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评 述

氨基酸感知系统mTORC1和GCN2调控机体免疫细胞发育、分化及功能的作用机制

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摘要 氨基酸感知系统感知细胞内外氨基酸水平, 不仅能够调节蛋白质的合成和降解, 还参与调控机体免疫细胞分化及功能. mTORC1和GCN2是真核生物体主要的氨基酸感知系统的组成部分, 本文简要综述了mTORC1和GCN2感知氨基酸水平的机制, 着重探讨了mTORC1和GCN2调控机体免疫细胞发育、分化和功能的研究进展及其在常见免疫相关疾病中的功能, 以期为预防或治疗常见免疫疾病提供新的思路和依据.

关键词 氨基酸, 免疫代谢, mTORC1, GCN2, 炎症

生命体通过感知环境中营养水平动态变化, 使营养物质的供应与机体生长发育的需要相协调. 氨基酸是蛋白质合成及细胞生长的基本单位, 也是维持细胞稳态的重要营养物质. 氨基酸感知系统能够感知细胞内外氨基酸水平, 调节蛋白质的合成与降解. 关于感知系统的组成, 原核生物主要通过化学受体和胞内传感器感知胞内外氨基酸水平的波动, 而真核生物不仅进化出了更复杂的胞外受体或氨基酸感受通路(如在酵母中的胞外氨基酸感知通路Ssy1-Ptr3-Ssy5(SPS)), 还含有两条重要的胞内氨基酸感知通路, 即哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)通路以及一般性调控阻遏蛋白激酶2(general control non-derepressible 2, GCN2)通路[1]. 这两条信号通路协同维持机体氨基酸的平衡. 当氨基酸充足时, mTORC1促进蛋白质合成, 同时抑制蛋白质分解, 从而降低胞内氨基酸的浓度; 当氨基酸缺乏或不足时, GCN2促进氨基酸的转运和合成, 从而恢复胞内氨基酸水平[2].

近年来, 研究表明mTORC1和GCN2对免疫细胞命运(如发育、分化、功能)的调节至关重要. 本文首先简述了mTORC1和GCN2在氨基酸感知中的研究进展, 随后重点阐述了mTORC1和GCN2在调控免疫细胞发育、分化和功能中的作用, 最后探讨了mTORC1和GCN2在免疫相关疾病的潜在作用, 为预防或治疗常见免疫疾病提供新的思路和依据.

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1　氨基酸感知系统mTORC1

mTOR是生命体调控细胞生长代谢的核心调节器, 包括mTORC1和mTORC2两种多蛋白复合物, 可通过蛋白组成和效应底物的不同区分二者[3].

mTORC1与机体多种合成代谢反应密切相关, 其重要特征之一是可感知并响应胞内外营养水平改变, 如ATP水平变化、氨基酸含量波动等[1,4]. 在除*S. cerevisiae*酿酒酵母外的绝大多数真核生物中, mTORC1主要由mTOR、mTOR调控相关蛋白(regulatory-associated protein of mTOR, Raptor)和哺乳动物SEC13蛋白8致死因子(mammalian lethal with sec-13 protein 8, mLST8/GβL)三种核心蛋白构成[1,4~6], 同时还包括多种结合蛋白, 如40 kD富含脯氨酸的Akt底物(proline-rich Akt/PKB substrate 40 kD, PRAS40)和包含DEP域的mTOR互作蛋白(DEP-domain containing mTOR-interacting protein, Deptor)等[7,8].

