



评述

氨基酸调控猪免疫细胞命运的分子机制研究进展

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摘要 氨基酸在免疫细胞的增殖、发育和免疫应答中发挥关键作用。本文总结了氨基酸对仔猪肠道免疫功能的调控作用和谷氨酰胺、 γ -氨基丁酸、精氨酸和色氨酸调控免疫细胞命运的作用机制, 并系统综述了氨基酸通过重塑免疫细胞代谢、调控信号通路活化和表观遗传修饰等途径调控免疫细胞命运的分子机制。为通过营养(氨基酸)策略改善仔猪肠道免疫功能, 降低仔猪死淘率提供了理论基础。

关键词 猪, 氨基酸, 免疫细胞, 肠道免疫

仔猪死淘率高一直是生猪养殖业的行业难题, 其中, 断奶期死亡的仔猪占据养殖全程的80%, 每年给我国生猪养殖业造成的经济损失高达1500亿元。病原菌感染导致的腹泻是断奶仔猪死亡的主要诱因^[1]。饲料、环境等多方面的应激因素导致断奶仔猪对病原微生物的易感性提高。断奶仔猪缺乏母源抗体的保护, 且集约化养殖普遍采取早期断奶技术(3~4周龄), 但断奶

仔猪的肠道免疫系统在7周龄才能发育成熟^[2,3]。因此, 改善断奶仔猪肠道免疫功能, 是增强仔猪抗病能力, 降低仔猪腹泻率和死亡率的重要手段。

仔猪在遭遇病原菌感染时, 免疫系统激活, 机体氨基酸代谢发生改变。通常, 氨基酸的功能主要被认为是作为蛋白质的基本合成单元, 以维持动物的生长和发育, 但近年来的研究表明, 谷氨酰胺、 γ -氨基丁酸(γ -

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aminobutyric acid, GABA)和精氨酸等多种氨基酸可调控断奶仔猪肠道免疫功能,然而,其分子机制和应用方式仍不明确.免疫细胞活化时,胞内氨基酸的代谢和转运也会发生改变,以适应其生物学功能(增殖、分泌细胞因子等)的需要.在多种细胞模型中的研究表明,谷氨酰胺、GABA、精氨酸等氨基酸可调控免疫细胞的增殖、分化和功能^[4].因此,揭示氨基酸调控免疫细胞增殖、存活和活化的分子机制,对于开发调控断奶仔猪肠道免疫功能,降低仔猪腹泻率和死亡率的营养策略具有重要意义.

本综述旨在总结氨基酸对仔猪肠道免疫功能的调控作用,讨论谷氨酰胺、GABA、精氨酸和色氨酸等关键氨基酸对免疫细胞命运的调控机制,并系统总结氨基酸介导免疫细胞代谢重塑、信号通路活化和表观遗传修饰等途径调控免疫细胞命运的潜在分子机制.为通过营养(氨基酸)策略调控仔猪肠道免疫稳态,增强仔猪抗病能力,降低仔猪死淘率提供理论基础.

1 氨基酸对断奶仔猪肠道免疫的调控作用

病原菌感染是导致断奶仔猪腹泻和死亡的关键因

素.肠道是动物最大的免疫器官,因此,通过营养调控改善断奶仔猪肠道免疫功能是提高断奶仔猪抗病能力的有效措施.近年来多篇研究表明,氨基酸不仅是维持动物生长的基础营养物质,其还在调节仔猪肠道免疫功能中发挥关键作用(表1).

在断奶仔猪中的研究表明,饲料添加0.2%的谷氨酰胺改善了仔猪肠道形态,但不影响仔猪血清脂多糖(lipopolysaccharide, LPS)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和白介素-8(interleukin-8, IL-8)的浓度^[5].饲料添加0.002%的GABA显著下调断奶仔猪肠道促炎细胞因子IL-1和IL-18的mRNA表达,上调抗炎因子IL-4和IL-10的mRNA表达^[6].2 mg/kg褪黑素(色氨酸代谢物)处理上调了断奶仔猪回肠IL-4和IL-17的mRNA表达,降低了回肠IL-6的mRNA表达^[7].支链氨基酸(0.19%异亮氨酸+0.27%缬氨酸+0.07%亮氨酸)导致小肠淋巴细胞数量减少,免疫球蛋白含量显著升高^[8].饲料添加1%的L型天冬氨酸对断奶仔猪的生长性能和肠道免疫功能无显著影响,但1%的D型天冬氨酸导致断奶仔猪生长性能降低,血清免疫球蛋白(immune globulin, Ig)M浓度下降^[9].这些研究表明,在断奶仔猪饲料中添加适量浓度的GABA可缓解仔猪肠道

表1 氨基酸对仔猪肠道免疫的调控作用^{a)}

Table 1 Effects of amino acid on intestinal immune function in piglets

处理方式和剂量	动物模型	作用效果	参考文献
0.2% Gln	断奶仔猪	血清LPS、TNF- α 和IL-8浓度无显著变化	[5]
0.002% GABA	断奶仔猪	肠道IL-1 $\downarrow$ 、IL-18 $\downarrow$ 、IL-4 $\uparrow$ 、IL-10 $\uparrow$	[6]
0.0002% Mel	断奶仔猪	肠道IL-4 $\uparrow$ 、IL-17 $\uparrow$ 、IL-6 $\downarrow$	[7]
0.19% Ile+0.27% Val+0.07% Leu	断奶仔猪	小肠淋巴细胞数量 $\downarrow$ 、免疫球蛋白含量 $\uparrow$	[8]
1% D-Asp	断奶仔猪	血清IgM $\downarrow$	[9]
0.5% Gln	<i>E. coli</i> F4感染仔猪	细胞因子的mRNA表达无显著变化	[10]
1% Gln	LPS攻毒仔猪	血清促炎细胞因子 $\downarrow$ 、Th17免疫应答 $\downarrow$ 、Treg介导的免疫耐受 $\uparrow$	[11]
1% Gln	双酚A诱导的肠炎仔猪	血清促炎细胞因子 $\downarrow$ 、抗炎细胞因子 $\uparrow$	[12]
4.4% Gln	<i>E. coli</i> 感染仔猪	细胞因子的mRNA表达无显著变化	[13]
0.5% Arg	<i>E. coli</i> F4感染仔猪	粪便IgA $\uparrow$	[10]
0.004% GABA	ETEC感染仔猪	肠道IgA $\uparrow$ 、空肠IL-1 β $\uparrow$ 、IL-4 $\uparrow$ 、IL-17 $\uparrow$	[14]
0.5%或1% Arg	LPS攻毒仔猪	小肠肥大细胞 $\downarrow$ 、CD4 ⁺ T细胞 $\downarrow$ 、IgA释放细胞 $\uparrow$ 、CD8 ⁺ T细胞 $\uparrow$	[15]
0.1% Met	LPS攻毒仔猪	血清IL-8 $\downarrow$	[16]
0.12% Met	IUGR仔猪	空肠IL-10 $\uparrow$	[17]
0.21% Trp	<i>E. coli</i> F4感染仔猪	血清IL-6 $\downarrow$ 、TNF- α $\downarrow$	[18]
0.0002% Mel	敌草快处理仔猪	血清IgM的浓度 $\uparrow$ 、肠道IL-10 $\uparrow$	[7]

a) Arg, 精氨酸; D-Asp, D型天冬氨酸; ETEC, 肠产毒素性大肠杆菌; GABA, γ -氨基丁酸; Gln, 谷氨酰胺; IgM, 免疫球蛋白M; IL, 白介素; Ile, 异亮氨酸; IUGR, 宫内发育迟缓; Leu, 亮氨酸; LPS, 脂多糖; Mel, 褪黑素; Val, 缬氨酸; Met, 蛋氨酸; Th17, 辅助性T细胞17; TNF- α , 肿瘤坏死因子- α ; Treg, 调节性T细胞; Trp, 色氨酸; $\uparrow$, 升高; $\downarrow$, 降低

