

胆盐刺激性脂肪酶功能研究进展

邹芸霞¹ 孟庆勇² 戴蕴平² 张雅丽^{1*}

(1. 中国农业大学食品科学与营养工程学院, 北京 100083; 2. 中国农业大学生物学院, 北京 100083)

摘要:胆盐刺激性脂肪酶(bile salt-stimulated lipase, BSSL)是一种脂肪分解酶。人体中的BSSL主要来自胰腺,也存在于人哺乳期乳腺中,并随乳汁分泌,是含量最丰富的乳清蛋白之一。BSSL能够作用于多种底物,包括甘油三酯(triglyceride, TG)、胆固醇酯、脂溶性维生素、神经酰胺等,对新生儿早期消化吸收乳汁中的脂类物质至关重要。国内外研究发现,BSSL不仅能够促进婴幼儿对乳脂的消化,其在调节血栓、炎症反应、动脉粥样硬化等方面也具有重要功能。作者综述了BSSL的特点及其功能,并对其在婴幼儿配方奶粉中的应用进行了展望。

关键词:脂肪酶;消化脂肪;乳清蛋白;婴儿

Research Progress on the Functions of Bile Salt-Stimulated Lipase

ZOU Yunxia¹ MENG Qingyong² DAI Yunping² ZHANG Yali^{1*}

(1. College of Food Science and Nutritional Engineering, China Agricultural University, Beijing 100083; 2. College of Biological Sciences, China Agricultural University, Beijing 100083)

Abstract: Bile salt-stimulated lipase (BSSL) is a lipolytic enzyme. In the human body, BSSL is primarily secreted by the pancreas and is also found in the mammary glands during lactation, secreted with milk, which is one of the most abundant whey proteins. BSSL can hydrolyze a variety of substrates, including cholesteryl esters, fat-soluble vitamins, ceramide, etc., and plays a crucial role in the early digestion and absorption of milk lipids by newborns. Recent domestic and international studies have shown that in addition to promoting the digestion of milk fat in infants and young children, BSSL also plays significant roles in pathogen resistance, thrombosis regulation, inflammation modulation, atherosclerosis prevention and so on. The author summarizes the characteristics and functions of BSSL and explores its potential applications in infant formula.

Keywords: lipase; digest fat; whey protein; infant

BSSL是一种具有广泛底物特异性的脂肪分解酶,主要在胰腺的腺泡细胞中合成。当胰液分泌到十二指肠肠腔时,BSSL被胆盐激活参与膳食脂肪的水解^[1]。此外,BSSL也存在于一些哺乳动物(如人类、大猩猩、狗、猫、雪貂和海豹)的乳汁中^[2]。因此,人类母乳中的BSSL对于新生儿或早产儿(小于37周胎龄)是否有特殊的生理功能是母乳成分研究中的一个关注点。随着对BSSL的深入研究发现,

BSSL不仅是婴幼儿消化吸收乳脂的重要物质,还在抗病原体、抗炎、调节血栓和动脉粥样硬化等方面具有重要的作用。作者主要从BSSL的表达水平、水解特性、纯化和杀菌方法以及功能等方面总结了BSSL的研究现状,并探讨了BSSL在婴幼儿配方奶粉中的应用前景。

1 BSSL的表达水平

人类母乳中BSSL的质量浓度为100~200 mg/L,

基金项目:农业生物育种国家科技重大专项项目(2023ZD0404905)。

通信作者:张雅丽(1975—),女,博士,副教授,博士研究生导师,主要从事天然产物与人体健康研究。E-mail:zhangyali@cau.edu.cn

收稿日期:2023-05-23 修回日期:2023-10-22

是母乳中最丰富的乳清蛋白之一^[3]。人类母乳中的 BSSL 由 722 个氨基酸残基组成,其肽链与胰腺中的 BSSL 肽链一样,两者由相同的基因编码^[4]。然而人类母乳和胰腺中 BSSL 的相对分子质量存在差异,这可能是由它们本身不同的糖基化水平引起的^[5]。母乳中的 BSSL 是高度糖基化的蛋白质,修饰的单糖有岩藻糖、半乳糖、葡萄糖胺、半乳糖胺和神经氨酸,各单糖摩尔比为 1:3:2:1:0.3^[6]。其糖基化程度与母体的血型有关,且哺乳期第一个月的糖基化程度高于后期^[7]。

人类母乳中的 BSSL 水平与母体的体质指数 (body mass index, BMI) 有关^[8]。初乳(胎儿出生后 2~3 d 收集的母乳)中的 BSSL 水平与孕前和孕后母体的 BMI 呈负相关,成熟乳(胎儿出生后 14 d 收集的母乳)中的 BSSL 水平与孕妇妊娠期间的 BMI 呈正相关。这可能是由于人类母乳中的 BSSL 水平受到妊娠期间孕妇体内激素(如催乳素)变化的影响。催乳素能够调节核因子 1-C2 的水平,该蛋白质可激活和调节乳腺上皮细胞核中 BSSL 的基因表达^[9]。由于肥胖母亲哺乳期间催乳素水平较低,可能导致 BSSL 分泌减少^[10]。相关研究还发现,早产儿母亲的乳汁中 BSSL 水平高于足月儿母亲的乳汁,因此母乳中的 BSSL 水平对于早产儿获取能量可能有重要作用。成熟乳中 BSSL 的水平高于初乳,这种高水平的 BSSL 一直持续到婴儿出生后的 6 个月,之后母乳中的 BSSL 水平逐渐下降。由此可以推断,在婴儿尤其是早产儿的胰脂肪酶(pancreatic lipase, PL)分泌不足时,从母乳中获得的 BSSL 可能弥补了早产儿体内低水平的 PL,从而促进了婴儿对脂肪的有效消化和吸收。随着婴儿胰腺逐渐发育,母乳中的 BSSL 水平也逐渐下降。此外,患有高血糖或者高血压的母亲乳汁中 BSSL 的水平较低^[8]。

研究发现,人体中 BSSL 的基因不仅在胰腺的腺泡细胞和乳腺中表达,在人体其他细胞中也有少量表达,如肝脏细胞、内皮细胞、嗜酸性粒细胞、巨噬细胞、血小板、垂体细胞等^[11-16]。在健康人体血液中,BSSL 质量浓度(1.5 $\mu\text{g/L}$)较低,当人体患有急性胰腺炎时,BSSL 质量浓度会有所上升,达到 3.5 $\mu\text{g/L}$ ^[17-18]。血液中的 BSSL 与低密度脂蛋白(low density lipoprotein, LDL)的载脂蛋白 B100 形成复合物,负责调节多种组织中的胆固醇稳态,

