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·综述·

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支链氨基酸代谢及其与疾病的关系

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摘要 亮氨酸、异亮氨酸和缬氨酸的疏水侧链都具有分支的甲基基团,因而被统称为支链氨基酸(branched chain amino acids, BCAAs)。作为机体的必需氨基酸,除了作为蛋白质合成的基本原料,BCAAs 及其各种分解代谢产物还可以作为信号分子,调控从蛋白质合成到胰岛素分泌等众多生理过程。因此,它们的正常代谢对机体生命活动至关重要。越来越多的证据表明,BCAAs 代谢异常与多种疾病关系密切,包括枫糖尿病、神经系统疾病、糖尿病、心血管疾病、肝疾病和癌症等。本文详细概述了哺乳动物中 BCAAs 分解代谢的基本模式、调控机制(主要关注对 2 个关键代谢酶 BCAT 和 BCKDH 的调控)以及 BCAAs 参与 mTOR 和 AMPK 信号通路在机体代谢中发挥的作用。总结了 BCAAs 代谢异常与多种疾病的关系,并对有关的矛盾观点进行阐述和解释。近年来,BCAAs 代谢及调控在疾病发生发展中的作用成为研究热点,为相关疾病预防和治疗提供了新视角。本综述将为进一步研究提供线索。

关键词 支链氨基酸; 代谢; 调控; 癌症

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Branched Chain Amino Acid Metabolism and Its Relationship with Diseases

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Abstract Leucine, isoleucine and valine, are referred to as branched chain amino acids (BCAAs) for their hydrophobic side chains with branched methyl groups. As essential amino acids, in addition to being the raw material of protein synthesis, BCAAs and various catabolic products act as signaling molecules, regulating biological processes ranging from protein synthesis to insulin secretion. Therefore, the normal metabolism of BCAAs is crucial to cellular activities. Accumulating evidence demonstrates that the dysregulation of BCAA metabolism is closely related to numerous diseases, including the maple syrup urine disease, nervous system disease, diabetes, cardiovascular disease, liver disease and cancer. Here, we review the regulatory mechanisms of BCAA catabolism in mammals, mainly focusing on the regulation of two key metabolic enzymes (BCAT and BCKDH), and summarize the role of BCAAs in mTOR and AMPK signaling pathways. Furthermore, we also summarize the relationship of abnormal BCAA metabolism with many diseases and expound some contradictory views. In recent years, the role of BCAA metabolism and regulation in the development of diseases has gradually become a hot spot, providing a new perspective for the disease prevention and treatment, and we hope to provide a basis for further reseach.

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Key words　branched chain amino acids(BCAAs); metabolism; regulation; cancer

支链氨基酸(branched chain amino acids, BCAAs)包括亮氨酸(leucine, Leu)、异亮氨酸(isoleucine, Ile)和缬氨酸(valine, Val),由于它们的疏水侧链都具有分支的甲基基团而得名。作为机体必需氨基酸,BCAAs 约占血浆游离必需氨基酸的 40%[1],除了参与合成蛋白质外,其发挥营养信号和代谢调节的作用也不可小觑。近年来,越来越多的研究关注 BCAAs 代谢与信号通路、物质代谢及疾病之间关系密切,但结论并不完全一致。本文对 BCAAs 代谢的功能调控及其与疾病的关系进行了全面的回顾和总结,以期为进一步研究指出方向。

1　支链氨基酸的分解代谢

BCAAs 分解代谢的起始阶段有着相似的步骤——转氨基、氧化脱羧再脱氢,随后进入各自分解途径。首先,由支链氨基转移酶(branched-chain amino acids aminotransferase, BCAT)催化,可逆地将 α-氨基转移至 α-酮戊二酸,生成谷氨酸(glutamate, Glu)。脱氨基后的碳骨架生成支链 α-酮酸(branched chain ketoacid, BCKA),Leu、Ile、Val 通过此步反应分别产生 α-酮异丙酸酯(α-ketoisocaproate, KIC)、α-酮-β-甲基戊二酸(α-keto-β-methylvalerate, KMV)和 α-酮异戊酸(α-ketoisovalerate, KIV)。随后,由支链 α-酮酸脱氢酶(branched-chain α-ketoacid dehydrogenase, BCKDH)复合物催化氧化脱羧,不可逆地生成相应的脂酰 CoA。最终,Leu 降解为乙酰乙酸和乙酰 CoA、Ile 降解为丙酰 CoA 和乙酰 CoA、Val 降解为琥珀酰 CoA。在大多数组织中,这些分解代谢产物分别进入三羧酸循环(tricarboxylic acid cycle, TCA)(Fig. 1),以肌肉、褐色脂肪、肝、肾和心血管为著[2],或进入糖酵解和其他代谢途径。

