturated fatty acids，PUFAs)的共轭转化[7-10]产生共轭脂肪酸受到广泛关注，对宿主脂代谢的影响尤为重要。BSH 能够降解人体分泌的胆汁酸(bile acids，BAs)，进而降低机体胆固醇及脂质的消化吸收[5]，并且能够通过抑制体内脂质的合成和促进脂质分解来影响机体脂代谢[6]。共轭脂肪酸能够通过抑制宿主体内脂肪酸合成、促进脂肪酸氧化分解、防止脂质积聚来影响机体脂代谢[9-10]。本文总结了乳酸菌 BSH 及共轭脂肪酸的产生及影响因素，并重点阐述了BSH及共轭脂肪酸对宿主脂代谢影响的分子机制，进一步对国内外相关报道进行了总结和展望，以期为乳酸菌应用于脂代谢调控提供更多的理论依据。

1 乳酸菌 BSH 的产生

1.1 BSH 简介

胆盐水解酶(BSH)属于 N 端亲核(Ntn)水解酶超家族，BSH 在 N 端半胱氨酸残基催化核心部位具有 αββα 结构[11]。目前的研究表明 BSH 为胞内酶，而且主要分布在脆弱拟杆菌(*Bacteroides fragilis*)、外阴拟杆菌(*Bacteroides vulgatus*)、产气荚膜梭菌(*Clostridium perfringens*)、单核细胞增生李斯特菌(*Listeria mono-cytogenes*)、乳杆菌(*Lactobacillus*)和双歧杆菌(*Bifidobacterium*)中[12]。BSH 在不同地理区域人群中的分布有所不同。有研究对全球 11 个健康状况不同的人群分析，共发现 591 种 BSH 酶，归属于 117 个属 447 个菌株[13]。截至目前，关于 BSH 分子结构的研究较少，仅报道了来自长双歧杆菌(*B. longum*)[14]、唾液联合乳杆菌(*Ligilactobacillus salivarius*)[15]、粪肠球菌(*Enterococcus faecalis*)[11]、产气荚膜梭菌(*C. perfringens*)[16]、多形拟杆菌(*B. thetaiotaomicron*)[17]和小克里斯滕森氏菌(*Christensenella minuta*)[18]中 6 种 BSH 三维空间结构。众多菌种中，乳酸菌是产生 BSH 的重要菌种，所产生的 BSH 酶在宿主中发挥广泛的代谢调节作用，其中对脂代谢的影响研究较为广泛[19]。

1.2 BSH 对机体胆固醇消化吸收及平衡的影响

人体胆固醇稳态主要取决于肠道对胆固醇的吸收、内源性胆固醇合成及胆固醇消耗用于合成胆汁酸和类固醇这几方面的平衡[20]。BSH 能够降解人体分泌的 BAs，对胆固醇的消化吸收及体内胆固醇的消耗具有一定的影响，已被认为是潜在的肥胖防治靶点。人体对脂质的消化吸收离不了 BAs 的作用，人体分泌的 BAs 的主要存在形式为结合态胆汁酸(图 1)，结合态胆盐因其两亲性而表现出很强的界面活性，对脂类物质的消化吸收及维持胆汁中胆固醇的溶解起着重要作用[5,21]。食品中胆固醇的吸收需将其酯化成胆固醇酯，进而组装形成脂蛋白，而结合态胆汁酸在小肠中作为乳化液能够通过降低脂、水两相之间的表面张力，从而促进脂蛋白的形成，促进游离胆固醇、磷脂、甘油三酯及由肠粘膜细胞合成的脱辅基蛋白一起形成乳糜微粒，在胆固醇小肠上皮细胞吸收关键蛋白 NPC1L1 的作用下，乳糜微粒从小肠上皮细胞经淋巴系统转运至肝细胞进入血液循环[22]。食物中胆固醇的吸收不仅与饮食供给量和其他饮食组分的影响有关[20,22]，也与肠道微生物密切相关[23-24]。肠道中乳酸菌含有的 BSH 能将结合态胆汁酸水解产生游离胆汁酸和氨基酸(图 1)，游离的胆汁酸会被降解为次级胆汁酸脱氧胆酸(deoxycholic acid，DCA)和石胆酸(lithocholic

acid，LCA)，解缀的胆汁酸乳化能力降低，更容易溶解在粪便中被排出[24](图 1)。同时，乳酸菌 BSH 能够降低胆固醇小肠上皮细胞吸收关键蛋白 NPC1L1 (Niemann-pick C1 like 1)的表达[23]，抑制脂质的吸收，达到降低体内血清胆固醇水平的目的。

另外，胆固醇是胆汁酸生物合成的前体，大约 30%−40%的胆固醇在肝脏中通过两种途径转化为初级胆汁酸，其中胆固醇 7α-羟化酶(cholesterol 7α-hydroxylase，CYP7A1)是经典途径中的限速酶，甾醇 27α-羟化酶(sterol 27α-hydroxylase，CYP27A1)是另一途径中关键调节酶，甾醇 12α-羟化酶(sterol 12α-hydroxylase，CYP8B1)则控制合成的胆酸和鹅去氧胆酸(chenodeoxycholic acid，CDCA)的比例[25]，BSH 主要能够影响 CYP7A1 的表达，促进胆汁酸的合成[26]。合成的初级胆汁酸包括胆酸(cholic acid，CA)，以及 CDCA 与牛磺酸或甘氨酸结合形成的结合态胆汁酸，包括甘氨胆酸(glycocholic acid，GCA)、鹅去氧胆酸(glycochenodeoxycholic acid，GCDCA)、牛磺胆酸(taurocholic acid，TCA)和牛磺鹅去氧胆酸(taurochenodeoxycholic acid，TCDCA)，并暂时储存在胆囊中，通常是由于进餐使得胆囊收缩素产生，进而刺激结合态胆汁酸通过胆管释放到十二指肠[24](图 1)。大约 90%−95%的胆汁酸通过被动扩散和载体介导的运输进入肠肝循环，沿着肠被重吸收，特别是在回肠被吸收，以维持胆汁酸库稳态[27]。在每个