部分 BSSL 被肾小球过滤并随尿液排出^[19-20]。目前,对于血液中 BSSL 的来源尚不清楚。Bruneau 等^[21]认为血液中的 BSSL 源于胰腺,通过肠上皮细胞胞吞作用进入血液,也有研究认为血液中的 BSSL 来自内皮细胞和巨噬细胞的分泌表达,表明血液中的 BSSL 在细胞和组织的脂质代谢方面有重要影响。

2 BSSL 的水解特性

BSSL 具有广泛的底物特异性,可以水解多种底物,包括 TG、*Sn*-1 单酰甘油酯、*Sn*-2 单酰甘油酯、*Sn*-3 单酰甘油酯、胆甾醇酯、视黄醇棕榈酸酯、对硝基苯乙酸以及二辛磷脂酰胆碱等^[2,22]。BSSL 还具有促进肠道吸收脂溶性维生素的作用^[23]。与胰腺分泌的 PL 相比,BSSL 可以更好地水解 *Sn*-2 单酰甘油酯。BSSL 和胰脂肪酶相关蛋白 2 (pancreatic lipase-related protein 2, PLRP2) 具有协同作用,但是 BSSL 对于中链和长链 TG 的水解活性更高^[24]。胃脂肪酶(human gastric lipase, HGL)水解 TG 的主要作用位点是 *Sn*-3 位,这种预消化可能会增强 PLRP2 和 BSSL 的水解能力。

BSSL 水解一些底物(如胆固醇酯和 TG)时需要被胆汁盐激活,而水解另外一些底物(如溶血磷脂)时无需被激活。能够激活 BSSL 的胆汁盐具有高度的特异性,虽然原发性胆汁盐(如胆酸盐和鹅去氧胆酸盐)和次级胆汁盐(如去氧胆酸盐)都能与 BSSL 结合,但是只有原发性胆汁盐能激活 BSSL,同时胆汁盐也可以保护 BSSL 不被肠道蛋白酶灭活^[25]。胆汁盐对 BSSL 的激活作用受到 BSSL 结构的影响,BSSL 蛋白质羧基端有一个保守的 6-氨基酸序列,其前面有一系列富含编码脯氨酸的可变数量串联重复序列(variable number of tandem repeats, VNTR),缺失 VNTR 可能会降低 BSSL 与胆汁盐的相互作用力^[23,26]。同时,BSSL 中的精氨酸残基对其与胆汁盐的相互作用也有重要影响。有研究表明,BSSL 中的精氨酸-63 和精氨酸-423 分别突变为丙氨酸和甘氨酸后,显著降低了 BSSL 水解胆固醇酯的活性^[27-28]。不同物种之间 BSSL 的特性存在差异,VNTR 的数目也不同(见表 1)。此外,胆汁盐的种类也会影响其对 BSSL 的激活作用,激活效果最好的胆汁盐是牛磺胆酸盐(taurocholate, TCH)^[29]。而磷脂酸(phosphatidic acid, PA)、溶血

表1 不同物种中BSSL的特点
Table 1 Characteristics of BSSL in different species

物种	来源	氨基酸残基数目/个	VNTR数目/个
人	乳腺/胰腺	722	16
牛	胰腺	578	3
大鼠	胰腺	592	4
兔	胰腺	556	2或3
三文鱼	胰腺	540	0

磷脂酸(lysophosphatidic acid, LPA)和血小板激活因子(platelet activating factor, PAF)可能是肠外BSSL的激活因子^[30]。磷脂酰胆碱会抑制BSSL对TG的水解,加入磷脂酶A2会缓解这种抑制^[31]。

3 BSSL的纯化和杀菌方法

猪胰液被认为是人胰液良好的替代品,通常用于外分泌胰腺功能不全患者的治疗,但是与人胰液相比,其BSSL的活性水平较低^[32]。BSSL已从人乳、胰液和胰腺中分离出来,由于胰腺提取物中的蛋白质水解率高,造成胰液或胰腺来源的酶在分离过程中不太稳定。从人乳中纯化BSSL可以采用硫酸铵沉淀法、离子交换层析法、分子筛层析法和亲和层析法,其中亲和层析法可以快速纯化BSSL^[33]。因为BSSL含有肝素结合位点,可以与肝素亲和结合,所以通常采用固定化肝素凝胶色谱来纯化人类母乳中的BSSL^[34-35]。BSSL的酯酶活性由对硝基苯己酸酯水解成显色对硝基苯酚的速率来确定,而其胆固醇酯酶活性是由水解胆固醇油酸酯的速率确定^[36-37]。天然人乳中BSSL的相对分子质量为100 000~130 000,可以利用蛋白质免疫印迹鉴定BSSL,采用酶联免疫吸附法测定BSSL的表达水平^[38]。此外,也可以采用液相色谱串联质谱法来测定BSSL的水平^[39]。

BSSL对温度敏感,经巴氏杀菌(62.5 °C、30 min)后易发生变性,导致其完全失活^[40]。因此,将BSSL添加到婴幼儿配方奶粉中时需要注意灭菌方法。与巴氏杀菌相比,对母乳高压处理(500 MPa、9 min)和高温短时处理(72 °C、15 s)可以减少细菌并提高BSSL等活性成分的保留率。但与未处理的母乳相比,BSSL的活性仍显著降低^[41]。Kontopodi等^[42]比较了不同杀菌方法对母乳的影响,结果显示高压处理(400 MPa、5~30 min; 500 MPa、1.5~5.0 min; 600 MPa、1.5~5.0 min)和紫

外线照射均能有效减少细菌数量,并且没有显著降低BSSL的活性。此外,静水高压处理(400 MPa、5 min)也在保证微生物安全的同时保护了BSSL的活性^[43]。由此可见,高压处理、静水高压处理、紫外线照射方法优于巴氏杀菌和高温短时处理。为了使BSSL更好地发挥作用,也有研究采用微胶囊技术对BSSL进行包埋,进一步提高了BSSL的热稳定性和生物利用率^[44]。