炎症, 添加支链氨基酸(branched chain amino acid, BCAA)可增强B细胞产生免疫球蛋白的能力, 但D型天冬氨酸可损伤肠道B细胞功能。

肠产毒素性大肠杆菌(enterotoxigenic *Escherichia coli*, ETEC)等病原菌诱导的肠道炎症是导致断奶仔猪腹泻和死亡的主要原因, 因此, 大肠杆菌和大肠杆菌来源的LPS常被用作构建病原感染的肠炎模型。此外, 在少量研究中, 敌草快和双酚A也被用来构建仔猪肠炎或氧化应激模型。最近的研究发现, 饲料添加0.5%的谷氨酰胺或0.5%的精氨酸均无法缓解*Escherichia coli* F4导致的断奶仔猪腹泻, 但精氨酸提高了粪便中IgA的含量^[10]。在LPS攻毒仔猪中, 饲料添加1%谷氨酰胺显著改善断奶仔猪生长性能和肠道形态, 降低了血清中多种促炎因子的含量, 抑制辅助性T细胞(helper T cells, Th)17免疫应答, 促进调节性T细胞(regulatory T cells, Treg)介导的免疫耐受^[11]。在*Escherichia coli*感染的断奶仔猪中, 尽管4.4%的谷氨酰胺改善了仔猪的肠道屏障功能, 但对肠道促炎细胞因子的mRNA表达无显著影响^[13]。在双酚A诱导的仔猪肠道炎症模型中, 添加1%的谷氨酰胺可降低血清中IL-1 β 、IL-6和TNF- α 的含量, 升高IL-10的含量^[12]。这些不一致的结果可能是由于这些研究中谷氨酰胺的添加量存在差异。在ETEC感染仔猪中, GABA可促进空肠IgA的分泌, 并提高空肠细胞因子IL-1 β 、IL-4和IL-17的浓度^[14]。在LPS处理的仔猪中, 0.5%或1%的精氨酸可显著降低空肠和回肠的肥大细胞数量和CD4⁺ T细胞数量, 提高回肠IgA释放细胞和CD8⁺ T细胞的数量^[15]。在LPS诱导的仔猪肠道炎症模型中, 0.1%的蛋氨酸可显著降低血清IL-8的浓度^[16]。0.12%的蛋氨酸处理可提高宫内发育迟缓(intrauterine growth retardation, IUGR)仔猪空肠抗炎细胞因子IL-10的分泌^[17]。与基础日粮相比, 饲料添加0.21%的色氨酸可降低*Escherichia coli* F4感染断奶仔猪血清IL-6和TNF- α 的浓度^[18]。在敌草快处理的仔猪中, 褪黑素提高了仔猪提高血清IgM的浓度和肠道IL-10的mRNA表达^[7]。

总的来说, 目前的研究表明, 在肠道炎症仔猪模型中, 饲料添加谷氨酰胺、精氨酸、蛋氨酸、色氨酸或褪黑素可缓解其肠道炎症, 谷氨酰胺可促进Treg介导的免疫耐受, 精氨酸、GABA和褪黑素可促进肠道IgA等抗体的分泌。然而, 在正常断奶仔猪和肠道炎症仔猪模型中, 谷氨酰胺等氨基酸的作用并不完全一致, 这可

能是由于仔猪正常生长和病原感染时的氨基酸营养需求存在差异。因此, 在探究氨基酸对仔猪的肠道免疫调控作用时, 可将病原感染仔猪模型分为不同的阶段(病原感染前和病原感染后)分别进行营养调控, 探究不同状态下断奶仔猪的营养需要, 并在养殖生产中区分腹泻和未腹泻仔猪, 实施不同的营养调控策略, 从而高效地增强仔猪的抗病能力, 促进病猪生理健康的恢复。此外, 尽管谷氨酰胺等氨基酸具有调控断奶仔猪肠道免疫的潜在功能, 但目前的研究大多局限于分析氨基酸对仔猪细胞因子表达或含量的影响, 未深入探究其分子机制。因此, 本文基于多种动物或细胞模型, 系统讨论氨基酸调控免疫细胞命运的潜在机制, 为通过氨基酸调控断奶仔猪肠道免疫, 降低断奶仔猪腹泻率和死亡率提供理论依据。

2 关键氨基酸调控免疫细胞命运的分子机制

2.1 谷氨酰胺

多个代谢途径提供中间体, 在巨噬细胞中, 谷氨酰胺为UDP-GlcNAc的合成提供氮源, 调控M2巨噬细胞标记蛋白的糖基化。谷氨酰胺分解代谢产生的 α -酮戊二酸(α -ketoglutaric acid, α -KG)可通过参与脂肪酸氧化(fatty acid oxidation, FAO)和Jumonji结构域(Jumonji domain-containing, Jmid3)依赖的H3K27去乙酰化促进巨噬细胞M2极化^[19]。但谷氨酰胺在M1巨噬细胞的极化中的作用还存在争议。在LPS刺激的小鼠巨噬细胞中, α -KG通过脯氨酸羟化酶结构域(prolyl hydroxylase domain, PHD)抑制核因子- κ B(nuclear factor- κ B, NF- κ B)激酶抑制剂I κ B激酶(I κ B kinase, IKK)的激活, 以及通过IKK β 的P191位点的羟基化抑制IKK β 的活化, 从而抑制巨噬细胞的M1极化^[19,20]。但也有研究表明, 谷氨酰胺被用于细胞中琥珀酸积累, 从而稳定缺氧诱导因子缺氧诱导因子1 α (hypoxia-inducible factor, HIF-1 α), 特异性促进M1巨噬细胞IL-1 β 的合成^[21]。

谷氨酰胺在淋巴细胞的分化和功能中也发挥关键作用。在naïve T细胞中, 谷氨酰胺通过氧化途径满足其基础代谢需要; 但在T细胞被抗原激活后, Slc38a1和Sc38a2等谷氨酰胺转运载体表达增强, T细胞谷氨酰胺分解代谢增强。与静息T细胞相比, 活化的小鼠脾T细胞显示出更高的谷氨酰胺酶(glutaminase, GLS)和谷氨酸脱氢酶(glutamate dehydrogenase, GDH)活性^[22]。谷

氨酰胺可经GLS催化水解为谷氨酸和氨, 促进谷胱甘肽(glutathione, GSH)的合成; 谷氨酰胺由谷氨酸脱氢酶(glutamate dehydrogenase, GDH)转化为 α -KG, 从而进入三羧酸(tricarboxylic acid, TCA)循环为细胞提供能量. 在B细胞中, 谷氨酰胺也作为碳源为B细胞提供能量^[23], 胞外谷氨酰胺浓度和摄取效率与B细胞胞内UDP-Gal的利用率正相关^[24]. 在病毒感染条件下, 自然杀伤(natural killer, NK)细胞Slc7a5和Slc3a2的表达升高, 从而促进亮氨酸内流和谷氨酰胺外排^[25,26], 但该机制在NK细胞的抗病毒功能中的作用还有待揭示. 谷氨酰胺的剥夺将抑制小鼠T细胞的增殖和细胞因子的产生^[27]. 谷氨酰胺也参与T细胞分化的调控, 在人和小鼠CD4⁺ T细胞中, 谷氨酰胺剥夺抑制Th1细胞分化, 促进Foxp3⁺ Treg细胞的分化^[27]. 而外源添加谷氨酰胺可促进T细胞增殖, 促进Th1免疫应答, 抑制Th2免疫应答^[28].

