色氨酸及其代谢物对细胞增殖的影响

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摘要 色氨酸作为机体必需氨基酸, 参与蛋白质合成, 还通过5-羟色胺和犬尿氨酸代谢途径产生重要的活性化合物, 诱导激活细胞内多种信号通路, 在细胞生长、增殖以及代谢平衡等过程中发挥重要作用, 且呈剂量依赖性。色氨酸可通过激活哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)、酪氨酸蛋白激酶2/信号转导与转录激活因子3(Janus kinase 2/signal transducer and activator of transcription 3, JAK2/STAT3)信号通路和一般性调控阻遏蛋白激酶2(general control non-derepressible 2, GCN2)经典应激反应促进细胞增殖; 5-羟色胺经其受体(5-hydroxytryptamine receptor, 5-HTR)和转运体(serotonin transporter, SETR)内化后激活下游信号分子, 促进细胞增殖。然而高表达的吲哚胺-2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)大量消耗色氨酸, 导致色氨酸耗竭和代谢物大量累积, 从而抑制细胞增殖; 同时犬尿氨酸激活芳烃受体(aryl hydrocarbon receptor, AhR), 阻滞细胞周期进程, 抑制细胞增殖。该文综述了色氨酸代谢途径及其代谢物诱导的多种信号通路对细胞增殖的调控机理, 旨在临床靶向治疗时, 可通过精准地调控色氨酸代谢的限速酶来治疗由细胞异常增殖而引起的代谢性疾病。

关键词 色氨酸; 5-羟色胺; 犬尿氨酸; mTOR; GCN2; JAK2/STAT3; AhR; 细胞增殖

Effects of Tryptophan and Its Metabolites on Cell Proliferation

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Abstract Tryptophan, as an essential amino acid in the body, is involved in protein synthesis. It also produces important active compounds through the metabolic pathway of 5-hydroxytryptophan and kynurenine, inducing and activating various intracellular signaling pathways, and plays an important role in the process of cell growth, proliferation and metabolic balance, which is dose-dependent. Tryptophan can promote cell proliferation by activating mTOR (mammalian target of rapamycin) and JAK2/STAT3 (Janus kinase 2/signal transducer and activator of transcription 3) signaling pathways and GCN2 (general control non-derepressible 2) classical stress response. 5-HTR (5-hydroxytryptamine receptor) and SETR (serotonin transporter) internalize 5-hydroxytryptamine to activate downstream signaling molecules and promote cell proliferation. However, highly expressed IDO (indoleamine 2,3-bioxygenase) consumes a large amount of tryptophan, resulting in tryptophan depletion and mass accumulation

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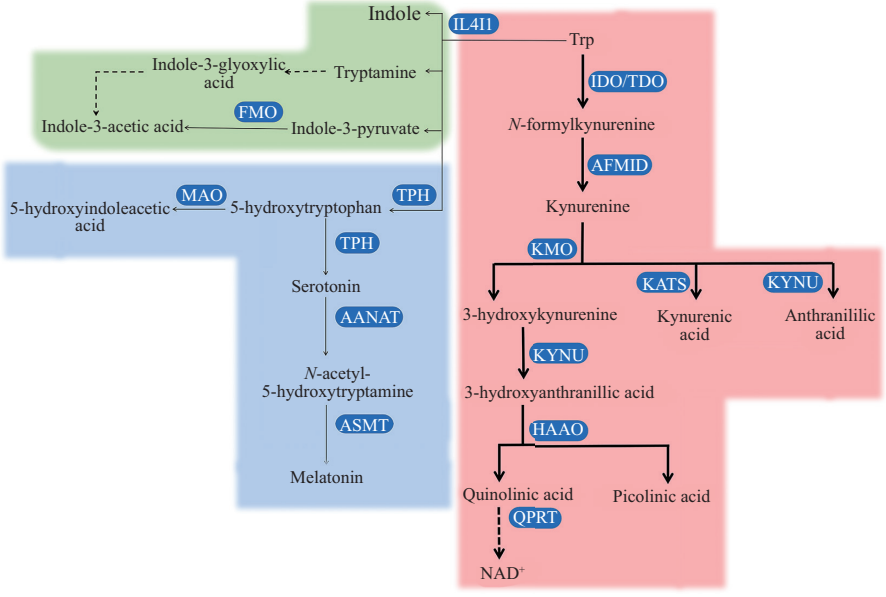
of metabolites, which can inhibit cell proliferation. At the same time, kynurenine activates AhR (aryl hydrocarbon receptor) signaling pathway, which blocks cell cycle process and inhibites cell proliferation. This paper reviews the metabolic pathways of tryptophan and its down-regulated metabolites that regulated cell proliferation. In brief, when applied to clinical targeted therapies, the rate-limiting enzymes of tryptophan metabolism could be precisely regulated for the treatment of metabolic diseases caused by abnormal cell proliferation.