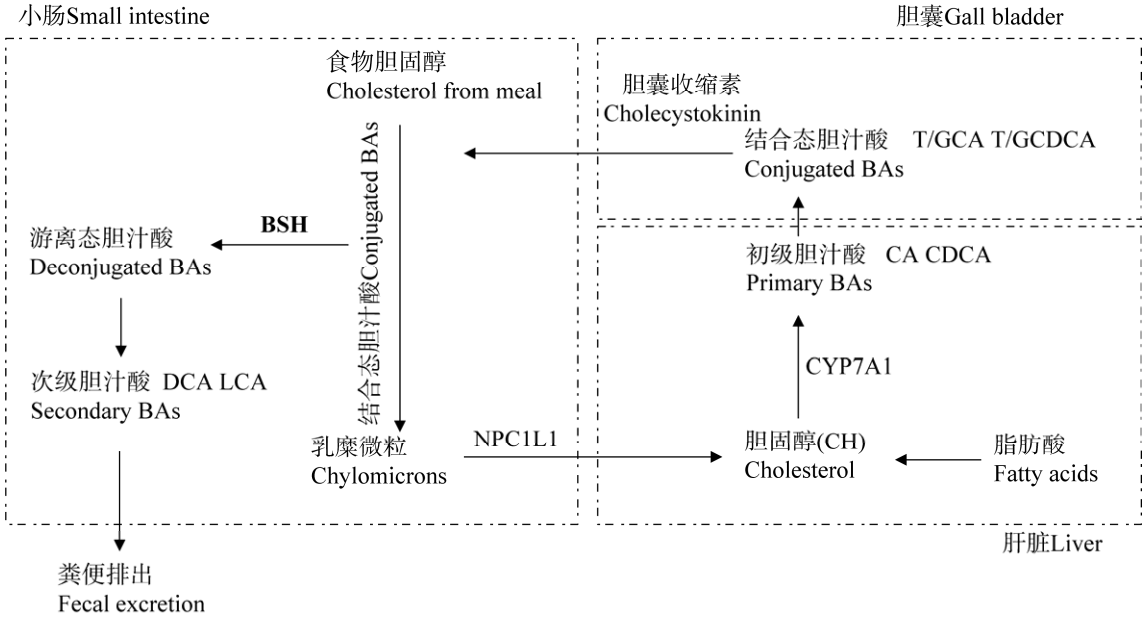

图 1　乳酸菌胆盐水解酶(BSH)对宿主胆固醇消化吸收影响机制[22,24]　BSH：胆盐水解酶；NPC1L1：胆固醇小肠上皮细胞吸收关键蛋白；CYP7A1：胆固醇 7α-羟化酶；BAs：胆汁酸；DCA：胆汁酸脱氧胆酸；LCA：石胆酸；TCA：牛磺胆酸；GCA：甘氨胆酸；TCDCA：牛磺鹅去氧胆酸；GCDCA：鹅去氧胆酸；CA：胆酸；CDCA：鹅去氧胆酸

Figure 1　Effects of bile salt hydrolase (BSH) of lactic acid bacteria on host digestion and absorption of cholesterol[22,24]. BSH: Bile salt hydrolase; NPC1L1: Niemann-pick C1 like 1; CYP7A1: Cholesterol 7α-hydroxylase; BAs: Bile acids; DCA: Deoxycholic acid; LCA: Lithocholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid.

周期中，近 4%−9%的胆汁酸随粪便排出，这被胆固醇在肝脏从头合成的胆汁酸所抵消[27]。显然，胆固醇向胆汁酸的转化是体内胆固醇排泄的主要途径。然而乳酸菌 BSH 的产生有助于粪便中游离胆汁酸排出的增加，进而有利于胆固醇向胆汁酸转化，并减少其向体循环的释放[28-29]。此外，新的胆固醇部分由脂肪转化而来，周而复始，更多的胆汁盐排出，越来越多的胆固醇和脂肪从血液中去除[5,30-31]。

1.3 影响乳酸菌 BSH 产生的因素

菌株差异及宿主饮食因素为影响乳酸菌 BSH 产生的重要因素。部分乳酸菌种所分泌的高活性和高表达量的 BSH 具有降脂作用，已得到广泛认可。如 Hou 等指出德氏乳杆菌(*L. delbrueckii*)促进了猪粪便总胆固醇(total cholesterol，TC)和总胆汁酸(total bile acids，TBA)的排出，血清 TC 和低密度脂蛋白胆固醇(low density lipoprotein cholesterol，LDL-C)的含量也对应显著降低[5]。有报道指出，不同乳杆菌(*Lactobacillus*)、双歧杆菌(*Bifidobacterium*)种类，包括长双歧杆菌(*B. longum*)[32]、唾液联合乳杆菌(*Ligilactobacillus salivarius*)[15]、植物乳植杆菌(*Lactiplantibacillus plantarum*)[33]和罗伊氏乳杆菌(*Limosilactobacillus reuteri*)等[34-35]分泌的 BSH 活性高，能够显著降低循环系统 TC 和/或甘油三酯水平。然而也有研究指出，具有高活性BSH的乳酸菌菌株对脂代谢的调节作用可能不同，如 Zhang 等的研究表明干酪乳杆菌 YRL577 和副干酪乳杆菌 X11 均具有较高的 BSH 活性，但干酪乳杆菌 YRL577 显著降低了肝脏重量和肝脏指数，并调节了脂质代谢，而副干酪乳杆菌 X11 并未表现出类似作用[36]。这种差异可能是由于宿主饮食差异所引起，饮食成分不仅会引起肠道菌群改变[37-38]，也会影响乳酸菌 BSH 的表达及活性[38]。Jia 等比较了生酮饮食(ketogenetic diet，KD)、常规饮食(baseline diet，BD)、过量饮食(overfeeding diet，OFD)、不足饮食(underfeeding diet，UFD)和低碳饮食(low-carbohydrate diet，LCD)对人体肠道微生物分泌 BSH 的影响。结果表明，KD 饮食能够显著增加 BSH 的产生，并导致 BSH 产生菌丰度增加；KD 中 80%的物质是脂类，可见脂类物质对乳酸菌的生长繁殖及 BSH 产生影响显著[37]。脂类中特别是 PUFAs 对乳酸菌代谢的影响不可忽视，PUFAs 影响乳酸菌 BSH 的产生，是其发挥降脂作用的重要途径[39]。有研究表明，当基质中 PUFAs 含量升高时，乳酸菌 BSH 合成量更多、活性更强，对应的宿主机体对胆固醇和脂肪的吸收显著降低[40-41]。