Slc1a5、Slc6a14/Slc6a19(B0AT1)、Slc38a1(SNAT1)、Slc38a2(SNAT2)、Slc38a4(SNAT4)、Slc38a3(SNAT3)和Slc38a5(SNAT5)等8种氨基酸转运蛋白介导谷氨酰胺的转运. 通过抑制Slc7a5的表达阻断谷氨酰胺的摄取将抑制Th1、Th17和细胞毒性T细胞(cytotoxic T cell, CTL)的分化, Slc7a5介导的谷氨酰胺摄取通过激活c-Myc调控效应T细胞(effector T cell, Teff)的功能^[29]. Slc1a5缺失T细胞的谷氨酰胺摄取能力受损, 雷帕霉素哺乳动物靶蛋白(mammalian target of rapamycin, mTOR)和T细胞受体(T cell receptor, TCR)的激活受损, Th1和Th17分化被阻断^[27]. 有研究探究了不同生命阶段Slc1a5缺失对T细胞的影响, 幼龄小鼠(6~7周龄)Slc1a5缺失不影响脾脏T细胞、naïve CD4⁺ T细胞和naïve CD8⁺ T细胞的数量; 但在5~6月龄时, Slc1a5缺失导致小鼠CD4⁺ T细胞的数量和比例降低, CD44^{lo}CD62L^{hi} naïve CD4⁺ T细胞比例显著降低^[30]. 以上研究结果表明, Slc1a5在维持年轻小鼠外周初始T细胞稳态中几乎没有作用, 但可能影响T细胞的激活及分化和老年小鼠初始T细胞稳态. 寄生虫或LPS感染的动物体内, Slc38a2介导树突状细胞(dendritic cell, DCs)谷氨酰胺的转运上调趋化因子受体Cxcr4的表达, 促进DCs的迁移^[31]. 在肿瘤微环境中, DCs通过转运蛋白Slc38a2和肿瘤细胞竞争谷氨酰胺, 通过卵巢滤泡激素(folliculin, FLCN)损害DCs抗原呈递功能, 促进CD8⁺ T细胞的增殖和抗肿瘤细胞因子的表达^[32]. 在缺氧条

件下, 谷氨酰胺对于B细胞的存活至关重要, 且谷氨酰胺可促进B细胞分化为浆细胞. 谷氨酰胺转运载体Slc1a5和谷氨酰胺酶(glutaminase, GLS)的抑制, 会干扰B细胞IgG和IgM的产生^[33].

综上所述, 巨噬细胞中, 谷氨酰胺通过代谢产物 α -KG促进FAO和组蛋白去乙酰化修饰促进巨噬细胞M2极化, 但其M1巨噬细胞中的功能仍存在争议. 在T细胞和B细胞中, 谷氨酰胺可进入TCA循环为细胞功能, 促进T细胞活化和B细胞抗体的产生. 谷氨酰胺还介导c-Myc、mTOR和TCR等多个信号途径促进Tff的功能以及Th1和Th17的分化. Slc38a2介导的谷氨酰胺转运在树突状细胞的迁移和抗原呈递功能中发挥着至关重要的作用.

2.2 γ -氨基丁酸

GABA由谷氨酸脱羧反应生成, 该代谢旁路是谷氨酰胺参与TCA循环的关键环节. 腹腔巨噬细胞高表达GABA转运载体GAT2(Slc6a13)和GAT4(Slc6a12), 但在M1极化时Slc6a13表达降低、Slc6a12表达升高, 同时胞内GABA含量显著降低^[34]. 外源添加GABA对M1巨噬细胞的IL-1 β 分泌无显著影响^[34], 但在巨噬细胞成熟阶段, GABA可通过增强琥珀酸-黄素腺嘌呤二核苷酸-赖氨酸特异性去甲基化酶1(lysine-specific demethylase 1, LSD1)信号通路, 调节细胞凋亡促进因子(Bcl-2-like protein, Bcl2l1)和双特异性磷酸酶(dual-specificity phosphatase, Dusp2)的组蛋白去甲基化, 减少NOD-样受体蛋白3(NOD like receptor protein 3, NLRP3)-凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)-半胱氨酸天冬氨酸蛋白酶-1(cysteiny aspartate specific proteinase, Caspase-1)复合体的形成, 从而抑制M1巨噬细胞IL-1 β 的分泌^[35]. 此外, GABA可促进单核细胞分化为抗炎巨噬细胞^[36]. Slc6a13缺失促进巨噬细胞胞内次黄嘌呤的积累, 不仅阻断了NLRP3/ASC/Caspase-1复合体的形成, 而且通过甲基化降低转录因子KID3的表达, 增强了氧化磷酸化(oxidative phosphorylation, OXPHOS)相关基因的表达, 从而抑制M1巨噬细胞IL-1 β 的合成和分泌^[34].

Th17免疫细胞和naïve T细胞的胞内GABA的代谢特征存在显著差异, Th17细胞的GABA分流途径代谢物(谷氨酸和GABA)含量显著较高^[37], 胞膜GABA转运

载体GAT2(Slc6a13)的表达也显著较高。肠道微生物可通过调控GABA的产生,介导mTORC1-SK激酶(S6 kinase, S6K1)信号作用于Th17免疫细胞促进IL-17的产生和分泌^[38]。T细胞可表达Slc6a1、Slc6a13和Slc6a12三种GABA转运载体^[37]。Slc6a1的敲除不影响小鼠初始T细胞的稳态^[39],但会增强T细胞介导的免疫应答,上调干扰素- γ (Interferon- γ , IFN- γ)、肿瘤坏死因子- α (tumour necrosis factor- α , TNF- α)、IL-6、IL-23、IL-17和IL-12等炎症细胞因子的表达,导致小鼠更容易发生实验性自身免疫性脑脊髓炎^[40]。Slc6a13缺失对T细胞发育和外周T细胞稳态影响不大,但可通过激活GABA-mTOR信号通路促进Th17细胞分化和Th17细胞反应^[37]。Slc6a13也参与B细胞的分化和功能的调控,Slc6a13缺失通过激活GABA-mTORC1信号诱发生发中心B细胞的分化,加剧IgA肾病的临床症状^[41]。

以上研究表明,GABA可促进单核细胞分化为巨噬细胞,在巨噬细胞成熟阶段,GABA可通过组蛋白去甲基化抑制M1巨噬细胞IL-1 β 的分泌;GABA转运载体Slc6a13的缺失会抑制M1巨噬细胞促炎细胞因子的合成和分泌。在T细胞中,GABA可促进Th17细胞免疫应答,但在GABA转运载体Slc6a1/13缺失的小鼠中,T细胞免疫应答也被增强,这种不一致的结果可能是由于GABA具有多个转运载体,其他未缺失的转运载体的功能被代偿性增强,Slc6a13的缺失还促进了生发中心B细胞的分化。

2.3 精氨酸

精氨酸的代谢主要包括精氨酸酶(arginase, ARG)途径、一氧化氮合酶(inducible NO synthase, iNOS)途径、肌酸途径以及胍丁胺酸和多胺途径。精氨酸代谢的改变是定义巨噬细胞极化的特征之一,M1型炎症巨噬细胞iNOS活性升高,精氨酸转化为NO抑制TCA循环和OXPHOS;相反,在M2型巨噬细胞中,精氨酸被精氨酸酶ARG1代谢分解为鸟氨酸,促进抗炎细胞因子的产生。M1和M2巨噬细胞的极化都依赖于阳离子氨基酸转运蛋白(cationic amino acid transporter 2, CAT2)(Slc7a2)摄取精氨酸,而静息态巨噬细胞通过Slc7a6、Slc7a7系统摄取精氨酸^[42]。Slc7a2的缺失导致巨噬细胞向M2表型极化,机体对炎症性肠病的易感性升高,对利士曼原虫的易感性降低^[43,44]。牛分歧杆菌感染后,DCs的精氨酸转运载体Slc7a1和Slc7a2升高,精

氨酸iNOS代谢途径增强,且该代谢变化与DCs的凋亡相关^[45]。在炎症条件下,DCs在吞噬凋亡细胞时,会上调Slc7a5和Slc7a11的表达以抑制胞葬作用,并抑制伤口的愈合^[46]。与巨噬细胞类似,DCs也可动态利用精氨酸的不同代谢途径,在活化的DCs中,microRNA-155沉默Arg2的表达,且该过程是DCs诱导T细胞启动的先决条件^[47,48]。在肿瘤微环境中,肿瘤浸润树突状细胞耗竭微环境精氨酸,从而抑制CD8⁺ T细胞的增殖,削弱T细胞的抗肿瘤免疫功能^[49]。

