•综述•

犬尿氨酸3-单加氧酶在疾病中的作用及其靶向药物研究进展

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摘要: 犬尿氨酸3-单加氧酶 (kynurenine 3-monooxygenase, KMO) 是机体犬尿氨酸代谢途径 (kynurenine pathway, KP) 分解代谢下游的一种关键限速酶。在KMO催化下, 中间产物犬尿氨酸被代谢为多种活性代谢物, 包括3-羟基犬尿氨酸 (3-hydroxykynurenine, 3-HK)、喹啉酸 (quinolinic acid, QA) 和烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+) 等。越来越多的研究表明, KMO表达活性异常介导KP代谢紊乱, 参与了神经系统疾病、自身免疫病、感染性疾病及肿瘤等的发生发展, 提示其可作为一个潜在、有效的药物治疗靶点。本文重点介绍KMO在多种疾病病理机制中的作用, 并总结了已有的KMO抑制剂, 为靶向KMO治疗提供方法和思路。

关键词: 犬尿氨酸3-单加氧酶; 犬尿氨酸途径; 肿瘤; 神经系统; 免疫系统

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2024)05-1101-12

Advances in the role of kynurenine 3-monooxygenase in disease and its target drugs

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Abstract: Kynurenine 3-monooxygenase (KMO) is a key rate-limiting enzyme in the downstream catabolism of kynurenine pathway (KP). Under the catalysis of KMO, the intermediate product kynurenine is metabolized into various active metabolites, including 3-hydroxykynurenine (3-HK), quinolinic acid (QA) and nicotinamide adenine dinucleotide (NAD^+). More and more studies have shown that abnormal KMO expression activity mediates KP metabolic disorders, and is involved in the occurrence and development of nervous system diseases, autoimmune diseases, infectious diseases and tumors, suggesting that KMO can be used as a potential and effective drug therapeutic target. This article focuses on the role of KMO in the pathological mechanism of various diseases, and summarizes the existing KMO inhibitors to provide methods and ideas for targeted KMO therapy.

Key words: kynurenine 3-monooxygenase; kynurenine pathway; tumour; nervous system; immune system

色氨酸 (tryptophan, Trp) 是机体必需氨基酸之一, 机体超过95%的Trp通过犬尿氨酸途径 (kynurenine pathway, KP) 代谢, 研究表明KP代谢通路紊乱与机体多种疾病发生发展密切相关[1]。犬尿氨酸3-单加氧酶 (kynurenine 3-monooxygenase, KMO) 是一种含有黄素腺嘌呤二核苷酸 (flavin adenine dinucleotide, FAD) 的KP代谢途径关键限速酶[2]。KMO通过调节底物犬尿氨酸 (kynurenine, Kyn) 水平与下游代谢物的平衡参与机体正常Trp-kyn代谢。近年来多项研究结果表明,

收稿日期: 2023-11-02; 修回日期: 2024-02-05.

基金项目: 安徽省自然科学基金面上资助项目 (2108085MH320); 省留学人员创新项目择优资助计划项目 (200LCX019).

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DOI: 10.16438/j.0513-4870.2023-1236

KMO活性与表达升高参与了中枢神经系统疾病、感染性疾病、自身免疫病和肿瘤等疾病的病理进展[3], 提示KMO有望成为治疗这些疾病的一个潜在的有效药物靶点 (图1)。本文就KMO在机体多种病理疾病中的作用以及对于目前KMO抑制剂的相关研究进展作一综述。

1 KMO的结构特征

KMO是一种定位于线粒体外膜的NADPH依赖型氧化还原酶。KMO在人肝肾组织中高表达, 在脑组织中低表达, 主要表达于巨噬细胞和单核细胞中。KMO由一个基因编码, 以黄素腺嘌呤二核苷酸为辅基, 催化NADPH或NADH转变为NADP/NAD, 并具有一个二核苷酸结合域, 因其结构域特点KMO被归类为A类黄素蛋白芳香族羟化酶[4]。人KMO (h-KMO)由486个氨基酸组成, 分子量约为50 kDa[5]。对KMO真核序列的研究结果显示, 其C端有一个约50个氨基酸残基长度的跨膜螺旋结构域, 该结构域主要与线粒体外膜结合[6]。小鼠KMO (mouse-KMO) 由479个氨基酸组成, 与人KMO具有80%一致性, 其主链结构与h-KMO相同, 其C端跨膜结构域氨基酸组成与h-KMO存在显著差异。大鼠KMO (rat-KMO) 结构与人KMO具有78%的一致性, 其主链结构相同, 但C端结构域的氨基酸残基与人类KMO也有显著不同, α12螺旋残基显示出低保守性[7] (图2)。通过对KMO结构的不断深入研究也有助于其抑制剂的设计和进一步作用机制的阐明, 为靶向KMO来治疗相关疾病打下坚实基础。