由氨基酸介导的mTORC1激活涉及多种途径[2]. 有研究表明, 氨基酸激活mTORC1起始于溶酶体内部并主要依赖于溶酶体膜上的多蛋白复合体和两种不同的小GTP酶, 包括Rag鸟苷三磷酸酶(Rag guanosine triphosphatases, Rag GTPases或Rags)以及脑Ras同源蛋白(Ras homolog enriched in brain, Rheb GTPases或RHEB)[1,9]. 实际上, 这两种不同的小GTP酶都属于Ras样GTPases超家族并以异源二聚体的形式存在[1,10], 但二者组成和分工不同: Rags由两个GTPase亚基组成(RagA或RagB与RagC或RagD结合)并通过整合氨基酸信号调控mTORC1亚细胞定位; RHEB由Rheb1和Rheb2两个亚基组成并通过整合生长因子和能量水平调控mTORC1活性[1,8]. 而溶酶体膜上的蛋白复合体包括Ragulator复合物和液泡ATP酶(vacuolar H+-ATPase, v-ATPase)复合物[9]. Ragulator复合物主要连接v-ATPase和Rags, 同时将Rags锚定于溶酶体上, 与其在溶酶体表面形成聚合体作为mTORC1转位到溶酶体上的停留位点[9,11].

氨基酸进入溶酶体后不断积累, 被v-ATPase所感知, 通过Ragulator与v-ATPase互作使氨基酸信号得以传递并激活Rags, 活化的Rags与mTORC1的Raptor亚基结合, 从而将mTORC1靶向招募到溶酶体上[6,9,12,13]. mTORC1易位到溶酶体上后, mTORC1可以与被生长因子激活的RHEB相互作用而被激活[1]. mTORC1激活后通过磷酸化翻译起始相关的两个关键蛋白: p70核糖体S6蛋白激酶K1(p70 ribosomal protein S6 kinases 1, S6K1)和真核翻译起始因子4E结合蛋白1(eukaryotic translation initiation factor 4E-binding proteins 1, 4E-BP1)来刺激生物大分子的合成, 包括蛋白质合成[3,8]. 在非激活状态下, 4E-BP1与真核生物翻译启动因子4E (eukaryotic translation initiation factor 4E, eIF4E)紧密结合, 导致5′末端帽状结构区的mRNA翻译被抑制[4]. 而当mTORC1被激活后, 磷酸化4E-BP1, 使其与eIF4E解离; 同时直接磷酸化S6K1, 促进核糖体的生物发生并启动翻译[6].

氨基酸感知蛋白也参与了mTORC1活性的调控[2]. 氨基酸感知蛋白和Rags发挥作用依赖于GATOR2 (GAP activity towards the Rags 2)-GATOR1(GAP activity towards the Rags 1)复合物(其中GATOR1包含DEPDC5, NPRL2和NPRL3; GATOR2包含Mios, WDR24, WDR59, Seh1L和Sec13)[14]. GATOR1以GTP酶激活蛋白(GTPase activating protein, GAP)形式与Rags互作, 抑制mTORC1, 而GATOR2可抑制GATOR1的活性, 从而正向调控mTORC1[14,15]. 如亮氨酸和精氨酸浓度较高时, 会分别与各自的感受蛋白相结合(亮氨酸感受蛋白为Sestrin-2: encoded by SESN2; 精氨酸感受蛋白为CASTOR1: cytosolic arginine sensor for mTORC1 subunit 1), 从而阻断感受蛋白对GATOR2的结合和抑制, 因此GATOR2能结合并抑制GATOR1, 最终激活mTORC1[15~17]. 最新研究发现, SAR1基因同源物B(SAR1 gene homolog B, SAR1B)也可作为亮氨酸感知受体[18]. 类似地, 甲硫氨酸缺乏导致*S*-腺苷甲硫氨酸(*S*-adenosyl-L-methionine, SAM)含量减少, 甲硫氨酸感知蛋白*S*-腺苷甲硫氨酸感应器(*S*-adenosylmethionine sensor, SAMTOR)会与GATOR1结合, 进而抑制mTORC1[19,20]. 位于溶酶体表面的溶质载体蛋白家族38成员9(solute carrier family 38, member 9, SLC38A9)能够感知并转运溶酶体内的精氨酸和谷氨酰胺以激活mTORC1, 这个感知蛋白的发现也有力地说明了mTORC1在溶酶体上能由内而外感知氨基酸[9,16](图1). 此外, 值得注意的是, 巨胞饮降解蛋白产生的氨基酸可通过不依赖于GATOR-Rags途径调控晚期体内mTORC1活性[21].