Keywords tryptophan; serotonin; kynurenine; mTOR; GCN2; JAK2/STAT3; AhR; cell proliferation

色氨酸(tryptophan, Trp)是蛋白质合成的一种必需氨基酸, 在体内所有氨基酸中, 其总浓度最低, 因而在蛋白质合成中主要起限速作用[1]; 同时, 其参与犬尿氨酸和5-羟色胺代谢途径, 是合成辅酶烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NAD)和褪黑素(melatonin, MLT)的底物[2]。色氨酸及其代谢物在多种生物学过程中通过某种信号通路的调节发挥着重要的生理作用, 涉及细胞生长和维持机体代谢平衡等, 并可能促进或抑制细胞的增殖[3-4]。近年来相关研究表明, 色氨酸在机体中可引起细胞内的级联反应, 诱导淋巴细胞[5]和角膜上皮细胞[6]增殖; 且其代谢物5-羟色胺可促进肝细胞再生[7], 以及肺动脉平滑肌细胞[8]和成纤维细胞[9]增殖。也有研究指出色氨酸及其代谢物通过其他调节通路抑制细胞增殖, 如色氨酸经过犬尿氨酸代谢途径激活AhR信号通路并抑制黑色素瘤细胞[10]、结肠癌细胞[11]、外胚层细胞[4]和肝细胞[12]等的增殖。本文综述了色氨酸及其代谢物通过激活各种信号通路调节细胞生长和增殖的作用。

1 色氨酸代谢

在人体中, 色氨酸作为必需氨基酸仅从膳食中摄取获得, 广泛分布于不同细胞、组织中, 其代谢物受到严格调控并且在不同生理过程中起着关键作用。例如, 从细胞的生长和增殖, 到机体对外环境变化的协调反应, 色氨酸及其代谢物都充当着重要的神经递质和信号分子的角色[13]。色氨酸及其代谢物水平的失衡与多种人类疾病包括抑郁症、精神分裂症、自身免疫和癌症等相关[14]。在tRNA转运下, 色氨酸参与蛋白质的合成, 其分解代谢颇为复杂[15]。如图1所示,



AFMID: 犬尿氨酸甲酰胺; KYNU: 犬尿氨酸酶; KATs: 犬尿氨酸氨基转移酶I~III; KMO: 犬尿氨酸-3-单加氧酶; HAAO: 3-羟基邻氨基苯甲酸3,4-双加氧酶; QPRT: 喹啉酸磷酸核糖转移酶; FMO: 黄素单加氧酶; MAO: 单胺氧化酶; ASMT: *N*-乙酰基-5-羟色胺-甲基转移酶。

AFMID: kynurenine formamidase; KYNU: kynureninase; KATs: kynurenine aminotransferases I-III; KMO: kynurenine-3-monooxygenase; HAAO: 3-hydroxyanthranilate 3,4-dioxygenase; QPRT: quinolinic acid phosphoribosyl transferase; FMO: flavin-containing monooxygenases; MAO: mono-amineoxidase; ASMT: *N*-acetylserotonin methyltransferase.

图1 色氨酸代谢通路

Fig.1 Pathways of tryptophan metabolism

色氨酸代谢途径主要有3种：其中约95%的色氨酸经过犬尿氨酸代谢途径(kynurenine pathway, KP)生成犬尿氨酸及其衍生物，该产物在免疫反应和神经传递中产生不同的生物学活性；剩余约5%的色氨酸可通过5-羟色胺和色胺的代谢途径分别生成褪黑素和吲哚衍生物[15-16]，这两种产物可作为神经递质参与神经调节等生理功能。

Trp在体内主要经过KP，第一步，Trp进行氧化分解形成*N*-甲酰犬尿氨酸(*N*-formylkynurenine, NFK)，催化此反应的酶为色氨酸-2,3-双加氧酶(tryptophan 2,3-dioxygenase, TDO)或吲哚胺-2,3-双加氧酶(indoleamine 2,3-bioxygenase, IDO)，此反应为该代谢途径的限速步骤[17]。癌症中，IDO和TDO的异常激活会导致抗肿瘤免疫的抑制；而在自身免疫中，IDO和TDO的激活或者KP代谢物均可缓解该疾病[18]。第二步，NFK在犬尿氨酸甲酰胺酶的催化下水解生成中间产物犬尿氨酸(kynurenine, Kyn)[19]。Kyn再经3种代谢途径，生成不同的代谢产物，包括邻氨基苯甲酸(anthranili acid, AA)、犬尿酸(kynurenic, KynA)和3-羟基邻氨基苯甲酸(3-hydroxyanthranilic acid, 3-HAA)。其中3-HAA参与喹啉酸(quinolinic acid, QUIN)的合成，最终QUIN逐步生成NAD^+[15]。KP代谢物多具有神经活性，如KynA是离子型谷氨酸受体的拮抗剂，与精神分裂症的认知功能障碍有关[20]；QUIN通过与*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid, NMDA)受体结合，介导兴奋性毒性和神经变性[21]。

剩余约2%的Trp可经过5-羟色胺途径代谢。色氨酸羟化酶(tryptophan hydroxylase, TPH)是此代谢途径的限速酶，催化Trp生成5-羟基色氨酸(5-hydroxytryptophan, 5-HTP)。 5-HTP再经氨基酸脱羧酶快速脱羧生成5-羟色胺(serotonin, 5-HT)，最后5-HT在乙酰化和甲基化作用下逐步生成MLT[15,22]。MLT作为启动睡眠的神经递质，调节生物节律；可清除自由基、降低过氧化物含量，保护细胞结构、防止DNA受损[23-24]。5-HT聚集于血小板上通过氧化脱氢转化为5-羟基吲哚乙酸(5-hydroxyindoleacetic acid, 5-HIAA)。5-HIAA作为G蛋白偶联受体35的配体，与其结合有助于单核细胞和中性粒细胞聚集到炎症部位，并增强该细胞的细菌清除能力[25]。SLABA等[26]研究发现，5-HIAA与血小板激活因子、黏附因子和趋化因子协同作用，促进中性粒细胞向组织内的迁移。此外还有少部分Trp在白介素4诱导蛋白1(interleukin-4-induced-1, IL4I1)的作用下代谢为吲哚-3-丙酮酸(indole-3-pyruvate, IPA)等吲哚衍生物[27]。研究表明，Trp代谢物吲哚类与AhR结合可调节中枢神经系统局部和远端的炎症[28]。

