安昊杰,高江梅,钟秀玲,等. 罗伊氏乳杆菌降胆固醇的作用与机制研究进展[J]. 中国实验动物学报,2025,33(1):108-116.

AN H J, GAO J M, ZHONG X L, et al. Progress in studies on the action and mechanism of *Lactobacillus reuteri* in lowering cholesterol [J]. Acta Lab Anim Sci Sin, 2025, 33(1): 108-116.

Doi:10.3969/j.issn.1005-4847.2025.01.011

罗伊氏乳杆菌降胆固醇的作用与机制研究进展

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【摘要】 由高胆固醇血症引起的动脉粥样硬化心血管疾病已成为影响人类生命健康的主要威胁之一。近年来,具有降胆固醇作用的益生菌已成为研究热点。研究表明,罗伊氏乳杆菌能够通过调节宿主肝与肠上皮细胞固醇调节元件结合蛋白 2、3-羟基-3-甲基戊二酰辅酶 A 还原酶、胆固醇 7α 羟化酶等的基因表达,减少内源胆固醇合成、调节胆固醇转运和促进胆固醇分解,从而降低宿主血清中总胆固醇和低密度脂蛋白胆固醇的水平。本文对已报道的罗伊氏乳杆菌降胆固醇作用与机制的研究进行综述,旨在为高胆固醇血症的治疗及降胆固醇益生菌的研发提供参考。

【关键词】 益生菌;罗伊氏乳杆菌;降胆固醇;作用与机制

【中图分类号】 Q95-33 **【文献标志码】** A **【文章编号】** 1005-4847(2025) 01-0108-09

Progress in studies on the action and mechanism of *Lactobacillus reuteri* in lowering cholesterol

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【Abstract】 Cardiovascular diseases that develop from hypercholesterolemia-induced atherosclerosis have emerged as a significant threat to human health. Recently, probiotics exhibiting cholesterol-lowering properties have emerged as a prominent area of research. Numerous studies have demonstrated that *Lactobacillus reuteri* can effectively reduce endogenous cholesterol synthesis, regulate cholesterol transport, and promote cholesterol degradation by

[**基金项目**]国家自然科学基金(82200966),广东省科学院科技发展专项(2022GDASZH-2022010110)。

Funded by National Natural Science Foundation of China (82200966), GDAS Special Project of Science and Technology Development (2022GDASZH-2022010110).

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modulating the expression of key genes, such as sterol-regulatory element binding protein 2, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, and cholesterol 7 alpha-hydroxylase, in both the liver and intestinal epithelial cells of the host. This leads to a notable decrease in total cholesterol and low-density lipoprotein cholesterol levels in the host serum. The present paper offers a comprehensive overview of the underlying mechanisms responsible for the cholesterol-lowering effects exerted by *L. reuteri*, aiming to provide valuable insights into the treatment of hypercholesterolemia and the development of probiotics with cholesterol-lowering properties.

【Keywords】 probiotics; *Lactobacillus reuteri*; cholesterol-lowering; action and mechanisms

Conflicts of Interest: The authors declare no conflict of interest.

高胆固醇血症是一类胆固醇代谢疾病,血清中过高的总胆固醇(total cholesterol,TC)和低密度脂蛋白胆固醇(low-density lipoprotein cholesterol,LDL-C)水平是影响动脉粥样硬化心血管疾病最重要的风险因素[1-3]。益生菌是指一类活的微生物,当摄入足够数量时对宿主起有益健康的作用[4-5]。以乳杆菌属为主的多种益生菌均被证实具有降低 TC 和 LDL-C 的功效[6-8]。近年来,具有降胆固醇作用的益生菌已成为研究热点之一,其降胆固醇机制主要包括:调节肠道中短链脂肪酸含量、促进胆盐水解酶表达、调节胆固醇转运、抑制胆固醇重吸收等[8-10]。