4 BSSL的功能

4.1 BSSL促进乳脂消化与吸收

乳脂是婴儿从母乳中获取能量的主要来源,提供了总能量的45%~55%^[45]。母乳和婴儿配方奶粉中95%以上的乳脂以TG的形式存在。成人肠道中主要通过PL和胰磷脂酶A2(pancreatic phospholipase A2, PLA2)分别消化TG和磷脂^[46]。但是新生儿,特别是早产儿体内,PL和PLA2在胰腺中的表达量很低,胆汁盐水平也较低,所以新生儿容易出现脂肪吸收不良的现象。多项研究证实^[47-48],母乳中的BSSL可以促进新生儿吸收脂肪。Alemi等^[49]研究发现,用未经加热的母乳或含有BSSL补充剂的配方奶喂养的新生儿体质量和脂肪吸收增加,脂肪排泄物减少。Miller等^[50]测定了野生型(母乳含有BSSL)和BSSL的基因缺陷型母鼠喂养方式下,幼鼠粪便中的脂肪组成,结果显示,BSSL的基因缺陷型母鼠喂养时,幼鼠粪便中含有较多未消化脂质,而野生型母鼠喂养的小鼠则表现出正常的脂肪吸收能力。同时,Wang等^[27]发现与正常早产小鼠相比,乳中高表达人类BSSL的母鼠喂养的早产小鼠存活率显著提高,并且体质量提高了43.8%,粪便中粗脂肪质量分数减少了33.3%,表明乳中高水平的BSSL可促进早产小鼠的生长发育和脂肪吸收。Wang等^[51]发现,用添加BSSL的配方奶喂养幼猫时,其体质量的日均增加量是对照组的2倍。基于这些研究结果可知,新生儿(特别是早产儿)对母乳中的TG可以有效利用的主要原因是乳中含有BSSL。BSSL在促进早产儿和低体质量新生儿的脂肪吸收方面具有重要作用,其有效解决了早产儿和低体质量新生儿体内PL分泌不足导致的脂类消化吸收问题。同时,添加BSSL可以水解单酰甘油,TG消化的最终产物由Sn-2-单甘油酯和游离脂肪酸转变为甘油和游

离脂肪酸,促进了脂肪的高效吸收^[52]。这对于新生儿十分有益,因为在胆汁盐水平较低的情况下,脂肪酸比单酰甘油更容易被吸收^[53-54]。

乳腺分泌的 BSSL 还可促进胆固醇以及长链多不饱和脂肪酸(long-chain polyunsaturated fatty acids, LC-PUFA)的利用^[2]。新生儿体内的 LC-PUFA 大部分由乳中的 TG 提供,LC-PUFA 不仅是大脑和视网膜的结构成分,而且是合成类十二烷酸的前体物质。LC-PUFA 被证实是新生儿的必需营养物质。在成人体内,LC-PUFA 分别由 *n*-6 和 *n*-3 系列的前体脂肪酸(即亚油酸和 α -亚麻酸)通过脱饱和反应和伸长反应合成,但新生儿并不完全具备这种能力。由相关研究可以推断,BSSL 的存在能够确保母乳喂养的新生儿体内有足量的 LC-PUFA,以促进其生长发育^[55-56]。

鞘磷脂是母乳中主要的磷脂。在胃中,酸性鞘磷脂酶可催化鞘磷脂降解为神经酰胺和磷酸胆碱。BSSL 能水解神经酰胺,因此可能在新生儿对鞘磷脂的消化吸收中起作用^[57]。神经酰胺能够抑制垂体激素分泌^[58],BSSL 可通过水解神经酰胺参与调节正常垂体细胞和腺瘤性垂体细胞的垂体激素分泌^[16]。同时,BSSL 可减轻神经酰胺对细胞内脂质运输的抑制,从而促进近端肠道中大乳糜微粒的产生^[59]。

4.2 BSSL 的抗病原体功能

母乳喂养的新生儿比配方乳喂养的新生儿具有更强的抵抗传染病的能力。母乳可以通过多种机制帮助新生儿预防传染病,相关研究表明,BSSL 也参与了某种保护机制^[60]。

人类免疫缺陷病毒 1 型(human immunodeficiency virus, HIV-1)可以与树突状细胞特异性细胞间黏附分子-3-结合非整合素因子(dendritic cell-specific ICAM-3-grabbing nonintegrin, DC-SIGN)相互作用,促进病毒向 CD4⁺T 淋巴细胞传递,增加感染程度。母乳中的 3-岩藻糖基-N-乙酰乳糖胺(3-fucosyl-N-acetyllactosamine, Le^x)可以与 DC-SIGN 结合,从而防止 DC-SIGN 与 HIV-1 相互作用,并抑制病毒向 CD4⁺T 淋巴细胞转移^[61]。Le^x通常与乳糖衍生的低聚糖(相对分子质量<10 000)或高相对分子质量(>100 000)蛋白质以结合的形式存在^[62]。研究发现,母乳中的 BSSL 携带 Le^x^[63],因此 BSSL 可以与 DC-SIGN 结合,从而阻断 DC-SIGN 介

导的 CD4⁺T 淋巴细胞与 HIV-1 的反式感染。BSSL 与 DC-SIGN 的结合能力可能与 VNTR 的重复次数有关。研究表明,母乳中 VNTR 少于 16 个重复次数的 BSSL 比 VNTR 重复次数更多的 BSSL 有更强的 DC-SIGN 结合能力^[64]。此外,DC-SIGN 基因内单核苷酸多态性与丙型肝炎病毒(hepatitis C virus, HCV)传播相关^[65],虽然 BSSL 能与 DC-SIGN 结合,但是 BSSL 的 VNTR 重复次数并不影响 HCV 的易感性^[66]。

贾第鞭毛虫(*Giardia lamblia*, GL)是常见的致病性肠道寄生虫,其引起的贾第鞭毛虫病可使人衰弱,并伴有严重的腹泻和吸收不良。这种寄生虫常感染儿童,会导致儿童发育不良。研究显示,母乳可以杀灭 GL 滋养体,这个过程可能与 BSSL 有关^[67]。在乳脂存在的条件下可以杀灭 GL,这可能归因于 BSSL 水解乳脂的产物为游离脂肪酸^[68-69],游离脂肪酸可能与寄生虫的质膜结合,扰乱其结构和流动性,最终导致病原体溶解。只有质子化的不饱和游离脂肪酸顺式异构体,如棕榈油酸、油酸、亚油酸、亚麻酸和花生四烯酸等对寄生虫有杀灭作用^[60]。此外,母乳对许多其他病原体,如痢疾内变形虫(EH)、阴道毛滴虫(TV)、单纯疱疹 II 型病毒(HSV II)和金黄色葡萄球菌(*S. aureus*)等的杀灭作用也归因于 BSSL 水解脂质后的活性产物^[70]。

4.3 BSSL 的抗炎功能

新生儿发育早期,肠道上皮细胞分化和营养物质运输过程会发生显著变化,使新生儿能够适应子宫外生活。在这个关键时期,小肠容易受到细菌感染和食物抗原的损害^[60]。

坏死性小肠结肠炎(necrotizing enterocolitis, NEC)是早产儿常见的胃肠道急症,主要特征是肠黏膜或肠道深层细胞坏死及出现炎症,通常发生在回肠末端,严重时会导致肠壁破裂和败血症。NEC 是导致早产儿和低体质量新生儿发病率和死亡率高的主要原因^[71]。人体中的 HGL 能部分水解 TG 和三丁酸甘油酯,而甘油二酯和游离脂肪酸等需要在十二指肠中进一步消化后才能被肠道上皮细胞摄取,再与其他物质结合形成乳糜微粒^[72]。新生儿由于胰腺发育不成熟,胰脂肪酶活性不足,导致消化和吸收脂肪能力不足,乳糜微粒合成能力弱。这进一步导致未被完全消化的脂质在小肠回肠中积累,其中的不饱和脂肪酸被氧化产生的