一般而言,BCAAs 的分解代谢开始于许多表达 BCAT 酶的外周组织,例如骨骼肌,生成的 BCKA 释放到血液循环中,再进入肝代谢[2]。这形成了 BCAAs 产物的特殊代谢模式,主要从骨骼肌释放,在器官间大量穿梭,随后在肝内氧化[3]。BCAAs 在器官间穿梭有助于其发挥营养信号和代谢调节的作用。

2　支链氨基酸代谢的调控

代谢调控通常是通过调节代谢途径的关键酶实现的。BCAAs 代谢调控的重点是对支链氨基转移酶(BCAT)和支链 α-酮酸脱氢酶(BCKDH)2 个关键酶的调节。

BCAT 作为 BCAAs 分解代谢的第 1 个关键酶,有 BCATm 和 BCATc 2 种同工酶[4],BCATm 主要定位于线粒体,在除肝外的各种组织中表达。其中,在胃中表达水平最高[5]。BCATc 主要定位于胞质,主要表达于大脑、卵巢和胎盘等组织[6]。BCATm 在转录水平受到过氧化物酶体增殖物激活受体 γ 辅激活因子 1α(PPARγ coactivator-1α, PGC-1α)[7]、甾醇调节元件结合蛋白 1(sterol regulatory element-binding protein 1, SREBP1)[8]和 Krüppel 样因子 15(Krüppel-like factor 15, KLF15)[9]的调节。在翻译后水平,cAMP 反应元件结合结合蛋白(cAMP-responsive element-binding (CREB)-binding protein, CBP)和 SIRT4 调控 BCATm 第 44 位赖氨酸的乙酰化水平,剥夺 BCAAs 能够增加 BCATm 乙酰化并促进其泛素-蛋白酶体依赖的降解[10]。

BCKDH 位于线粒体内膜,由 BCKA 脱羧酶(E1)、二氢硫辛酰胺酰基转移酶(E2)和二氢硫辛酰胺脱氢酶(E3)3 个亚基组成[11],其中 E1 和 E2 具有特异性,而 E3 是与丙酮酸脱氢酶(pyruvate dehydrogenase, PDH)复合物和 α-酮戊二酸脱氢酶复合物共有的组分。因为 BCKDH 是 BCAAs 分解代谢的限速酶,因此,受着更为严格的调控。在转录水平,BCKDH 也受到转录因子 KLF15 的调控[9]。在翻译后水平,支链 α-酮酸脱氢酶激酶(branched chain ketoacid dehydrogenase kinase, BCKDK)通过磷酸化 BCKDH 复合物的 E1 亚基抑制其脱氢酶活性[12]。线粒体靶向 2C 型丝氨酸/苏氨酸蛋白磷酸酶(mitochondrial-targeted 2C-type Ser/Thr protein phosphatase, PPM1K)作为 BCKDH 的磷酸酶,与 BCKDK 竞争 BCKDH 的 E2 亚基结合位点,随后使 E1 去磷酸化而激活 BCKDH[13]。BCKDK-PPM1K 轴作为 BCAA 代谢调控节点,能够根据 BCAAs 的浓度实现对 BCKDH 的调节[13],当膳食蛋白质缺乏时,BCKDH 转化为非活性的磷酸化状态,以保存用于蛋白质合成的 BCAAs。当膳食蛋白质过量时,其处于活性的去磷酸化状态,负责降解过量的 BCAAs。