罗伊氏乳杆菌(*Lactobacillus reuteri*, *L. reuteri*)呈白色短棒状,是乳杆菌科(Lactobacillaceae)、乳杆菌属(*Lactobacillus*)的一种革兰氏阳性菌,2003 年被正式批准为保健益生菌[11-13]。临床前研究表明, *L. reuteri* NCIMB 30242[14]、*L. reuteri* MG5149[15]、*L. reuteri* A9[16]、*L. reuteri* HI120[17]等多个菌株均具有降低高脂血症啮齿类动物血清中 TC 和 LDL-C 的作用,能够有效缓解肝脂质累积与病变[18],并发挥保护肠粘膜屏障[19-21]、调节宿主免疫[22-24]、改善肠道菌群[25-26]的作用。临床研究发现:相较于服用安慰剂,患者连续 9 周服用 *L. reuteri* NCIMB 30242,其血清 TC(9.14%, $P < 0.001$)和 LDL-C(11.64%, $P < 0.001$)水平明显降低,且无不良反应发生[27]。

近年来研究发现,*L. reuteri* 可以通过调节啮齿类动物肝细胞中固醇调节元件结合蛋白 2(sterol-regulatory element binding proteins-2, SREBP-2)和 3-羟基-3-甲基戊二酰辅酶 A 还原酶(3-hydroxy-3-methyl glutaryl coenzyme A reductase, HMGCR)的基因表达来减少内源胆固醇的合成[14,17],通过调节肝细胞和肠上皮细胞中低密度脂蛋白受体(low-density lipoprotein receptor, LDLR)、ATP 结合盒转运体 G5/8(ATP-binding cassette transporters G5/8, ABCG5/8)、ATP 结合盒转运体 A1(ATP-binding cassette transporters A1, ABCA1)、类尼曼-匹克 C1 蛋白 1(niemann-pick C1 like 1, NPC1L1)等的基因表达调节胆固醇摄入与排出[16,18],并经上调肝细胞中甾醇 27 羟化酶(sterol 27-hydroxylase, CYP27A1)等的基因表达水平促进胆固醇的分解[28-29]。本文结合近年来的相关报道,首次对 *L. reuteri* 降胆固醇的作用(表 1)与机制进行综述,旨在为高胆固醇血症的治疗及降胆固醇益生菌的研发提供参考。

1　减少胆固醇的合成

固醇调节元件结合蛋白(sterol-regulatory element binding proteins, SREBPs)是肝细胞胆固醇合成、摄取,脂质代谢等生理活动的主要调控因子[37-39]。SREBPs 具有三个亚型,其中 SREBP-2 蛋白参与 *LDLR*、*HMGCR* 等基因的转录调控,进而调节胆固醇稳态[40-42]。HMGCR 是内源性胆固醇合成的重要限速酶,可将 3-羟基-3-甲基戊二酰辅酶 A(3-hydroxy-3-methyl glutaryl coenzyme A, HMG-CoA)还原成甲羟戊酸,*HMGCR* 基因表达增强将促进内源性胆固醇的合成[42-43]。

研究发现,*L. reuteri* 可下调宿主肝细胞中 *SREBP*-2 和 *HMGCR* 基因转录和表达水平。*L. reuteri* NCIMB 30242[14]、*L. reuteri* A9[16]、*L. reuteri* HI120[17]和 *L. reuteri* DSM20016[17]等多个菌株可明显下调高脂血症 SD 大鼠和 C57BL/6 小鼠肝细胞中 *SREBP*-2($P < 0.05$)和 *HMGCR*($P < 0.05$)基因与肠上皮细胞中 *SREBP*-2($P < 0.05$)基因转录和表达水平。肝细胞中 *SREBP*-2 基因表达水平降低可能导致高尔基体膜上

表 1 不同 *L. reuteri* 菌株降胆固醇的作用与机制比较

Table 1 Comparison of the action and mechanism of *L. reuteri* strains on cholesterol-lowering