2 KMO是KP代谢途径重要限速酶之一

Trp在吲哚胺-2, 3-双加氧酶1 (indoleamine 2, 3-dioxygenase 1, IDO1)、吲哚胺-2, 3-双加氧酶2 (indoleamine 2,3-dioxygenase 2, IDO2)及色氨酸2,3-双加氧酶2 (tryptophan 2,3-dioxygenase 2, TDO2)的酶促作用下将底物Trp转变为重要中间产物Kyn[8]。Kyn在KMO催化下产生下游代谢物3-羟基犬尿氨酸 (3-hydroxykynurenine, 3-HK)、3-羟基-2-氨基苯甲酸 (3-hydroxyanthranilic acid, 3-HAA)及喹啉酸 (quinolinic acid, QA), QA经过一系列酶促作用生成最终产物烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD^+)[9] (图3)。在KP代谢通路另一分支上Kyn经犬尿氨酸氨基转移酶I/II (kynurenine aminitricoxide transferase I and II, KAT I/II)代谢为犬尿喹啉酸 (kynurenicacid, KA)。KMO是KP代谢过程中的关键限速酶, 机体通过动态调节KMO活性与水平, 使Kyn与KMO下游代谢物始终保持在稳定水平, 进而调节机体各项生理功能。

3 KMO介导KP代谢失衡在疾病中的作用

3.1 中枢神经系统疾病

3.1.1 亨廷顿舞蹈症 亨廷顿舞蹈症 (Huntington's disease, HD)是一种遗传性神经退行性疾病[10]。KP异常与包括HD在内的几种神经退行性疾病发病机制密切相关[11]。在疾病进展早期, HD患者大脑新纹状体和皮层中3-HK和QA水平升高[12]。3-HK通过氧化还原反应生成超氧化物和过氧化氢引起神经元细胞损伤和

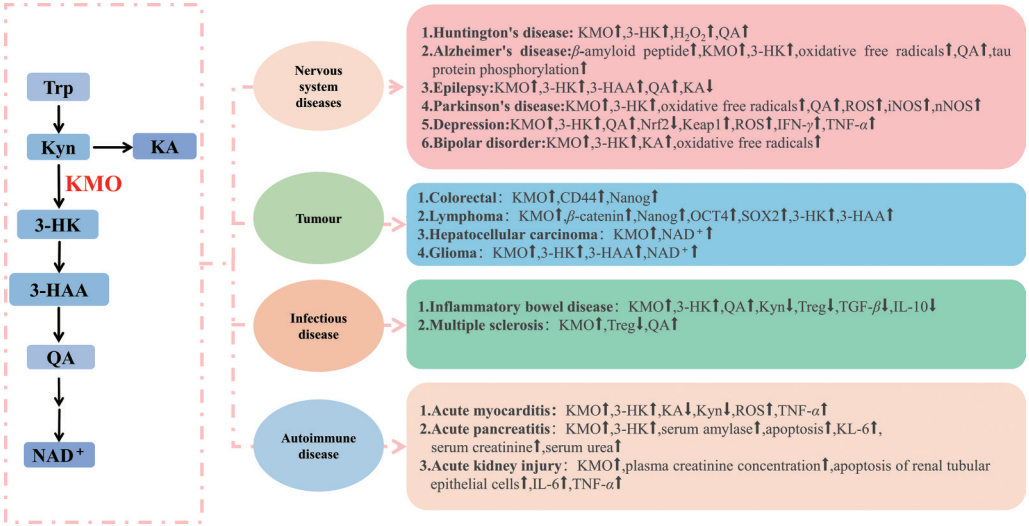


Figure 1 The involvement of KMO in diversity diseases. KMO: Kynurenine 3-monooxygenase; Trp: Tryptophan; Kyn: Kynurenine; KA: Kynurenic acid; 3-HK: 3-Hydroxykynurenine; 3-HAA: 3-Hydroxyanthranillic acid; QA: Quinolinic acid; NAD^+: Nicotinamide adenine dinucleotide; ROS: Reactive oxygen species; iNOS: Inducible nitric oxide synthase; nNOS: Neuronsal nitric oxide synthase; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; IFN-γ: Interferon γ; TNF-α: Tumor necrosis factor-α; OCT4: Octamer-binding transcription factor 4; SOX2: SRY-box transcription factor 2; Treg: Regulatory T cell; TGF-β: Transforming growth factor β; IL-10: Interleukin 10; KL-6: Krebs von den Lungen-6; IL-6: Interleukin 6

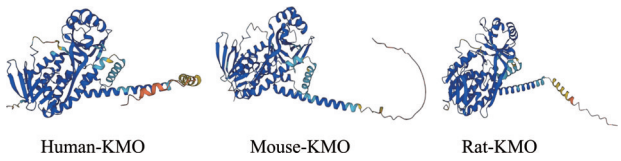


Figure 2　Three-dimensional structure of human-KMO, mouse-KMO and rat-KMO in complex

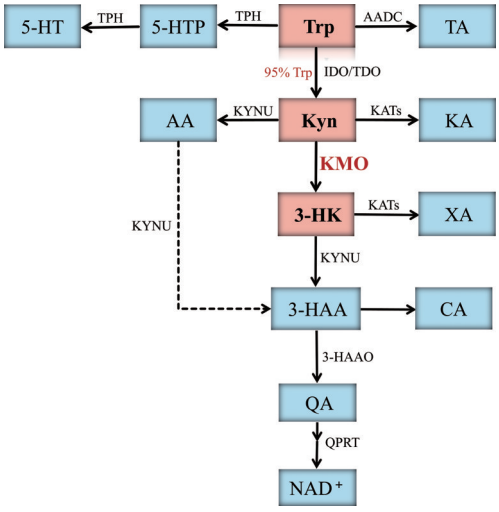


Figure 3　Trp-Kyn metabolic pathway. 5-HTP: 5-Hydroxytryptopha; 5-HT: Serotonin; TA: Tryptamine; AA: Anthranillic acid; XA: Xanthurenic acid; CA: Cinnabarinic acid; TPH: Tryptophan hydroxylase; AADC: Amino acid decarboxylase; IDO: Indoleamine 2, 3-dioxygenase; TDO: Indoleamine 2, 3-dioxygenase; KYNU: Kynureninase; KATs: Kynurenic aminotransferase; 3-HAAO: 3-Hydroxyanthranilate 3, 4-dioxygenase; QPRT: Quinolinate phosphoribosyltransferase