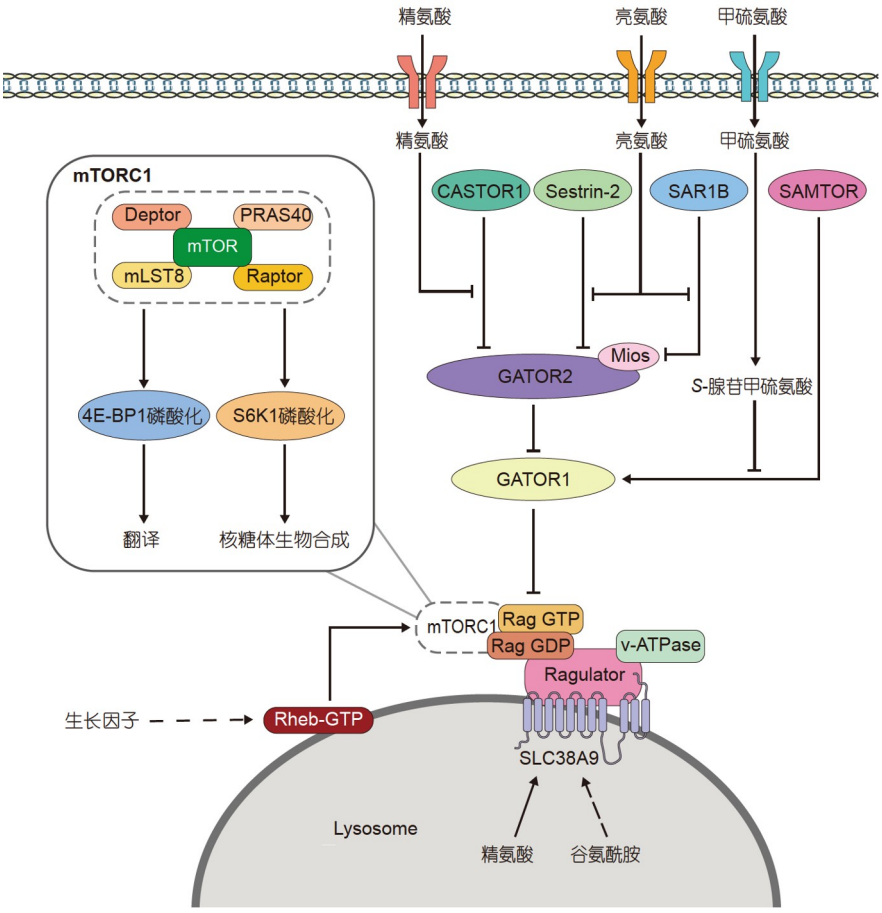

图 1 mTORC1通过不同的机制感知氨基酸浓度

Figure 1 mTORC1 senses amino acid concentrations through various mechanisms

2 氨基酸感知系统GCN2

GCN2通路是酵母和哺乳动物中重要的氨基酸感知系统，主要参与氨基酸限制条件下的代谢反应[22]. 当氨基酸浓度较低或缺失时, 细胞内空载的tRNA积累并与GCN2结合，使GCN2发生二聚化而被激活，促使eIF2α在51位点的丝氨酸处发生磷酸化而失活, 减少翻译起始所需的eIF2, 从而抑制蛋白质合成; 同时也特异性地上调与氨基酸缺乏有关的转录因子ATF4，增强自噬和氨基酸转运与代谢相关基因(如氨基酸合成酶和转运载体、氨基酸酰基tRNA合成酶等)的表达[2,23,24]. 这种调节机制能在营养匮乏的条件下限制细胞对氨基酸的消耗，增加氨基酸周转和合成以满足机体的需求[24]. 除了参与调节氨基酸代谢，GCN2-ATF4通路还参与调节氨基酸缺失诱导的其他反应，比如亮氨酸缺乏导致的白色脂肪褐色化反应[25].