菌株 Bacterial strain	来源 Source	实验动物 Laboratory animal	血脂水平 Blood lipid level				基因转录与表达 Gene transcription and expression	参考文献 Reference
			TC	TG	LDL-C	HDL-C		
L. reuteri NCIMB30242	猪粪便 Pig feces	SD 大鼠（雄性） SD rats (male)	↓	↓	↓	↑	*SREBP*-2 和 *HMGCR* 基因转录和表达水平降低，*CYP7A*1、*LDLR* 基因转录和表达水平升高（肝） Decreased transcription and expression levels of *SREBP*-2 and *HMGCR* genes, increased transcription and expression levels of *CYP7A*1 and *LDLR* genes (liver)	[14]
L. reuteri SY523	小鼠粪便 Mouse feces	C57BL/6（雄性） C57BL/6 (male)	↓	↓	↓	↑	未检测 Not done	[30]
L. reuteri Fn041	人类母乳 Human breast milk	C57BL/6N（雄性） C57BL/6N (male)	↓	–	↓	–	*CYP7A*1、*LXR* 基因转录水平升高（肝）；*SLC10A2* 基因转录水平降低（回肠） Increased transcription levels of *CYP7A*1 and *LXR* genes (liver); decreased transcription level of *SLC10A2* gene (ileum)	[19,28]
L. reuteri CGMCC 17942	成人粪便 Adult feces	C57BL/6J（雄性） C57BL/6J (male)	↓	↓	↓	–	*CYP7A*1 和 *CYP7B*1 基因转录水平显著降低，*CYP27A*1 基因转录水平显著升高（肝） Decreased transcription and expression levels of *CYP7A*1 and *CYP7B*1 genes, increased transcription and expression levels of *CYP27A*1 gene (liver)	[29]
L. reuteri MJM60668	婴儿粪便 Infant feces	C57BL/6（雄性） C57BL/6 (male)	↓	↓	未检测 Not done	–	*SREBP* 基因转录和表达水平降低（肝） Decreased transcription and expression levels of *SREBP* gene (liver)	[31]
L. reuteri CCFM8631	人类粪便 Human feces	C57BL/6J（雌性） C57BL/6J (female)	↓	–	↓	–	未检测 Not done	[32]
L. reuteri FYNLJ109L1	猪粪便 Pig feces	C57BL/6J（雄性） C57BL/6J (male)	–	–	↓	–	未检测 Not done	[33]
L. reuteri FGSZY33L6	儿童粪便 Children feces	C57BL/6（雄性） C57BL/6 (male)	↓	–	↓	–	未检测 Not done	[34]
L. reuteri FGSYC2L3	成人粪便 Adult feces	C57BL/6（雄性） C57BL/6 (male)	–	–	↓	–	未检测 Not done	[34]
L. reuteri 8513d	未知 Unknown	SD 大鼠 SD rats	↓	–	–	–	*ABCA*1 基因转录水平降低，*LDLR* 和 *ABCG5* 基因转录水平升高（肝） Decreased transcription and expression levels of *ABCA*1 gene, increased transcription and expression levels of *LDLR* and *ABCG5* genes (liver)	[18]
L. reuteri HI120	儿童粪便 Children feces	C57BL/6（雄性） C57BL/6 (male)	↓	–	未检测 Not done	未检测 Not done	*NPC1L1* 和 *SREBP*-2 基因转录和表达水平降低（小肠）；*SREBP*-2、*HMGCR* 基因转录和表达水平降低，*CYP7A*1 基因转录和表达水平不变（肝） Decreased transcription and expression levels of *NPC1L1* and *SREBP*-2 genes (small intestine); decreased transcription and expression levels of *SREBP*-2 and *HMGCR* genes, unchanged in *CYP7A*1 gene (liver)	[17]