凋亡[13,14]。QA水平升高通过激活*N*-甲基-*D*-天冬氨酸受体 (*N*-methyl-*D*-aspartate receptor, NMDAR) 导致神经元细胞过度去极化、钙离子内流增加及神经毒性[15]。HD由亨廷顿蛋白 (Huntingtin, HTT) 结构末端谷氨酰胺残基 (polyQ) 不稳定扩增导致, 有研究表明KMO与HTT可在线粒体内膜处发生相互作用, 当HTT的polyQ扩增时会破坏这种相互作用导致疾病发生[16]。在R6/2转基因HD模型小鼠及HTT突变的HD模型小鼠中, 给予KMO抑制剂后导致Kyn升高, 进而引起KA增加, 而KA作为NMDAR的拮抗剂能防止神经元过度去极化产生神经保护作用, 进而改善疾病症状[17-20]。

3.1.2　阿尔茨海默病　阿尔茨海默病 (Alzheimer disease, AD) 是一种慢性进行性神经退行性疾病, AD患者认知能力逐渐下降的病理机制在于大脑中产生聚集性的淀粉样蛋白, 淀粉样蛋白的前体为37～43个氨基酸组成的不溶性结构, 称为Aβs[21]。临床前研究结果表明, 在AD模型小鼠大脑斑块中A$\beta_{1\text{-}42}$ (β淀粉样多肽) 升高以及神经促炎细胞因子上调了KMO活性[22]。多项研究表明, AD患者血清3-HK和QA浓度升高, KA水平下降[23-25]。3-HK通过产生过量自由基损伤神经元以及QA过度激活NMDAR导致神经毒性。研究发现, QA诱导人类神经元细胞中tau蛋白磷酸化, 而高水平磷酸化的tau蛋白则与AD发病机制密切相关[26]。在神经细胞β-淀粉样前体蛋白 (APP) 转基因动物 (APPtg) 的AD自发性小鼠模型中, 给予KMO抑制剂JM6可以减轻AD小鼠神经元损伤和突触损伤, 这可能与其上调模型小鼠大脑斑块中KA浓度从而抑制兴奋性神经元过度激活有关[17]。

3.1.3　帕金森病　帕金森病 (Parkinson disease, PD) 是一种慢性进行性神经退行性疾病, 其主要特征性病理表现为PD患者大脑黑质致密部多巴胺能神经元功能选择性病变[27]。研究发现, PD患者大脑硬壳核、前额皮质和黑质致密部中KMO表达上调, KMO代谢产物3-HK和QA水平明显升高, PD和AD相似, 3-HK通过产生自由基、过氧化氢和超氧离子导致神经元变性和细胞凋亡[28,29]。动物实验结果显示, 在多巴胺能神经毒素处理的猕猴模型大脑中, 中脑黑质区域的小胶质细胞被激活后产生大量QA[30], 而QA通过过度激活NMDAR导致神经毒性[31]。QA还通过促进神经元细胞释放谷氨酸、阻断星形胶质细胞摄取及合成谷氨酰胺酶, 从而引起微环境谷氨酸增高以及神经毒性的产生[32]。研究发现氧化应激导致线粒体功能障碍会诱导PD患者大脑黑质致密部神经元发生非功能性和错误折叠[33], 而QA除了介导兴奋性毒性外, 还与Fe^{2+}形成络合物发生氧化还原反应产生大量活性氧 (reactive oxygen species, ROS) 导致神经元细胞诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 及神经元型一氧化氮合酶 (neuronsal nitric oxide synthase, nNOS) 表达升高[34], 降低电子传递链线粒体复合物I活性, 继而引起线粒体功能障碍有关[35]。以上研究结果显示, 抑制KMO活性进而减少3-HK和QA产生可能是治疗PD的一种潜在有效策略。

3.1.4　癫痫　癫痫是最常见的神经系统疾病之一, 可在任何年龄发病, 影响着全球7 000多万人[36]。人类癫痫的发作和维持与机体兴奋性氨基酸产生过多有关。研究表明, 癫痫模型小鼠大脑皮层中KMO表达增加, 3-HK、3-HAA和QA浓度升高, 而神经保护性产物KA水平明显降低[37]。Heyes等[38]在一项临床研究中发现癫痫患者脑脊液和血清中3-HK与QA水平升高, QA通过激活NMDAR促进神经元细胞释放谷氨酸, 增加神经元活动并诱导其癫痫样放电。动物实验发现过高