色氨酸及其代谢物作为机体重要的营养物质及信号分子影响着细胞行为以及代谢调节。犬尿氨酸代谢途径(kynurenine pathway, KP)的代谢物作用于神经元，显示出不同的神经活性：QUIN刺激NMDA受体，介导神经元兴奋性；KynA则是离子型谷氨酸受体的拮抗剂，可控制谷氨酸、多巴胺、乙酰胆碱的水平，缓解神经元毒性[20]。色氨酸经KP产生的NAD^+作为DNA修复酶唯一的内源性底物，可促进细胞内DNA氧化损伤的清除[29]；且NAD^+对胚胎干细胞发育十分重要，研究发现NAD^+可预防因胚胎干细胞的犬尿氨酸酶(kynureninase, KYNU)缺失而导致的先天性器官畸形[30]。KP代谢物会影响细胞衰老，OXENK-RUG等[31]发现，Kyn/Trp值与细胞衰老呈正相关，Trp通过影响胰岛素/胰岛素样生长因子-1和mTOR信号通路来调控细胞衰老进程。多数情况下，细胞对Trp摄取的增加或TDO活性的抑制可减缓细胞衰老并延长机体寿命[32]。此外，KP下游代谢物也参与了细胞衰老调节，用Kyn喂养果蝇会缩短其寿命[33]。色氨酸及其代谢物也可通过多种信号通路的调节影响细胞的生长和增殖。以下将重点阐述色氨酸及其代谢物对细胞增殖的影响。

2 色氨酸及其代谢物促进细胞增殖

细胞增殖是生物繁殖、生长和发育的基础，是生物体重要的生命特征。所有生物都是以细胞分裂的方式进行增殖，从而产生新的细胞以补充机体内衰老或死亡的细胞。Trp除了参与蛋白质合成外，也是细胞生存和增殖不可或缺的物质，可诱导角膜上皮细胞[6]、人胚胎干细胞[34]和淋巴细胞[5]等细胞的增殖。Trp在体内还起着重要的生理作用，其代谢物通过转运体进入细胞激发下游信号分子，能促进肝细胞[7]、成纤维细胞[8]和肌细胞[9]等细胞的生长。

2.1 色氨酸促进细胞增殖的作用机理

Trp只能通过人类饮食摄取获得，可参与调节人体内大分子物质的合成，同时也是细胞增殖所必需的氨基酸，可促进免疫细胞的增殖和分化。Trp经过光分解得到产物6-甲酰基吲哚并[3,2-b]咔唑(6-formylindolo[3,2-b]carbazole, FICZ)，VILLA等[35]发

现, 用250 nmol/L FICZ处理B细胞可有效提高Cyclin O基因的表达量, 该基因表达的产物参与控制细胞周期, 从而促进B细胞增殖。Trp在体内能促使骨髓T细胞前体增殖并分化为成熟T细胞[36], 同时Trp还可通过mTOR信号通路[37]以及GCN2经典应激反应[5]来促进肠道上皮细胞和淋巴细胞的增殖。

2.1.1 Trp激活mTOR信号通路 mTORC1是一种丝氨酸/苏氨酸蛋白激酶, 可在某种类型细胞中对Trp作出反应, 并调节蛋白质合成和细胞生长[38]。Trp在猪肠道上皮细胞中难以降解, 与基础培养液相比, 添加适当Trp的培养液可显著促进细胞增殖。Trp可通过磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)/蛋白激酶B(AKT)激活mTOR信号通路, 从而促进猪肠道上皮细胞增殖[37]。如图2所示, Trp通过其转运体进入细胞, 促使细胞内Trp浓度增加, 导致PI3K被激活, 进而催化细胞膜内表面的PIP2生成PIP3, PIP3作为第二信使与3-磷酸肌醇依赖性蛋白激酶1(3-phosphoinositide-dependent protein kinase 1, PDK1)结合, 促使AKT磷酸化, 活化后的AKT可通过结节性硬化蛋白复合体(tuberous sclerosis complex 1/2, TSC1/TSC2)间接作用于mTORC1[39], 也可直接磷酸化脯氨酸富集蛋白(Proline-rich Akt substrate 40 kDa, PRAS40), 使其对mTORC1的抑制作用消失, 从而激活mTORC1通路[40]。mTORC1的下游信号分子真核起始因子4E结合蛋白1(eIF4E-binding protein, 4E-BP1)进行磷酸化, 最终启动翻译并编码调节细胞周期的蛋白, 促进细胞增殖[41]。体外实验中, 通过在常规培养液中添加Trp可有效促进人多能干细胞的增殖, 并使蛋白质合成速率增加[34]。

2.1.2 Trp激活JAK2/STAT3通路 JAK2/STAT3作为应激的炎症信号通路, 反应迅速, 可调节细胞的生长增殖[42]。在浅层点状角膜炎、持续性角膜上皮细胞缺损的疾病中, 增加Trp可使细胞代谢增强, 修复角膜上皮细胞。研究发现, 角膜细胞中高浓度的Trp及其代谢物犬尿酸可使IL-6的释放量增加[43]。IL-6可激活JAK2/STAT3信号通路, 影响下游多种效应分子活化, 从而维持角膜上皮细胞的状态, 并选择性刺激细胞分裂, 诱导细胞增殖[44]。体外培养角膜上皮细胞的实验已证实, 暴露于Trp的角膜上皮细胞, 其活性和增殖能力也得到轻微增强[6]。