续表 1

菌株 Bacterial strain	来源 Source	实验动物 Laboratory animal	血脂水平 Blood lipid level				基因转录与表达 Gene transcription and expression	参考文献 Reference
			TC	TG	LDL-C	HDL-C		
L. reuteri DSM20016	人类粪便 Human feces	C57BL/6（雄性）C57BL/6 (male)	↓	–	未检测 Not done	未检测 Not done	*NPC1L1* 和 *SREBP*-2 基因转录和表达水平降低（小肠）；*SREBP*-2、*HMGCR* 基因转录和表达水平降低，*CYP7A1* 基因转录和表达水平不变（肝）Decreased transcription and expression levels of *NPC1L1* and *SREBP*-2 genes (small intestine); decreased transcription and expression levels of *SREBP*-2 and *HMGCR* genes, unchanged in *CYP7A1* gene (liver).	[17]
L. reuteri A9	老人粪便 Elderly feces	Wistar 大鼠（雄性）Wistar rats (male)	↓	–	↓	–	*SREBP*-2 和 *LDLR* 转录水平升高，*LXR*、*CYP7A1* 转录水平不变（肝）Increased transcription levels of *SREBP*2 and *LDLR* genes, unchanged in *LXR* and *CYP7A1* gene (liver)	[16]
L. reuteri GMNL-263	未知 Unknown	SD 大鼠（雄性）SD rats (male)	↓	↓	未检测 Not done	未检测 Not done	未检测 Not done	[35]
		金黄地鼠（雄性）Golden Syrian hamsters (male)	↓	↓	↓	↑	未检测 Not done	[36]

注：TG：甘油三酯；HDL-C：高密度脂蛋白胆固醇；↑：升高或增加；↓：降低或减少；–：无差异。
Note. TG. Triglyceride. HDL-C. High-density lipoprotein cholesterol. ↑. Indicates increase or elevation. ↓. Indicates decrease or reduction. –. Indicates no difference.

SREBP-2 无法被裁切形成 n-SREBP2（图 1，路径①），进而引起 *HMGCR* 基因转录和表达水平降低（图 1，路径②），肝内源性胆固醇合成受阻（图 1，路径③）。SUN 等[17]经体外实验证明，*L. reuteri* 可能将肠道中的亚油酸转变为共轭亚油酸，从而发挥降低血清中 TC 水平的作用。