剂量QA引起正常大鼠大脑海马体锥体细胞和颗粒细胞发生变性进而引发癫痫症状[39]。因此, 抑制KMO活性、降低QA含量并增加KA水平可能有助于缓解癫痫症状。

3.1.5 抑郁症 KP代谢异常被认为是抑郁症发病的一个重要因素[40]。动物实验结果发现, 在坐骨神经损伤 (sciatic nerve injury, SNI) 小鼠模型中诱导神经性疼痛与抑郁样行为, 结果显示, 与对照组小鼠比较, SNI模型小鼠神经损伤后出现炎性症状, 小鼠海马体神经元中KMO表达升高, KMO代谢物3-HK与QA水平增加, 给予KMO抑制剂后显著逆转了神经损伤带来的抑郁样行为[41]。Bansal等[42]在分子对接实验中发现QA与泛素蛋白酶体复合物以及磷脂酰肌醇3-激酶 (phosphoinositide 3-kinase, PI3K) 具有良好的亲和力, QA通过PI3K/蛋白激酶B (protein kinase B, AKT) 及糖原合酶激酶3β (glycogen synthase kinase3β, GSK3β) 途径抑制了核转录因子红系2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 的表达, 与此同时促进了kelch样ECH关联蛋白1 (kelch-like ECH-associated protein 1, Keap1) 表达, 促进小胶质细胞ROS以及干扰素γ (interferon γ, IFN-γ) 和肿瘤坏死因子α (tumor necrosis factor α,TNF-α) 等炎症因子产生。给予KMO抑制剂后, 模型小鼠海马体与前额叶皮层中Nrf2 mRNA水平升高, Keap1蛋白表达降低, ROS水平降低, 五羟色胺 (5-hydroxytryptamine, 5-HT) 和五羟吲哚乙酸水平上升。Mori等[43]一项动物实验结果显示, 与WT小鼠相比, KMO-KO小鼠大脑前额叶皮层中KAT I和α7烟碱型乙酰胆碱受体 (α7 nicotinic acetylcholine receptor, α7nAChR) 的mRNA水平升高, 代谢物KA水平升高, KA对于α7nAChR的非竞争拮抗作用比NMDAR更强, KMO-KO小鼠表现出强烈的抑郁样行为。这些数据表明, KMO可能参与了与炎症和Kyn代谢改变相关抑郁行为的发病机制, 提示KMO可能成为未来治愈抑郁症的新方向。

3.1.6 双相情感障碍 双相情感障碍 (bipolar disorder, BD) 是一种伴有非特异性大脑结构变化和认知能力下降的慢性精神疾病[44-46]。Johansson等[47]研究发现, 分离培养BD患者皮肤成纤维细胞, 给予IFN-γ、TNF-α、白介素1β (interleukin-1β, IL-1β) 及白介素6 (interleukin-6, IL-6) 等细胞因子进行刺激后, KP代谢物3-HK和KA水平均明显增加。Birner等[48]临床研究表明, Trp分解代谢产物异常参与了BD病理过程。在143名BD患者和101名健康人血清中, BD患者3-HK/Kyn比值升高, KMO催化Kyn产生3-HK水平上升, 进而产生氧化自由基导致神经毒性产生。

3.2 肿瘤

3.2.1 结直肠癌 结直肠癌 (colorectal cancer, CRC) 是常见的恶性肿瘤之一, 其发病率和死亡率呈逐年上升趋势[49]。KP通路异常在促进癌症进展过程中发挥关键作用, Kyn及其下游代谢产物与CRC发生密切相关[50]。研究发现, CRC患者肿瘤组织中KMO表达高于健康组织和肠道息肉组织, 而高水平KMO与低水平生存率相关, 给予KMO特异性抑制剂Ro 61-8048后可明显抑制SW480、HCT-116、HCT-15和Lovo等结直肠癌细胞系球体的形成、侵袭和转移等, 并降低了CD44 (也被称为Hermes、Pgp1、H-CAM或Hutch, 是一种复杂的跨膜黏附糖蛋白) 及Nanog (一种DNA结合同源框转录因子) 表达[51]。CD44是结直肠肿瘤干细胞 (colorectal stem cell, CSC) 的表面标志物[52], CSC参与结直肠癌的生长、转移和复发[53]。转录因子Nanog能够调节多能干细胞的增殖与分化, 研究显示Nanog高表达与CRC预后不良和淋巴结转移有关[54]。以上结果提示, 靶向抑制KMO在CRC中会产生积极作用, 但是KMO对于CRC的免疫调节的生物学机制还未明确阐明, 因此抑制KMO表达在CRC细胞中的抗癌作用机制需要进一步研究。

3.2.2 乳腺癌 乳腺癌是仅次于肺癌的全球第二大常见癌症, 也是女性癌症死亡的主要原因[55]。Tsang等[56]利用分子表征的方法对TCGA和GTEx等数据库进行分析, 结果表明乳腺癌患者肿瘤组织中KMO表达显著升高, KMO水平与乳腺癌患者生存率呈负相关, 而与其复发率呈正相关, 其机制可能与KMO促进肿瘤组织中CXC趋化因子配体10、CXC趋化因子配体11、干扰素调节因子1等趋化因子以及IL-6、白介素12 (interleukin-12, IL-12) 和TNF-α等促炎因子表达有关, 进而促进了乳腺癌的发生发展。研究表明, 在健康人群与不同亚型的乳腺癌患者血清中, 乳腺癌患者尤其是在富含人表皮生长因子受体2 (human epidermal growth factor receptor 2, HER2) 的乳腺癌分型中, KMO表达及其下游代谢物3-HK与3-HAA的水平明显升高[57]。Fallarino等[58]发现3-HK能够抑制$CD4^+$ T细胞增殖, 而3-HAA也被证明可以抑制$CD8^+$ T细胞增殖[59]。三阴性乳腺癌 (triple negative breast cancer, TNBC) 患者占乳腺癌总人数的15%～20%, TNBC患者其雌激素受体、孕激素受体和人表皮生长因子受体均为阴性, 是一种预后较差的乳腺癌亚型[60]。β-catenin作为一种转录因子, 介导Wnt信号传导, 控制细胞正常生长、增殖以及维持干细胞的特征[61]。研究发现与癌旁组织对比, KMO在TNBC患者肿瘤组织中表达明显升高; 免疫共沉淀方法发现, 人源乳腺癌细胞