3　支链氨基酸调控的信号通路

BCAAs 不仅作为体内氨基酸的氮供体和蛋白

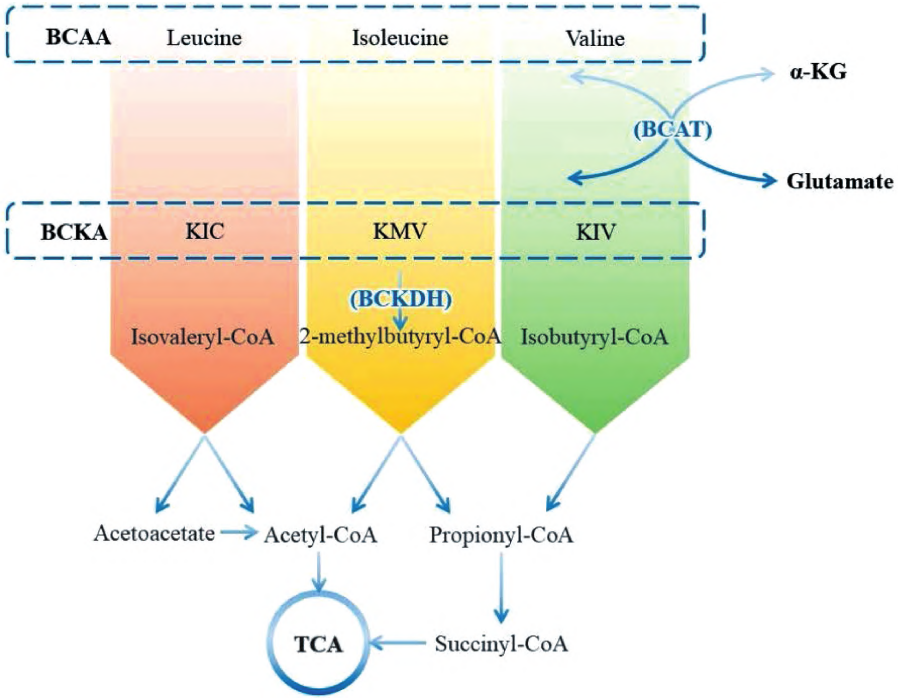

Fig. 1 Summary of branched chain amino acid catabolism Branched-chain amino acid (BCAA) metabolism in the body can be divided into two steps. The first step is reversible transamination to form α-ketoisocaproate (KIC), α-keto-β-methylvalerate (KMV) and α-ketoisovalerate (KIV) respectively, by branched-chain amino acids aminotransferase (BCAT), with concomitant production of Glu from α-ketoglutarate (α-KG). The second step is irreversible oxidative decarboxylation catalyzed by the mitochondrial branched-chain α-ketoacid dehydrogenase (BCKDH) complex. The final metabolites enter the tricarboxylic acid (TCA) cycle. BCKA, branched chain ketoacid

质合成的底物,同时也是一种重要的营养信号,通过激活不同的信号通路发挥作用。

哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)信号通路作为蛋白质代谢的调节中枢,可被 BCAAs 激活。mTOR 有 mTORC1 和 mTORC2 两种复合体,其中 mTORC1 对氨基酸信号非常敏感。BCAAs 通过多种途径激活 mTORC1。抗氧化应激蛋白 Sestrin2 抑制 mTORC1 信号传导,Leu 可以直接结合 Sestrin2 促进 mTORC1 的激活[14]。此外,亮氨酰 tRNA 合成酶(leucyl-tRNA synthetase,LRS)是细胞内 Leu 的传感器,通过 Vps34-PLD1 激活 mTORC1[15]。肌醇多磷酸激酶(inositol polyphosphate multikinase, IPMK)以辅因子的形式参与 Leu 对 mTOR 的激活,并增强 mTORC1 的下游信号传导[16]。也有研究指出,BCAAs 通过 V-ATP 酶(v-ATPase)的级联反应招募 mTORC1 至溶酶体后被激活[17]。BCAAs 通过激活 mTORC1,使其下游不同的信号分子发生磷酸化,从而产生不同的生物学效应,例如在心肌组织中通过激活 PPAR-α 促进脂肪酸氧化[18],在下丘脑中通过核糖体蛋白 S6 激酶 1(S6 Kinase1, S6K1)影响机体对食物的摄取[19],在肌肉组织中促进蛋白质合成[20],在肝组织中抑制脂肪生成[21]。