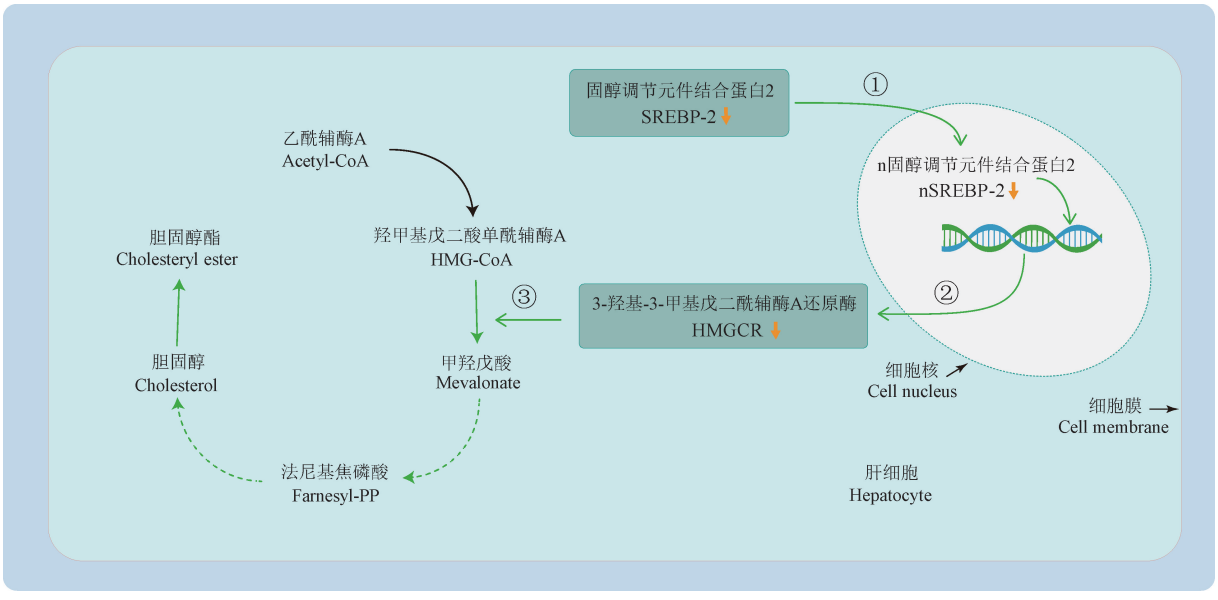
2　促进胆固醇的分解

胆固醇在肝中被分解为胆汁酸是胆固醇代谢的主要途径，根据胆固醇被羟基化的方式可以分为经典途径和替代途径[44]。在经典途径中，胆固醇被胆固醇 7α 羟化酶（cholesterol 7 alpha-hydroxylase，CYP7A1）羟基化为 7α-羟基胆固醇，并最终形成胆酸和脱氧胆酸[45-46]。研究发现，*L. reuteri* 可促进 *CYP7A1* 基因转录与表达，促进胆固醇分解为胆汁酸，并抑制胆汁酸的重吸收。研究发现，经 *L. reuteri* NCIMB 30242[14] 和 *L. reuteri* Fn041[28] 干预，高脂饮食诱导的啮齿类动物肝中 *CYP7A1* 基因转录和表达水平显著升高（$P < 0.05$），表明 *L. reuteri* 可通过经典途径促进胆固醇的降解（图 2，路径①）[13]。此外，LU 等[28]发现，经 *L. reuteri* Fn041 干预的高脂饮食诱导的 C57BL/6 N 小鼠粪便中总胆汁酸含量显著上升（$P < 0.01$），且回肠中与胆汁酸重吸收有关的溶质转运蛋白家族 10 成员 2（solute carrier family 10 member 2，SLC10A2）的基因转录水平降低（$P < 0.05$）。

在替代途径中，胆固醇经 CYP27A1 羟基化并由氧固醇 7α 羟化酶（oxysterol 7-alpha-hydroxylase，CYP7B1）等催化后，主要形成脱氧胆酸[47-48]。此外，*L. reuteri* 可通过上调 *CYP27A1* 基因表达，促进胆固醇经替代途径分解。YE 等[29]研究发现：*L. reuteri* CGMCC 17942 可显著降低高胆固醇 C57BL/6J 小鼠肝中 *CYP7A1* 基因转录水平（$P < 0.05$），*CYP27A1* 基因转录水平显著升高（$P < 0.05$），表明 *L. reuteri* 可能通过促进胆固醇降解的替代途径生成胆汁酸（图 2，路径②）。