1.4 乳酸菌BSH影响宿主脂代谢的分子机制

乳酸菌BSH能够影响宿主胆固醇和脂肪酸代谢信号通路及关键基因表达。BSH 水解 BAs 产物 LCA、DCA 等会影响宿主胆汁酸组成和法尼类 X 受体(farnesoid X receptor，FXR)信号传导。已有研究证明，FXR 活性降低会下调小异二聚体伴侣(small heterodimer partner，SHP)，并通过限速酶 CYP7A1 增加胆固醇合成胆汁酸[41]。SHP 下调促进肝脏 X 受体(liver X receptor，LXR)激活，进而上调三磷酸腺苷结合转运蛋白 G5 和 G8 (ATP-binding cassette subfamily G5/G8，ABCG5/G8)，促进胆固醇转运到胆汁中[41-43](图 2)。此外，Huang 等采用非酒精性脂肪肝(nonalcoholic fatty liver disease，NAFLD) HepG2 细胞模型分析指出，干酪乳杆菌 pWQH01 和植物乳杆菌 AR113 中高活性的 BSH 能够降低肝细胞 TC 合成关键酶 3-羟基-3-甲基-戊二酰 CoA 还原酶(3-hydroxy-3-methyl glutaryl coenzyme A reductase，EC1.1.1.34，HMG-CoA)的表达，进而降低肝细胞 TC 含量；BSH 也能够降低信号通路固醇调节元件结合蛋白 1c (sterol regulatory

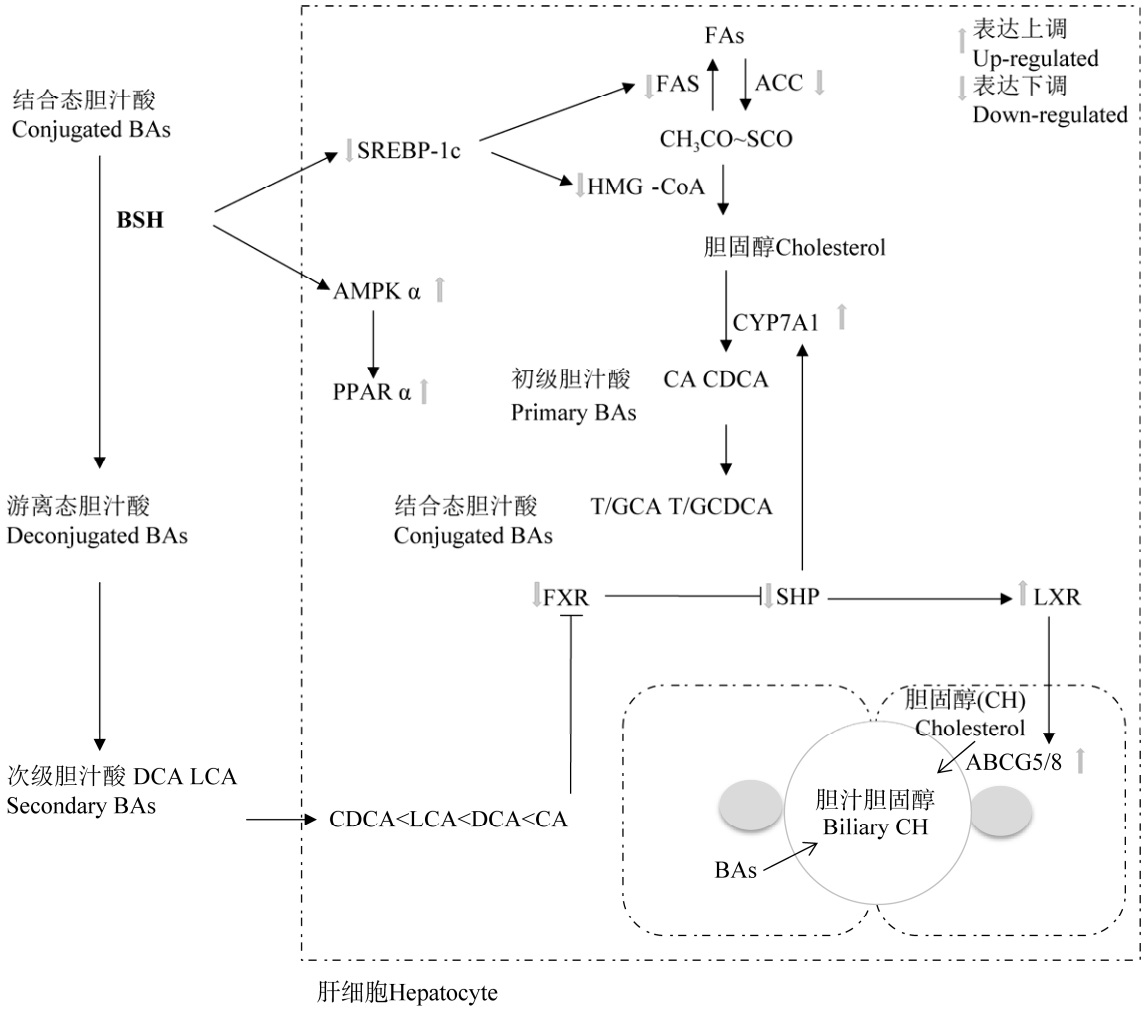

图 2　乳酸菌胆盐水解酶(BSH)对宿主脂代谢影响分子机制[41-42,44]　BSH：胆盐水解酶；BAs：胆汁酸；DCA：胆汁酸脱氧胆酸；LCA：石胆酸；TCA：牛磺胆酸；GCA：甘氨胆酸；TCDCA：牛磺鹅去氧胆酸；GCDCA：鹅去氧胆酸；CA：胆酸；CDCA：鹅去氧胆酸；SREBP-1c：固醇调节元件结合蛋白 1c；ACC：乙酰-CoA 羧化酶；FAS：脂肪酸合成酶；HMG-CoA：3-羟基-3-甲基-戊二酰 CoA 还原酶；CYP7A1：胆固醇 7α-羟化酶；FXR：法尼类 X 受体；SHP：小异二聚体伴侣；LXR：肝脏 X 受体；ABCG5/G8：三磷酸腺苷结合转运蛋白 G5 和 G8；AMPKα：5'-腺苷单磷酸激活蛋白激酶 α；PPARα：过氧化物酶体增殖物激活受体 α