静息态和激活的CD8⁺ T细胞的精氨酸转运载体Slc7a3表达较高,但Slc7a3敲除并不影响T细胞的精氨酸摄取、细胞的发育、活化和增殖^[50],这可能是由于Slc7a1和Slc7a2也介导精氨酸的摄取。研究表明,精氨酸缺乏通过激活一般性调控阻遏蛋白激酶2(general controlled non-repressed kinase 2, GCN2)下调T细胞TCR复合物的CD3 ζ 亚基的表达诱导T细胞周期阻滞,抑制T细胞增殖和细胞因子的产生^[51]。精氨酸缺乏导致T细胞CD25和CD69表达下调,mRNA翻译功能受损,从而抑制T细胞增殖和IL-2的产生^[52]。氨基酸代谢产生的副产物氨会损害细胞寿命,CD8⁺ T细胞可通过利用胞质精氨酸代谢途径清除氨,促进CD8⁺ Tm细胞发育^[53],增强CD8⁺ T细胞介导的抗肿瘤活性^[27]。这些研究表明精氨酸在T细胞的增殖、活化和效应功能中至关重要。然而当T细胞激活时,胞内精氨酸iNOS上调,NO积累,从而介导p53聚集和CD95信号促进细胞凋亡,该机制被认为是T细胞的一种自我限制机制^[54]。较早的体内研究表明,精氨酸缺乏抑制骨髓B细胞的发育,降低次级淋巴器官中的B细胞数量,抑制特异性IgA的产生^[55,56]。近期的研究发现,浆细胞摄入亮氨酸和精氨酸等氨基酸激活mTORC1,从而促进抗体的产生^[24]。体内补充精氨酸可促进CD56⁺ NK细胞的细胞毒性和活性,其机制是通过iNOS代谢途径产生的NO促进靶细胞和DNA碎片的溶解,而精氨酸缺乏会限制NK细胞的增殖,抑制IFN- γ 的分泌^[57,58]。

精氨酸是巨噬细胞极化的重要生物标志,在M1和M2巨噬细胞中,精氨酸分别被代谢iNOS和ARG代谢为NO和鸟氨酸调控巨噬细胞功能;在炎症或肿瘤微环境中,DC细胞也可动态利用精氨酸的不同代谢途径,启动T细胞或抑制T细胞的抗肿瘤免疫功能。精氨酸可通过清除氨促进CD8⁺ Tm细胞发育,增强其抗肿瘤活性,精氨酸缺乏将介导细胞周期阻滞和mRNA转

录导致T细胞增殖和功能受损. 此外, 精氨酸也是影响B细胞发育和功能的关键氨基酸.

2.4 色氨酸

色氨酸在体内主要包含犬尿氨酸、5-羟色胺和吲哚代谢3个代谢途径, 吲哚代谢主要由微生物调控^[59]. 肿瘤相关树突状细胞的色氨酸代谢限速酶吲哚胺2, 3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)的表达升高, 导致Treg细胞的分化和抗肿瘤免疫功能的削弱^[60]. 在缺氧条件下, HIF-1 α 通过上调色氨酸、谷氨酰胺和脯氨酸的转运载体Slc36a4和色氨酸分解代谢限速酶IDO1的表达维持NK细胞生理稳态^[61]. 色氨酸可促进巨噬细胞的M1极化, 但色氨酸犬尿氨酸和吲哚代谢途径代谢物作为芳香烃受体(aryl hydrocarbon receptor, AhR)的激动剂, 可通过NF- κ B信号抑制巨噬细胞的M1极化^[62-65]. 吲哚-3-乳酸(indole-3-lactic acid, ILA)(吲哚代谢途径代谢物)通过抑制上皮细胞趋化因子CCL2/7的产生, 抑制促炎巨噬细胞的迁移^[66]. 褪黑素(色氨酸5-羟色胺途径代谢物)可通过褪黑素受体MT1-无活性糖原合成酶激酶(glycogen synthase kinase 3, GSK3) β -热休克因子(heat shock factor, Hsf)1轴, 抑制巨噬细胞干扰素调节因子-7(interferon regulatory factor, IRF-7)的表达和IL-1 β 的产生^[67]. 色氨酸剥夺导致DCs呈现免疫耐受性表型, 高表达抑制性受体免疫球蛋白样转录物(immunoglobulin-like transcript 2, ILT2), ILT3和ILT4, 诱导T细胞向Foxp3⁺Treg细胞分化, 褪黑素^[68]和吲哚丙酮酸(indole-3-propionic acid, IPA)IPA^[69]也具有促进DCs向免疫耐受表型分化的潜在作用, 但色氨酸犬尿氨酸代谢途径的代谢物不影响DCs的表型和抗原呈递能力^[70,71].

芳香烃受体是多种色氨酸代谢物的受体, 通过负调控维甲酸受体相关孤儿受体- γ t(retinoic acid receptor-related orphan receptor- γ t, ROR γ t)抑制Th17细胞的分化^[72]. 色氨酸剥夺通过GCN2上调Slca7a5的表达, 促进naïve CD4⁺ T细胞对犬尿氨酸的摄取, 从而激活AhR, 上调Foxp3的表达, 促进Treg细胞的分化^[73], 但近期的研究表明I3A可通过改变Treg细胞对TGF- β 的感知, 抑制Treg的发育和CD4⁺ T细胞对抗原的识别^[74]. 吲哚代谢途径代谢物吲哚-3-乙醛(indole-3-carboxaldehyde, I3A)可介导AhR促进产IFN- γ 的CD8⁺ T细胞的分化^[75]. 褪黑素也是关键的淋巴细胞调节因子^[76], 体内

研究表明, 褪黑素可介导AMP依赖的蛋白激酶(AMP activated protein kinase, AMPK)/沉默信息调节因子(silent information regulator 1, SIRT1)轴调控Treg/Th17细胞的平衡, 抑制Th17分化, 促进Treg分化^[77]. 有体内研究表明, 色氨酸限制会抑制骨髓B淋巴细胞的发育, 并导致外周B细胞数量减少^[78], 且有研究暗示色氨酸代谢参与B淋巴细胞功能的调控^[79], 但目前仍缺乏色氨酸调控B细胞增殖或功能的直接证据.

总的来说, 目前的研究表明色氨酸可促进巨噬细胞M1极化, 但其下游代谢产物, 如犬尿氨酸、褪黑素和吲哚类代谢物可抑制巨噬细胞的M1极化和迁移. 色氨酸的剥夺或色氨酸代谢产物(褪黑素和吲哚代谢物)均可导致DC细胞和T呈现免疫耐受表型.

3 氨基酸调控免疫细胞命运的分子机制

3.1 氨基酸重塑免疫细胞代谢

免疫细胞在对感染和组织环境变化做出反应时, 其动态激活状态严重依赖于自身的代谢状态. 本团队近年来的研究发现, 巨噬细胞在M1极化时, 丙氨酸、天冬氨酸、谷氨酸、甘氨酸、丝氨酸、苏氨酸、脯氨酸等的代谢和转运也发生改变, 其中, 胞内GABA、天冬氨酸、天冬酰胺、丝氨酸、脯氨酸的含量降低^[34,80], 胞内甘氨酸和甘氨酸代谢物, 如GSH和S-腺苷蛋氨酸(S-adenosyl methionine, SAM)水平升高^[81]. 氨基酸可通过多种途径参与其他的代谢通路^[82], 如嘌呤和嘧啶从头合成需要谷氨酰胺和天冬氨酸^[80]; 谷氨酰胺和谷氨酸可用于增殖活跃的细胞, 作为TCA循环的替代输入物, 用于支持ATP生成或脂肪酸合成^[83]; 其他氨基酸, 包括精氨酸和色氨酸, 通过各种代谢途径以支持髓系细胞和淋巴细胞的增殖、分化和功能(图1)^[54].