脂质过氧化物诱导产生氧化应激和炎症,导致脂质依赖性损伤和NEC的加重^[73-77]。

母乳喂养对NEC有预防作用。纯配方奶喂养比纯母乳喂养的早产儿的NEC发病率高6~10倍。虽然配方奶的营养和热量组成与母乳相似,但配方奶缺乏母乳含有的多种生物活性成分,如BSSL。BSSL可以通过促进LC-PUFA的吸收和代谢,对新生儿起保护作用。而LC-PUFA不仅有助于新生儿生长发育,还可作为免疫调节剂增强机体抵抗力,例如二十二碳六烯酸(docosahexaenoic acid, DHA)和二十碳五烯酸

(eicosapentaenoic acid, EPA)可通过影响免疫反应的不同步骤降低NEC、早产儿视网膜病变(ROP)、支气管肺发育不良(BPD)等疾病的发生率^[78]。Howles等^[79]研究发现,无BSSL摄入的新生小鼠和摄入BSSL但用BSSL特异性抑制剂灌胃的新生小鼠的回肠绒毛上皮细胞中均有脂滴积累,从而导致其回肠绒毛上皮细胞结构的损伤。因此,对于早产儿和低体质量的新生儿,母乳中的BSSL对保护未成熟的小肠上皮细胞结构具有重要影响^[80]。BSSL在乳汁中的功能主要概括为4个方面,见图1^[32]。

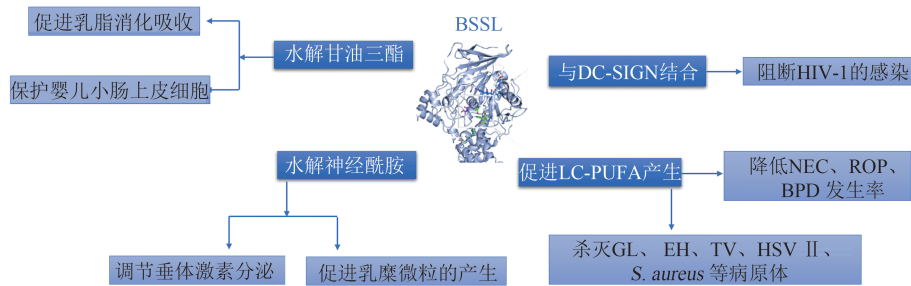


图1 BSSL在乳汁中的功能及其对婴幼儿的影响

Fig. 1 Function of BSSL in breast milk and its influence on infants

4.4 BSSL调节血栓的功能

基质细胞衍生因子-1(stromal cell-derived factor-1, SDF-1)是储存在血小板颗粒中并在血小板激活时释放的趋化因子^[81-82]。SDF-1通过结合趋化因子受体4(C-X-C chemokine receptor type 4, CXCR4)诱导血小板细胞内钙动员,增加凝血酶或ADP诱导的血小板聚集^[83-84]。研究表明,BSSL与SDF-1作用效果类似,通过与血小板上的CXCR4相互作用,在血小板活化中发挥作用^[15]。在小鼠血栓形成模型中,BSSL在血管壁损伤部位积累。与野生型小鼠相比,无BSSL的小鼠血小板细胞内钙动员和血栓形成减弱,尾出血次数增加。综上所述,BSSL作为一种趋化因子,会与血小板上的受体CXCR4相互作用,从而调节血栓形成。

4.5 BSSL调节动脉粥样硬化的功能

动脉粥样硬化(atherosclerosis, AS)是各种动脉硬化中最常见的一种。动脉硬化的共同特点是动脉管壁增厚变硬、失去弹性和管腔变小。在动脉粥样硬化斑块形成过程中,血液循环中的单核细胞进入血管壁的内皮下层转变为巨噬细胞,随

后吞噬氧化型低密度脂蛋白(oxidized low density lipoprotein, OxLDL)及其他经过修饰的脂蛋白,进而发展成泡沫细胞,而泡沫细胞是粥样硬化斑块形成的主要标志。在巨噬细胞中,BSSL与OxLDL孵育后分泌增加,这表明BSSL在调节动脉粥样硬化中具有潜在作用^[14]。OxLDL是AS斑块形成的一个主要因素,除了促使泡沫细胞的形成,还直接参与形成AS的其他方面^[85-86]。比如在LDL氧化过程中,磷脂水解的副产物溶血磷脂酰胆碱(lysophosphatidylcholine, L-PC)是导致动脉粥样硬化的主要原因。在体外试验中,L-PC可以作为单核细胞的趋化剂,减弱内皮依赖性动脉舒张,诱导单核细胞黏附到动脉内皮细胞上,并促进巨噬细胞增殖,从而导致泡沫细胞形成^[87-90]。Shamir等^[91]研究表明,OxLDL与BSSL共同培养4 h后,L-PC的质量分数降低了43%。由此可知,BSSL可能通过减少L-PC来降低AS的风险。神经酰胺是OxLDL中存在的一种导致AS的脂质信号分子。研究表明,神经酰胺能促进平滑肌细胞增殖,与其同源物共同促使AS的加重^[92-93]。BSSL

可以水解神经酰胺,因此 BSSL 可能通过降低神经酰胺的水平来抑制 AS 的加重^[57]。

4.6 BSSL 的其他功能

短肠综合征(short bowel syndrome, SBS)被定义为一种吸收不良状态,是由于小肠大规模切除术(mSBR)后肠道吸收面积减少导致的。研究表明,口服 BSSL 能够通过促进肠上皮细胞增殖和抑制肠上皮细胞凋亡来保护 SBS 诱导的肠损伤^[94]。

Qiu 等^[19]研究发现,BSSL 可以通过 LRP6 受体激活 Wnt/ β -连环蛋白信号通路恢复被乙醇破坏的肠道细胞上皮屏障功能。BSSL 还可以促进人脐静脉内皮细胞(human umbilical vein endothelial cells, HUVEC)的增殖、迁移、愈合以及毛细血管网的形成,表明血液中循环的 BSSL 可能参与血管的生成^[95]。

另外,人丁酰胆碱酯酶(human butyrylcholinesterase, BChE)是目前最先进的生物毒性清除剂,可以高效抵抗神经毒剂的毒性作用^[96]。研究发现,人体中的 BSSL 在蛋白质高级结构上与 BChE 有 34% 的相似性,可以作为 BChE 的替代品用于清除神经毒性^[97]。