3　调节胆固醇的转运

肝和肠上皮细胞负责胆固醇跨膜运输的膜

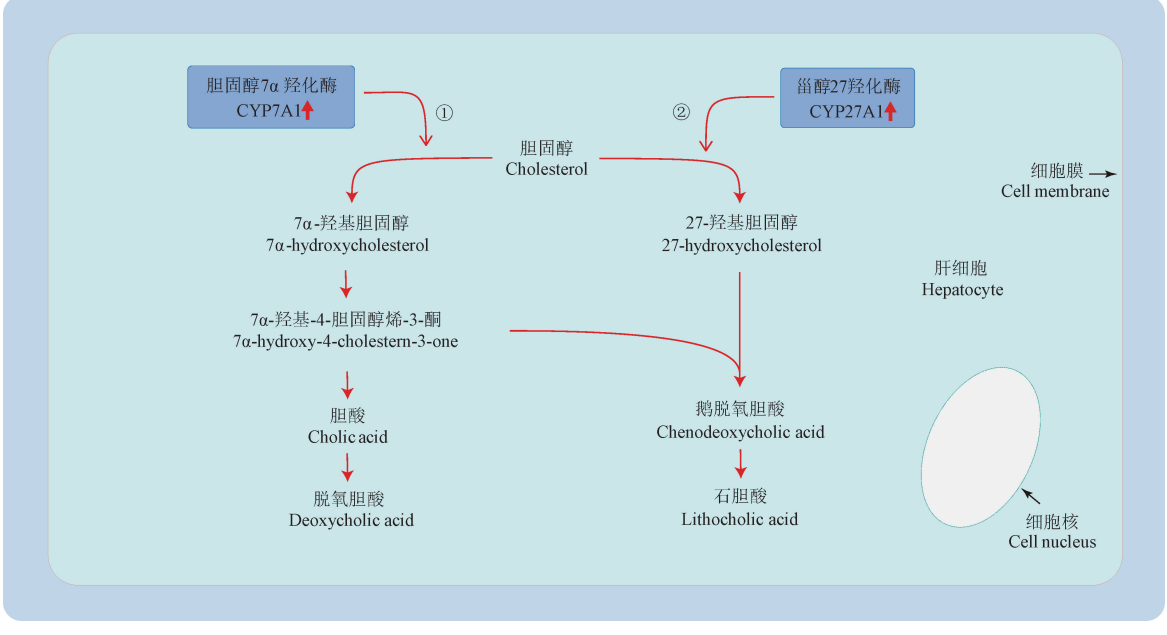


注:①:*SREBP*-2 基因表达量降低,进而导致细胞核内 nSREBP-2 水平降低;②:nSREBP-2 水平降低导致 *HMGCR* 基因表达下调;③:HMGCR 水平降低导致 HMG-CoA 合成甲羟戊酸受阻,影响内源性胆固醇合成。

图 1 *L. reuteri* 减少内源性胆固醇合成的作用机制

Note. ①. Expression of *SREBP*-2 is downregulated, resulting in a reduction in the nuclear levels of nSREBP-2. ②. Reduction in nSREBP-2 levels results in the downregulation of *HMGCR* gene expression. ③. Reduction in HMGCR levels results in compromised synthesis of HMG-CoA, consequently impacting the biosynthesis of endogenous cholesterol.

Figure 1 Mechanism of *L. reuteri* on decreasing the synthesis of endogenous cholesterol



注:①:*CYP7A1* 基因表达量升高,促进胆固醇被催化为 7α-羟基胆固醇(经典途径);②:*CYP27A1* 基因表达量升高,促进胆固醇被催化为 27α-羟基胆固醇(替代途径)。