2.1.3 Trp缺乏激活GCN2通路 GCN2是一种传感蛋白, 根据营养供应情况控制细胞周期相关基因的表达, 调节细胞代谢[45]。Trp大量消耗时, GCN2通过检测任何不带电荷的tRNA来发挥作用, 引发细胞代谢的两条途径。一般情况下GCN2检测到环境中氨基酸受限制时, 会阻碍蛋白质合成, 使内质网压力增大, 从而导致细胞死亡。例如在$CD4^+$T细胞中, GCN2感应到Trp消耗因无法调整内质网应激反应而导致细胞死亡[46]。然而这一途径与GCN2激活的经典应激反应不相同, 在经典应激反应下, 转录激活因子4(activating transcription factor 4, ATF4)和内质网

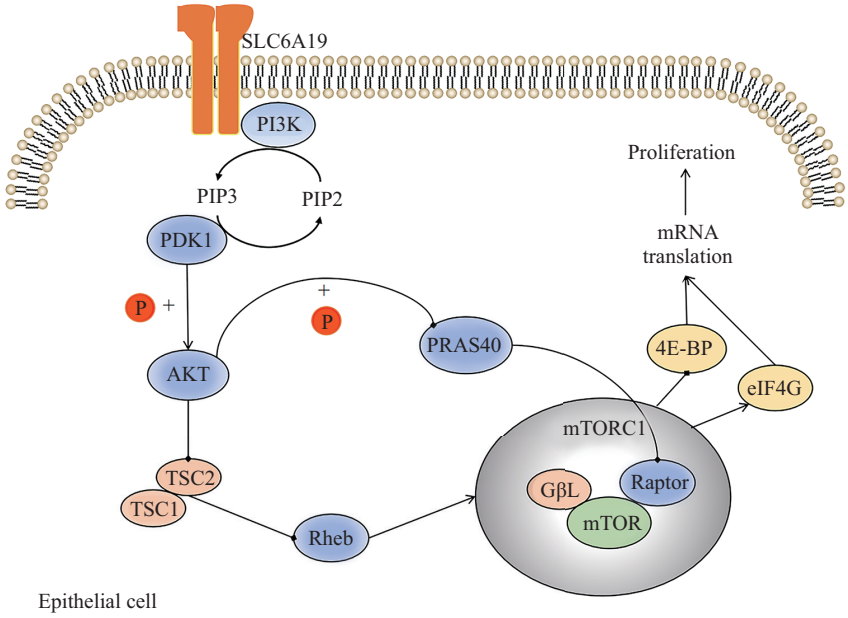


图2 色氨酸通过mTOR信号通路促进肠道上皮细胞增殖

Fig.2 Tryptophan promotes intestinal epithelial cell proliferation via mTOR signaling pathway

应激基因表达量增加, 从而调控细胞周期, 促进细胞增殖[47]。

Trp的大量消耗可使GCN2激活, 引发的经典应激反应能促进某些T淋巴细胞的生长和增殖。RASHIDI等[48]研究发现脑肿瘤患者中, 低水平的Trp引起GCN2的激活对于$CD8^+$T细胞的功能、生存和增殖都是必需的。如图3所示在胶质瘤背景下, 骨髓来源的抑制性细胞和肿瘤细胞表达的IDO和TDO介导Trp的耗竭, 两种细胞通过协同作用, 从肿瘤微环境中去除Trp[49]。GCN2感应到Trp的缺失, 使真核翻译起始因子2α磷酸化从而抑制机体内蛋白质的翻译并上调内质网应激基因的表达, 最终缓解因Trp缺乏而导致的内质网压力[50-51]。因此在肿瘤介导下Trp的消耗引起GCN2的激活, 促进ATF4以及内质网应激基因表达, 使得$CD8^+$T细胞增殖。

2.2 5-羟色胺促进细胞增殖的作用机理

5-羟色胺(serotonin, 5-HT)是一种在整个进化过程中高度保守的单胺, 它来源于必需氨基酸色氨酸, 可从饮食中所获取。作为中枢神经系统中一种重要的神经递质, 5-HT参与了认知、注意力、情绪、疼痛、睡眠和觉醒等方面的活动[52]; 外周5-HT主要由胃肠道产生, 并被血小板吸收和储存, 当血小板凝结成块时释放的5-HT将增强血管和平滑肌收缩, 促进血液凝固和止血[53]。同时5-HT也在细胞中通过其受体5-HTR或转运体SETR起着促进细胞增殖的作用[54]。

2.2.1 5-HTR介导的信号机制 机体中5-HT通过激活7种不同类型受体(5-HT1~5-HT7)中的任意一种受体来产生细胞效应。研究发现, 在部分小鼠的肝切除模型中, 由血小板衍生的5-HT在残肝中迅速集结, 通过5-HT2A和5-HT2B受体的信号转导促进肝细胞再生[55]。5-HTR位于细胞膜上, 属于G蛋白偶联受体, 可激活细胞内第二信使引发级联反应。5-HT通过5-HT2受体增加细胞内二脂酰甘油和三磷酸肌醇的水平[54], 由此激活蛋白激酶C(protein kinase C, PKC), 活化的PKC使底物蛋白磷酸化, 从而引起细胞反应; IP3诱导内质网钙泵打开并动员细胞的内源钙扩散到细胞质基质中, 使细胞质中游离的钙离子浓度增高[56], Ca^{2+}也可激活PKC, 使转录因子磷酸化从而促进包括细胞增殖在内的众多生物学过程的发生[57]。

