IDO1介导的色氨酸代谢在脓毒症中的研究进展

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摘要: 脓毒症是由感染引起的全身炎症反应导致的器官功能障碍, 过度炎症和免疫抑制交织存在, 严重者甚至可发展为多器官功能衰竭。研究表明, 吲哚胺-2,3-双加氧酶1 (indoleamine 2,3-dioxygenase 1, IDO1) 介导的色氨酸代谢参与了脓毒症的发生发展过程, 血浆犬尿氨酸水平和犬尿氨酸/色氨酸 (kynurenine/tryptophan, Kyn/Trp) 比值升高是败血症发展的早期指标。本文系统总结了IDO1在脓毒症急性炎症期、后期免疫抑制及器官损害过程中所发挥的作用, 主要包括对炎症状态、免疫细胞功能、血压及其他环节的调节, 同时对靶向IDO1药物临床前研究进行了分析。深入了解和研究IDO1可能有助于从全新的角度认识脓毒症和多器官损害的发病机制及临床意义, 并为探索其防治方法提供新的研究思路。

关键词: 脓毒症; 吲哚胺-2,3-双加氧酶1; 免疫激活; 炎症; 低血压
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Research progress of IDO1-mediated tryptophan metabolism in sepsis

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Abstract: Sepsis is a condition characterized by organ dysfunction resulting from the systemic inflammatory response triggered by an infection. Excessive inflammation and immunosuppression are intertwined, and severe cases may even develop into multiple organ failure. Studies have shown that indoleamine 2,3-dioxygenase 1-mediated tryptophan metabolism is involved in the occurrence and development of sepsis, and elevated plasma kynurenine levels and Kyn/Trp ratios are early indicators of sepsis development. In this paper, we provide a comprehensive summary of the role of IDO1 in the acute inflammatory phase of sepsis, late immunosuppression, and organ damage. This includes its regulation of inflammatory state, immune cell function, blood pressure, and other aspects. Additionally, we analyze preclinical studies on targeted IDO1 drugs. An in-depth understanding and study of IDO may help to understand the pathogenesis and clinical significance of sepsis and multiple organ damage from a new perspective and provide new research ideas for exploring its prevention and treatment methods.

Key words: sepsis; indoleamine 2,3-dioxygenase 1; immune activation; inflammation; hypotension

1 脓毒症

脓毒症是宿主对感染反应失调而导致的危及生命的多器官功能障碍的综合征, 感染后发病率高、死亡率高, 被认为是影响患者健康的重要原因[1,2]。脓毒症类疾病根据其严重程度分为脓毒症、重症脓毒症和脓毒症休克, 而脓毒症休克死亡率高达50%[3], 是导致脓毒症患者死亡的主要原因。肺炎是导致脓毒症最常见的原因, 其次是尿路感染[4]。在脓毒症急性期, 剧烈的炎症反应可能会带来多器官功能的障碍: 包括心肌抑制、

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心源性肺水肿、脓毒症相关急性肾损伤、肝功能衰竭等, 增加脓毒症患者死亡的风险[5]。根据《柳叶刀》数据, 从1990～2017年, 脓毒症发病率下降了37.0%, 死亡率下降了52.8%。尽管对脓毒症防治取得了可喜的成绩, 但脓毒症所带来的后遗症依然严重威胁患者的健康, 如身体残疾、认知障碍和再次入院等[6,7], 因此还需要继续丰富治疗手段。