5 展望

人体中 BSSL 的基因位于染色体 9q34.3 上,第 1 或第 4 个 VNTR 内的单碱基缺失会导致 8 型青少年起病的成熟发病型糖尿病(maturity-onset diabetes of the young type 8, MODY8)。MODY8 是一种以外分泌胰腺功能障碍和糖尿病为特征的遗传性疾病^[98-99]。因此,未来可以进一步探索 BSSL 的基因与胰腺疾病的关系。

基于 BSSL 在脂质代谢中的重要作用,可以将其应用于脂肪吸收障碍人群。母乳是新生儿最理想的食物,但是由于母亲的身体状况或者一些社会原因不能进行母乳喂养,而在牛乳和婴幼儿配方奶粉中都没有检测到 BSSL^[100]。因此,将 BSSL 添加在配方奶粉中,可以提高新生儿对脂肪,特别是 LC-PUFA 的消化吸收。

受来源限制的影响,从人乳中纯化 BSSL 并不适合大规模商业化生产。目前,有研究者在转基因克隆奶牛的乳汁中构建了高效表达重组人胆盐刺激性脂肪酶(recombinant human bile salt-stimulated lipase, rhBSSL)的载体,成功将 rhBSSL

在牛乳中稳定表达,并证明了从转基因牛乳中纯化得到的 rhBSSL 与天然 BSSL 在热稳定性、pH 稳定性、对 TG 的水解活性、抗胰蛋白酶水解的稳定性等方面没有显著差异。有关 rhBSSL 转基因母鼠代养幼鼠的试验结果表明,rhBSSL 可以促进幼鼠对乳脂的利用,减少粪便中脂肪的含量^[38]。这为 rhBSSL 未来在婴幼儿配方奶粉中的应用提供了依据。

近几年,有关 BSSL 的研究较少,且还有很多问题有待研究,比如在调节动脉粥样硬化方面的具体机制、在婴幼儿胃肠道环境中 BSSL 消化脂肪的活性以及对成人和婴幼儿肠道健康方面的直接影响等。此外,目前 BSSL 在免疫调节方面的作用鲜少研究,母乳中的 BSSL 具有丰富的糖基修饰,说明其可能存在潜在的调节肠道菌群的作用^[101]。对于人乳中 BSSL 的功能仍需要进一步探索,从而可以更好地开发利用,以促进婴幼儿配方奶粉母乳化产品的开发。

参考文献

- [1] 沙丽君,李晓南. 胆盐刺激性脂酶的发育、生物学特征和功能的研究进展[J]. 中国儿童保健杂志,2014,22(8):829-832. SHA L J, LI X N. Research progress on the development, biological characteristics and function of bile salt-stimulated lipase [J]. Chinese Journal of Child Health Care, 2014, 22(8): 829-832. (in Chinese)
- [2] HERNELL O, BLÄCKBERG L. Human milk bile salt-stimulated lipase: functional and molecular aspects [J]. The Journal of Pediatrics, 1994, 125(5): S56-S61.
- [3] STRÖMQVIST M, LINDGREN K, HANSSON L, et al. Differences in the glycosylation of recombinant and native human milk bile salt-stimulated lipase revealed by peptide mapping [J]. Journal of Chromatography A, 1995, 718(1): 53-58.
- [4] NILSSON J, BLÄCKBERG L, CARLSSON P, et al. cDNA cloning of human-milk bile-salt-stimulated lipase and evidence for its identity to pancreatic carboxylic ester hydrolase [J]. European Journal of Biochemistry, 1990, 192(2): 543-550.
- [5] ABOUAKIL N, ROGALSKA E, BONICEL J, et al. Purification of pancreatic carboxylic-ester hydrolase by immunoaffinity and its application to the human bile-salt-stimulated lipase [J]. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism, 1988, 961(3): 299-308.
- [6] WANG C S, DASHTI A, JACKSON K W, et al. Isolation and characterization of human milk bile salt-activated lipase C-tail fragment [J]. Biochemistry, 1995, 34(33): 10639-10644.
- [7] LANDBERG E, HUANG Y, STRÖMQVIST M, et al.