2.2.2 SETR介导的信号机制 SETR是一种相对较小的膜蛋白, 全部包埋于细胞膜中, 随着构象的改变而转运5-HT产生细胞效应。在肺动脉高压(pulmonary arterial hypertension, PAH)患者中由于缺氧诱导了色氨酸羟化酶表达, 使5-HT从头合成。通过SETR内化的5-HT激活下游信号分子促进成纤维细胞和肺动脉平滑肌细胞的增殖[8]。如图4所示, 5-HT由SETR进入细胞内, 激活SETR依赖的细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)、活性氧(reactive oxygen species, ROS)和Rho激酶(Rho-associated kinase, ROCK), 进而促使磷酸化的ERK转位进入细胞核增加转录因子GATA-4表达, 最终促进细胞增殖[58]。5-HT只能在牛的肺动

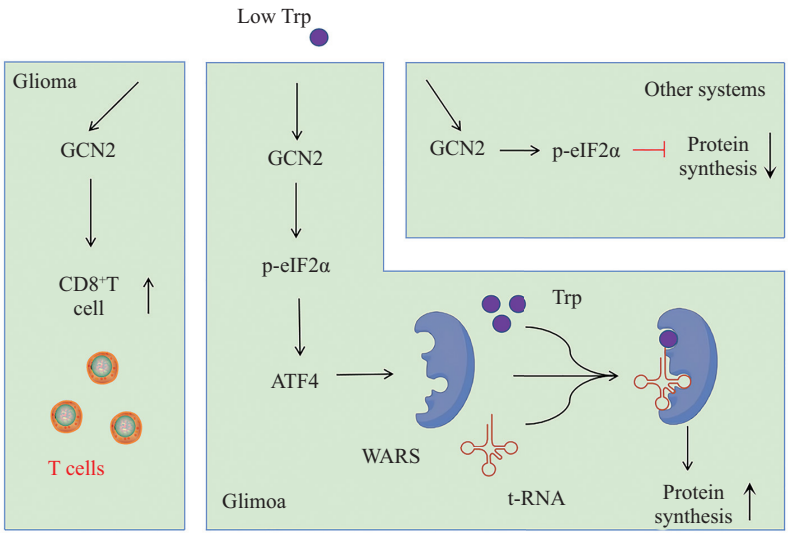


图3 色氨酸耗竭对胶质瘤模型或其他系统的影响(根据参考文献[1]修改)

Fig.3 Effects of tryptophan deprivation in glioma models or other systems (modified from the reference [1])

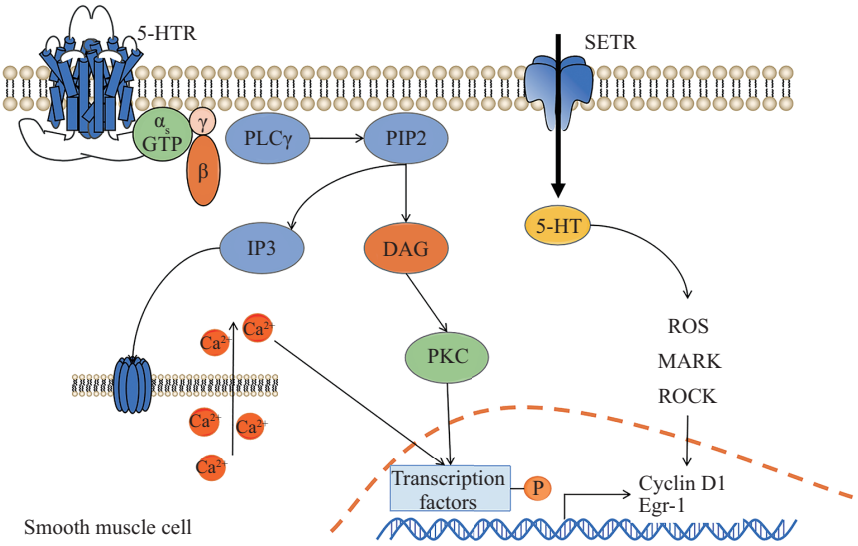


图4 5-羟色胺在平滑肌细胞中的信号转导

Fig.4 Serotonin-induced signaling in smooth muscle cells

脉平滑肌细胞中特异性地激活NADP+, 进而产生氧化应激反应。 生成的ROS激活细胞中ERK1/2的磷酸化, 最终pERK1/2核转位增加转录因子的表达。ROCK在细胞增殖、迁移以及细胞骨架重排等多种生物学过程中发挥着重要作用。内化后5-HT激活ROCK通路, ROCK介导肺成纤维细胞中磷酸化的ERK转位进入细胞核, 从而导致转录因子GATA-4、Cyclin D1和早期生长反应因子-1的表达量增加, 促进细胞增殖[59]。

2.2.3 5-HT激活mTOR通路 HT也是一种强大的有丝分裂原, 已被证明可促进神经[60]和血管[61]生成。5-HT可激活由5-HT2B受体介导的SCR/PI3K/AKT/mTOR信号途径, mTOR被激活后, 通过磷酸化4E-BP来刺激细胞增殖。在体外培养的胚胎中, 5-HT摄取抑制剂已被证实抑制了神经嵴细胞的迁移和外胚间充质的增殖, 造成了严重的颅面畸形。同时在体外5-HT能够诱导培养的$CD34^+$细胞扩增[54]。