在细胞增殖和转录中, 核苷酸是支持DNA和RNA合成的基本底物. 天冬氨酸是次黄嘌呤核苷酸在嘌呤的从头合成中转化为腺嘌呤核糖核苷酸所必需的, 并为嘧啶的从头合成提供碳主链^[84]. 本团队前期的研究发现, 巨噬细胞M1极化时, 胞内核苷酸代谢物含量显著降低, 天冬氨酸可通过重塑细胞天冬氨酸/天冬酰胺/核苷酸代谢促进M1型巨噬细胞促炎因子IL-1 β 的分泌. 蛋氨酸可通过上调巨噬细胞胞内的iNOS活性和ATP酶/ADP酶的活性, 改变细胞氧化还原稳态和嘌呤代谢,

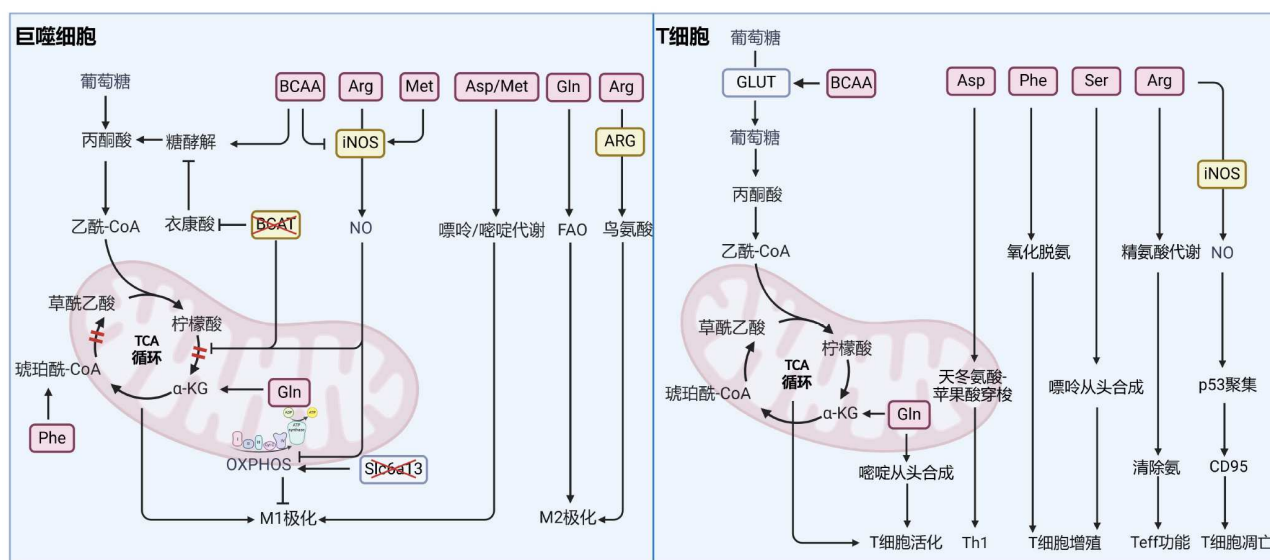


图1 氨基酸通过代谢重塑调控巨噬细胞和T细胞命运. α -KG, α -酮戊二酸; Arg, 精氨酸; ARG, 精氨酸酶; Asp, 天冬氨酸; BCAA, 支链氨基酸; BCAT, 支链氨基酸转氨酶; Gln, 谷氨酰胺; GLUT, 葡萄糖转运体; iNOS, 一氧化氮合酶; Met, 蛋氨酸; NO, 一氧化氮; OXPHOS, 氧化磷酸化; Phe, 苯丙氨酸; Ser, 丝氨酸; TCA, 三羧酸; $\rightarrow$, 促进; $\downarrow$, 抑制

Figure 1 Mechanisms associated with metabolic pathways whereby amino acids influence macrophage and T cell fate. α -KG, α -Ketoglutaric acid; Arg, arginine; ARG, arginase; Asp, aspartate; BCAA, branched chain amino acid; BCAT, BCAA transaminase; Gln, glutamine; GLUT, glucose transporter; iNOS, inducible NO synthase; Met, methionine; NO, nitric oxide; OXPHOS, oxidative phosphorylation; Phe, phenylalanine; Ser, serine; TCA, tricarboxylic acid; $\rightarrow$, promote; $\downarrow$, inhibit

促进巨噬细胞的M1极化^[85,86]. 核苷酸可通过影响细胞周期促进T细胞活化. 丝氨酸通过为甘氨酸和嘌呤的从头合成提供一碳单位支持T细胞增殖^[87]. 谷氨酰胺可为嘧啶提供碳主链, 核苷酸可缓解谷氨酰胺剥夺对T细胞活化的影响, 暗示谷氨酰胺可通过核苷酸代谢支持T细胞活化^[42]. 这些研究表明天冬氨酸和蛋氨酸可通过支持嘧啶和嘌呤的代谢促进巨噬细胞M1极化, 丝氨酸和谷氨酰胺可通过核苷酸代谢促进T细胞的增殖和活化.

氨基酸可通过参与糖酵解、TCA循环和线粒体氧化磷酸化等能量代谢途径调控免疫细胞的命运和功能. 精氨酸通过iNOS途径代谢产生的NO参与了巨噬细胞M1极化期间线粒体电子传递链的动态重塑和TCA循环的改变, 并介导了M1巨噬细胞的细胞毒性和杀菌作用. GABA转运载体Slc6a13的缺失会通过甲基化降低转录因子KID3的表达, 增强OXPHOS相关基因的表达, 从而抑制M1巨噬细胞IL-1 β 的合成和分泌^[34]. BCAA可通过mTORC1/HIF-1 α /糖酵解通路促进巨噬细胞M1极化^[88,89], BCAA可由支链氨基酸转氨酶(BCAA transaminase, BCAT)催化分解代谢为支链酮酸

(branched-chain ketoacids, BCKA); 抑制巨噬细胞BCAT的功能将通过激活核呼吸因子2(nuclear respiratory factor 2, NRF2)信号抑制TCA循环^[90]. 此外, BCAT的抑制还将介导免疫应答基因1蛋白(immune-responsive gene 1 protein)IRG1/衣康酸轴导致巨噬细胞耗氧量和糖酵解减少, 抑制M1巨噬细胞促炎因子的产生^[91]. 苯丙氨酸可介导缬氨酸-琥珀酰-辅酶A轴重塑细胞线粒体代谢, 促进OXPHOS水平, 进而抑制Caspase-1的激活, 降低巨噬细胞促炎因子IL-1 β 和TNF- α 的分泌, 并缓解LPS和多杀性巴氏杆菌血清型A株CQ2感染诱发的炎症反应^[92]. 在活化的T细胞内, 谷氨酰胺由谷氨酰胺脱氢酶(glutamate dehydrogenase, GDH)转化为 α -KG, 从而进入TCA循环为T细胞提供能量^[83]. CD8⁺ T细胞胞内BCAA的富集将上调胞膜葡萄糖转运蛋白1(glucose transporter, GLUT)的表达, 促进细胞对葡萄糖的摄取, 增强糖酵解和OXPHOS水平, 上调CD107A的表达, 促进促炎细胞因子IFN- γ 、TNF- α 的产生^[93]. 细胞因子刺激的NK细胞的激活高度依赖氨基酸, 尤其是通过Slc7a5转运的中性氨基酸, 以支持其cMyc的表达^[25]. cMyc可通过调节糖酵解、戊糖磷酸途径(糖酵

解的分支途径)和OXPHOS等多种代谢过程来促进细胞生长和增殖. TLR7/8配体蛋白RNA(protamine-RNA, pRNA)刺激pDCs后, pDCs摄入高水平的BCAA, 摄入的氨基酸通过促进线粒体生物发生支持脂肪酸氧化(fatty acid oxidation, FAO)和细胞功能^[94].

以上研究表明, 精氨酸和BCAA可通过参与巨噬细胞的TCA循环和糖酵解代谢促进巨噬细胞M1极化, 外源添加苯丙氨酸、抑制GABA的转运或抑制BCAA的分解代谢可介导TCA循环/糖酵解/或OXPHOS抑制巨噬细胞的M1极化. 谷氨酰胺和BCAA可通过TCA循环/糖酵解/或OXPHOS为T细胞提供能量, 促进T细胞的增殖和活化. 在NK细胞和DCs中, 中性氨基酸和BCAA也通过参与能量代谢支持其生长、增殖和功能.