3 氨基酸感知系统对免疫细胞发育、分化和功能的调控

3.1 mTORC1对免疫细胞发育、分化和功能的调控

(1) mTORC1调控中性粒细胞趋化和功能. 中性粒细胞来源于骨髓造血干细胞, 表达IgG Fc受体, 具有很强的变形运动和穿越毛细血管壁的能力[26]. 激活的中性粒细胞形成胞外陷阱(neutrophil extracellular trap, NET)参与捕获和杀灭病原菌，而NADPH氧化酶产生的ROS和自噬是影响NETs形成的决定因素[27,28]. mTORC1作为调节胞内代谢和自噬的关键信号通路, 对中性粒细胞增殖、分化和功能有重要的作用[27].

当mTORC1被抑制时，中性粒细胞自噬小体形成加速，影响ROS产生和NETs释放[28]. 此外，抑制mTORC1或敲除其下游低氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)会抑制脂多糖刺激下的中性

粒细胞NETs的形成并降低其抗菌活性[29]. mTORC1被激活后, 通过ATP-P2Y2受体(识别ATP和其他核苷酸的受体)通路引起中性粒细胞的趋化反应; 雷帕霉素抑制mTORC1活性则会降低线粒体中ATP的释放, 最终影响中性粒细胞的趋化作用[27]. 此外, mTORC1还调节NF-κB的磷酸化, 从而影响中性粒细胞环氧合酶2、前列腺素以及炎性因子(如IL-6, IL-8和TNF-α)的产生[30,31].

综上所述, mTORC1参与中性粒细胞的趋化作用、炎症反应以及NETs的形成. 尽管雷帕霉素在体内外能抑制嗜酸性粒细胞分化和功能[32], 但mTORC1在嗜酸或嗜碱性粒细胞中的作用仍需进一步研究.

(2) mTORC1调控NK细胞发育、增殖、活化和功能. 自然杀伤细胞(natural killer, NK)属于先天淋巴细胞, 产生IFN-γ以及颗粒酶B, 具有抗菌和免疫调节功能[33]. 小鼠mTOR缺失时, NK细胞发育相关因子(如Eomes, T-bet)表达下降, 因此骨髓中NK细胞分化受阻和NK细胞数量减少[34], 表明mTOR信号对NK细胞发育至关重要. 同时, 胞内mTORC1信号也影响NK细胞的增殖, 如雷帕霉素处理能抑制NK细胞从G1期到S期[35]. 当NK细胞活化时, 胞内mTORC1-Akt信号通路被激活, 上调淋巴细胞功能相关抗原1(lymphocyte function-associated antigen 1, LFA-1)整合素的表达, 从而影响NK细胞活化[36]. 活化的NK细胞还依赖于mTORC1上调葡萄糖摄取以及糖酵解的速率, 影响其胞内代谢重编程[33,37]. 另外, mTORC1信号对NK细胞IFN-γ分泌和抑菌功能也有作用[38]. 其机制可能依赖于mTORC1介导的糖酵解: 正常情况下, 糖酵解酶GAPDH与IFN-γ mRNA的3′UTR富AU元件结合并抑制IFN-γ的表达; 而糖酵解速率增加时, GAPDH参与糖酵解, 从而减少与IFN-γ mRNA的结合[33]. 因此, mTORC1作为NK细胞发育、增殖、活化以及功能的关键调节因子, 对维持NK细胞介导的免疫反应具有重要作用.

(3) mTORC1调控巨噬细胞成熟、极化和功能. 巨噬细胞由单核细胞成熟而来, 在不同的刺激下极化为M1型或M2型巨噬细胞, 具有抵抗病原菌感染和促进组织修复等功能. mTORC1通路与巨噬细胞成熟有关, 且影响巨噬细胞功能. 例如, Rheb1的缺失抑制单核细胞向巨噬细胞成熟, 并影响巨噬细胞的吞噬功能[39]. 结节性硬化症复合物(tuberous sclerosis complex, TSC)由TSC1, TSC2和Tre2-Bub2-Cdc16-1结构域家族成员7(Tre2-Bub2-Cdc16-1 domain family member 7, TBC1D7)组成, 负向调控胞内mTORC1信号[40]. 敲除TSC1, 促进M1型巨噬细胞极化, 降低M2型巨噬细胞极化[41]. 另外, 抑制AKT1时促进巨噬细胞M1型极化, 而抑制AKT2时促进M2型极化[42]. 这些结果表明, mTORC1信号与巨噬细胞极化相关. 此外, 本课题组前期研究发现, 阻断mTORC1信号抑制M1巨噬细胞极化[43]. 值得注意的是, 敲除TSC2可通过细胞周期蛋白依赖性激酶4(cyclin-dependent kinase 4, CDK4)促进代谢重编程, 促进巨噬细胞增殖[44], 表明mTORC1信号也可能影响巨噬细胞增殖. 以上结果表明, 巨噬细胞成熟、极化和功能都可能受mTORC1影响, 然而巨噬细胞具有明显的异质性, 因此mTORC1信号通路对不同来源的巨噬细胞或者不同微环境中巨噬细胞命运的影响需要深入探究.