Figure 2　Molecular mechanism of effect of bile salt hydrolase (BSH) from lactic acid bacteria on host lipid metabolism[41-42,44]. BSH: Bile salt hydrolase; BAs: Bile acids; DCA: Deoxycholic acid; LCA: Lithocholic acid; TCA: Taurocholic acid; GCA: Glycocholic acid; TCDCA: Taurochenodeoxycholic acid; GCDCA: Glycochenodeoxycholic acid; CA: Cholic acid; CDCA: Chenodeoxycholic acid; SREBP-1c: Sterol regulatory element binding protein 1c; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; HMG-CoA: 3-hydroxy-3-methyl glutaryl coenzyme A reductase; CYP7A1: Cholesterol 7α-hydroxylase; FXR: Farnesoid X receptor; SHP: Small heterodimer partner; LXR: Liver X receptor; ABCG5/G8: ATP-binding cassette subfamily G5/G8; AMPKα: 5′-AMP activated protein kinaseα; PPARα: Peroxisome proliferator-activated receptor α.

element binding protein 1c，SREBP-1c)的表达，相关脂代谢途径关键酶乙酰-CoA 羧化酶(acetyl-CoA carboxylase，ACC)和脂肪酸合成酶(fatty acid synthase，FAS)的表达下调[44](图 2)。另外，BSH 能够促使脂质分解途径的 5'-腺苷单磷酸激活蛋白激酶 α (5′-AMP activated protein kinase α，AMPKα)和过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor α，PPARα)的表达显著上升(图 2)，脂质分解代谢显著加强，包括脂肪酸氧化、甘油三酯分解、脂蛋白代谢、胆汁酸代谢和糖异生[44-45]。

1.5 乳酸菌 BSH 应用潜在风险

肠内乳酸菌 BSH 对宿主脂代谢的影响受到广泛认可，但 BSH 活性的增加也会带来潜在的不利影响。高 BSH 浓度被认为会产生大量未结合的 BAs，这可能会导致脂质吸收不良并引发腹泻[46-47]。BSH 活性增加也会损害结肠黏膜功能，从而诱发胆结石形成和结肠癌的产生[48]。因此，高浓度和高活性的 BSH 均可对宿主产生不良影响。尽管如此，研究表明，通常情况下适宜的乳酸菌 BSH 确实能够有效达到宿主脂代谢调节作用[41]，但目前关于肠内乳酸菌产生 BSH 的安全剂量范围未见相关报道。可见，促进乳酸菌适宜 BSH 的产生可作为宿主脂代谢紊乱调控的有效策略，确定其有效且安全的剂量范围，对于临床应用具有重要的意义。

2 乳酸菌共轭脂肪酸的产生

2.1 共轭脂肪酸的来源

乳酸菌能够通过对外源 PUFAs 营养物质转化产生共轭脂肪酸。乳酸菌在生长发酵过程中主要合成 $C_{6:0}$、$C_{8:0}$、$C_{10:0}$、$C_{12:0}$、$C_{14:0}$、$C_{16:0}$、$C_{16:1\Delta9}$、$C_{18:0}$、$C_{18:1\Delta11}$ 和 $C_{18:1\Delta9}$ 等脂肪酸[49-51]。当基质中存在脂肪酸营养物质时，乳酸菌会吸收利用这些营养成分，自身合成的脂肪酸会降低[49]。同时，在利用外来脂肪酸时，PUFAs 会被绝大多数乳酸菌饱和化，以满足生长需求，饱和化的过程中会产生羟基脂肪酸、氧代脂肪酸和共轭脂肪酸这些中间产物，这些中间产物具有多种生理功能，如抗癌、抗动脉粥样硬化、抑制炎症、抑制肥胖、抑制糖尿病、促进生长和促进骨骼形成等[10,52-54]，而降脂减肥作用是共轭脂肪酸的一项重要功能。小鼠、仓鼠、猪及人类补充共轭脂肪酸均已被证明有降脂减肥作用[55]。

亚油酸(ω-6)和 α-亚麻酸(ω-3)为膳食中来源最广泛的 PUFAs，也为人体必需脂肪酸。乳酸菌对亚油酸、α-亚麻酸进行异构化代谢，可以将其转化为共轭亚油酸(conjugated linoleic acid，CLA)和共轭亚麻酸(conjugated linolenic acid，CLNA)[9-10]。CLA 是多种含有共轭双键的十八碳二烯酸的总称，CLNA 是具有共轭双键的十八碳三烯酸的总称，它们是乳酸菌对膳食中亚油酸和亚麻酸生物还原饱和化过程的中间产物。有研究表明补充亚油酸后小鼠肠道 CLA 代谢产物水平显著增加，而补充亚麻酸后转化产生的 CLNA 不如前者显著[56]，这说明 CLA 的脂代谢调控作用可能更显著，目前能够检测到 28 种 CLA 异构体[57]。

2.2 PUFAs 转化为 CLA 的代谢路径

乳酸菌转化亚油酸产生 CLA 的催化酶系已被鉴定(采用模式植物乳杆菌 AKU1009a)[58]，CLA 的产生需要完整的亚油酸异构酶系。亚油酸异构酶系中的短链脱氢酶(conjugated linoleic hydratase，CLA-HY)、氧化还原酶(hydroxy fatty acid dehydrogenase，CLA-DH)、乙酰乙酸脱羧酶(acetoacetate decarboxylase，CLA-DC)和碳-碳双键饱和酶(carbon-carbon double bond saturase，CLA-ER)是催化其生成 CLA 的关键酶(图 3)[58-59]，其中 CLA-HY、CLA-DH 和 CLA-DC 在催化产生 CLA 途径中必不可少。不同菌种催

