色氨酸与肿瘤免疫

张 弛, 严时佳, 万国辉*

(中山大学药学院, 广东 广州 510006)

摘要: 色氨酸 (tryptophan, Trp) 作为人体必需氨基酸, 生理功能多样, 在肿瘤的代谢过程中具有重要意义。在人体中, 色氨酸主要经犬尿氨酸代谢, 既促进肿瘤细胞固有的恶性特性, 又限制肿瘤免疫, 因此它是癌症免疫治疗的重要药物开发靶点。肿瘤中色氨酸代谢的改变常伴随色氨酸相关酶基因表达的异常, 其中以吲哚胺2,3-双加氧酶 (indoleamine 2,3-bioxygenase, IDO) 相关基因表达和色氨酸2,3-双加氧酶 (tryptophan 2,3-dioxygenase, TDO) 相关基因改变最为常见。基于此, IDO抑制剂、TDO抑制剂及联合治疗被应用于大量的临床试验中。本文从色氨酸代谢出发, 阐述肿瘤中犬尿氨酸代谢途径、肿瘤细胞IDO、TDO、犬尿氨酸 (kynurenine, KYN) 相关基因的表达调控, 并概述色氨酸相关肿瘤治疗方案的新进展, 为肿瘤治疗方案的进一步探索提供新思路。

关键词: 肿瘤; 色氨酸代谢; 基因表达调控; 肠道菌群; IDO1/TDO2-KYN-AhR; 抑制剂

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Tryptophan and tumor immunity

ZHANG Chi, YAN Shi-jia, WAN Guo-hui*

(*School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, China*)

Abstract: As an essential amino acid, tryptophan (Trp) has various physiological functions and is of great significance in the metabolic process of tumors. In the human body, tryptophan is mainly transformed through kynurenine metabolic pathway, which not only promotes the inherent malignant properties of tumor cells, but also leads to immune-suppressive tumor microenvironment. Changes in tryptophan metabolism often occur in tumors, accompanied by abnormal gene expression of tryptophan-related enzymes, among which indoleamine 2,3-bioxygenase (IDO)-related gene expression and tryptophan 2,3-dioxygenase (TDO)-related gene changes are the most significant. A large number of clinical trials on IDO inhibitors, TDO inhibitors and combination therapy have been carried out. This paper reviewed the tryptophan metabolic pathway, regulation of IDO (TDO), kynurenine (KYN) and other related genes in tumor cells, and outlined the development of therapeutic schedule targeting tryptophan-related genes. The new progress provides new ideas for the further exploration of tumor treatment options.

Key words: tumor; tryptophan metabolism; regulation of gene expression; intestinal flora; IDO1/TDO2-KYN-AhR; inhibitor

肿瘤是影响人类健康的重要疾病, 现在已经成为全球第二大死因[1]。肿瘤免疫是利用人体自身的免疫系统对抗肿瘤, 清除肿瘤细胞, 达到治疗肿瘤的目的, 并保持持续的免疫记忆。随着免疫检查点抑制剂等肿瘤免疫治疗手段的发展, 使患者获益[2]。尽管在黑色素瘤等获得较好的响应, 但免疫检查点抑制剂对大部分实体瘤疗效甚微, 如何解决免疫治疗抵抗、提高患者对程序性死亡受体1/细胞程序性死亡配体1 (programmed cell death protein 1/programmed cell death 1 ligand 1, PD-1/PD-L1) 等免疫检查点抑制剂的响应是当前肿瘤免疫疗法的重中之重。

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*通讯作者 Tel: 86-20-39943495, E-mail: wanguoh@mail.sysu.edu.cn

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肿瘤代谢造成的免疫抑制性肿瘤微环境, 在肿瘤的形成和发展中具有重要作用, 其特点就是低氧和偏酸性。色氨酸 (tryptophan, Trp) 作为人体必需氨基酸, 它的生理功能多样, 如影响人体的新陈代谢、蛋白质合成及产生多种生物活性物质, 在肿瘤的代谢过程中具有重要意义[3]。而色氨酸经过犬尿氨酸代谢参与调节炎症反应、氧化应激和免疫激活反应, 在肿瘤微环境和肿瘤代谢中起到十分重要的作用。在人体中, 肿瘤的形成和发展通常出现色氨酸代谢的改变, 并伴随着色氨酸相关酶基因表达的异常, 其中以吲哚胺 2,3-双加氧酶 (indoleamine 2,3-bioxygenase, IDO) 相关基因表达改变最为常见。