AMP 蛋白激酶(adenosine 5′-monophosphate-activated protein kinase, AMPK)是肌细胞能量平衡的调节器,在葡萄糖、脂质和蛋白质代谢中发挥着重要作用。当能量缺乏时,补充不同 BCAAs 比例的低蛋白质饮食可激活 AMPK[22],刺激分解代谢途径并抑制合成代谢途径,为细胞存活提供 ATP[23]。AMPK 抑制肌肉蛋白质合成是通过抑制 mTORC1 复合物实现的[24],在缺氧、剧烈运动或葡萄糖匮乏等能量应激条件下,能够降低肌肉蛋白质合成[25]。例如,在骨肉瘤细胞中,为了满足能量和代谢的需要 AMPK 活性增加而 mTORC1 的表达下调即印证了上述观点[23]。

4 支链氨基酸代谢与疾病的关系

作为机体含量最多的必需氨基酸,BCAAs 的代谢异常会引发一系列疾病。BCAAs 代谢酶异常会引起相关的先天性代谢疾病,例如枫糖尿病(maple syrup urine disease, MSUD)和自闭症谱系障碍(autism spectrum disorders, ASD)伴癫痫。此外,糖尿

病、肝疾病和癌症等则可能与 BCAAs 的代谢改变和信号功能有关。

4.1　枫糖尿病

MSUD 是一种常染色体隐性的先天性代谢紊乱疾病,由线粒体 BCKDH 的功能性突变引起,BCAAs 代谢受阻,相应的酮酸衍生物在体内蓄积,造成线粒体生物能功能障碍[26]。BCAAs 浓度升高,与其他氨基酸竞争大型中性氨基酸转运蛋白 1(large neutral amino acid transporter, LAT1)进入中枢神经系统,从而造成多种神经损伤[27];而 BCAAs 积累的代谢物本身也具有神经毒性,其中以 Leu 及其代谢产物最为显著[28]。

4.2　神经系统疾病

BCAAs 与芳香族氨基酸竞争,通过血脑屏障从而影响神经递质水平。血脑屏障上的 LAT1 可以转运 BCAAs 和芳香族氨基酸,而 BCAAs 相对于芳香族氨基酸更具有竞争性[4]。这种竞争的结果可能影响某些神经递质的合成,尤其是多巴胺、去甲肾上腺素和 5-羟色胺[4],从而影响大脑功能和行为。而如果缺乏 BCAAs,芳香族氨基酸将有更多机会到达中枢神经系统并产生相关的神经递质[29]。

此外,BCAAs 在大脑代谢中作为氮供体发挥着重要作用。研究已证实,Leu 是大脑中合成 Glu 和 Gln 的主要氮供体[3]。Hutson 等人[30]提出,BCAAs 的氮穿梭在谷氨酸能神经元中发挥重要作用。在阿尔茨海默病(Alzheimer's disease, AD)、血管性痴呆(vascular dementia, VaD)和路易体痴呆(dementia with Lewy bodies, DLB)患者的大脑中发现,BCATm 蛋白的表达显著增加,提示 BCAAs 可能参与到 Glu 的神经兴奋性毒性中[31]。

BCAAs 稳态对神经系统发挥正常功能至关重要。人类星形胶质细胞中存在活跃的 BCAAs 代谢,若代谢受损,会导致 AD 患者大脑中的神经递质失衡[32]。在糖尿病和 AD 患者中,血浆 BCAAs 水平显著上升,BCAAs 的积累可能是由于大脑中 BCATc 的下调,导致 Leu 积累,从而以 mTOR 依赖性方式促进 Tau 蛋白的磷酸化,随后导致糖尿病相关 AD 的发展[33]。*BCKDK* 基因突变可导致 ASD 伴癫痫,这种先天性代谢缺陷的直接后果是 BCAAs 的分解代谢提高,血清和大脑 BCAAs 水平异常降低[34]。