化酶的表达水平差异是造成亚油酸转化产生CLA不同的内在原因，某些乳酸菌该酶系中亚油酸异构酶系蛋白酶表达量高且活性强，对亚油酸异构化转化率也高[60-62]。也有研究表明CLA-HY是肠道乳酸菌产生CLA代谢的关键酶[56,63]，通过调控该酶表达，可以有效调控CLA的产生量及各组分的比例。另外，许多种类的乳酸菌并不完全具有催化酶系。例如唾液联合乳杆菌(*Ligilactobacillus salivarius*)含有CLA-DC、CLA-ER和CLA-HY；淀粉乳杆菌(*L. amylovorus*)、约翰逊乳杆菌(*L. johnsonii*)、瑞士乳杆菌(*L. helveticus*)和卷曲乳杆菌(*L. crispatus*)仅具有CLA-DH、CLA-ER和CLA-HY (www.genome.jp/kegg)。可见宿主菌群的分布，以及不同菌群之间对PUFAs代谢的协同作用是产生CLA的必备条件，与对宿主的脂代谢作用也有着密切关系。

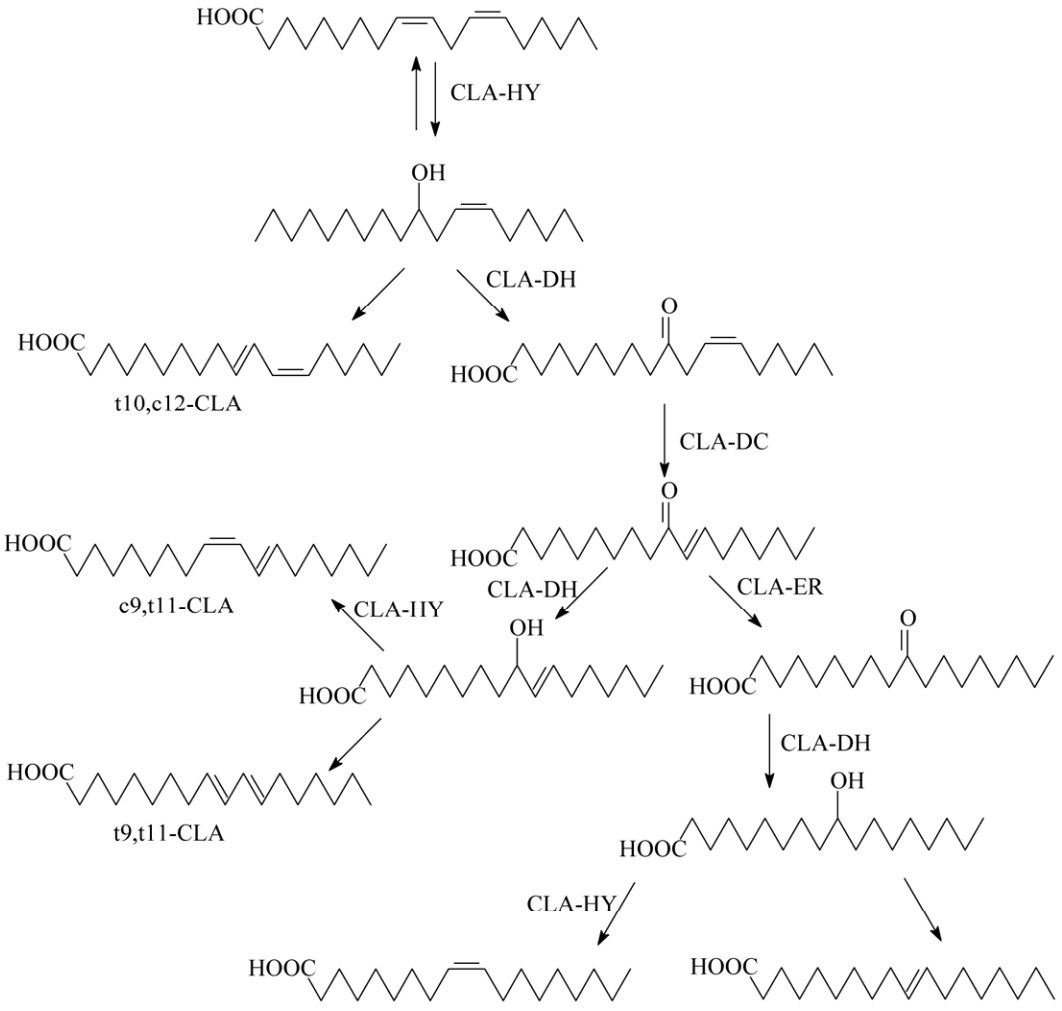

图 3 植物乳杆菌 AKU1009a 中亚油酸异构为 CLA 的反应历程[58-59] CLA-HY：短链脱氢酶；CLA-DH：氧化还原酶；CLA-DC：乙酰乙酸脱羧酶；CLA-ER：碳-碳双键饱和酶；t10,c12-CLA：t10,c12-共轭亚油酸；c9,t11-CLA：c9,t11-共轭亚油酸；t9,t11-CLA：t9,t11-共轭亚油酸

Figure 3 Reaction scheme of linoleic acid isomerized to CLA in *L. plantarum* AKU1009a[58-59]. CLA-HY: Conjugated linoleic hydratase; CLA-DH: Hydroxy fatty acid dehydrogenase; CLA-DC: Acetoacetate decarboxylase; CLA-ER: Carbon-carbon double bond saturase; t10,c12-CLA: t10,c12-conjugated linoleic acid; c9,t11-CLA: c9,t11-conjugated linoleic acid; t9,t11-CLA: t9,t11-conjugated linoleic acid.