1　色氨酸代谢

色氨酸是人体无法合成的必需氨基酸。在人体中, 色氨酸代谢有 3 种途径, 除了参与蛋白质的合成, 色氨酸还有两条其他的代谢途径, 如图 1 所示, 其中约有 5% 的 *L*-色氨酸会进行蛋白质合成及 5-羟色胺途径代谢成褪黑素, 而其余的约 95% 的 *L*-色氨酸通过犬尿氨酸 (kynurenine, KYN) 途径代谢成系列犬尿氨酸衍生物[4]。

由图 1 可以看出, 犬尿氨酸代谢途径分为以下几个步骤: 第一步是 *L*-色氨酸在 IDO 和色氨酸 2,3-双加氧酶 (tryptophan 2,3-dioxygenase, TDO) 的催化下转化为 *N*-甲酰犬尿氨酸 (*N*-formyl-*L*-kynurenine, NFK), 是该代谢途径中的限速步骤[5]; 第二步, NFK 可以在犬尿氨酸甲酰胺酶的作用下水解成第一个稳定的中间代谢产物——*L*-KYN。KYN 又有 3 条代谢途径生成不同的代谢产物:它可以在犬尿氨酸氨基转移酶 (kynurenine aminotransferase, KATs) 的作用下生成犬尿喹啉酸 (kynurenic acid, KYNA); 在犬尿氨酸-3-单加氧酶 (kynurenine-3-monooxygenase, KMO) 的作用下生成 3-羟基犬尿氨酸 (3-hydroxy-kynurenine, 3-HK), 并进一步在犬尿氨酸酶 (kynureninase, KYNU) 的作用下转化成 3-羟基邻氨基苯甲酸 (3-hydroxyanthranilic acid, 3-HAA); 此外, 在 KYNU 的作用下, KYN 还可以直接被催化成邻氨基苯甲酸 (anthranili acid, AA) 进而转化成 3-HAA。两种途径生成的 3-HAA 都可以经过系列反应生成人体所必需的吡啶甲酸 (picolinic acid, PIC)、喹啉酸 (quinolinic acid, QUIN) 及烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+)。

色氨酸代谢是促进肿瘤细胞固有的恶性特性, 限制抗肿瘤免疫的主要代谢途径, 因此它也成为癌症免疫治疗的药物开发靶点。

2　色氨酸代谢通路调控

2.1　IDO1

IDO 由免疫细胞和肿瘤细胞共同表达, 可以分解含有吲哚环的化合物。它有两种亚型, IDO1 与 IDO2, 其中 IDO1 的酶活性形式是单体, 是在多种组织内广泛表达的一种诱导酶, IDO2 与 IDO1 相比, 具有更高的组织特异性和更低的生物活性[6]。在乳腺癌[7]、肺癌[8]等

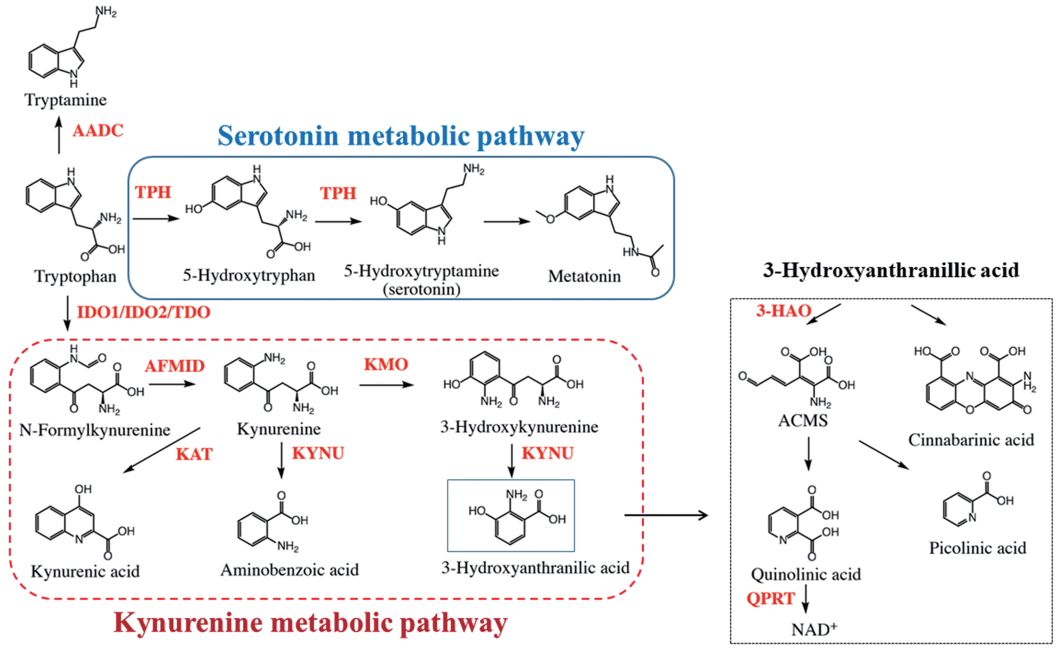

Figure 1　The kynurenine (KYN) metabolic pathway. It shows the enzymes and main products related to the kynurenine metabolic pathway. IDO: Indoleamine 2,3-dioxygenase; KAT: Kynurenine aminotransferase; KMO: Kynurenine-3-monoox-ygenase; TDO: Tryptophan 2,3-dioxygenase; KYNU: Kynureninase