(4) mTORC1调控T细胞迁移、分化和功能. T细胞在胸腺中发育成熟, 然后循环于外周血液和淋巴组织, 在受到抗原的刺激下分化为效应T细胞和记忆T细胞[45]. mTORC1通路与T细胞外周迁移以及凋亡相关[46]. T细胞迁移需要CC-趋化因子受体7(CC-chemokine receptor 7, CCR7), CD26L以及氨醇-1-磷酸受体1(sphingosine-1-phosphate receptor 1, S1PR1)介导[47]. Krüppel样因子2(Krüppel-like factor 2, KLF2)调控CCR7, CD62L和S1PR1基因的表达[47]. mTORC1信号通路可能是下调KLF2的关键, 并能在免疫激活期间抑制趋化因子和黏附受体网络的表达[48], 从而影响T细胞的迁移. 除了KLF2, mTORC1也可通过T-bet介导的促炎趋化因子(如CXC趋化因子受体3(CXC-chemokine receptor 3, CXCR3))的表达来调控T细胞的迁移[49]. mTORC1通路还调控T细胞分化和功能. $CD4^+$ T细胞分化时受到微环境中细胞因子等因素的影响, 可分化成不同的亚型(如Th1, Th17, Treg)[45]. 例如, 初始$CD4^+$ T细胞在IFN-γ和IL-12的刺激下分化为Th1细胞(T helper 1 cells, Th1), 在IL-23,TGF-β和IL-6等刺激下分化为Th17细胞[45]. mTORC1对Th细胞亚型的分化至关重要. 例如, mTORC1通过细胞因子信号转导抑制因子3(suppressor of cytokine signalling 3, SOCS3)、IL-12R信号等促进Th1细胞分化[46]; 通过S6K1、生长因子独立蛋白1(growth factor-independent protein 1, Gfi1)、HIF-1α等促进Th17分化[50,51]. $CD8^+$ T细胞依赖于转录

因子T-bet和Eomes可分化为效应T细胞和记忆T细胞. mTORC1调控T-bet和Eomes的表达, 从而影响效应$CD8^+$ T细胞和记忆$CD8^+$ T细胞生成, 抑制mTORC1后, 引起T-bet的减少以及Eomes的增加从而促进记忆性T细胞的产生[52]. 此外, 产肠毒素大肠杆菌(*Enterotoxigenic Escherichia coli*., ETEC)感染导致的氨基酸含量变化会激活mTORC1进而促进Th17分化和增强IL-17的表达, 表明mTORC1可以通过调控Th17的分化和IL-17参与维持肠道免疫稳态[51]. 综上所述, mTORC1在T细胞的迁移、分化及功能上发挥重要的调控作用.

(5) mTORC1调控B细胞发育和功能. B细胞在骨髓中发育, 后进入外周分化为浆细胞和记忆B细胞. 早期pro-B细胞发育与胞内糖酵解水平有关, mTORC1在早期pro-B细胞发育过程中高度活化并刺激糖酵解发生[53]. 在小鼠早期发育B细胞中敲除Raptor, 氧化磷酸化和糖酵解显著降低, 导致早期B细胞发育受阻[54]. 此外, mTORC1在类转换过程中诱导胞嘧啶脱氨酶AID选择IgG1重链区域, 促进生发中心形成, 体细胞超突变和记忆性B细胞生成[55]. 本课题组最新研究发现, GAT2(GABA转运载体)敲除也会通过mTORC1影响生发中心B细胞的功能(未发表数据). 因此, mTORC1在早期B细胞发育中具有重要的调控作用, 对于B细胞功能也至关重要.