2.3 t10,c12-CLA

大量研究表明，乳酸菌产生 CLA 的大多数生物效应归因于 c9,t11-CLA 和 t10,c12-CLA 两种异构体[55]，而 t10,c12-CLA 异构体脂代谢调控作用更显著[56]。t10,c12-CLA 是 CLA-HY 作用后亚油酸代谢的初级产物(图 3)。前人对 22 株乳酸杆菌进行了比较，发现不同乳酸菌产生 t10,c12-CLA 的效率不同，如唾液联合乳杆菌(*L. salivarius*)和加氏乳杆菌(*L. gasseri*)可以高效转化亚油酸(ω-6)产生 t10,c12-CLA，而嗜酸乳杆菌(*L. acidophilus*)和约翰逊乳杆菌(*L. johnsonii*)转化产生 t10,c12-CLA 的效率则较低[56]。相对应地，对高脂模型小鼠补充 t10,c12-CLA 则能够显著提升肠道特定乳酸菌属的含量和丰度，促进脂质分解代谢，增加肠道蠕动，降低脂质吸收[56]。可见，促进乳酸菌 t10,c12-CLA 的产生是促进降脂作用的有效途径。

2.4 CLA 混合物及单体 t10,c12-CLA 降脂机制

CLA 的降脂机制已有报道，但 CLA 混合物与单体物质 t10,c12-CLA 的降脂机制有所不同。CLA 混合物主要通过增加瘦素(leptin，LP)和 PPARα 基因表达来促进脂肪酸的氧化分解[58,64-65](图 4A)。LP 具有抑制食欲、促进能量消耗从而减少脂肪含量的功能，在体重的生理学调节方面具有举足轻重的作用[66-67]。PPARα 可增强靶酶——肉毒碱脂酰辅酶 A 转移酶 1 (carnitine acyl-CoA transferase 1，CPT1)和肉毒碱脂酰辅酶 A 转移酶 2 (CPT2)等脂肪酸氧化酶的表达，可促使脂酰肉毒碱(acyl-carnitine)转化为脂酰辅酶 A (acyl CoA)，促进脂质氧化；PPARα 还可促进细胞色素 P450 4A (cytochrome P450 4A，CYP4A)的表达，催化不饱和脂肪酸在 ω 和 ω1 位点羟基化，加速脂肪酸氧化[58,64-65](图 4A)。然

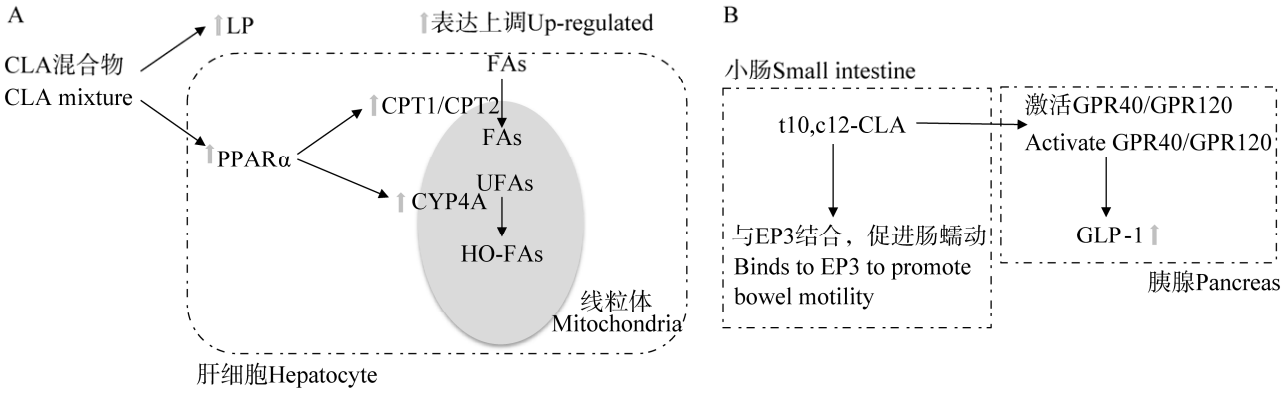

图 4 CLA 混合物(A)[58,64-65]及单体 t10,c12-CLA (B)[56]降脂分子机制 CLA：共轭亚油酸；LP：瘦素；FAs：脂肪酸；UFAs：不饱和脂肪酸；HO-FAs：羟基化脂肪酸；CPT1/2：肉毒碱脂酰辅酶 A 转移酶 1/2；CYP4A：细胞色素 P450 4A；t10,c12-CLA：t10,c12-共轭亚油酸；EP3：前列腺素 E 受体 3；GPR40/120 G：蛋白偶联受体 40/120；GLP-1：胰高血糖素样肽 1

Figure 4 The molecular mechanism of lipid-lowering effect of CLA mixture (A)[58,64-65] and monomer t10,c12-CLA (B)[56]. CLA: Conjugated linoleic acid; LP: Leptin; FAs: Fatty acids; UFAs: Unsaturated fatty acids; HO-FAs: Hydroxylated fatty acids; CPT1/2: Carnitine acyl-CoA transferase 1/2; CYP4A: Cytochrome P450 4A; t10,c12-CLA: t10,c12-conjugated linoleic acid; EP3: Prostaglandin E receptor 3; GPR40/120 G: Protein-coupled receptor 40/120; GLP-1: Glucagon like peptide-1.

而单体 t10,c12-CLA 主要通过激活 G 蛋白偶联受体 40/120 (G protein-coupled receptor 40/120，GPR40/120)促进胰高血糖素样肽 1 (glucagon like peptide-1，GLP-1)分泌，降低血糖，促进脂质分解；t10,c12-CLA 也可与前列腺素 E 受体 3 (prostaglandin E receptor 3，EP3)结合，促进肠蠕动，抑制脂质吸收[56](图 4B)。单体与混合物降脂机制的差异可能是由于不同物质之间的共同作用与单体物质的作用有所差异，然而具体原因还有待于进一步研究分析。