许多肿瘤中都发现IDO的过表达, IDO的过表达与肿瘤免疫抑制有着密切的联系。IDO的过表达与2号染色体上的肿瘤抑制基因*BIN1* (bridging integrator 1) 的失活也有着密切联系。*BIN1*参与调控编码IDO酶的Indo基因的表达[9], 在许多肿瘤发生发展中都表现出失活或活性减弱, 通过上调IDO表达抑制T细胞功能。另外, 缺氧时环加氧酶2 (cyclooxygenase-2, COX-2) 表达减少[10], 而COX-2的上调可以使其代谢产物前列腺素E_2 (prostaglandin E_2, PGE_2) 生成增多, 从而通过自分泌信号通路与前列腺素E_2受体 (prostaglandin E2 receptor, EP receptor) 结合, 再通过蛋白激酶C和PI3K途径激活IDO1, 因此, 缺氧会导致IDO1表达减少[11]。

2.2 TDO

虽然TDO和IDO都可以催化Trp代谢中相同的生化反应, 但是它们具有不同的组织分布和生理功能。TDO主要存在于动物肝脏和神经元细胞中, 受糖皮质激素和色氨酸水平的调节[11], 并且对于*L*-色氨酸具有高度特异性, TDO2酶的活性形式是同四聚体。研究结果表明TDO阻断有利于TDO阴性肿瘤的免疫治疗, 通过增加Trp来克服IDO1介导的免疫抑制, 但是TDO在稳态中的作用尚不清楚[12]。

2.3 KYN

KYN、3-HK、3-HAA和QUIN等代谢产物可以促进肿瘤增殖并调节免疫细胞群[13]。其中IDO和TDO产生的KYN是芳烃受体 (aromatic hydrocarbon receptors, AhR) 的内源性激动剂。KYN可以通过自分泌或者旁分泌的形式与AhR相互作用, 从而抑制抗肿瘤免疫反应, 抑制免疫细胞的分化和活性, 导致对肿瘤的免疫作用受损, 促进肿瘤细胞存活[14]。

KYN的下游代谢产物可以选择性抑制T细胞的增殖和活化, 3-HAA和QUIN还可以通过激活caspase-8, 促进线粒体释放细胞色素C, 从而诱导T细胞的选择性凋亡[15]。此外, 3-HAA可以通过抑制磷酸肌醇依赖性激酶1的磷酸化, 从而显著抑制T细胞增殖[16]。

KMO是犬尿氨酸通路中十分重要的酶, 它可以通过催化KYN羟基化为3-HK, 产生自由基从而导致细胞凋亡。在体外实验中, 相比于人正常肝细胞, KMO酶水平在HCC细胞中上调, KMO可能在促进肿瘤增殖、转移和侵袭方面发挥作用, 并且敲低KMO酶可以降低癌细胞的增殖, KMO可能是肝癌治疗的新靶标[13]。

2.4 AhR

AhR是KYN的直接受体。它的配体种类和来源多种多样, AhR被激活后, 发生构象改变, 进入细胞核后与AhR核易位体蛋白 (aryl receptor nuclear translocator, ARNT) 结合形成二聚体, 调控一系列与代谢有关的基因的表达, 活化相关代谢酶, 参与诸如信号转导、细胞增殖与分化、细胞凋亡等重要的生物学过程, 可以促进癌细胞增殖、组织侵袭、转移和血管生成, 与肿瘤的发生发展密切相关[17]。同时, AhR还有助于IDO1的转录, 还通过影响蛋白质半衰期的非基因组机制来促进IDO1的调节[18]。

AhR激活与肿瘤细胞生长相关。当利用2,3,7,8-四氯二苯并二恶英 (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD) 激活AhR时, 可以减少雌激素反应元件与雌激素受体β (estrogen receptor β, ERβ) 的结合, 从而抑制肿瘤的生长[19]。