3.2 氨基酸调控信号通路活化

多种信号通路参与免疫细胞的增殖、分化和活化的调控. mTOR是氨基酸的感知中枢, 包含mTOR复合体1(mTORC1)和mTOR复合体2(mTORC2). mTOR通路的激活通常促进合成代谢反应, 促进mRNA翻译, 驱动蛋白质和脂质合成, 以支持免疫细胞的生长、增殖和发挥效应功能^[95](图2). 在巨噬细胞中的研究表明, 丝氨酸、谷氨酸可介导mTOR/HIF-1 α /糖酵解通路, 促进巨噬细胞M1极化^[96,97]. 本团队近期的研究发现, 溶酶体Slc1a2介导溶酶体谷氨酸和天冬氨酸外排维持V-ATP酶的激活, 从而支持巨噬细胞功能和mTOR的活化促进巨噬细胞M1极化^[97]. 在Treg细胞中, 丝氨酸介导mTOR抑制Foxp3的表达及其免疫抑制功能; 但同时, 丝氨酸代谢产生的GSH, 可通过抑制NRF2, 从而

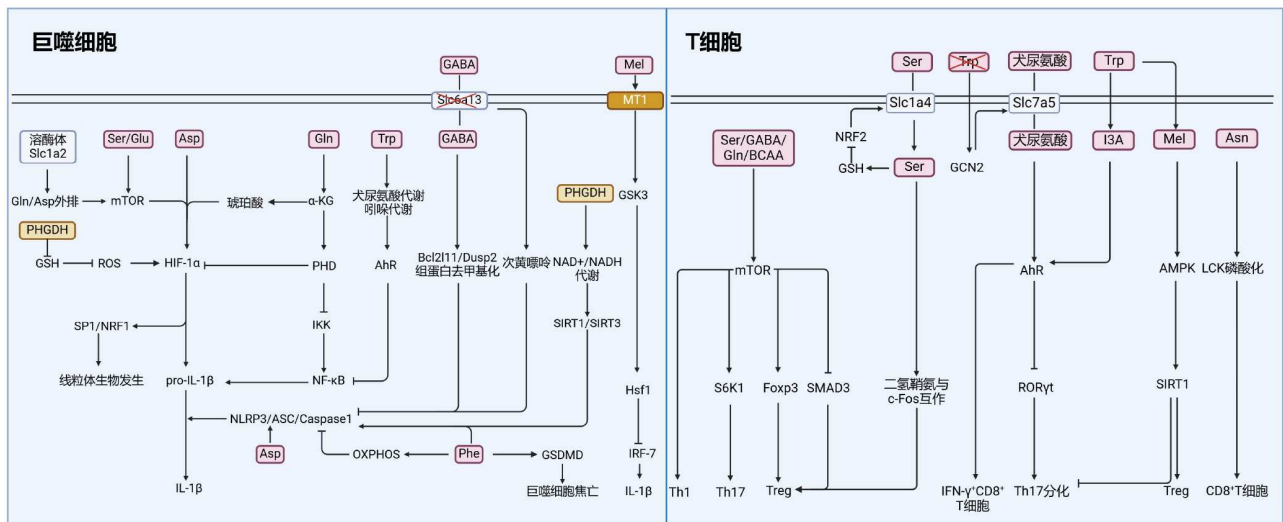


图2 氨基酸通过信号通路调控巨噬细胞和T细胞命运. AhR, 芳香烃受体; AMPK, AMP依赖的蛋白激酶; ASC, 凋亡相关斑点样蛋白; Bcl2l11, 细胞凋亡促进因子; Caspase1, 半胱氨酸天冬氨酸蛋白酶-1; Dusp2, 双特异性磷酸酶; GABA, γ -氨基丁酸; GCN2, 一般性调控阻遏蛋白激酶2; GLS, 谷氨酰胺酶; GSH, 谷胱甘肽; Glu, 谷氨酸; GSDMD, Gasdermin D; GSK3, 无活性糖原合成酶激酶; Foxp3, 叉头样转录因子家族; HIF-1 α , 缺氧诱导因子-1 α ; Hsf1, β -热休克因子; I3A, 吲哚-3-乙醛; IKK, I κ B激酶; IRF-7, 干扰素调节因子-7; LCK, 淋巴细胞细胞特异性蛋白酪氨酸激酶; Mel, 褪黑素; MT1, 褪黑素受体1; mTOR, 哺乳动物雷帕霉素靶蛋白; NAD⁺, 烟酰胺腺嘌呤二核苷酸; NADH, 还原型烟酰胺腺嘌呤二核苷酸; NF- κ B, 核因子 κ B; NLRP3, NOD样受体蛋白3; NRF2, 核呼吸因子2; PHD, 脯氨酸羟化酶结构域; PHGDH, 磷酸甘油酸脱氢酶; ROR γ T, 维甲酸受体相关孤儿受体- γ T; ROS, 活性氧; S6K1, S6激酶; SIRT1/3, 沉默信息调节因子; SMAD3; $\rightarrow$, 促进; $\downarrow$, 抑制

Figure 2 Mechanisms associated with signaling pathways whereby amino acids influence macrophage and T cell fate. AhR, aryl hydrocarbon receptor; AMPK, adenosine 5'-monophosphate(AMP)-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a CARD; Bcl2l11, bcl-2-like protein 11; GSDMD, Gasdermin D; Caspase1, cysteinyl aspartate specific proteinase; Dusp2, dual-specificity phosphatase; GABA, γ -aminobutyric acid; GCN2, general controlled non-repressed kinase 2; GLS, glutaminase; Glu, glutamate; GSH, glutathione; GSK3, glycogen synthase kinase; Foxp3, forkhead transcription factor; HIF-1 α , hypoxia-inducible factor 1 α ; Hsf1, heat shock factor; I3A, indole-3-acetaldehyde; IKK, I κ B kinase; IRF-4, interferon regulatory factor-4; LCK, lymphocyte Cell-Specific Protein-Tyrosine Kinase; Mel, melatonin; MT1, melatonin receptor 1; mTOR, mammalian target of rapamycin; NAD⁺, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide reduced; NF- κ B, nuclear factor kappa-B; NLRP3, NOD like receptor protein 3; NRF2, nuclear respiratory factor 2; PHD, prolyl hydroxylase domain; PHGDH, phosphoglycerate dehydrogenase; ROR γ T, retinoic acid receptor-related orphan receptor- γ T; ROS, reactive oxygen species; S6K1, S6 kinase; SIRT1, silent information regulator 1; $\rightarrow$, promote; $\downarrow$, inhibit

下调丝氨酸转运载体Slc1a4的表达限制丝氨酸的摄入,从而维持Treg细胞的免疫稳态^[98]。Slc1a5缺失T细胞的谷氨酰胺摄取能力受损,mTOR和TCR的激活受损,Th1和Th17分化被阻断^[27]。微生物可通过调控GABA的产生,介导mTORC1-SK激酶(S6 kinase, S6K1)信号作用于Th17免疫细胞促进IL-17的产生和分泌^[38]。GABA转运载体Slc6a13的缺失对T细胞发育和外周T细胞稳态影响较小,但可通过激活GABA-mTOR信号通路促进Th17细胞分化和Th17细胞反应^[37]。Slc3a2介导的BCAA的摄取通过mTOR激活维持Foxp3⁺Treg细胞的增殖状态^[99]。天冬氨酸和谷氨酰胺在天冬酰胺合成酶(asparagine synthetase, ASNS)的作用下代谢为天冬酰胺,ASNS直接参与T细胞的功能调控,在体外激活早期阶段,CD8⁺T细胞的ASNS表达较低,天冬酰胺剥夺导致T细胞的活力、生长和功能受损。但在激活后期(激活24 h以上),TCR介导mTOR激活ASNS,维持T细胞活性和功能^[100]。氨基酸的消耗与浆细胞产生抗体的能力相关,浆细胞摄入亮氨酸和精氨酸等氨基酸激活mTORC1,从而促进抗体的产生;其中,亮氨酸和精氨酸是IgG产量最相关的氨基酸^[24]。艾巴氏病毒(Epstein-Barr virus, EBV)感染人原代B细胞可上调氨基酸转运蛋白Slc1a4和Slc1a5、中性氨基酸转运蛋白Slc7a5和Slc7a11的表达,并导致氨基酸的快速内流,激活mTOR以及支持合成代谢反应^[101]。GABA转运载体Slc6a13也参与B细胞的分化和功能的调控,Slc6a13缺失通过激活GABA-mTORC1信号诱发生发中心B细胞的分化,加剧IgA肾病的临床症状^[41]。支链氨基酸(branched chain amino acid, BCAA),尤其是缬氨酸,可介导mTOR促进单核细胞衍生的树突状细胞(monocyte-derived dendritic cells, moDCs)的成熟,缬氨酸和亮氨酸还可介导mTOR/S6K信号促进DC的IL-12和IFN- γ 产生^[102,103]。这些研究表明,mTOR是一种关键的氨基酸感知受体,在巨噬细胞中mTOR可感知丝氨酸、谷氨酸促进巨噬细胞M1极化;在T细胞中,mTOR可感知丝氨酸和BCAA维持Treg的增殖和免疫抑制功能,感知GABA促进Th17的分化和IL-17的产生;在B细胞中,亮氨酸,精氨酸,中性氨基酸和GABA可激活mTOR,促进抗体的产生;在树突状细胞中,BCAA也通过mTOR促进DCs的成熟和细胞因子的分泌。