2.5 CLA 的应用风险

目前，多数研究显示 CLA 或单体 t10,c12-CLA 在一定浓度范围的使用是安全的[9,55,63]，但关于 CLA 的安全使用剂量范围未见相关报道。如 Blankson 等进行了不同浓度 CLA 混合物对超重或肥胖志愿者(体重指数 25−35 kg/m^2)体脂量(body fat mass，BFM)的影响，结果表明当 CLA 剂量为 1.7 g/d 时，对体脂及健康水平并未产生额外影响，然而当 CLA 剂量为 3.4/6.8 g/d 能够显著降低体脂含量[68]，这说明当 CLA 使用剂量为 3.4−6.8 g/d 会产生降脂减肥作用，而且不会带来健康隐患。另外，有文献报道高剂量的 CLA 使用可能会产生不良反应。例如：Oliveira 等研究表明，30 g/d 的 CLA 补充量减少了奶牛/母羊的产奶量[69]；Foote 等发现高剂量 t10,c12-CLA (饮食质量 0.5%)会导致雌性 FVB 小鼠乳腺发育障碍，引起高胰岛素血症和肝脏脂质积聚，这说明高剂量的 CLA 确实对机体存在有害影响[70]。总之，过量的 CLA 混合物及单体均会带来健康隐患，因此直接补充 CLA 可能会导致剂量过高，存在一定风险。可见，通过日常饮食摄入适量的 PUFAs 进行体内转化产生共轭脂肪酸进行补充，或通过摄入富含 CLA 的食品(如奶制品)[71]更加安全，这些方法中 CLA 一般在安全剂量范围内。

3 乳酸菌影响宿主脂代谢作用分子机制小结

综上所述，乳酸菌对宿主脂代谢调节作用主要为：(1) 乳酸菌合成的 BSH 通过加强宿主消化系统结合态 BAs 分解，从而抑制 NPC1L1 表达，降低宿主饮食中胆固醇等脂类物质的吸收[23]；通过降低机体信号转导途径 FXR 和 SHP 表达，调控关键酶 CYP7A1 表达促进胆固醇向胆汁酸转化[41]，SHP 下调促进 LXR 激活，上调 ABCG5/G8，促进胆固醇转运到胆汁中[41-43]；同时通过增加信号转导途径 AMPKα 和 PPARα 表达，降低 SREBP-1c 及关键酶 HMG-CoA、ACC 和 FAS 等表达，抑制胆固醇合成，促进脂质的分解代谢[41,44](图 5)。(2) 乳酸菌转化 PUFAs 为共轭脂肪酸，共轭脂肪酸 CLA/CLNA 能够促进 LP 的产生，抑制食欲，促进能量消耗[58]；能够通过激活 PPARα，增强靶酶 CPT1、CPT2 和 CYP4A 的表达，促进人体脂肪酸的氧化分解[64-65](图 5)。

4 展望

本文重点从两个方面阐述了乳酸菌对宿主脂代谢的调节作用，即乳酸菌 BSH 的产生及对 PUFAs 转化产生共轭脂肪酸，并最终对其内在分子机制进行了总结阐述。

BSH 酶在宿主代谢过程中发挥广泛的作用，包括胆固醇代谢、能量和炎症稳态的调节。对肠道微生物群的功能分析显示，乳酸菌能够产生 BSH 促进体内胆固醇的排出，抑制饮食中脂类的吸收[5,21]。不同菌株 BSH 的产生存在差异[15,32-35]，不同饮食成分，如 PUFAs 对乳酸菌这种酶的产生及活性存在影响也已经得到证实[37,39]。作为参与关键解偶联反应的独特酶，通过补充特定菌株，

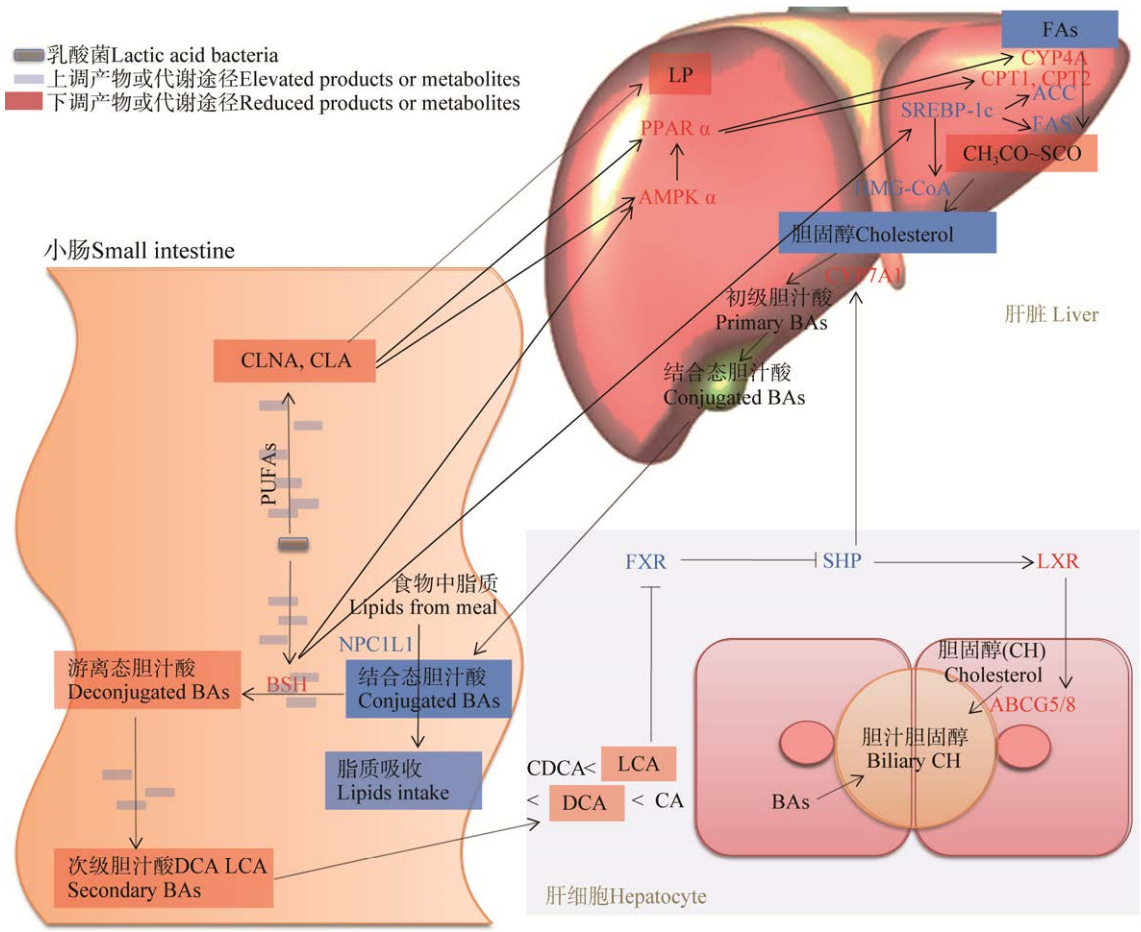

图 5　乳酸菌通过产生胆盐水解酶(BSH)、共轭脂肪酸(CLA/CLNA)对宿主脂代谢调节分子机制[23,41,44,58,66-67]