- Changes in glycosylation of human bile-salt-stimulated lipase during lactation[J]. *Archives of Biochemistry and Biophysics*, 2000, 377(2):246-254.
- [8] SHA L J, ZHOU S S, XI Y Y, et al. The level of bile salt-stimulated lipase in the milk of Chinese women and its association with maternal BMI[J]. *Journal of Biomedical Research*, 2019, 34(2):122-128.
- [9] JOHANSSON E M, KANNIUS-JANSON M, GRITTLINDE A, et al. Nuclear factor 1-C2 is regulated by prolactin and shows a distinct expression pattern in the mouse mammary epithelial cells during development[J]. *Molecular Endocrinology*, 2005, 19(4):992-1003.
- [10] ASAI-SATO M, OKAMOTO M, ENDO M, et al. Hypoadiponectinemia in lean lactating women: prolactin inhibits adiponectin secretion from human adipocytes[J]. *Endocrine Journal*, 2006, 53(4):555-562.
- [11] CAMULLI E D, LINKE M J, BROCKMAN H L, et al. Identity of a cytosolic neutral cholesterol esterase in rat liver with the bile salt stimulated cholesterol esterase in pancreas [J]. *Biochimica et Biophysica Acta (BBA) -Lipids and Lipid Metabolism*, 1989, 1005(2):177-182.
- [12] LI F, HUI D Y. Synthesis and secretion of the pancreatic-type carboxyl ester lipase by human endothelial cells[J]. *Biochemical Journal*, 1998, 329(3):675-679.
- [13] HOLTSBERG F W, OZGUR L E, GARSETTI D E, et al. Presence in human eosinophils of a lysophospholipase similar to that found in the pancreas [J]. *Biochemical Journal*, 1995, 309(Pt 1):141-144.
- [14] LI F, HUI D Y. Modified low density lipoprotein enhances the secretion of bile salt-stimulated cholesterol esterase by human monocyte-macrophages species-specific difference in macrophage cholesteryl ester hydrolase [J]. *Journal of Biological Chemistry*, 1997, 272(45):28666-28671.
- [15] PANICOT-DUBOIS L, THOMAS G M, FURIE B C, et al. Bile salt-dependent lipase interacts with platelet CXCR4 and modulates thrombus formation in mice and humans [J]. *Journal of Clinical Investigation*, 2007, 117(12):3708-3719.
- [16] LA ROSA S, VIGETTI D, PLACIDI C, et al. Localization of carboxyl ester lipase in human pituitary gland and pituitary adenomas[J]. *Journal of Histochemistry and Cytochemistry*, 2010, 58(10):881-889.
- [17] BLIND P J, BÜCHLER M, BLÄCKBERG L, et al. Carboxylic ester hydrolase: a sensitive serum marker and indicator of severity of acute pancreatitis [J]. *International Journal of Pancreatology*, 1991, 8(1):65-73.
- [18] LOMBARDO D, MONTALTO G, ROUDANI S, et al. Is bile salt-dependent lipase concentration in serum of any help in pancreatic cancer diagnosis?[J]. *Pancreas*, 1993, 8(5):581-588.
- [19] QIU Y Q, ZHOU J F, ZHANG D D, et al. Bile salt-dependent lipase promotes the barrier integrity of Caco-2 cells by activating Wnt/ β -catenin signaling via LRP6 receptor[J]. *Cell and Tissue Research*, 2021, 383(3):1077-1092.
- [20] COMTE B, FRANCESCHI C, SADOULET M O, et al. Detection of bile salt-dependent lipase, a 110 kDa pancreatic protein, in urines of healthy subjects [J]. *Kidney International*, 2006, 69(6):1048-1055.
- [21] BRUNEAU N, BENDAYAN M, GINGRAS D, et al. Circulating bile salt-dependent lipase originates from the pancreas via intestinal transcytosis[J]. *Gastroenterology*, 2003, 124(2):470-480.
- [22] CARRIÈRE F, WITHERS-MARTINEZ C, VAN TILBEURGH H, et al. Structural basis for the substrate selectivity of pancreatic lipases and some related proteins[J]. *Biochimica et Biophysica Acta*, 1998, 1376(3):417-432.
- [23] HUI D Y, HOWLES P N. Carboxyl ester lipase: structure-function relationship and physiological role in lipoprotein metabolism and atherosclerosis [J]. *Journal of Lipid Research*, 2002, 43(12):2017-2030.
- [24] XIAO X J, MUKHERJEE A, ROSS L E, et al. Pancreatic lipase-related protein-2 (PLRP2) can contribute to dietary fat digestion in human newborns [J]. *Journal of Biological Chemistry*, 2011, 286(30):26353-26363.
- [25] HERNELL O, OLIVECRONA T. Human milk lipases II. Bile salt-stimulated lipase [J]. *Biochimica et Biophysica Acta(BBA)-Lipids and Lipid Metabolism*, 1974, 369(2):234-244.
- [26] MOORE S A, KINGSTON R L, LOOMES K M, et al. The structure of truncated recombinant human bile salt-stimulated lipase reveals bile salt-independent conformational flexibility at the active-site loop and provides insights into heparin binding [J]. *Journal of Molecular Biology*, 2001, 312(3):511-523.
- [27] WANG Y Y, SHENG Z Y, WANG Y H, et al. Transgenic mouse milk expressing human bile salt-stimulated lipase improves the survival and growth status of premature mice[J]. *Molecular Biotechnology*, 2015, 57(3):287-297.
- [28] LIANG Y, MEDHEKAR R, BROCKMAN H L, et al. Importance of arginines 63 and 423 in modulating the bile salt-dependent and bile salt-independent hydrolytic activities of rat carboxyl ester lipase [J]. *Journal of Biological Chemistry*, 2000, 275(31):24040-24046.
- [29] JOHN S, THANGAPANDIAN S, LAZAR P, et al. New insights in the activation of human cholesterol esterase to design potent anti-cholesterol drugs [J]. *Molecular Diversity*, 2014, 18(1):119-131.

- [30] FONTBONNE H, PUIGSERVER A, BOUZA B, et al. Activation of bile salt dependent lipase by (lyso) phosphatidic acid and platelet activating factor[J]. FEBS Letters, 2013, 587(18):3002-3007.
- [31] VENUTI E, SHISHMAREV D, KUCHEL P W, et al. Bile salt stimulated lipase: inhibition by phospholipids and relief by phospholipase A₂[J]. Journal of Cystic Fibrosis, 2017, 16(6):763-770.
- [32] SALHI A, AMARA S, MANSUELLE P, et al. Characterization of all the lipolytic activities in pancreatin and comparison with porcine and human pancreatic juices [J]. Biochimie, 2020, 169:106-120.
- [33] WANG C S, HARTSUCK J A. Bile salt-activated lipase. A multiple function lipolytic enzyme[J]. Biochimica et Biophysica Acta (BBA) -Lipids and Lipid Metabolism, 1993, 1166(1):1-19.
- [34] BLÄCKBERG L, HERNELL O. The bile-salt-stimulated lipase in human milk: purification and characterization[J]. European Journal of Biochemistry, 1981, 116(2):221-225.
- [35] 王宇航. 利用牛乳腺生物反应器表达重组人胆盐激活酯酶的研究[D]. 北京:中国农业大学, 2016.
- [36] VÉRINE A, BRUNEAU N, VALETTE A, et al. Immunodetection and molecular cloning of a bile-salt-dependent lipase isoform in HepG2 cells [J]. Biochemical Journal, 1999, 342(1):179-187.
- [37] AUGÉ N, REBAÏ O, LEPETIT-THÉVENIN J, et al. Pancreatic bile salt-dependent lipase induces smooth muscle cells proliferation[J]. Circulation, 2003, 108(1):86-91.
- [38] WANG Y H, DING F R, WANG T, et al. Purification and characterization of recombinant human bile salt-stimulated lipase expressed in milk of transgenic cloned cows[J]. PLoS ONE, 2017, 12(5):e0176864.
- [39] LIU Y W, XIONG L, KONTOPODI E, et al. Changes in the milk serum proteome after thermal and non-thermal treatment [J]. Innovative Food Science & Emerging Technologies, 2020, 66:102544.
- [40] BINTEABUBAKAR S Y, SALIM M, CLULOW A J, et al. Human milk composition and the effects of pasteurisation on the activity of its components[J]. Trends in Food Science & Technology, 2021, 111:166-174.
- [41] LIANG N J, MOHAMED H M, KIM B J, et al. High-pressure processing of human milk: a balance between microbial inactivation and bioactive protein preservation[J]. The Journal of Nutrition, 2023, 153(9):2598-2611.
- [42] KONTOPODI E, STAHL B, GOUDOEVER J B, et al. Effects of high-pressure processing, UV-C irradiation and thermoultrasonication on donor human milk safety and quality[J]. Frontiers in Pediatrics, 2022, 10:828448.
- [43] ZHANG J, LEE N A, DULEY J A, et al. Comparing the effects of hydrostatic high-pressure processing vs holder pasteurisation on the microbial, biochemical and digestion properties of donor human milk[J]. Food Chemistry, 2022, 373(Pt B):131545.
- [44] 杨宝嘉. 胆盐激活脂肪酶微胶囊的制备及稳定性研究 [D]. 大庆:黑龙江八一农垦大学, 2022.
- [45] KOLETZKO B, AGOSTONI C, BERGMANN R, et al. Physiological aspects of human milk lipids and implications for infant feeding: a workshop report[J]. Acta Paediatrica, 2011, 100(11):1405-1415.
- [46] LINDQUIST S, HERNELL O. Lipid digestion and absorption in early life: an update[J]. Current Opinion in Clinical Nutrition and Metabolic Care, 2010, 13(3):314-320.
- [47] YANG Y, SANCHEZ D, FIGARELLA C, et al. Discoordinate expression of pancreatic lipase and two related proteins in the human fetal pancreas[J]. Pediatric Research, 2000, 47(2):184-188.
- [48] HE X, MCCLORRY S, HERNELL O, et al. Digestion of human milk fat in healthy infants [J]. Nutrition Research, 2020, 83:15-29.
- [49] ALEMI B, HAMOSH M, SCANLON J W, et al. Fat digestion in very low-birth-weight infants: effect of addition of human milk to low-birth-weight formula[J]. Pediatrics, 1981, 68(4):484-489.
- [50] MILLER R, LOWE M E. Carboxyl ester lipase from either mother's milk or the pancreas is required for efficient dietary triglyceride digestion in suckling mice 1, 2[J]. The Journal of Nutrition, 2008, 138(5):927-930.
- [51] WANG C S, MARTINDALE M E, KING M M, et al. Bile-salt-activated lipase: effect on kitten growth rate[J]. The American Journal of Clinical Nutrition, 1989, 49(3):457-463.
- [52] BERNBÄCK S, BLÄCKBERG L, HERNELL O. The complete digestion of human milk triacylglycerol *in vitro* requires gastric lipase, pancreatic colipase-dependent lipase, and bile salt-stimulated lipase [J]. Journal of Clinical Investigation, 1990, 85(4):1221-1226.
- [53] HOFMANN A F, KERN F J. The significance of bile acids in gastrointestinal and hepatic disease[J]. Disease-a-Month, 1971, 1(1):3-38.
- [54] MORGAN R G H, BORGSTRÖM B. The mechanism of fat absorption in the bile fistula rat[J]. Quarterly Journal of Experimental Physiology and Cognate Medical Sciences, 1969, 54(2):228-243.
- [55] CHEN Q, BLÄCKBERG L, NILSSON A, et al. Digestion of triacylglycerols containing long-chain polyenoic fatty acids *in vitro* by colipase-dependent