3 色氨酸缺乏及其代谢物抑制细胞增殖

Trp及其代谢物广泛参与机体的新陈代谢, 有助于蛋白质更新, 是维持细胞生长和增殖所必需的物质, 但同时也有研究发现Trp缺乏及其代谢物对细胞增殖有抑制作用。FRUMENTO等[62]研究发现免疫细胞对Trp缺乏极为敏感, 从而导致其细胞周期停滞。同时XU等[4]研究发现Kyn通过激活AhR抑制猪滋养外胚层细胞的增殖, 诱导细胞周期停滞于G_1期。

3.1 色氨酸缺乏抑制细胞增殖的作用机理

Trp是机体内所必需的营养物质, 可影响细胞的生长和机体代谢的平衡。研究发现高表达的IDO大量消耗Trp导致营养物质缺乏, 使细胞增殖受到抑制[63]。同时也有研究认为由于Trp耗竭产生的代谢物大量累积是导致细胞增殖受到抑制的主要因素[64]。

3.1.1 Trp缺乏抑制细胞增殖 在Trp缺乏的条件下, 虽然通过GCN2的激活引发的经典应激反应能促使蛋白质合成引起细胞分裂, 但GCN2也可导致免疫细胞周期阻断, 抑制其增殖[65]。研究发现巨噬细胞(macrophages, Mø)等产生的IDO介导了Trp分解代谢, 使Trp浓度低于1 μmol/L,从而抑制T细胞增殖[66]。体内过表达IDO的细胞能形成Trp含量较低的局部微环境, 虽然机体可以补充Trp, 但当底物通过细胞膜运输时会受到扩散速率的严格限制, 从而导致Trp浓度迅速下降到细胞内无法检测的水平[67]。由于表达IDO的Mø消耗Trp的速率比正常代谢需求高出几个数量级, 因此Mø会造成Trp浓度较低的局部条件。Trp水平低于0.5~1 μmol/L时, T细胞存在的色氨酸敏感检查点会阻断G_1期, 抑制T细胞增殖[67]。

3.1.2 Trp代谢物累积抑制细胞增殖 Trp在高表达的IDO催化下逐步分解成Kyn、3-HK、AA、QUIN等使其代谢物大量积累[47-48,68]。Kyn和QUIN等是NMDA受体激活剂, 过量的谷氨酸盐激活NMDA受

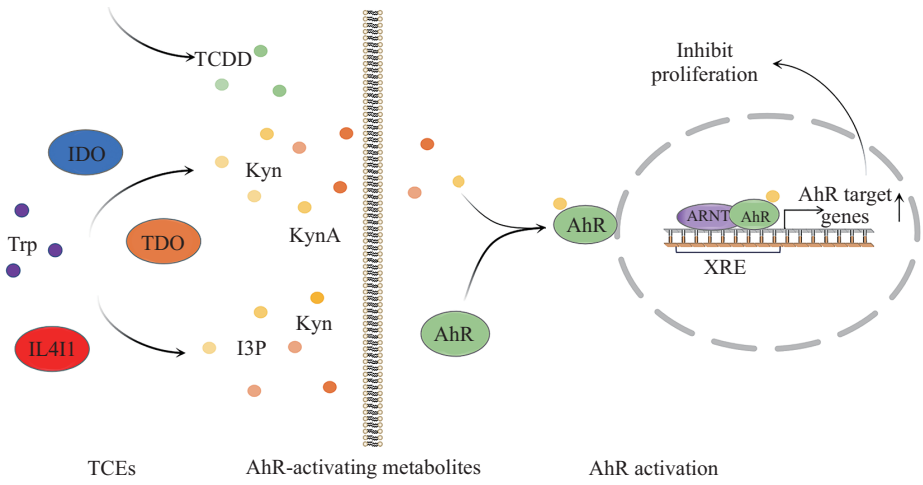


图5 色氨酸分解代谢通过激活芳香烃受体(AhR)抑制细胞增殖(根据参考文献[1]修改)

Fig.5 Tryptophan catabolism inhibits cell proliferation via activation of the aryl hydrocarbon receptor (AhR) (modified from the reference [1])

体打开离子通道, 细胞外的Na^+和Ca^{2+}内流进入细胞, 致使神经元内钙离子过载, 引发线粒体损伤、钙蛋白酶激活等一系列下游促死信号, 最终导致细胞凋亡[69]。NMDA受体及其介导的分子机制也存在于免疫细胞中。在大鼠的体内及体外研究中发现, IDO催化Trp代谢, 产生的Kyn、3-HK、QUIN等都可显著抑制T细胞、B细胞和NK细胞增殖[70]。

3.2 犬尿氨酸抑制细胞增殖的作用机理

Kyn是犬尿氨酸代谢途径中最主要的代谢物, 调节神经元兴奋性和免疫细胞反应。同时Kyn作为AhR的内源性激动剂[71], 可以通过自分泌或旁分泌的形式与AhR相互作用, 阻断细胞周期, 使其停滞在G_1/G_0期, 从而抑制细胞的增殖[72]。