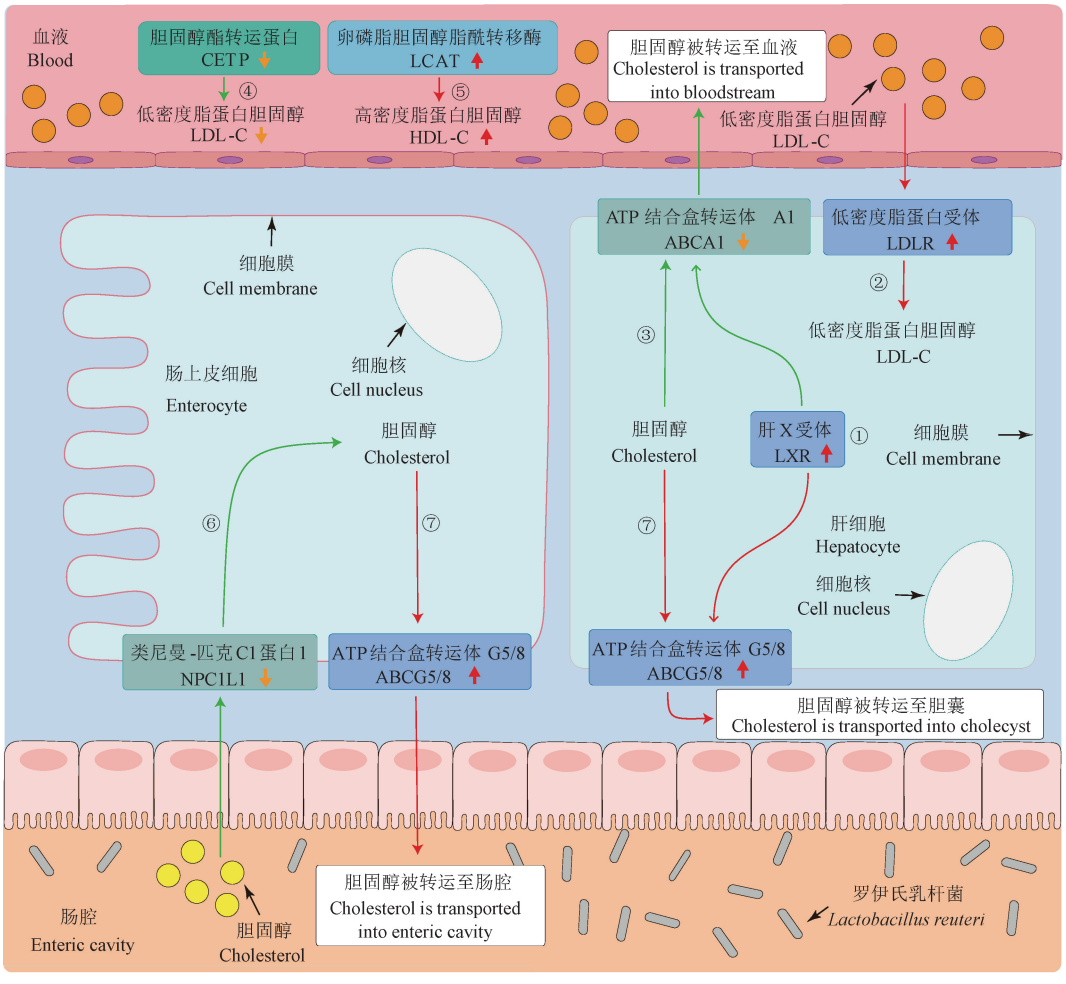
图 2 *L. reuteri* 促进胆固醇分解的作用机制

Note. ①. Expression of the *CYP7A1* gene is upregulated, thereby enhancing the catalytic conversion of cholesterol into 7α-hydroxycholesterol (classical pathway). ②. Expression of the *CYP27A1* gene is elevated, thereby facilitating the catalytic conversion of cholesterol to 27α (alternative pathway).

Figure 2 Mechanism of *L. reuteri* on promoting the degradation of cholesterol

蛋白主要有 ABC 超家族(ABCA1、ABCG5 和 ABCG8 等)、LDLR、NPC1L1 等[49-51]。其中 ABCA1 与 ATP 结合盒转运体 G1(ATP-binding cassette transporter G1, ABCG1)可将胞内多余胆固醇向血液排放[49-50],ABCG5 与 ABCG8 可将胆固醇排至胆囊和肠腔[49,51],而 LDLR 可从血液中吸收 LDL-C[52],NPC1L1 可吸收小肠中的外源胆固醇[53],这些跨膜转运蛋白共同维持胆固醇在各脏器之间的转运与平衡。此外,肝 X 受体(liver X receptor, LXR)作为 ABC 超家族重要的调控因子,与配体结合后可调控 *ABCA1*、*ABCG5*、*ABCG8* 等基因的表达[54]。

研究发现,经 *L. reuteri* 干预的高脂血症啮齿类动物体内胆固醇转运发生变化,血清中 TC 和 LDL-C 的含量降低,粪便和肠道中胆固醇的含量升高[28]。其可能的机制是:(1)肝对血清中胆固



注:①:肝细胞的 *LXR* 基因表达量升高,调控 ABC 超家族的转录与表达;②:肝细胞的 *LDLR* 基因表达量升高,促进肝细胞回收 LDL-C;③:肝细胞 *ABCA1* 基因表达量降低,减少向血液中排出胆固醇;④:血液中 CETP 含量升高,减少 LDL-C 的合成;⑤:血液中 LCAT 含量升高,促进 HDL-C 的合成;⑥:肠上皮细胞 *NPC1L1* 表达量降低,减少从肠腔中摄入胆固醇;⑦:肝细胞和肠上皮细胞的 *ABCG5/8* 基因表达量升高,促进胆固醇排出至肠腔和胆囊。

图 3　*L. reuteri* 调节胆固醇转运的作用机制

Note. ①. Elevated *LXR* gene expression in hepatocytes regulates ABC superfamily transcription and expression. ②. Elevated *LDLR* gene expression in hepatocytes promotes the recycling of LDL-C by hepatocytes. ③. Decreased *ABCA1* gene expression in hepatocytes reduces cholesterol efflux into the bloodstream. ④. Elevated levels of CETP in the blood reduce LDL-C synthesis. ⑤. Elevated levels of LCAT in the blood promote HDL-C synthesis. ⑥. Decreased expression of the *NPC1L1* gene in enterocytes reduces the uptake of cholesterol from the enteric cavity. ⑦. Elevated expression of the *ABCG5/8* genes in the hepatocytes and enterocytes promotes the efflux of cholesterol to the enteric cavity and the cholecystic.