3 色氨酸代谢调控肿瘤发生发展

3.1 信号通路

IDO1的活性主要在转录水平上受到调节: 干扰素 (interferon, IFN)、病原体相关分子模式 (pathogen-associated molecular patterns, PAMP)、损伤相关的分子模式 (damage associated molecular patterns, DAMPs) 都通过核因子κB (nuclear factor kappa-B, NF-κB) 或细胞因子和生长因子的主要信号传导通路——Jak/STAT通路激活IDO转录[20], 诱导IDO表达, 如图2所示; 翻译水平的调节也可以影响IDO1的活性和半衰期, 如血红素酶调节剂NO可以作用于IDO1上的血红素从而导致酶活性的剂量依赖和可逆抑制[21]。

恶性胶质瘤中的TDO除受色氨酸水平影响调节外, 还受到胆固醇及PGE_2的调节。PGE_2可以与G蛋白偶联受体相结合, 从而上调TDO的表达, 前列腺素还可以通过激活前列腺素E_2受体-4 (EP4) 来增强TDO的表达, EP4的敲低可以抑制TDO的活性及表达[22], 并且在TDO过表达的细胞中, EP4和产生PGE_2的酶COX-2表达增加, 说明这是正反馈调节。

3.2 免疫细胞

IDO能够通过抑制淋巴T细胞和自然杀伤细胞 (natural kill cell, NK) 的活性引起肿瘤细胞的免疫逃逸[23]。由于IDO1在肿瘤微环境中的肿瘤细胞、树突状细胞 (dendritic cell, DC) 和巨噬细胞中高度表达, Trp分解代谢导致Trp消耗和积累Trp相关代谢物, 介导肿瘤免疫逃逸。一方面, 初始T细胞转变为效应T细胞时, 其代谢需求有明显增加。在效应T细胞的活化、增殖和分化过程中, 氨基酸既是生物合成 (如蛋白质和核酸) 的能量来源, 也是底物。当Trp消耗时, 效应T细胞减少, 免疫功能降低[24]。IDO1还可以通过一种丝氨酸/苏氨酸激酶一般性调控阻遏蛋白激酶2 (general control nonderepressible 2, GCN2) 的活化, 下调相关基因影响脂肪酸的合成[25]。当色氨酸的浓度低时,

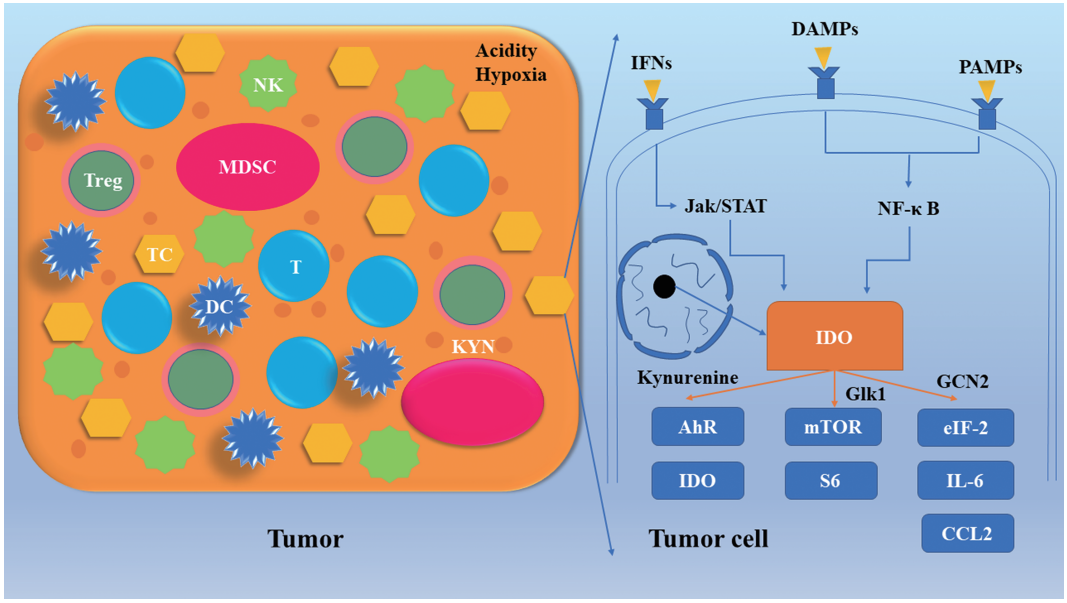

Figure 2　IDO regulation and effector signaling pathways. It shows the microenvironment of tumor cells and several IDO regulation and signaling pathways. Tumor cells are depicted on the right. AhR: Aromatic hydrocarbon receptors; KYN: Kynurenine; NK: Natural kill cell; TC: Tumor cell; DC: Dendritic cell; Treg: Regulatory T cells