AhR是细胞质的转录因子, 在非激活状态下与几个分子伴侣形成复合物, 其分子伴侣包括两个热休克蛋白90、辅助伴侣P23和芳烃受体互作蛋白[73]。在与Kyn等配体结合后, AhR被激活。伴随着热休克蛋白90的解离, AhR构象发生改变, 从而移位到细胞核中[74]。AhR进入细胞核后与其核转运体蛋白(aryl receptor nuclear translocator, ARNT)结合形成异二聚体, 此异二聚体通过与异源反应元件结合来调节AhR靶基因的表达[75](图5)。在某些上皮细胞或滋养层细胞中, AhR靶基因所表达的蛋白, 如细胞色素P450和细胞周期依赖蛋白激酶抑制物P27kip1等[76], 经AhR配体处理后水平均有所增加, 从而促使细胞周期停滞于G_1期, 最终导致细胞增殖的抑制[77]。因此, AhR活性可能是调节细胞增殖和细胞周期进展所需的。有研究表明持续的二恶英暴露促使AhR激活, 导致多种细胞的细胞周期停滞, 使细胞增殖受到抑制[78]。活化的AhR还可以通过调节促增殖因子E2F的功能来影响细胞增殖和细胞周期相关基因的表达[79]。AhR和低磷酸化视网膜母细胞瘤蛋白相互作用, 使其与E2F转录因子结合来抑制G_1期向S期的转变, 从而阻碍S期所需蛋白的表达, 使细胞周期停滞, 抑制细胞增殖[80]。

3.3 3-羟基邻氨基苯甲酸抑制细胞增殖的作用机理

在犬尿氨酸代谢途径中, Kyn的下游代谢产物也能对细胞增殖和活性进行选择性抑制。3-羟基犬尿氨酸在犬尿氨酸酶催化下生成的3-HAA可以通过激活caspase-8, 促进线粒体释放细胞色素C, 从而使体外诱导的小鼠胸腺细胞和T细胞选择性凋亡[49,67]。此外, 3-HAA以特定构象与PDK1结合, 导致PDK1在Ser-241处无法磷酸化, 同时3-HAA特异性地抑制了Toll样受体诱导的核因子κB的激活, 使活化的T细胞功能紊乱, 从而显著抑制了T细胞增殖[81]。

综上, 色氨酸及其代谢物进入细胞激活某种信号通路, 引起胞内级联反应, 从而影响细胞增殖(表1)。基于色氨酸及其代谢物对细胞生长和增殖的作用, 以不同细胞类型进行归纳总结色氨酸及其代谢物的调控机理。

4 临床应用

Trp及其代谢物在胞内通过某种信号通路影响细胞生长、增殖, 然而异常的细胞增殖可导致某些

疾病发生。研究发现, Trp代谢在癌症中发挥着重要作用, 其可通过犬尿氨酸代谢途径抑制抗肿瘤免疫反应并增加癌细胞的恶性程度促进肿瘤发展[82]。其他一些疾病也和Trp代谢相关, 如肺动脉高压(pulmonary arterial hypertension, PAH)可由5-HT通过其转运体和受体引起的异常血管增殖而引起[83]; Trp及其代谢物在沙眼、角膜炎和角膜上皮细胞缺损疾病中起重要作用, 有助于抗炎、抗氧化、神经保护和维持角膜完整的特性[84]。

在某些癌症中, 由于细胞代谢调控紊乱导致其恶性增殖, 而犬尿氨酸代谢途径可进一步加剧肿瘤细胞的恶性程度。近年来研究表明, 肿瘤细胞将Trp逐步代谢成Kyn后, 将Kyn转移到CD^{8+}T细胞中以AhR依赖的方式上调其靶基因程序性死亡蛋白1的表达, 抑制CD^{8+}T细胞的增殖, 促使肿瘤细胞免疫逃逸[85]。同时, Trp分解代谢导致的Trp耗竭也介导肿瘤细胞免疫逃逸。起始T细胞在转变为效应T细胞时, 需要大量营养供给。因此在效应T细胞增殖、活化过程中, Trp既是蛋白质合成的底物也是能量的来源。Trp消耗, 抑制效应T细胞增殖, 使得细胞免疫功能降低, 促进肿瘤细胞逃逸[86]。因此, Trp耗竭及代谢成Kyn可促进肿瘤细胞免疫逃逸。在临床前模型中, 采用药物抑制IDO和TDO活性, 阻碍Trp代谢及消耗可减少小鼠肺癌模型中肿瘤结节数[87]。目前, IDO抑制剂依卡多司特(INCB024360)、那福莫特(NLG-919/GDC919)和BMS-986205(F001287)已用于癌症治疗; KHK2455、LY3381916和MK-7162作为IDO抑制剂进入临床评估阶段[88-89]。

PAH疾病中低氧导致的肺血压升高与血管异常增殖相关, 并且5-HT会促进血管增殖[90]。在慢性缺氧的小鼠模型中, 低氧导致5-HT2B受体显著高表达[91], 5-HT激活5-HT2B受体使血管异常增殖是PAH发展的关键性步骤[8], 而慢性缺氧的小鼠暴露于5-HT2B受体拮抗剂中, 会抑制该疾病的发生。因此, 5-HT2B受体可作为PAH的诊断指标和潜在治疗靶点, 5-HT2B受体拮抗剂可用于开发新的PAH治疗药物。同时研究发现, 厌食患者在服用药物芬氟拉明和氨氯地平后也会患上PAH[8,92]。两种药物都是

表1 色氨酸及其代谢物促进或抑制细胞增殖的作用机理

Table 1 Mechanism of tryptophan and its metabolites in promoting or inhibiting cell proliferation