系MDA-MB-468细胞中KMO与β-catenin发生相互作用, KMO通过调节β-catenin表达, 进一步调节Nanog、OCT4和SOX2等基因表达, 促进肿瘤的生长、侵袭和转移, 在动物实验中, 将CRISPR KMO-KD细胞与对照MDA-MB-231细胞静脉注射到NOD-SCID免疫缺陷小鼠尾静脉中构建乳腺癌模型, 结果表明注射CRISPR KMO-KD细胞的模型小鼠乳腺肿瘤生长及转移减少, 生存率也明显提高[62], 提示靶向KMO/β-catenin轴是治疗TNBC的一种潜在有效的方法。

3.2.3　肝细胞癌　肝细胞癌 (hepatocellular carcinoma, HCC) 是世界上第五大常见癌症[63]。多项研究表明, KP下游代谢产物3-HK、QA及KA等与HCC的病理过程相关[64-66]。与邻近非肿瘤肝组织相比, HCC患者肿瘤组织中KMO水平异常升高, KMO表达增加导致HCC肿瘤组织中NAD^+水平升高, 进而参与HCC进展[67]。但另一项研究表明, KMO及其底物3-HAA在人源HCC细胞系HepG2等细胞及HCC组织中均降低, KMO过表达以及3-HAA治疗逆转了Kyn的促肿瘤作用, 并显著提高了IDO1/2抑制剂对肝癌异种移植的疗效[68]。目前, KMO在HCC中的作用尚未明确, 还需要更多的证据来阐明其功能。

3.2.4　神经胶质瘤　神经胶质瘤是最常见的大脑原发性中枢神经系统肿瘤[69]。研究发现, 与未刺激的胶质瘤细胞相比, IFN-γ刺激的胶质瘤细胞中KMO表达上调[70], 大脑胶质瘤组织中KMO和犬尿氨酸酶 (kynureninase, KYNU) 上调导致3-HK和3-HAA产生增加, 发挥免疫抑制作用。Vázquez等[71]发现, 多形性胶质母细胞瘤 (glioblastoma multiforme, GBM) 多种肿瘤细胞系中KMO表达均升高, 与其他神经系统疾病的患者脑组织相比, KMO表达在GBM患者肿瘤组织中升高。可能与KMO的表达升高导致下游NAD^+水平增加有关, 而NAD^+代谢可通过$CD8^+$ T细胞依赖的方式驱动肿瘤免疫逃避, 从而促进恶性肿瘤发展[72]。也有相反的研究显示, KMO下游代谢物3-HK、3-HAA及QA可降低GBM细胞增殖, 增加其凋亡[73]。由于KMO在肿瘤代谢和免疫抑制中的作用, 可能会成为神经胶质瘤的潜在重要研究靶点。

3.3　自身免疫病

3.3.1　炎症性肠病　炎症性肠病 (inflammatory bowel disease, IBD) 是以临床病理特征为慢性肠道炎症导致肠黏膜损伤的一种自身免疫病[74]。Nikolaus[75]收集了IBD患者和健康人群外周血, 结果显示IBD患者血清中3-HK及QA水平较健康对照组明显升高。体内2,4,6-三硝基苯磺酸诱导的溃疡性结肠炎小鼠模型中, KMO在模型小鼠结肠组织中表达增加, 敲除KMO基因后Kyn浓度增加, 小鼠结肠组织当中调节性T细胞 (regulatory T cells, Tregs) 增多[76], 而Treg可以分泌转化生长因子β (transforming growth factor-β, TGF-β) 抑制结肠组织中辅助T细胞1及辅助T细胞17的活化, 从而减轻炎性症状[77]。另外, 体内给予Kyn治疗后可减轻小鼠结肠炎性症状, 抗炎因子TGF-β和IL-10水平升高。结果表明, 给予Kyn或抑制KMO对Treg诱导非常重要。

3.3.2　多发性硬化症　多发性硬化症 (multiple sclerosis, MS) 是一种以中枢神经系统神经元脱髓鞘为特征的炎症性神经退行性疾病[78]。Sundaram等[79]研究表明, 体内给予KMO特异性抑制剂Ro 61-8048后显著改善实验性自身免疫性脑脊髓炎 (experimental autoimmune encephalomyelitis, EAE) 小鼠临床评分, 大脑和脊髓中QA水平下降, KA水平增加, Treg数量显著增加。而在EAE小鼠模型中, QA与小胶质细胞显示出强烈共定位, 过高水平QA可作用于NMDA受体, 会导致神经炎症与神经变性, 诱导神经元和神经胶质细胞死亡, 进而导致神经元脱髓鞘形成, 引发MS[80]。