GCN2会磷酸化真核生物起始因子2a激酶, 导致蛋白质生产能力下降[26]。

另一方面, 代谢产物AhR的积累诱导调节性T细胞 (regulatory T cells, Tregs) 分化[27], 降低DC功能, 抑制效应T细胞功能。AhR还可以驱动巨噬细胞CD39表达, 从而抑制T细胞活化。AhR促进趋化因子受体CCR2, 而CCR2基因的缺失可以显著降低肿瘤的生长速度[28]。AhR抑制巨噬细胞的核因子NF-κB激活[29], NF-κB可以刺激很多种蛋白的表达, 如肿瘤坏死因子、白细胞介素、CD95等。在蛋白质水平上, IDO1主要通过被蛋白酶体降解来应对免疫原性刺激, IDO1降解可以将耐受性DC转化为免疫原性细胞[30]。肝脏外的IDO1受到促炎细胞因子 (尤其是干扰素γ[31]) 的刺激, 如肿瘤坏死因子α (tumor necrosis factor α,TNFα)、白细胞介素1 (interleukin-1, IL-1) 和IL-2[32], 此外脂多糖 (lipopolysaccharide, LPS) 的影响也十分显著。

因此, Trp耗竭和犬尿氨酸相关代谢物有利于肿瘤免疫逃逸。

3.3　肠道菌群

动物肠道中存在数量庞大的微生物, 肠道菌群是人体中最庞大也是最复杂的微生态系统。存在于肠道中的微生物可以通过合成神经递质、短链脂肪酸或者通过调节免疫反应及氨基酸的代谢来影响大脑的活动[33], 引发脑瘤等多种疾病。

肠道微生物群也会影响犬尿氨酸代谢途径中的酶, 尤其是影响IDO1, 这是因为IDO2与TDO在肠道中不表达。肠道中AhR的活性主要被微生物代谢影响, 肠道菌群的一些代谢产物可以激活AhR, 菌群代谢生成AhR的能力、产生AhR配体的能力及AhR的活性较正常肠道明显降低, 可能会引起肠道屏障损伤[34], 而犬尿氨酸代谢途径的失调可以通过破坏抗肿瘤免疫反应来促进癌症的发展。

肠道中多种细菌门 (放线菌、厚壁菌、拟杆菌、变形杆菌和梭杆菌) 可以代谢色氨酸并产生神经活性代谢物, 如犬尿氨酸、吲哚及衍生物等[35], 吲哚基代谢物可以与AhR结合并不同程度地激活AhR[36], 进一步调节IDO1的活性从而影响肿瘤的发生发展。在Trp耗竭的情况下, 肠道微生物群可以通过同化肠道中可用的Trp, 帮助癌细胞逃避人体免疫作用[37]。

4　色氨酸代谢相关抑制剂

IDO1参与检查点抑制剂的耐药机制, 使IDO1抑制剂与检查点抑制剂的组合成为一种扩大免疫治疗患者群体的有希望的策略[34]。

色氨酸代谢相关抑制剂已经广泛应用于临床前和临床试验。目前靶向色氨酸的药物, 包括IDO抑制剂 (如*D*-1MT)、TDO抑制剂 (如LM10) 及IDO1/TDO双重抑制剂 (如HTI-1090)。

4.1　IDO1抑制剂

几种IDO1抑制剂具有不同的模式作用, 或与Trp竞争IDO1的催化位点, 或与IDO1高亲和力不可逆结合。在过去的几十年里, IDO1在肿瘤发生发展中的作用及机制研究取得了重要进展, 但仅有几个候选化合

物进入临床研究。下面介绍几种常见的IDO1抑制剂。

4.1.1 Trp类似物

4.1.1.1 Indoximod (*D*-1MT) Indoximod是最具代表性的色氨酸类似物抑制剂, 但不是IDO1通路的直接抑制剂: indoximod的一种可能作用机制是调节Trp跨膜运输或模拟Trp调控IDO1下游信号通路。哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 是细胞生长和增殖的重要调节因子, mTOR会参与细胞生长与自噬决策, mTOR的活性会被IDO1抑制, *D*-1MT可以专一性地在Trp耗竭时恢复mTOR的活性, 而不能恢复其他氨基酸 (如亮氨酸、谷氨酰胺和精氨酸) 耗竭时产生的影响[38]。Indoximod能够减轻mTORC1信号通路因为色氨酸消耗而受到的影响。即可以上调mTORC1的活性, 间接地抑制IDO1的作用[20]。

在docetaxel与indoximod联用的I期临床试验时, 显示出较好的耐受性[39], 单药使用时, 也有I期临床试验 (表1) 证明indoximod的安全性、药代动力学性质和免疫学效果良好, 毒性特征较弱, 这也对indoximod未来的持续发展有利。由于缺乏显著的单药活性, 进一步发展的主要重点是研究吲哚莫德与其他免疫疗法和化疗的组合[40]。