4.3　糖尿病

许多报道都表明,BCAAs 调控机体的糖代谢,与胰岛素抵抗(insulin resistance, IR)、肥胖和糖尿病风险呈正相关[35]。BCAAs 可以通过刺激 mTOR 和 S6K1 使胰岛素受体底物-1(insulin receptor substrate 1, IRS-1)的丝氨酸残基发生磷酸化,进而干扰胰岛素信号传导[36],在高脂/BCAA 饮食诱导 IR 发生中具有重要作用[37]。研究发现,BCAAs 是机体胰岛素分泌所必需的,缺乏 BCAAs 会破坏机体的糖代谢稳态。例如,BCAAs 会刺激胰岛素和胰高血糖素的分泌[38];而高 BCAAs 暴露会导致 IRS-1/蛋白激酶 B(Akt)信号传导受损和胰岛素刺激的糖原合成受损[39]。然而,BCAAs 是否会导致 IR 的发展或恶化尚未得出结论。有研究发现,在高脂饮食的动物中,富含 BCAAs 的乳清蛋白饮食不会导致 IR[40];补充 BCAAs 不会损害肥胖、糖尿病前期受试者的糖代谢,也不是 IR 患者 BCAAs 升高的原因[41]。另有研究报道,IR 是 BCAAs 的代谢酶表达下调使 BCKAs 积聚导致的[42]。

上述 2 种观点聚焦于是否是 BCAAs 导致了胰岛素抵抗。但另一思路是,肌肉发生的 BCAAs 代谢改变使 BCAAs 水平升高,而 BCAAs 分解代谢受损可通过扰乱氨基酸和脂肪酸代谢来促进 IR 的发展[2]。例如,氨基受体减少导致 BCAAs 转氨基障碍,以及脂肪酸氧化中产生的 NADH 和酰基辅酶 A 对 BCKA 脱氢的抑制作用,导致 1 型糖尿病(diabetes mellitus type 1, T1DM)患者的血浆 BCAAs 水平增加[43]。而对于 T2DM 患者肌肉中 BCAT 和 BCKDH 表达降低、BCAAs 水平升高的机制,可以通过糖酵解受损和脂肪供应过多对肌肉 BCAAs 转氨和脱羧的抑制作用来解释[44]。基于这种观点,针对 BCAAs 代谢的治疗可使糖尿病患者受益。

4.4　肝疾病

BCAAs 与肝疾病关系密切。严重缺乏蛋白质的饮食与肝内脂肪积累和非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)有关。BCAAs 减少也是肝硬化患者血液的特征性改变,这一特征与肝性脑病(hepatic encephalopathy, HE)、肌肉萎缩和肝癌(hepatocellular carcinoma, HCC)的发生及患者的不良预后相关[45]。BCAAs 可通过抑制 *FAS* 基因的表达减轻非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)相关的肝脂肪变性和肝损伤[46]。BCAAs 和 BCKAs 可以通过 mTOR 途径阻断 Akt2-INSIG2a 信号传导,抑制肝内脂肪生成,诱导肝、肌肉和肾内脂质的再分配[21],而 PPM1K 调节 BCAAs 代谢中的代谢转录因子 ChREBP-β 能激活肝内脂肪生成[47]。有研究发现,血浆 BCAAs 浓度与 NAFLD 严重程度的相关性具有性别差异,女性

血浆 BCAAs 浓度随着 NAFLD 和肝纤维化程度加重而增加[48]。

在肝硬化早期代偿时期,肝内下降的氨解毒能力被骨骼肌代偿;而随着疾病进展,当骨骼肌无法代偿、发生低白蛋白血症或高氨血症时,则被认为是肝硬化失代偿期[49]。因此,维持骨骼肌质量并改善糖耐量可能有助于肝硬化患者预后[50]。肝硬化患者的 BCAAs 全身清除率增加,可能主要通过骨骼肌增加对 BCAAs 的代谢需求,骨骼肌从血浆中吸收氨和释放谷氨酰胺,从而调节血氨水平[51]。

尽管 BCAAs 水平与肝疾病的发病机制尚未完全清楚,针对 BCAAs 和富含 BCAAs 的补充剂的研究已广泛开展,并常被推荐作为肝病的治疗方法。补充 BCAAs 可改善肝硬化患者的氮平衡和肝功能,提高白蛋白水平,减少 HE 等并发症,显著提高生活质量和预后。虽然补充 BCAAs 可能促使器官间的氨转移,但体内的氮总量是增加的,这可能导致氨积累形成恶性循环,有学者提出可以通过锌补充治疗来改善[49]。