3.4　感染性疾病

3.4.1　急性心肌炎　急性心肌炎是扩张型心肌病和心源性猝死的常见原因, 通常由嗜心肌病毒 (encephalomyocarditis virus, EMCV) 感染引起, 随后导致心肌炎症性破坏[81]。病毒性心肌炎常因中性粒细胞和嗜酸性粒细胞浸润心肌而产生一系列炎性症状[82]。小鼠EMCV感染是病毒性心肌炎的常用模型[83]。Kubo等[84]构建了WT与KMO-KO EMCV小鼠模型, 研究结果显示, 与正常对照组相比, WT-EMCV小鼠心肌组织KMO表达和血清3-HK水平升高。与WT-EMCV小鼠相比, KMO-KO模型小鼠死亡率下降, 心肌组织中中性粒细胞和巨噬细胞浸润减少, 血清炎性因子TNF-α、IL-6以及趋化因子配体3、趋化因子配体4和趋化因子配体2水平下降, KP代谢物KA和Kyn水平上升。而Kyn可以通过产生ROS抑制T细胞与自然杀伤细胞增殖, KA激活G蛋白偶联受体35 (G protein-coupled receptor 35, GPR35) 进而抑制巨噬细胞产生TNF-α[85-87]。趋化因子产生受核因子κB (nuclear factor kappa-B, NF-κB) 信号通路的调节[88,89], 而KP代谢物3-HAA可抑制NF-κB活化[90], 故推测KP代谢物可能通过抑制NF-κB信号传导抑制趋化因子配体2、趋化因子配体3、趋化因子配体4及CXC趋化因子配体1产生, 从而提高小鼠EMCV感染时的存活率。因此, 抑制KMO表达可能通过调节免疫细胞募集及NF-κB信号通路改善小鼠急性心肌炎的炎性症状。

3.4.2　急性胰腺炎　急性胰腺炎 (acute pancreatitis,

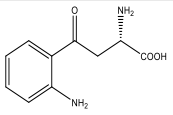
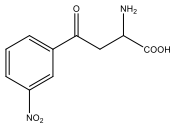
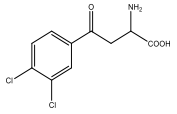
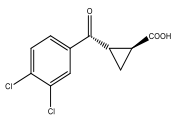
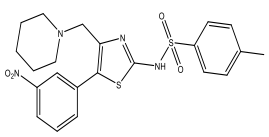
AP) 是一种无菌胰腺组织局部炎症性疾病, 大约25%的AP患者会产生全身性炎症反应, 从而导致多器官功能障碍综合征 (multiple organ dysfunction syndrome, MODS)[91]。引起AP-MODS的确切病理机制尚不清楚, 但KP代谢通路异常已经被认为是导致AP-MODS的一个重要原因[3,92]。一项临床试验发现, 通过检测血清C反应蛋白水平、血清淀粉酶浓度和炎性细胞因子含量将受试者病情分为轻、中、重度, 随后测量3种类型受试者血浆中KP代谢物水平和KMO表达, 结果发现KMO水平及其下游代谢物3-HK浓度升高与AP患者机体炎性表现、器官功能障碍发生率和疾病严重程度呈正相关[93]。Mole等[3]构建实验性AP模型发现, WT模型小鼠与KMO-KO模型小鼠的胰腺组织学评分无明显差异, 但KMO-KO模型小鼠血清淀粉酶浓度较低, 肺组织和肾脏组织中凋亡细胞数量明显减少, 肝细胞坏死标志物丙氨酸氨基转移酶水平下降。在WT-AP小鼠中给予KMO抑制剂GSK180后, 胰腺组织学评分下降, 中性粒细胞与巨噬细胞浸润减少, 肺部支气管灌洗蛋白浓度及肺部损伤生物标志物涎液化糖链抗原 (Krebs von den Lungen-6, KL-6) 水平降低, 肾小管外髓质凋亡细胞减少, 血清肌酐和尿素浓度下降。机制可能是抑制KMO后KA水平升高, 进而激活GPR35, 抑制TNF-α释放, 发挥抗炎作用[94]。KMO抑制后, Kyn水平升高, 升高的Kyn与芳香烃受体结合后可抑制Th17细胞释放炎性细胞因子[95]、抑制$CD4^+$ T细胞和$CD8^+$ T细胞增殖[95]以及增加Treg产生[96]。此外, Kyn增加可能有助于机体自由基清除, 对活化的中性粒细胞产生ROS具有浓度依赖性抑制作用[97]。开发KMO抑制剂在未来对于治疗AP具有较好应用前景。

3.4.3 急性肾损伤 肾脏缺血再灌注损伤 (ischemia-reperfusion injury, IRI) 导致的急性肾损伤死亡率高, 并且缺乏特异性治疗[98]。Zheng等[99]构建了WT与KMO-KO的IRI小鼠模型, KMO-KO模型小鼠血浆肌酐浓度降低, 尿白蛋白/肌酐比值减少, 肾小管损伤程度改善, TUNEL染色结果显示KMO-KO模型小鼠肾小管上皮细胞凋亡减少, 中性粒细胞与巨噬细胞浸润降低, 促炎细胞因子IL-6与TNF-α水平下调, 趋化因子CXC配体1和CXC配体2 mRNA表达降低, 结果显示, 抑制KMO的表达对IRI导致的急性肾损伤具有缓解作用。