Table 1 Clinical trials of the IDO1 inhibitor indoximod

Drug	Stage	Cancer	Clinical trial	process
Indoximod	I	Advanced solid carcinoma	NCT00567931	Completed (good)
Indoximod	II	Prostate cancer	NCT01560923	Completed (good)

总之, indoximod是一种具有广泛潜在用途的重要的IDO抑制剂, 其安全性较好, 并有望改善肿瘤治疗现状[41], 但联合治疗的方案应继续进行临床试验验证。

4.1.1.2 PF-06840003 PF-06840003是一种高选择性IDO1抑制剂, 是活性 (PF-06840002) 和非活性 (PF-06840001) 对映异构体的外消旋混合物,与indoximod不同的是, 它是色氨酸非竞争性抑制剂, 并不会结合IDO1的血红素。目前, 已有针对恶性胶质瘤的I期临床试验证实了PF-06840003的安全性和耐受性及初步抗肿瘤活性[42], 并且PF-06840003联合抗PD-L1比单独使用PF-06840003或抗PD-L1具有更高的体内疗效[43]。

4.1.2 N-羟基脒类

Epacadostat是一种有效的选择性的IDO1抑制剂。Epacadostat可以与色氨酸竞争, 通过羟基脒上的氧原子与IDO1上血红素的铁离子发生配位, 与IDO1的催化结构域结合, 而其他的IDO1抑制剂一般是通过氮原子进行配位[44]。该药物在临床试验前期表现出巨大的潜力, 在药效、安全性、药代动力学、初步抗癌疗效等方面取得了可观的成绩[45], IDO1抑制的百分比最终被定义为血浆KYN水平从用药前到用药后值的降低, 但是epacadostat单药使用时缺乏抗癌活性[46]。

4.1.3 芳基咪唑类

Navoximod (GDC-0919) 也是IDO1的一种小分子抑制剂, 其咪唑环上的氮原子可以与血红素中铁离子形成配位键。它具有良好的口服利用度和药代动力学特征[47], 在高达800 mg BID的剂量下具有良好的耐药性[48]。当GDC-0919与PD-L1抑制剂atezolizumab联用进行I期临床试验时, 显示出良好的安全性、耐药性及药代动力学性质[49]。

4.1.4 喹啉类

Linrodostat (BMA-986205) 是一种高效的选择性的口服IDO1抑制剂, 是目前进入临床的唯一一种不可逆抑制剂。Linrodostat可以占据血红素辅因子结合位点, 以防止IDO1进一步活化, 从而减少犬尿氨酸的生成[50]。Linrodostat在I/II期临床试验中对人IDO1表现出很强的效力, linrodostat联合nivolumab在30例晚期膀胱癌患者中显示了临床活性[51], 并未观察到临床显著的不良反应, 表现出了符合期望的有效性与安全性[52]。目前, 正在进行III期临床试验。此外, 有研究证明linrodostat在与检查点抑制剂联合治疗时效果高于单药使用[53]。

4.2 TDO抑制剂

TDO也是色氨酸代谢的关键酶。过去几十年来, 越来越多的证据表明TDO参与各种疾病, 这促进了对TDO抑制剂的探索[54]。

680C91是一种有效的选择性TDO抑制剂, 680C91对色氨酸与血浆中血清白蛋白的结合没有影响, 可以与色氨酸竞争性抑制TDO[55], 但是溶解度低, 生物利用度差[56]。为了提升这一性质, 研究者们积极开发新的化合物, 最终发现了选择性TDO抑制剂LM10[57]。与680C91类似, LM10显示出对TDO的选择性, 然而LM10具有更加良好的溶解性和生物利用度[57], 进行全身治疗时可以促进表达TDO的肿瘤排斥反应, 毒副作用小。总之, TDO的药理学抑制可能提示了一种安全有效的癌症治疗方法——通过促进肿瘤免疫排斥反应, 从而利用癌症免疫治疗[58]。

4.3 IDO1/TDO双重抑制剂

开发IDO1/TDO双重抑制剂, 将有机会弥补IDO1或TDO抑制剂在临床试验中的不足, 同时扩大抑制剂的癌症治疗范围。IDO1/TDO双重抑制剂RY103可以

显著阻断犬尿氨酸代谢途径, 表现出临床前功效并改善小鼠的IDO1/TDO介导的免疫抑制[59]。除此之外, 还有很多化合物及其衍生物被发现具有IDO1/TDO双重抑制剂活性, 如1-1-苯基-1*H*-萘并[2,3-d][1,2,3]三唑-4,9-二酮衍生物[60]、色聚氰胺衍生物[61]、吲哚-2-羧酸衍生物[62]、4,6-取代-1*H*-吲唑衍生物[63]等。