在LPS刺激的小鼠巨噬细胞中,谷氨酰胺代谢产

物 α -KG通过脯氨酸羟化酶结构域(prolyl hydroxylase domain, PHD)抑制NF- κ B激酶抑制剂I κ B激酶(I κ B kinase, IKK)的激活,以及通过IKK β 的P191位点的羟基化抑制IKK β 的活化,从而抑制M1巨噬细胞的促炎细胞因子的转录^[19,20]。但也有研究表明,谷氨酰胺被用于细胞中琥珀酸积累,从而稳定缺氧诱导因子HIF-1 α ,特异性促进M1巨噬细胞IL-1 β 的合成^[21]。色氨酸犬尿氨酸和吲哚代谢途径代谢物作为芳香烃受体AhR的激动剂,可通过NF- κ B信号抑制巨噬细胞的M1极化^[62-65]。巨噬细胞中丝氨酸合成的限速酶磷酸甘油酸脱氢酶(phosphoglycerate dehydrogenase, PHGDH)的缺失,会抑制GSH的合成,促进线粒体活性氧的产生,从而激活HIF-1 α 信号,调控核特异性蛋白1(nuclear specificity protein 1, SP1)和核呼吸因子1(nuclear respiratory factor 1, NRF1)的表达,最终增强巨噬细胞的线粒体生物发生^[104]。本团队的研究发现,天冬氨酸也可通过激活HIF-1 α 和NLRP3炎性小体复合体促进M1型巨噬细胞促炎因子IL-1 β 的分泌^[80]。GABA可通过调节Bcl2l11和Dusp2的组蛋白去甲基化,抑制炎性小体NLRP3/ASC/Caspase-1复合体的形成,抑制M1巨噬细胞IL-1 β 的分泌^[35]。GABA转运载体Slc6a13的缺失会通过胞内次黄嘌呤积累抑制巨噬细胞NLRP3/ASC/Caspase-1复合体的形成,抑制M1巨噬细胞IL-1 β 的分泌^[35]。PHGDH通过烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD⁺)/还原型烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide reduced, NADH)代谢提高SIRT1和SIRT3的表达和活性,调控NLRP3和ASC的乙酰化修饰,促进IL-1 β 的成熟^[105]。苯丙氨酸可作用于NLRP3/ASC/Caspase-1复合体,但目前的研究结果并不一致,有研究表明苯丙氨酸可介导缬氨酸-琥珀酰-辅酶A轴重塑细胞线粒体代谢,促进OXPHOS水平,进而抑制Caspase-1的激活,降低巨噬细胞促炎因子IL-1 β 和TNF- α 的分泌;但也有研究发现苯丙氨酸可通过作用于NLRP3/ASC/Caspase1和Gasdermin D(GSDMD),促进巨噬细胞的焦亡和IL-1 β 的释放^[106]。色氨酸代谢产物褪黑素可通过褪黑素受体MT1-无活性糖原合成酶激酶(glycogen synthase kinase 3, GSK3) β -热休克因子(heat shock factor, Hsf)1轴,抑制巨噬细胞干扰素调节因子-7(interferon regulatory factor, IRF-7)的表达和IL-1 β 的产生^[67]。

3.3 氨基酸调控表观遗传修饰

组蛋白和DNA的甲基化修饰可改变细胞DNA的转录机制,从而调控免疫细胞命运(图3). 蛋氨酸是一种含硫必需氨基酸,是蛋白质和SAM合成必需的氨基酸, SAM是DNA、RNA和蛋白质甲基转移酶的通用甲基供体. 巨噬细胞在清除凋亡细胞时,凋亡细胞来源的蛋氨酸可通过转化为SAM,被DNA甲基转移酶3A (DNA methyltransferases 3A, DNMT3A)用于甲基化修饰Dusp4,进而促进巨噬细胞对凋亡细胞的识别和清除^[107]. 丝氨酸可为乙酰化和甲基化提供底物调节表观遗传修饰参与免疫细胞大量的生物过程^[108]. 外源添加丝氨酸可通过促进SAM合成以介导H3K27me3上调胰岛素样生长因子(insulin-like growth factor 1, IGF1)的表达, IGF1介导p38-酪氨酸激酶(tyrosine-protein kinase 2, JAK)-信号转导及转录激活蛋白(signal transducer and activator of transcription, STAT)轴促进巨噬细胞的M1极化,还可通过H3K36me3修饰直接上调IL-1 β 等促炎细胞因子mRNA的表达^[96,109~111]. PHGDH是丝

氨酸合成的限速酶, PHGDH通过NAD⁺/NADH代谢提高SIRT1和SIRT3的表达和活性,进而介导TLR-4的H3K9/27的乙酰化上调IL-1 β 的mRNA表达,并介导炎性小体复合体NLRP3的K21/22/24和ASC的K21/22/24位点的乙酰化修饰,促进IL-1 β 的成熟^[105]. 在巨噬细胞成熟阶段, GABA可通过增强琥珀酸-黄素腺嘌呤二核苷酸(flavin adenine dinucleotide, FAD)-赖氨酸特异性去甲基化酶1(Lysine-specific demethylase 1, LSD1)信号通路介导的去甲基化修饰,减少NLRP3/ASC/Caspase-1复合体的形成,从而抑制M1巨噬细胞IL-1 β 的分泌^[35]. GABA转运载体Slc6a13缺失促进巨噬细胞胞内次黄嘌呤的积累,而且通过甲基化降低转录因子KID3的表达,增强了OXPHOS相关基因的表达,从而抑制M1巨噬细胞IL-1 β 的合成和分泌^[34]. 谷氨酰胺分解代谢产生的 α -KG可通过参与FAO和Jumonji结构域依赖的H3K27去乙酰化促进巨噬细胞M2极化^[19]. 总的来说,在巨噬细胞内,蛋氨酸和丝氨酸可通过促进SAM的产生提供甲基供体,介导甲基化促进巨噬细胞的M1