4.5 心血管疾病

BCAAs 代谢失调日益成为心血管疾病的特征生化改变[52]。研究证实,BCAAs 的升高通过改变细胞电生理致心律失常[53];在一般人群中也发现,空腹 Val 血浆水平与心电图参数之间存在显著性关联[53]。血浆 BCAAs 水平升高与 ST 段抬高型心肌梗死和急性心力衰竭患者的长期不良心血管事件独立相关[54],其机制可能与氧化应激[18, 55]和代谢紊乱[9, 52, 56, 57]有关。二氢硫辛酸脱氢酶(dihydrolipoic acid dehydrogenase, PDH)作为丙酮酸氧化的限速酶,是葡萄糖氧化的关键调节剂。研究发现,BCAAs 可以通过其分解代谢缺陷导致的糖基化修饰和直接抑制两种方式调节 PDH,使得 PDH 通量降低并抑制心肌细胞的葡萄糖氧化[56]。在心血管中,BCAA 代谢的昼夜节律振荡由 KLF15 介导[9]。KLF15 通过 GLUT4 调节胰岛素分泌、组织胰岛素敏感性和葡萄糖吸收。葡萄糖选择性抑制心肌细胞中 KLF15 转录,下调 BCAA 分解代谢以促进心肌细胞肥大[57]。

此外,BCAAs 通过调节 GCN2/ATF6 信号通路激活 PPAR-α,增强了心肌组织中的脂肪酸氧化,加剧了脂质过氧化毒性,从而加重心肌损伤[18]。另有研究表明,BCAAs 通过 AMPK-ULK1 途径产生过量活性氧,通过自噬诱导心肌损伤[55]。

4.6 癌症

BCAAs 分解代谢在人类癌症中发挥重要作用。长期以来,癌症患者血浆 BCAAs 水平改变备受关注。一方面,正如 Warburg 效应提出的肿瘤相对于正常组织的糖酵解通量增加,与正常细胞相比,癌细胞对代谢的要求差异很大[58]。因此,以肿瘤细胞的营养来源为靶点的抗癌治疗策略成为一种可行的方法,而 BCAAs 正是肿瘤生长重要的氮源和碳源之一,在乳腺癌细胞 MCF-7 产生的能量中,高达 36% 是由 BCAAs 分解提供的[59]。另一方面,累积的 BCAAs 可作为信号分子,对肿瘤的生长发挥调节作用。

不同肿瘤对 BCAAs 的利用是不同的,这可能与不同细胞类型、组织起源或突变基因的肿瘤具有不同的首选能源有关(见 Table1)。例如胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)风险增加与血浆 BCAAs 水平升高有关,并且血浆 BCAAs 水平的升高先于临床表现多年[60],这一发现在 Kras 突变驱动的胰管腺癌小鼠实验中也得到证实[61]。胰腺导管内乳头状黏液肿瘤(intraductal papillary mucinous neoplasm, IPMN)恶性程度越高,血浆 BCAAs 水平也越高[62]。与此类似,在乳腺癌(breast cancer, BC)[63]和多囊卵巢综合征(polycystic ovary syndrome, PCOS)[64]患者中,也观察到血浆 BCAAs 水平升高。然而,高血浆 BCAAs 水平却与结直肠腺癌(colorectal adenocarcinoma, CRA)风险呈负相关[65]。体外研究证实,BCAAs 显著降低胰岛素引发的人结肠癌(colon cancer, CC)细胞系 HCT-116 和肝癌细胞系 HepG2 的增殖[66]。即使同样是由 Kras 和 p53 突变驱动的 PDAC 和非小细胞肺癌(non-small-cell lung cancer, NSCLC),利用 BCAAs 的方式也有所不同。PDAC 对 BCAAs 的依赖性很小,而 NSCLC 利用 BCAAs 作为氮源并增强 BCAAs 的摄取[67]。总而言之,BCAAs 在不同类型或不同阶段癌症中的作用是不同的,这对其临床应用是很大的挑战。

BCAAs 分解代谢酶 BCAT 和 BCKDH 也与肿瘤进展密切相关,是癌症预后标志物讨论的热点(见 Table2)。目前的研究表明,大多数癌症类型表达高水平 BCATc,并利用 BCAAs 分解代谢产生氮源、促进细胞增殖。然而,并非所有的癌症类型都表达高水平的 BCATc,例如 BCATc 在软骨肉瘤(SW1353)中表达下调[23]。也并非所有癌症对 BCAA 代谢物的需求都相同,并且 BCATc 的功能在不同类型的癌