5　联合治疗现状

目前, 临床试验表明单一使用IDO抑制剂只能起到控制部分病情的作用, 并不能直接杀死肿瘤细胞。而将IDO抑制剂与放疗、化疗等传统手段进行联合使用, 可以起到很好的辅助作用, 并且IDO抑制剂毒性小, 可以持续给药[64]。

5.1　与检查点抑制剂联用

免疫检查点抑制剂是继放疗化疗之后肿瘤治疗的新手段, 但是应用免疫检查点抑制剂单药时的效果也不可观, 研究发现IDO1的过表达仅限于肿瘤微环境[65], 可能是因为肿瘤微环境中存在炎症因子, IDO1的上调与对免疫检查点治疗 (如抗PD-1抑制剂) 的抵抗有关[66]。此外, 抗PD-L1治疗促进色氨酸分解代谢[67], Brown等[68]提出, IDO1酶抑制剂与免疫检查点抑制剂联合使用可能是肿瘤治疗的新疗法, 因此研究者迫切需要提高免疫检查点抑制剂的疗效[69]。各种IDO抑制剂与检查点抑制剂联用的具体情况见表2。

由于epacadostat的单药治疗效果不佳, 临床研究重新关注IDO1抑制剂与已批准的抗癌药物联合治疗。然而, 2018年, ECHO-301 (IDO1抑制剂epacadostat与PD-1检查点抑制剂pembrolizumab联合用药) 用于治疗不可切除或转移性黑色素瘤的III期临床试验以失败告终[46]。尽管如此, 仍有许多研究者认为对于那些具有自然免疫反应的患者而言, IDO1抑制剂epacadostat仍然有效[70], 对于导致ECHO-301研究失败的因素可能与epacadostat剂量低有关, 也可能与未做到精准联合有关[71], 但是研究者们对于IDO抑制剂的研究兴趣依旧高涨。

Epacadostat与一种抗细胞毒性T淋巴细胞相关蛋白 (cytotoxic T-lymphocyte-associated protein, CTLA) ipilimumab的联合使用进行到I/II期临床试验[72], 小于50 mg的epacadostat被证明具有临床和药理活性, 并且在黑色素瘤患者中的耐受性良好。GDC-0919与PD-L1抑制剂atezolizumab联用 (NCT01471846)[49]时也表现出良好的耐药性、药理活性及安全性。

5.2　与疫苗联合使用

肿瘤疫苗是指通过将肿瘤组织中或者人体体液中提取的肿瘤相关抗原注射于肿瘤患者体内, 激活机体免疫系统杀死肿瘤细胞的特异性免疫反应, 以达到控制和治疗肿瘤的目的。同样, 单纯使用疫苗较大程度受到肿瘤微环境等很多方面的影响, 联合用药再次成为研究的新热点。表3中列举了部分疫苗与IDO抑制

Table 2　Clinical trials of combination of IDO inhibitors and immune checkpoint inhibitors. It shows the basics of the combination of IDO inhibitors with immune checkpoint inhibitors. Ipilimumab is cytotoxic T-lymphocyte-associated protein. Pembrolizumab, nivolumab, durvalumab and atezolizumab are programmed death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors. Tamoxifen is a selective estrogen receptor modulator. Sirolimus is a macrolide antibiotic immunosuppressant

Drug combination	Stage	Cancer	Clinical trial	process
Epacadostat + ipilimumab	I/II	Metastatic melanoma	NCT01604889	Completed (poor)
Epacadostat + pembrolizumab	III	Metastatic melanoma	NCT02752074	Completed (good)
	I/II	Melanoma, non-small cell lung cancer, kidney cancer, uterine tumors	NCT02178722	Completed (good)
	III	Lung cancer	NCT03322540	Completed (good)
	II	Gastric cancer	NCT03196232	Completed (good)
	III	Locally advanced or metastatic renal cell carcinoma	NCT03260894	In progress
	II	Head and neck cancer	NCT03238638	Completed (poor)
	II	Ovarian cancer	NCT03602586	Completed (poor)
	II	Bladder cancer	NCT03832673	Completed (poor)
Epacadostat + nivolumab	III	Lung cancer	NCT03348904	Completed (poor)
	II	Advanced malignant melanoma	NCT02327078	Completed (good)
Epacadostat + durvalumab	I/II	Non-small cell lung cancer, head and neck cancer	NCT02318277	Completed (good)
	II	Advanced Epstein-Barr virus positive nasopharyngeal carcinoma	NCT04231864	Completed (poor)
	III	Muscle invasive bladder cancer	NCT03661320	Recruiting
Epacadostat + atezolizumab	I	Lung cancer	NCT02298153	Completed (poor)
Epacadostat + tamoxifen	II	Ovarian cancer	NCT01685255	Completed (poor)
Epacadostat + sirolimus	I	Non-small cell lung cancer	NCT03217669	In progress
GDC-0919 + atezolizumab	I	Solid tumors	NCT02471846	Completed (good)
Indoximod + pembrolizumab	II	Melanoma	NCT02073123	Completed (good)
Indoximod + pembrolizumab + nivolumab	II/III	Melanoma	NCT03301636	Completed (poor)