Figure 3　Mechanism of *L. reuteri* on regulating the transportation of cholesterol

醇的摄入量升高、排出量降低;(2)肠道对胆固醇的摄入量降低、排出量升高。

L. reuteri 可降低血浆中与 LDL-C 合成相关蛋白的含量,促进肝细胞从血清中摄取 LDL-C,减少肝细胞向血清中排出胆固醇,进而降低血清中 TC 和 LDL-C 水平。LU 等[28]研究发现,经 *L. reuteri* Fn041 干预的高胆固醇血症 C57BL/6 N 小鼠肝细胞中 *LXR* 基因的转录和表达水平升高($P < 0.05$),进而调控下游 ABC 超家族转录与表达(图 3,路径①)。据报道,经 *L. reuteri* NCIMB 30242[14]、*L. reuteri* A9[16]和 *L. reuteri* 8513d[18]干预后,高胆固醇血症啮齿类动物肝细胞中 *LDLR* 基因转录与表达水平上调($P < 0.05$,图 3,路径②),*ABCA*1 基因转录与表达水平下调($P < 0.01$,图 3,路径③),加快肝细胞从血液中吸收 LDL-C,减少向血液中排出胆固醇[50]。此外,LEE 等[14]研究发现,当 *L. reuteri* NCIMB 30242 的浓度达到 10^{10} CFU/mL 时,能显著降低高胆固醇血症 SD 大鼠血浆中胆固醇酯转运蛋白(cholesteryl ester transfer protein, CETP)含量($P < 0.05$),通过减少 LDL-C 合成,降低 LDL-C 水平(图 3,路径④)[14,55];显著升高卵磷脂胆固醇脂酰转移酶(lecithin cholesterol acyltransferase, LCAT)含量($P < 0.05$),提高血清中 HDL-C 水平(图 3,路径⑤)[14,56]。

L. reuteri 还可通过减少从胆囊和肠腔中摄入胆固醇,并促进肠上皮细胞向胆囊和肠腔中排出胆固醇。SUN 等[17]研究发现,*L. reuteri* HI120 和 *L. reuteri* DSM20016 可降低高胆固醇血症 C57BL/6 小鼠小肠上皮细胞中 *NPC*1*L*1 基因表达水平(图 3,路径⑥),减少外源性胆固醇摄入。此外,LEW 等[18]研究发现,采用 *L. reuteri* 8513 d 干预衰老高胆固醇血症 SD 大鼠后,大鼠肝和小肠上皮细胞中 *ABCG5* 基因转录($P < 0.05$)水平显著升高(图 3,路径⑦),促进胆固醇排向肠腔和胆囊。

4 总结与展望

L. reuteri 可通过多种不同的途径降低血清中胆固醇水平,研发成为益生菌的潜力巨大。目前,部分 *L. reuteri* 降胆固醇的机制尚不明确;不同来源的 *L. reuteri* 菌株降胆固醇效果差异较大[57];缺乏在非人灵长类实验动物上的验证研究。针对上述问题,亟待围绕以下领域开展深入研究:(1)利用无菌鼠、转基因鼠、非人灵长类动物等进行降胆固醇作用与机制研究;(2)筛选降胆固醇效果更好的 *L. reuteri* 菌株,并将其纳入降胆固醇益生菌的菌种库;(3)通过宏基因组学、代谢组学、转录组学等多组学技术深度解析 *L. reuteri* 降胆固醇的作用与机制;(4)通过合成生物学等技术获得具有降胆固醇功效的靶向代谢物质,为临床治疗高胆固醇血症提供安全有效的策略。

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[收稿日期] 2024-07-25