3.2 GCN2调控免疫细胞增殖、分化和功能

目前关于GCN2与免疫细胞增殖、分化和功能的研究较少, 少量的报道主要集中在T细胞上, 因此本部分主要总结GCN2对T细胞命运的影响. GCN2在ISR中处于核心地位, ISR导致早期T细胞活化过程中细胞周期的停滞, 进而导致T细胞功能受损[56]. 除此之外, GCN2也参与$CD4^+$ T细胞的分化, 例如, 缺失GCN2抑制Th9分化[57], 激活GCN2促进Treg分化[58]. 另外, 完整的GCN2感知系统对于维持$CD8^+$ T细胞的存活和功能至关重要[59]. 值得注意是, 当GCN2缺失时, 其他免疫细胞亚群(如$CD4^+$ T细胞、$CD19^+$ B细胞和$CD11b^+$白细胞)数量也发生显著变化[60], 提示GCN2对其他阶段的T细胞甚至其他类型的免疫细胞命运(如巨噬细胞和B细胞)也具有重要的调控作用. 然而, 关于GCN2信号对上述类型的免疫细胞命运的影响有待深入的研究.

4 氨基酸感知系统与免疫相关疾病

4.1 氨基酸感知系统与自身免疫性疾病

自身免疫性疾病是机体免疫系统反应异常, 将自身正常细胞当作外来抗原加以攻击. 常见的自身免疫性疾病, 包括系统性红斑狼疮(systemic lupus erythematosus, SLE)、类风湿性关节炎(rheumatoid arthritis, RA)、Ⅰ型糖尿病、自身免疫性甲状腺炎、原发性胆汁性肝硬化等[61]. 本部分将以SLE为例重点探讨mTORC1和GCN2信号在自身免疫性疾病中的作用.

SLE是典型的自身免疫性疾病, 主要表现为T细胞、B细胞增殖分化异常, 产生大量的自身抗体, 影响体内主要器官, 进而威胁生命. 目前的研究结果支持SLE患者中mTORC1被过度激活, 进而促进了SLE的发展. 例如, 在SLE小鼠模型中, mTORC1被激活后导致浆细胞数量增加、B细胞分化异常、自身抗体水平提高, 从而促进SLE的发展[62]; mTORC1在SLE Treg细胞内被IL-21激活, 进而抑制$CD4^+$ T细胞向Treg细胞的分化[63]; 在SLE患者中发现钙调蛋白激酶Ⅳ(calmodulin kinase Ⅳ, CaMK Ⅳ)增强mTORC1的活性, 刺激IL-4和IL-17的产生[64,65]. 凋亡细胞是SLE自身抗原的来源, 因此凋亡细胞的增加和清除系统的缺陷是SLE发生和发展的主要驱动力之一[66]. 凋亡细胞诱导色氨酸代谢酶IDO在巨噬细胞中表达, 耗竭胞内色氨酸水平, 从而激活GCN2; 而GCN2激活后能调节巨噬细胞因子(如IL-10和TGF-β)的分泌, 降低自身抗体的产生, 有效抑制炎症性自身免疫[67]. 因此, 靶向GCN2和mTORC1可能有效干预自身免疫疾病的病程.

4.2 氨基酸感知系统与免疫缺陷相关疾病

免疫缺陷相关疾病主要分为原发性免疫缺陷病和获得性免疫缺陷病. 原发性免疫缺陷主要与遗传相关; 而获得性免疫缺陷是由于严重感染所引起, 包括艾滋病病毒感染(human immunodeficiency virus type-1, HIV-1)、巨细胞病毒感染、风疹、麻疹等. 本部分主要以HIV为例简要阐述mTORC1和GCN2信号在免疫缺陷相关疾病的作用.