- pancreatic lipase and human milk bile salt-stimulated lipase[J]. *Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism*, 1994, 1210(2):239-243.
- [56] HERNELL O, BLÄCKBERG L, CHEN Q, et al. Does the bile salt-stimulated lipase of human milk have a role in the use of the milk long-chain polyunsaturated fatty acids?[J]. *Journal of Pediatric Gastroenterology and Nutrition*, 1993, 16(4):426-431.
- [57] NYBERG L, FAROOQI A, BLÄCKBERG L, et al. Digestion of ceramide by human milk bile salt-stimulated lipase [J]. *Journal of Pediatric Gastroenterology and Nutrition*, 1998, 27(5):560-567.
- [58] MATHIAS S, PEÑA L A, KOLESNICK R N. Signal transduction of stress *via* ceramide [J]. *Biochemical Journal*, 1998, 335(3):465-480.
- [59] KIRBY R J, ZHENG S Q, TSO P, et al. Bile salt-stimulated carboxyl ester lipase influences lipoprotein assembly and secretion in intestine: a process mediated *via* ceramide hydrolysis[J]. *Journal of Biological Chemistry*, 2002, 277(6):4104-4109.
- [60] LOMBARDO D. Bile salt-dependent lipase: its pathophysiological implications [J]. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, 2001, 1533(1):1-28.
- [61] NAARDING M A, LUDWIG I S, GROOT F, et al. Lewis X component in human milk binds DC-SIGN and inhibits HIV-1 transfer to CD4⁺T lymphocytes [J]. *Journal of Clinical Investigation*, 2005, 115(11):3256-3264.
- [62] SCHWERTMANN A, RUDLOFF S, KUNZ C. Potential ligands for cell adhesion molecules in human milk [J]. *Annals of Nutrition & Metabolism*, 1996, 40(5):252-262.
- [63] NAARDING M A, DIRAC A M, LUDWIG I S, et al. Bile salt-stimulated lipase from human milk binds DC-SIGN and inhibits human immunodeficiency virus type 1 transfer to CD4⁺T cells [J]. *Antimicrobial Agents and Chemotherapy*, 2006, 50(10):3367-3374.
- [64] STAX M J, NAARDING M A, TANCK M W, et al. Binding of human milk to pathogen receptor DC-SIGN varies with bile salt-stimulated lipase (BSSL) gene polymorphism[J]. *PLoS ONE*, 2011, 6(2):e17316.
- [65] STEBA G S, KOEKKOEK S M, VANHOMMERIG J W, et al. DC-SIGN polymorphisms associate with risk of hepatitis C virus infection among men who have sex with men but not among injecting drug users[J]. *The Journal of Infectious Diseases*, 2018, 217(3):353-357.
- [66] STEBA G S, KOEKKOEK S M, PRINS M, et al. Bile-salt stimulated lipase polymorphisms do not associate with HCV susceptibility[J]. *Virus Research*, 2019, 274:197715.
- [67] GILLIN F D, REINER D S, WANG C S. Human milk kills parasitic intestinal protozoa[J]. *Science*, 1983, 221(4617):1290-1292.
- [68] HERNELL O, WARD H, BLÄCKBERG L, et al. Killing of *Giardia lamblia* by human milk lipases: an effect mediated by lipolysis of milk lipids[J]. *The Journal of Infectious Diseases*, 1986, 153(4):715-720.
- [69] REINER D S, WANG C S, GILLIN F D. Human milk kills *Giardia lamblia* by generating toxic lipolytic products[J]. *The Journal of Infectious Diseases*, 1986, 154(5):825-832.
- [70] KABARA J J. Lipids as host-resistance factors of human milk[J]. *Nutrition Reviews*, 1980, 38(2):65-73.
- [71] NEU J, WALKER W A. Necrotizing enterocolitis [J]. *New England Journal of Medicine*, 2011, 364(3):255-264.
- [72] GARGOURI Y, PIERONI G, RIVIÈRE C, et al. Importance of human gastric lipase for intestinal lipolysis: an *in vitro* study [J]. *Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism*, 1986, 879(3):419-423.
- [73] MARTIN C R, CHEESMAN A, BROWN J, et al. Factors determining optimal fatty acid absorption in preterm infants[J]. *Journal of Pediatric Gastroenterology and Nutrition*, 2016, 62(1):130-136.
- [74] VELASQUEZ O R, PLACE A R, TSO P, et al. Developing intestine is injured during absorption of oleic acid but not its ethyl ester [J]. *Journal of Clinical Investigation*, 1994, 93(2):479-485.
- [75] CRISSINGER K D, BURNEY D L, VELASQUEZ O R, et al. An animal model of necrotizing enterocolitis induced by infant formula and ischemia in developing piglets[J]. *Gastroenterology*, 1994, 106(5):1215-1222.
- [76] VELASQUEZ O R, TSO P, CRISSINGER K D. Fatty acid-induced injury in developing piglet intestine: effect of degree of saturation and carbon chain length [J]. *Pediatric Research*, 1993, 33(6):543-547.
- [77] SODHI C P, FULTON W B, GOOD M, et al. Fat composition in infant formula contributes to the severity of necrotising enterocolitis [J]. *British Journal of Nutrition*, 2018, 120(6):665-680.
- [78] LAPILLONNE A, MOLTU S J. Long-chain polyunsaturated fatty acids and clinical outcomes of preterm infants[J]. *Annals of Nutrition & Metabolism*, 2016, 69(Suppl 1):35-44.
- [79] HOWLES P N, STEMMERMAN G N, FENOGLIO-PREISER C M, et al. Carboxyl ester lipase activity in milk prevents fat-derived intestinal injury in neonatal mice [J]. *American Journal of Physiology*, 1999, 277