细胞分类 Cell classification	细胞类型 Cell type	细胞增殖或抑制的机理 Mechanisms of cell proliferation or inhibition
Epithelial cells	Intestinal epithelial cells	Trp activates mTOR signaling pathway through PI3K/AKT to promote cell proliferation [37,40-41]
	Corneal epithelial cells	Trp drives the release of IL-6, which activates the JAK2/STAT3 signaling pathway to promote cell proliferation [43-44]
Endothelial cells	Vascular endothelial cells	5-HT is mediated by 5-HT2B receptor to activate SCR/PI3K/AKT/mTOR signaling pathway to promote cell proliferation [61]
Immune cells	CD^{8+}T cells	In tumors, IDO mediates Trp depletion, which induces a classical stress response of GCN2 to promote cell proliferation [47-48]
	B cells NK cells	Trp is gradually broken down into Kyn, 3-HK, AA, QUIN, etc. by IDO, the massive accumulation of metabolites activates NMDA receptors to open Na^+ and Ca^{2+} ion channels, causing a series of downstream pro-death signals, which in turn inhibits cell proliferation [69-70]
	T cells	3-HAA binds to PDK1 which hinders the phosphorylation process to inhibit cell proliferation [81]
Tumor cells	Colon cancer cells Melanoma cells Human cervical cancer cells	Kyn and other aromatic ligands bind to AhR so that the activated AhR regulates the expression of its target genes and interacts with RB to block the expression of S-phase genes to inhibit cell proliferation [10-11]
Others	Hepatocyte	5-HT is internalized by 5-HT2A and 5-HT2B receptors, activating intracellular second messengers to trigger cascade reactions that phosphorylate transcription factors to promote cell proliferation [55]
	Fibroblasts Pulmonary arterial smooth muscle cells	5-HT is internalized by SETR to enable signal transduction via ERK, ROS and ROCK to produce the initiating transcription factor GATA-4 expression to promote cell proliferation [58-59]

SERT的激动剂, 引起5-HT释放并逆转其正常流向, 介导肺动脉平滑肌细胞增殖, 最终导致PAH产生[92]。因此, 靶向色氨酸羟化酶1抑制5-HT合成可能是PAH治疗的新方法。

炎性角膜疾病和角膜氧化损伤中角膜细胞正常增殖受到阻碍加剧该疾病进程。临床试验结果表明, 适当浓度的Trp和KynA会促进角膜细胞增殖以及IL-6释放[43]。IL-6作为促炎因子, 促进角膜上皮伤口的愈合、参与维持角膜上皮细胞的状态[93]。因而, 在普通眼药水中添加Trp可用于治疗角膜上皮细胞缺损等眼表疾病。

综上, 基于色氨酸及其代谢物对细胞增殖的调控机理, 在某些癌症治疗中以AhR受体为靶点, 可阻碍免疫细胞程序性死亡蛋白的表达, 从而限制肿瘤细胞的免疫逃逸; 精准靶向IDO、TDO等限速酶来调控犬尿氨酸代谢途径, 可减少Trp消耗, 最终阻止肿瘤细胞的恶性发展; Trp代谢物5-HT影响着PAH疾病发展, 以此为治疗靶点, 可阻碍SETR和5-HT2B受体激活, 从而抑制血管异常增殖, 使疾病逐步缓解。

5 总结与展望

综上, 色氨酸及其代谢物进入细胞后通过激活某种信号通路, 促进或抑制细胞的增殖。外源添加色氨酸可通过细胞内特异性受体传递信号刺激mTOR和JAK2/STAT3信号通路, 然后通过磷酸化4E-BP1等下游信号分子, 使得调节细胞周期的蛋白表达量增加, 进而促进细胞的生长增殖。在胶质瘤模型中, 色氨酸等营养物质消耗可激活GCN2经典应激反应, 促使ATF4和内质网应激基因表达, 从而调控细胞周期, 促进细胞增殖。同时5-羟色胺经5-HTR和SETR进入细胞内, 激活ERK、ROS和ROCK等信号通路, 增加转录因子GATA-4表达促使细胞增殖。色氨酸及其代谢物因作用的细胞类型不同, 诱导细胞内不同的信号通路, 从而导致细胞增殖受到抑制。色氨酸被摄取进入细胞后, 由巨噬细胞高表达的IDO大量消耗色氨酸, 使色氨酸等营养物质耗竭或色氨酸下游代谢物大量积累, 引发一系列下游促凋亡信号, 从而抑制细胞的增殖。3-羟基邻氨基苯甲酸通过激活caspase-8, 使细胞选择性凋亡。同时犬尿氨酸通过与AhR相结合, 使得活化的AhR调控其靶基因表达, 从而阻滞细胞周期进程, 抑制细胞增殖。

细胞增殖是整个生命活动的基础, 影响着多细胞生物的生长、发育, 随着对细胞增殖和色氨酸代谢途径及其信号通路调控机理的深入研究, 以色氨酸及其代谢物为调控靶点的药物在细胞异常增殖的疾病中的应用越来越广泛。但细胞增殖调控是一个精密而复杂的过程, 需要各种通路相互作用, 从而成为一个巨大的调控网路。色氨酸及其代谢物通过调节不同的信号通路即可促进细胞增殖亦可使细胞周期停滞, 虽然色氨酸耗竭的效应机制已在代谢性疾病中明确, 并已开发以IDO、TDO等限速酶为靶点的治疗性药物, 但还需要进一步的研究来发现潜在的额外效应机制, 确定个别下游代谢物与细胞异常增殖的相关性, 并评估其他色氨酸代谢调控酶在治疗中的作用。

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