Table 3 Clinical trials of combination of IDO inhibitors and vaccine

Drug combination	Stage	Cancer	Clinical trial	Progress
Epacadostat + vaccine	II	Melanoma	NCT01961115	Completed (good)
	I/II	Ovarian cancer	NCT02166905	Completed (good)
Indoximod + vaccine	I/II	Metastatic breast cancer	NCT01042535	Completed (good)
Nivolumab + vaccine	II	Metastatic melanoma	NCT03047928	In progress

Table 4 Clinical trials of combination of IDO inhibitors and chemotherapy

Drug combination	Stage	Cancer	Clinical trial	Progress
Indoximod + temozolomide	I/II	Primary malignant brain tumor	NCT02052648	Completed (good)
	I	Primary brain tumor	NCT02502708	Completed (good)
Indoximod + docetaxel	II	Metastatic breast cancer	NCT01792050	Completed (poor)
Indoximod + gemcitabine/paclitaxel	I/II	Metastatic pancreatic cancer	NCT02077881	Completed (good)
Indoximod + docetaxel + vaccine	I/II	Non-small cell lung cancer	NCT02460367	Terminated

剂的联合用药情况。Nivolumab与一种针对IDO与PD-L1的疫苗联用 (NCT03047928) 时, 疫苗可以激活IDO/PD-L1特异性T细胞, 限制由免疫抑制细胞介导的免疫抑制信号的范围, 从而将肿瘤微环境恢复到适合免疫反应进行的正常环境, 联用组合中客观缓解率 (ORR) 达到80%[73]。IDO抑制剂*L*-1MT与DC疫苗联用时也优于单药使用[74]。

5.3 联合化疗

化疗药物和IDO抑制剂联合使用, 如表4所示, 可以展示良好的协同效应, 化疗药物直接杀死肿瘤细胞, 免疫疗法可以激活免疫系统从而杀死肿瘤细胞。另外, 二者在作用时间上也体现出互补性: 化疗药物作用快, 作用时间短, 而免疫治疗可以产生强烈而持久的抗肿瘤作用。化学免疫疗法可以在减少用药剂量的同时, 显著提升治疗效果, 有望成为临床治疗恶性肿瘤的一缕曙光。然而, 这种联合方法常见的问题是两种治疗药物的药代动力学性质、在体内的分布等性质不同, 而纳米药物递送系统具有较好地改善药物药代动力学性质、实现定向定点递送并释放的能力[75]。

最新研究出的混合纳米药物RPMANB NPs可以同时运载化疗药物和IDO抑制剂NLG919, 精准释放并且利用近红外光精准激活化疗药物, 从而放大疗效[76]。IDO抑制剂*D*-1MT联合放疗可以有效延缓荷肺癌小鼠的肿瘤生长[77], 肿瘤生长进展减缓30%[9], 研究者们发现IDO的抑制可以增强化疗的疗效。然而, 在一项针对紫杉烷联合或不联合*D*-1MT治疗转移性乳腺癌的II期临床试验 (NCT01792050) 中, 联合*D*-1MT并没有起到增强药效的作用[78]。

6 问题与展望

色氨酸作为人体必需氨基酸之一, 具有广泛的生理作用。随着PD-1/PD-L1抑制剂被批准应用, 癌症免疫治疗已经取得了巨大的成就。但是只有一小部分患者从中受益, 因此研究者需要开发新的策略来规避原发性或继发性耐药[79]。Trp-Kyn-AhR途径的免疫抑制作用是通过IDO1/TDO介导的Trp耗竭、KYN介导的T细胞相关的适应性免疫功能障碍及随后激活的AhR来介导的。总的来说, 过表达IDO1或TDO2的癌细胞可以逃避免疫监测, 而转录因子AhR通过结合IDO1/TDO2产物KYN参与癌症免疫逃逸。体外针对氨基酸代谢的靶向小分子抑制剂研究已经取得了很大的进展[80], 由于大多数代谢抑制剂无法作为单一有效的治疗药物, 因此联合治疗可能是较为合理的策略, Trp分解代谢靶向药物与免疫疗法的结合, 在免疫治疗领域被赋予了很高的期望。

作者贡献: 张弛负责研究选题、调研整理文献、文章撰写; 严时佳负责提出选题、设计论文框架、修订论文; 万国辉负责提出选题、终审论文。

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