- (3):G653-G661.
- [80] CASPER C, CARNIELLI V P, HASCOET J M, et al. RhBSSL improves growth and LCPUFA absorption in preterm infants fed formula or pasteurized breast milk[J]. *Journal of Pediatric Gastroenterology and Nutrition*, 2014, 59(1):61-69.
- [81] CLEMETSON K J, CLEMETSON J M, PROUDFOOT A E, et al. Functional expression of CCR1, CCR3, CCR4, and CXCR4 chemokine receptors on human platelets [J]. *Blood*, 2000, 96(13):4046-4054.
- [82] JIN D K, SHIDO K, KOPP H G, et al. Cytokine-mediated deployment of SDF-1 induces revascularization through recruitment of CXCR4⁺ hemangiocytes [J]. *Nature Medicine*, 2006, 12(5):557-567.
- [83] KOWALSKA M A, RATAJCZAK J, HOXIE J, et al. Megakaryocyte precursors, megakaryocytes and platelets express the HIV co-receptor CXCR4 on their surface: determination of response to stromal-derived factor-1 by megakaryocytes and platelets [J]. *British Journal of Haematology*, 1999, 104(2):220-229.
- [84] KOWALSKA M A, RATAJCZAK M Z, MAJKA M, et al. Stromal cell-derived factor-1 and macrophage-derived chemokine: 2 chemokines that activate platelets [J]. *Blood*, 2000, 96(1):50-57.
- [85] WITZTUM J L, STEINBERG D. Role of oxidized low density lipoprotein in atherogenesis [J]. *Journal of Clinical Investigation*, 1991, 88(6):1785-1792.
- [86] WITZTUM J L. The oxidation hypothesis of atherosclerosis[J]. *The Lancet*, 1994, 344(8925):793-795.
- [87] KUGIYAMA K, KERNS S A, MORRISSETT J D, et al. Impairment of endothelium-dependent arterial relaxation by lysolecithin in modified low-density lipoproteins [J]. *Nature*, 1990, 344(6262):160-162.
- [88] QUINN M T, PARTHASARATHY S, STEINBERG D. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 1988, 85(8):2805-2809.
- [89] KUME N, CYBULSKY M I, JR GIMBRONE M A. Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells [J]. *Journal of Clinical Investigation*, 1992, 90(3):1138-1144.
- [90] SAKAI M, MIYAZAKI A, HAKAMATA H, et al. Lysophosphatidylcholine plays an essential role in the mitogenic effect of oxidized low density lipoprotein on murine macrophages [J]. *Journal of Biological Chemistry*, 1994, 269(50):31430-31435.
- [91] SHAMIR R, JOHNSON W J, MORLOCK-FITZPATRICK K, et al. Pancreatic carboxyl ester lipase: a circulating enzyme that modifies normal and oxidized lipoproteins *in vitro* [J]. *Journal of Clinical Investigation*, 1996, 97(7):1696-1704.
- [92] AUGÉ N, ESCARGUEIL-BLANC I, LAJOIE-MAZENC I, et al. Potential role for ceramide in mitogen-activated protein kinase activation and proliferation of vascular smooth muscle cells induced by oxidized low density lipoprotein [J]. *Journal of Biological Chemistry*, 1998, 273(21):12893-12900.
- [93] AUGÉ N, NIKOLOVA-KARAKASHIAN M, CARPENTIER S, et al. Role of sphingosine 1-phosphate in the mitogenesis induced by oxidized low density lipoprotein in smooth muscle cells *via* activation of sphingomyelinase, ceramidase, and sphingosine kinase [J]. *Journal of Biological Chemistry*, 1999, 274(31):21533-21538.
- [94] YANG Y, ZHENG T, ZHOU J F, et al. Bile salt dependent lipase promotes intestinal adaptation in rats with massive small bowel resection [J]. *Bioscience Reports*, 2018, 38(3):BSR20180077.
- [95] REBAÍ O, LE PETIT-THEVENIN J, BRUNEAU N, et al. *In vitro* angiogenic effects of pancreatic bile salt-dependent lipase [J]. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2005, 25(2):359-364.
- [96] LUSHCHEKINA S, MASSON P. Catalytic bioscavengers against organophosphorus agents: mechanistic issues of self-reactivating cholinesterases [J]. *Toxicology*, 2018, 409:91-102.
- [97] TOUVREY C, COURAGEUX C, GUILLON V, et al. X-ray structures of human bile-salt activated lipase conjugated to nerve agents surrogates [J]. *Toxicology*, 2019, 411:15-23.
- [98] GRAVDAL A, XIAO X J, CNOP M, et al. The position of single-base deletions in the VNTR sequence of the carboxyl ester lipase (*CEL*) gene determines proteotoxicity [J]. *Journal of Biological Chemistry*, 2021, 296:100661.
- [99] JOHANSSON B B, FJELD K, EL JELLAS K, et al. The role of the carboxyl ester lipase (*CEL*) gene in pancreatic disease [J]. *Pancreatology*, 2018, 18(1):12-19.
- [100] ZHANG J, DULEY J A, COWLEY D M, et al. Adaption of a commercial lipase kit to measure bile salt-stimulated lipase in human milk [J]. *Food Bioscience*, 2022, 50:101993.
- [101] ZEINALI L I, GIULIANO S, LAKSHMINRUSIMHA S, et al. Intestinal dysbiosis in the infant and the future of lacto-engineering to shape the developing intestinal microbiome [J]. *Clinical Therapeutics*, 2022, 44(2):193-214.

(责任编辑:史润东东)