症中似乎有所不同。BCATc 在 BC[63, 70]、骨髓瘤[71]中过表达,通过激活 mTORC1 途径促进 EC 细胞增殖。在大脑中,BCATc 催化 BCAA 分解和 Glu 生成,以增强胶质母细胞瘤的生长[72]。与胶质母细胞瘤相似,软骨肉瘤经常携带 *IDH*1 基因,突变 IDH1 与 BCATc 之间存在联系[23]。

Table 1　Relationship between different cancers and BCAA levels

Cancers	Relationship with BCAAs level	References
PDAC	An association between increased plasma BCAAs level and increased risk of pancreatic cancer was found—particularly when the increase in BCAAs was observed at least 10 years before diagnosis.	[60]
IPMN	Circulating BCAAs levels were lower in low/moderate IPMN than in high-grade/invasive IPMN.	[62]
BC	The plasma and tissue levels of BCAAs are increased in breast cancer.	[63]
HCC	Progressive loss of BCAAs catabolism promotes HCC's development and growth. Dietary BCAAs intake also correlated with cancer mortality risk.	[68]
CRC	There are positive associations between higher intake of dietary BCAAs and risk of all-cause mortality in CRC patients.	[69]
CRA	High plasma concentrations of leucine, valine and total BCAAs were inversely associated with CRA risk after adjustment of BMI.	[65]
CC&HCC	BCAAs significantly decreased insulin-initiated proliferation of human colon and hepatic cancer cell lines in vitro.	[66]

Table 2　Relationship between BCAA metabolic enzymes and cancer development

Cancers	Targets	Relationship with cancer development	References
BC	BCATc	↑	[63, 70]
EOC	BCATc	↑	[73]
Glioblastoma	BCATc	↑	[74]
HCC	BCATc	↑	[75]
PDAC	BCATc	↑	[76]
myeloma	BCATc	↑	[71]
chondrosarcoma	BCATc	↓	[23]
AML	BCATc	↑	[77]
CML	BCATc	↑	[72]
PDCA	BCATm	↑	[58, 78]
EL-4 lymphoma	BCATm	↑	[79]
PDCA	BCKDHA	↑	[58]
CRC	BCKDK	↑	[80]
HCC	BCKDK	↑	[68]

↑: Overexpression in cancer or promoting cancer progression;
↓: Expression in cancer reduces or inhibits cancer progression.

BCAAs 代谢重编程不仅体现在癌细胞本身,肿瘤微环境中基质成分的代谢改变也对癌症发生发展发挥重要作用。在 PDAC 中,作为基质细胞的肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)参与调节癌细胞的 BCAA 代谢。CAFs 中高表达 BCATc,上调 BCAA 脱氨反应并为癌细胞提供

BCKA,从而在 BCATm 催化下实现蛋白质的从头合成[76]。这一发现有助于解释 BCATm 在 PDAC 中升高和癌细胞对 BCAAs 摄取增加的现象[78]。

5 问题与展望

近年来,BCAAs 代谢调控与疾病之间关系研究得愈发广泛和深入。本文对 BCAAs 代谢、调控以及和疾病的关系进行了综述,发现仍有很多问题亟待进一步研究和探讨。首先,在 BCAAs 的代谢调控方面,针对 BCAT 和 BCADH 的转录、转录后和翻译后修饰水平调控有待进一步深入探索,代谢调控的组织特异性也值得关注。更全面地了解代谢调控机制可以为疾病发生机制的解释和疾病预防提供线索。其次,在疾病层面,目前的证据支持 BCAAs 代谢、其衍生物和血浆水平与 IR、T2DM、肝疾病、心血管疾病和癌症等疾病有着密切的联系。然而,不同疾病与 BCAAs 水平有不同关系,甚至对同一疾病在不同背景下也有相反观点。BCAAs 可以通过其代谢改变和作为信号分子的两种作用对疾病的发生发展产生影响,但对于多数疾病,目前尚无法确定何种作用更为主要,需要更多的研究来进一步阐明,其中不同组织器官的代谢背景和不同疾病的发生机制等都应当纳入考虑。我们期待,以 BCAAs 代谢为靶点的干预措施能够改善这些疾病的预防和治疗现状。

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