BSH：胆盐水解酶；CLA：共轭亚油酸；CLNA：共轭亚麻酸；PUFAs：多不饱和脂肪酸；NPC1L1：胆固醇小肠上皮细胞吸收关键蛋白；CYP7A1：胆固醇 7α-羟化酶；CDCA：鹅去氧胆酸；CA：胆酸；DCA：胆汁酸脱氧胆酸；LCA：石胆酸；FXR：法尼类 X 受体；SHP：小异二聚体伴侣；LXR：肝脏 X 受体；ABCG5/G8：三磷酸腺苷结合转运蛋白 G5 和 G8；HMG-CoA：3-羟基-3-甲基-戊二酰 CoA 还原酶；SREBP-1c：固醇调节元件结合蛋白 1c；ACC：乙酰-CoA 羧化酶；FAS：脂肪酸合成酶；AMPKα：5′-腺苷单磷酸激活蛋白激酶 α；PPARα：过氧化物酶体增殖物激活受体 α；LP：瘦素；CPT1/2：肉毒碱脂酰辅酶 A 转移酶 1/2；CYP4A：细胞色素 P450 4A。上调蛋白：PPARα、AMPKα、CYP4A、CPT1、CPT2、CYP7A1、BSH、LXR、ABCG5/8；下调蛋白：SREBP-1c、ACC、FAS、HMGCoA、FXR、SHP。

Figure 5　The molecular mechanism of regulation of host lipid metabolism by lactic acid bacteria trough production of bile salt hydrolase (BSH) and conjugated fatty acids (CLA/CLNA)[23,41,44,58,66-67]. BSH: Bile salt hydrolase; CLA: Conjugated linoleic acid; CLNA: Conjugated linolenic acid; PUFAs: Polyunsaturated fatty acids; NPC1L1: Niemann-pick C1 like 1; CYP7A1: Cholesterol 7α-hydroxylase; CDCA: Chenodeoxycholic acid; CA: Cholic acid; DCA: Deoxycholic acid; LCA: Lithocholic acid; FXR: Farnesoid X receptor; SHP: Small heterodimer partner; LXR: Liver X receptor; ABCG5/G8: ATP-binding cassette subfamily G5/G8; HMG-CoA: 3-hydroxy-3-methyl glutaryl coenzyme A reductase; SREBP-1c: Sterol regulatory element binding protein 1c; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; AMPKα: 5′-AMP activated protein kinase; PPARα: Peroxisome proliferator-activated receptor α; LP: Leptin; CPT1/2: Carnitine acyl-CoA transferase 1/2; CYP4A: Cytochrome P450 4A. Upregulated proteins: PPARα, AMPKα, CYP4A, CPT1, CPT2, CYP7A1, BSH, LXR, ABCG5/8; Down regulated proteins: SREBP-1c, ACC, FAS, HMGCoA, FXR, SHP。

或通过调控饮食成分如 PUFAs 进而调节乳酸菌 BSH 的产生，可作为一种有前途的策略来控制肥胖疾病。然而高含量的 BSH 会对宿主产生不利影响[68-70]，目前涉及乳酸菌 BSH 有效安全剂量的文章很少，并且涉及饮食成分对 BSH 产生影响的文章也较少。因此，深入研究 BSH 的有效安全剂量，进一步分析宿主饮食成分如 PUFAs 对乳酸菌 BSH 产生的影响，对深入理解乳酸菌产生 BSH 的脂代谢调控机制有着重要意义。

在过去的几十年里，乳酸菌可将 PUFAs 转化为 CLA/CLNA 等异构体已达成共识，这些异构体在脂代谢调控、防治肥胖的作用已在体内外得到广泛证实[55-56,58]。总而言之，研究主要集中在亚油酸乳酸菌转化产物 CLA 中，对 CLNA 的研究较少[56]。目前，研究表明 CLA 对人类影响的研究比对动物少，并且相较于动物，其在人体观察到的作用要少得多，这可能是由于动物在体实验中所用的剂量远高于人体，然而 CLA 在动物和人体中的有效剂量仍不清楚。目前市场主要为 CLA 混合物产品，或者为 50:50 的 c9,t11-CLA 和 t10,c12-CLA，但不同的 CLA 对健康和疾病的影响不同，有些如 t10,c12-CLA 甚至可能在某些条件下表现出不良影响[69-70]。因此，后续进行不同共轭脂肪酸单体有效和安全剂量，以及脂代谢调控机制研究有助于更好地理解其结构-功能关系。

乳酸菌影响宿主脂代谢已经得到共识，如通过产生短链脂肪酸、丙酸盐和醋酸盐等物质调节脂肪的代谢，通过增强上皮细胞屏障、调节肠道微生物菌群和降低肠道内 pH 值等方法，进而刺激肠壁，增加肠道蠕动，促进肠液分泌、肠腔润滑和缩短食物在肠道中的停留时间等方式来调节脂质代谢[72]，但目前的研究主要集中在对单一途径的深入研究中。乳酸菌脂代谢调控涉及多种方式，如本文所论述，产生 BSH[5,12,21]及转化产物 CLA/CLNA[9-10]均可影响宿主脂代谢且调控机制有相似之处，而且都会受到饮食因素如 PUFAs 的影响。因此，进一步分析不同方式之间的相互作用及其影响因素，对深入理解乳酸菌宿主脂代谢调控作用及临床应用有着重要意义。

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