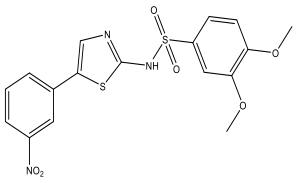
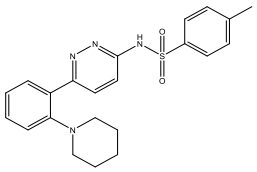
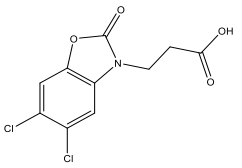
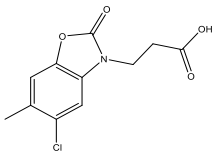
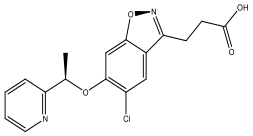
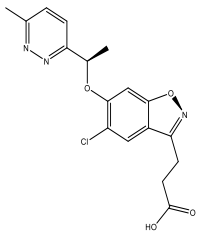
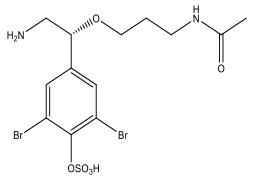
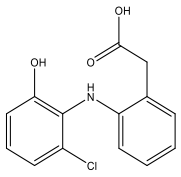
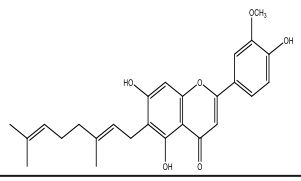
4 KMO抑制剂

近年来, 对KMO蛋白结构研究不断深入, 人们通过对酿酒酵母菌、荧光假单胞菌和大鼠中的KMO蛋白进行纯化和结晶, 并通过X射线衍射技术对其全长三维结构进行探究, 明确阐明了KMO蛋白活性位点结构, 新的KMO抑制剂开发也取得了重大进展, 在虚拟化合物库中进行高通量筛选, 并通过计算机辅助药物设计功能开发了多种新的KMO抑制剂。因此, 本文总结了几种KMO抑制剂, 并根据其化学类别进行了分类 (表1)[2,6,10,19,100-107]。

Table 1 KMO inhibitor

Name	Chemical structure	IC_{50}/μmol·L^{-1}	Disease	Ref.
L-Kynurenine		17.4	Not applied	[100]
m-NBA		0.90	Huntington's disease	[101]
FCE28833		0.20	Huntington's disease	[102]
UPF648		0.020	Huntington's disease, Alzheimer's disease, triple negative breast cancer	[103]
M6		0.037	Huntington's disease, Alzheimer's Disease	[19]

Continued

Name	Chemical structure	IC_{50}/μmol·L^{-1}	Disease	Ref.
Ro 61-8048		0.037	Depression/multiple sclerosis, ulcerative colitis, Huntington's disease, Alzheimer's disease, triple negative breast cancer	[104]
N-(6-Phenylpyridazin-3-yl) benzenesulfonamides		0.003 3	Huntington's disease	[19]
GSK180		0.006	Acute pancreatitis	[2]
GSK428		0.001	Acute pancreatitis	[6]
GSK065		0.000 002 3	Acute pancreatitis	[10]
GSK366		0.002 3	Acute pancreatitis, Huntington's disease	[10]
Ianthellamide A		0.001 5	Neurodegenerative disease	[105]
Diclofenac		0.013 6	Not applied	[106]
Cannflavin A (CFA)		0.029 4	Not applied	[107]

4.1　底物类似物

在KMO晶体结构被发现之前, 开发临床使用的KMO抑制剂十分困难。KMO结构信息缺乏导致早期开发KMO抑制剂只能模仿内源性配体*L*-Kyn类似物的结构[108]。烟酰丙氨酸在结构上与*L*-Kyn非常相似, 对KMO和KYNU都有微弱的非特异性抑制作用, 体

内给药后可导致大鼠脑组织中Kyn水平升高[100]。随着KMO晶体结构的发现, 研究人员开始基于结构设计KMO抑制剂。间硝基苯甲酰丙氨酸 (m-NBA) 是首个发表的KMO特异性抑制剂[109]。通过对于底物结构的修饰, 芳香环上第三和第四位置的卤素取代 (3,4二氯和3,4二氟衍生物) 证明可以产生更有效的抑制作用。紧接着3,4-二氯苯甲酰丙氨酸 (3,4-cba或FCE 28833) 被开发, 显示出与m-NBA相似且更有效的特点[102]。但底物类似物在结合KMO活性位点并抑制活性的同时, 还通过解偶联NAD(P)H和O_2的方式, 导致细胞毒性物质过氧化氢的产生[108]。UPF648, 化学名称为2-(3,4-二氯苯甲酰)-环丙烷-1-羧酸, 是另一种被广泛研究的KMO抑制剂。研究表明, 在啮齿动物模型中, UPF648通过降低神经毒素3-HK和QA浓度并产生神经保护代谢物KA发挥神经保护作用[103]。然而, 虽然UPF648抑制了KMO的活性, 但它也显著增加了近20倍的过氧化氢产生。此外, UPF648的最大弊端是不能穿过血脑屏障, 因此难以在神经系统疾病中发挥作用[17]。