HIV-1感染后, mTORC1被HIV-1的转录激活剂(transactivator of transcription, Tat)、包膜糖蛋白复合物(envelope glycoprotein complex, Env)等激活, 从而促进病毒整合和复制[68]. 另外mTORC1激活后导致$CD4^+$

T细胞耗竭和$CD4^+$ T细胞功能丧失. 具体机制如下: mTORC1通过CXCR4或CCR5[69]或者p53[70]诱导$CD4^+$ T细胞凋亡; 而HIV-1阴性的$CD4^+$ T细胞凋亡是导致患者$CD4^+$ T细胞耗竭的主要原因. HIV-1还以mTORC1依赖的形式诱导巨噬细胞、树突状细胞自噬活性下调, 进而损害机体免疫功能[71,72]. 在HIV-1病毒感染后期, 大量的病毒mRNA被翻译成蛋白质, 耗竭胞内的氨基酸水平从而激活GCN2, 随后磷酸化eIF2α, 进而抑制病毒蛋白质的合成; 但随着病毒RNA的翻译, HIV-1通过招募蛋白裂解酶使GCN2失活, 从而促进病毒的复制[73]. 由此可见, mTORC1和GCN2信号在HIV感染或者其他免疫抑制相关疫病中具有重要的作用.

5　总结与展望

综上所述, 宿主通过mTORC1和GCN2感知体内氨基酸水平, 调节蛋白质合成和分解. 胞内氨基酸浓度升高时, mTORC1被激活促进蛋白质合成, 从而降低胞内氨基酸水平; 而氨基酸缺乏时, mTORC1被抑制, GCN2被激活, 编码氨基酸合成酶和转运载体, 促进氨基酸合成和转运, 从而恢复胞内氨基酸水平. 目前发现了精氨酸、亮氨酸、甲硫氨酸以及谷氨酰胺的感知蛋白, 而其他氨基酸的感知蛋白尚不清楚.

mTORC1和GCN2在免疫细胞命运调控中有重要的作用. 目前关于mTORC1与中性粒细胞、NK细胞、巨噬细胞、T细胞以及B细胞的命运研究较多, 而对GCN2信号关注较少. 虽然有研究发现, 在亮氨酸缺失的前提下, GCN2可作为mTORC1信号通路上游的抑制因子[74], 然而GCN2能否在特定的条件下通过mTORC1调控免疫细胞命运需要深入研究. 此外, 虽然氨基酸代谢对免疫细胞命运有重要调控作用[75]; mTORC1和GCN2介导的免疫细胞命运决定机制也可能通过非氨基酸代谢依赖, 如mTORC1能够感知能量水平(ATP等)变化、调节线粒体的生物发生和功能等介导免疫细胞的功能[76]. 值得注意的是, 由于不同的免疫细胞所处的微环境差异, 且调控mTORC1或GCN2活性或者mTORC1或GCN2调控的下游通路不一, 因此mTORC1或GCN2对不同免疫细胞命运的影响甚至是对同一免疫细胞在不同微环境作用结果也不一样.

研究氨基酸感知系统具有广阔的前景和价值. 尽管有证据表明, 氨基酸感知系统mTORC1和GCN2能调控免疫细胞发育、分化和功能, 并且在常见免疫相关疾病中发挥着重要的作用, 然而氨基酸是否可以作为营养调控手段来预防或辅助治疗常见免疫性疾病仍需要进一步研究(特别是对疾病临床治疗效果以及安全性的探讨). 此外, 如何靶向病理条件下某一类细胞或者某一亚型细胞内的mTORC1和GCN2信号需要深入探索.

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Role of mTORC1 and GCN2 signaling in immune cells

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The amino acid sensing system senses amino acid levels both inside and outside the cell and regulates influences protein synthesis and degradation, but also the differentiation and function of the immune cells. The mammalian target of rapamycin (mTOR) and general control nonderepressible 2 (GCN2) are crucial components of amino acid sensing system. In the present study, we briefly show the progression of mTORC1 and GCN2 in amino acid sensing, and then highlight the importance of mTORC1 and GCN2 in immune cell differentiation and function, and their possible roles in immune-related diseases.

amino acids, immunometabolism, mTORC1, GCN2, inflammation

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