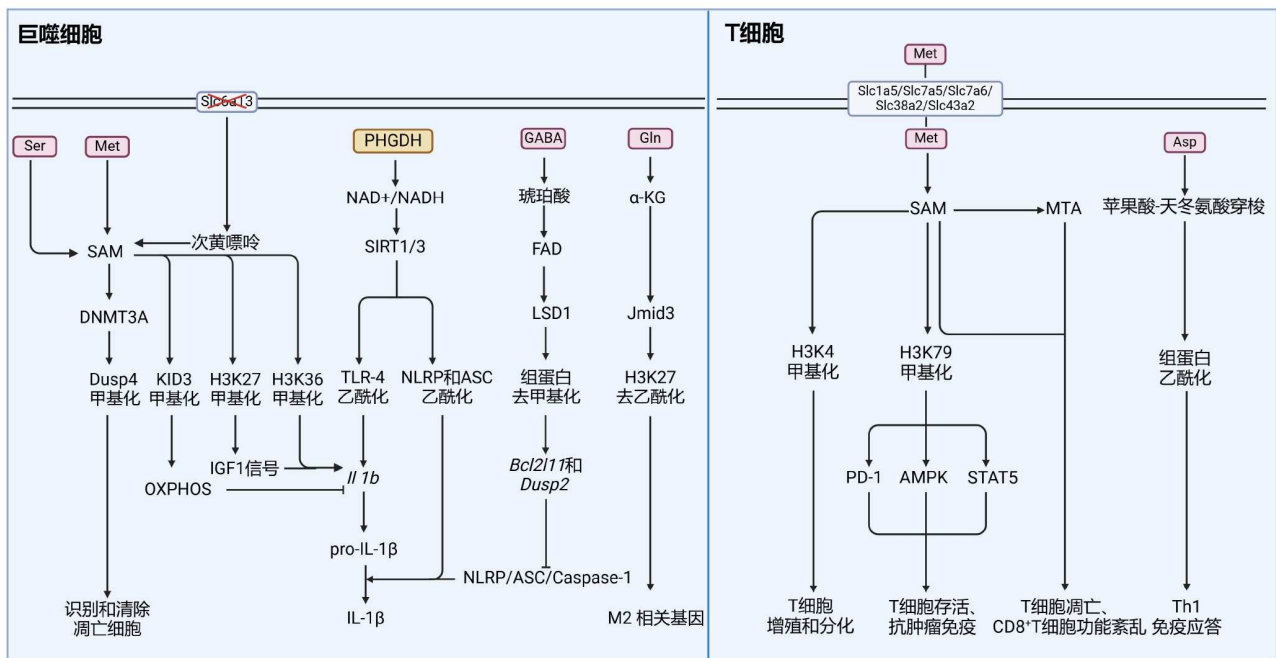


图3 氨基酸通过表观遗传修饰对免疫细胞的调控. DNMT3A, DNA甲基转移酶3A; FAD, 黄素腺嘌呤二核苷酸; IGF1, 胰岛素样生长因子; Jmjd3, Jumonji结构域; LSD1, 赖氨酸特异性去甲基化酶1; MTA, 甲硫基腺苷; PD-1, 程序性死亡受体1; SAM, S-腺苷蛋氨酸; STAT5, 信号转导及转录激活蛋白; TLR-4, Toll样受体4; $\rightarrow$, 促进; $\dashv$, 抑制

Figure 3 Mechanisms associated with epigenetic modifications whereby amino acids influence macrophage and T cell fate. DNMT3A, DNA methyltransferase 3A; FAD, flavin adenine dinucleotide; IGF1, insulin-like growth factor; Jmjd3, Jumonji domain-containing; LSD1, Lysine-specific demethylase 1; MTA, 5-methylthioadenosine; PD-1, programmed death receptor 1; SAM, S-Adenosyl methionine; STAT5, signal transducer and activator of transcription-5; TLR-4, Toll-like receptors-4; $\rightarrow$, promote; $\dashv$, inhibit

极化; 丝氨酸合成的限速酶PHGDH可介导TLR-4和NLRP3/ASC/Caspase-1炎性小体的乙酰化, 促进M1巨噬细胞IL-1 β 的合成和成熟; 而GABA转运体Slc6a13的抑制, 通过转录因子KID3的甲基化促进巨噬细胞的OXPHOS, 从而抑制M1巨噬细胞IL-1 β 的分泌; 谷氨酰胺通过组蛋白的去乙酰化促进巨噬细胞的M2极化。

与静息态T细胞相比, 抗原激活的T细胞胞膜蛋氨酸转载体Slc1a5、Slc7a5、Slc7a6、Slc38a2上调, 从而摄入蛋氨酸获得甲基供体, 驱动T细胞的核苷酸甲基化和遗传修饰重编程, 调控T细胞的增殖和分化^[112]。蛋氨酸剥夺降低Th17细胞中的SAM水平和组蛋白H3K4甲基化水平从而抑制Th17细胞的增殖和细胞因子的产生^[113]。人和小鼠肿瘤浸润CD8⁺ T细胞中Slc43a2表达降低, 导致T细胞中蛋氨酸和SAM水平降低, H3K79me2和STAT5表达受损, 细胞存活和功能降低^[114]。在肿瘤微环境中, 蛋氨酸剥夺导致的H3K79me2降低, 诱导CD4⁺ T细胞AMPK下调和PD-1上调损害T细胞的抗肿瘤免疫功能^[115]。但另一项在肝癌中的研究发现蛋氨酸通过5-甲基硫腺苷(5-methylthioadenosine, MTA)和SAM驱动T细胞耗竭和CD8⁺ T细胞功能紊乱^[116]。在Th1细胞分化和增殖过程中, 线粒体苹果酸-天冬氨酸穿梭和柠檬酸输出对组蛋白乙酰化和Th1细胞的增殖至关重要, 对苹果酸-天冬氨酸穿梭相关的转载体或酶的抑制都将导致细胞H3K9乙酰化水平的降低, 抑制Th1细胞IFN- γ 的产生^[117]。这些研究表明, 在活化的T细胞中, 其蛋氨酸转载体的表达上调, 从而摄取蛋氨酸获得甲基供体, 从而驱动T细胞的分化, 支持其效应功能, 但在某些特殊的微环境下(如肝癌), 蛋氨酸可能会介导甲基化导致T细胞的功能紊乱。此外, 天冬氨酸可通过线粒体苹果酸-天冬氨酸穿梭, 促进组蛋白的乙酰化, 支持Th1细胞的增殖和功能。

4 展望

氨基酸不仅可作为蛋白质的基本合成单元维持动物的生长和发育, 还可通过多种途径调控断奶仔猪肠道免疫功能。本文总结了氨基酸对断奶仔猪肠道免疫

功能的调控作用和谷氨酰胺、GABA、精氨酸和色氨酸调控免疫细胞命运的作用机制, 并系统总结了氨基酸介导免疫细胞代谢、信号通路活化和表观遗传修饰等途径调控免疫细胞命运的分子机制, 为解析氨基酸的免疫调节机制, 通过营养策略调控仔猪免疫应答, 增强仔猪抗病能力提供了理论基础。

尽管近年来营养代谢的免疫调节作用得到了极大的关注和发展, 但氨基酸对猪免疫细胞的命运决定研究领域仍存在较大发展空间, 主要包括: (1) 目前关于免疫代谢相关的研究主要以小鼠和人的免疫细胞为模型, 但猪和小鼠及人的免疫系统结构和营养代谢规律存在较大差异, 以小鼠和人为模型得出的研究结论在畜牧业中的参考价值有限。猪原代免疫细胞分离成本较高, 猪免疫细胞系较少, 且缺乏猪免疫细胞培养相关的细胞因子和生长因子, 限制了氨基酸对猪免疫细胞命运调控机制的研究领域的发展; (2) 目前关于免疫代谢的研究集中于巨噬细胞和T细胞, 且关于巨噬细胞的研究大多集中于M1巨噬细胞, 氨基酸对其他免疫细胞(如DCs、B细胞、NK细胞和肥大细胞等)命运的调控作用和分子机制研究较少; (3) 肠道微生物介导的氨基酸代谢(如色氨酸、精氨酸和BCAA)也在多种疾病的预防和治疗中发挥关键作用, 但肠道微生物介导的氨基酸代谢对猪免疫细胞的命运调控仍有待揭示; (4) 免疫细胞在不同的免疫应答阶段的细胞状态和效应功能存在差异, 如在病原菌感染前期, 免疫系统以促炎免疫应答为主, T细胞分化为Th1细胞, 巨噬细胞极化为促炎的M1巨噬细胞, 主要发挥识别和清除病原菌的效应功能。在病原菌感染后期, 以抗炎免疫应答为主, T细胞分化为Th2细胞, 巨噬细胞极化为抗炎的M2巨噬细胞, 主要发挥促进组织修复的效应功能。但氨基酸对不同状态的免疫细胞的调控作用具有较大差异, 因此, 在开展施展营养策略调控猪免疫系统功能相关研究时, 可将病原感染仔猪模型分为不同的阶段实施进行精准饲喂, 探究不同状态下断奶仔猪的营养需要, 并在养殖生产中区分腹泻仔猪和未腹泻仔猪, 实施不同的营养调控策略, 从而高效地增强仔猪的抗病能力, 促进病猪生理健康的恢复。

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Amino acids in fate decision of porcine immune cells

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Amino acids play a key role in the proliferation, development, and immune response of immune cells. This review summarizes the effects of amino acids on intestinal immune function of piglets, and the mechanism of glutamine, γ -aminobutyric acid, arginine and tryptophan in regulating immune cell fate by remodeling cellular metabolism, activation of signal pathways and epigenetic modification. This study provides a theoretical basis for improving the intestinal immune function of piglets through nutritional strategy.

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