4.2 磺胺类药物

Ro 61-8048是具有强效、选择性和最广泛的KMO抑制剂, 可有效治疗各种类型的神经退行性疾病[104]。研究表明, Ro 61-8048通过阻止底物进入或产物释放对KMO产生变构抑制作用, 这有助于进一步优化Ro 61-8048和开发新的KMO抑制剂[17]。Ro 61-8048的前药JM6尽管不能穿过血脑屏障, 但是临床前研究结果表明JM6可以减轻阿尔茨海默病模型小鼠神经退行性病变的临床表现。此外, *N*-(6-苯基吡啶嗪-3-基)苯磺酰胺是一种新型先导化合物, 与CHDI-340246相比, 对KMO表现出同等强度的抑制活性, 且在血脑屏障穿透方面优于CHDI-340246。该化合物通过抑制神经毒性产物3-HK产生, 并增加KA水平, 从而对R6/2小鼠产生神经保护作用[19], 服用该化合物可改善HD小鼠受损的认知功能。

4.3 恶唑烷酮类药物

GSK180是葛兰素史克公司开发的恶唑烷酮化合物, 是一种来自Kyn底物的强效特异性KMO抑制剂[2]。先前的研究已经证实GSK180可以对AP啮齿动物模型的多器官衰竭发挥治疗保护作用, 这为危重疾病的药物发现开辟了一个新的领域。GSK428也是一种具有结构修饰的底物竞争性结合化合物, 在与荧光假单胞菌KMO (Pf-KMO) 配合物的X射线结构中表现出更具吸引力的结合模式[6]。然而, GSK428的烷氧基吡啶衍生物GSK775和GSK891在非竞争行为中占据了*L*-Kyn位点, 这也进一步阐明了该化合物的结合动力学特征。Pf-KMO结构提供了更完整的催化位点图像, 并显著提高了基于KMO结构的药物设计能力。

4.4 苯并异恶唑类药物

在GSK775晶体结构的基础上, 通过修饰杂环核心基团设计出了更多的分子, 进一步改善了抑制剂的药物性能。如研究发现GSK065和GSK366在AP疾病模型中通过结合模式修饰进行临床前评估, 结果表明这两种化合物结合袋中黄素基团的转换能力能够促进新型KMO抑制剂的开发[10]。GSK3335065是一种新型KMO抑制剂, 正在开发用于治疗AP。在接受1.3 mg GSK3335065的单个受试者中, 发现Trp途径代谢物变化与临床前研究中观察到的变化一致, 表明KMO酶活性被抑制后AP临床症状也显著减轻[110]。

4.5 其他类药物

Ianthellamide A是从澳大利亚海洋植物角蕨中分离出来的衍生物。相关实验证明ianthellamide A能够选择性地抑制KMO的活性, 其IC_{50}为1.5 μmol·L^{-1}[105]。从结构上看, 该化合物明显不同于天然底物Kyn, 彻底改变了人们对KMO活性位点中基质刚性结合模式的理解。然而, ianthellamide A是否能在大脑中产生足够水平的KA作为神经保护剂仍有待观察。双氯芬酸作为抗炎药物已通过分子相似性方法被证实可以与h-KMO蛋白结合并抑制其活性[106]。对cannflavin A (CFA, 是一种从植物大麻中提取纯化的苜蓿类黄酮类物质) 和一系列植物大麻素抗KMO活性进行了评估, 结果表明CFA对KMO的抑制作用最强, 与阳性对照Ro 61-8048相当。此外, 分子对接研究阐明了CFA与KMO蛋白之间分子相互作用, 结果表明CFA与KMO蛋白的结合亲和力为4.1×10^{-5} mol·L^{-1}。SPR竞争性结合分析结果表明, CFA和Ro 61-8048以竞争性方式与KMO蛋白结合[107]。这些发现表明大麻衍生的植物化学物质包括CFA是潜在的KMO抑制剂, 这为针对KP及其相关病理疾病的治疗方法发展提供了新的思路。

5 结论与展望

KP是Trp代谢调控通路之一, 在多种生物代谢过程中发挥独特作用。KP代谢失衡与细胞活性、免疫细胞反应和组织损伤等多种生物过程相关。KMO是KP中关键限速酶, 它决定Kyn向3-HK的转化, 并影响下游代谢物如KA、3-HK、QA和NAD^+的产生。近年来, 随着对KMO研究的不断深入, KMO酶活性失调在神经系统疾病、肿瘤、自身免疫病及感染性疾病中均发挥重要作用, 可能成为多种疾病的潜在治疗靶点。KP代谢紊乱与多种炎症免疫相关疾病有关, 而KMO作为KP中重要限速酶之一, KMO及其下游代谢产物如何调节机体免疫功能、主要作用于机体哪些免疫细胞的

研究尚需进一步阐明。其次KMO是否可以通过非酶作用直接调节机体免疫细胞信号传导参与疾病进展,将是KMO功能研究的重点之一。随着对KMO蛋白结构的不断研究深入,已研发出多种KMO抑制剂,这些抑制剂在动物实验中应用较多,而目前进入临床试验的抑制剂较少,在未来研究者需要通过更多的临床试验来验证这些抑制剂的有效性,以期弥补目前临床治疗神经系统疾病、肿瘤及炎症免疫相关性疾病治疗药物的不足,具有重要意义。

作者贡献: 王燚负责撰写全文,并进行修改; 常艳和魏伟负责选题,并对文章进行指导并提出合理的修改意见。

利益冲突: 所有作者均声明不存在利益冲突。

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