由致病菌引起的感染是诱发脓毒症的主要原因之一。这些致病菌包括革兰阴性菌、革兰阳性菌和真菌等。致病率最高的是金葡菌 (20.5%), 其次还有假单胞菌 (19.9%)、肠杆菌 (主要是大肠杆菌, 16.0%) 和真菌 (19%) 等[3]。这些微生物入侵人体以后可以释放毒性物质刺激机体免疫系统, 导致免疫系统释放大量炎性介质来对抗致病菌, 最终导致脓毒症。参与脓毒症的主要炎性介质有肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素 (interleukin, IL)-1β、血小板活化因子、白三烯、血栓素A2和补体级联激活剂等[8]。另外, 疾病原因也可能导致脓毒症的发生, 如白血病、结石[9,10], 白血病造成患者体内的白细胞减少, 使患者很容易感染, 甚至出现败血症。尿石症可导致尿液淤滞, 使细菌黏附在尿路上皮并繁殖, 从而引起尿路感染导致脓毒症[11]。脓毒症引起的器官损伤主要在于血管供血供氧的能力和组织代谢不平衡, 脓毒症患者早期释放的大量炎性介质会导致血管内皮弥漫性损伤和功能障碍, 血压下降, 血管通透性增加, 有效血容量下降, 微循环功能障碍, 这使得脓毒症患者的器官损伤可能发生于除感染部位的其他部位, 主要包括肾、肺、心脏、神经系统等[12,13]。因此, 目前临床前药物治疗方法主要集中于改善循环灌注不足、促进细菌清除及抗炎研究。脓毒症的临床治疗通常是根据临床患者的状况进行综合治疗, 包括通过液体复苏 (推荐使用晶体液) 增加循环血量、抗微生物治疗、控制感染源、使用血管活性药物升压等[14], 其他有可能改善患者状况的措施有低潮气量时适当通气, 严格控制血糖等[15], 但这些措施治疗效果有限, 脓毒症的死亡率仍居高不下。近年来, 一些脓毒症的辅助治疗药物也处于不断开发中, 包括IL-1拮抗剂、抗脂多糖 (lipopolysaccharides, LPS) 抗体、Toll样受体4 (Toll-like receptor 4, TLR4) 拮抗剂等, 但这些药物临床试验均以失败告终或仅显现出微弱的疗效, 研发针对脓毒症的药物仍面临巨大的挑战[16]。

2 吲哚胺2,3-双加氧酶 (indoleamine 2,3-dioxygenas, IDO)

IDO是细胞内一种含有血红素的代谢酶[17,18], 在哺乳动物中可催化色氨酸 (tryptophan, Trp) 代谢生成中间产物*N*-甲酰犬尿氨酸[19], 是色氨酸代谢 (犬尿氨酸代谢途径, kynurenine pathway, KP) 的第一步和限速步骤, 产物*N*-甲酰基犬尿氨酸被快速转化为犬尿氨酸 (kynurenine, Kyn) 和甲酸[20,21]。Kyn被释放或进一步代谢为各种下游分解代谢物, 如3-羟基犬尿氨酸、3-羟基邻氨基苯甲酸和吡啶甲酸, 最终可产生烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide phosphate, NAD^+) (图1)[22]。Kyn/Trp比值常用来衡量IDO活性的强弱。在人体中KP代谢消耗大约95%的游离色氨酸[23,24], 参与许多体内生物活性物质的代谢, 形成犬尿氨酸代谢物, 与炎症、免疫反应、神经系统疾病及糖尿病的发生和发展相关[22]。

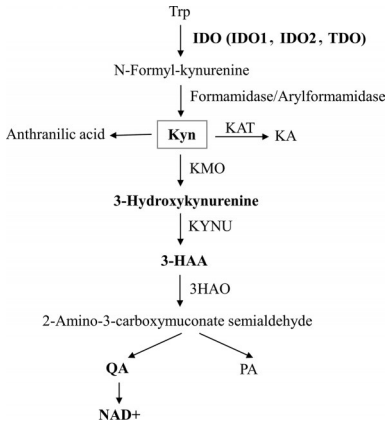

Figure 1 The major metabolites and enzymes involved in tryptophan metabolism. IDO: Indoleamine 2,3-dioxygenase; TDO: Tryptophan 2,3-dioxygenase; KAT: Kynurenine aminotrans ferase; KYNU: Kynureninase; KMO: Kynurenine 3-monooxygenase; 3-HAA: 3-Hydroxyanthranilic acid; 3HAO: 3-Hydroxyanthranilic acid oxygenase; QA: Quinolinic acid; PA: Picolinci acid; NAD: Nicotinamide adenine dinucleotide

目前已知IDO有3种亚型, IDO1、IDO2和色氨酸-2,3-双加氧酶 (tryptophan 2,3-dioxygenase, TDO)[25]。IDO1在全身表达, 与炎症信号相关, 主要由干扰素γ (interferon-γ, IFN-γ) 诱导产生[26]。IDO2主要存在于肝脏、大脑、睾丸、子宫内膜、胎盘和甲状腺中[27], 酶活性相对较弱[28], 且IFN-γ并不会诱导IDO2基因的表达[29]。而TDO是一种肝酶, 主要代谢存在于肝脏中的色氨酸, TDO基因可被与压力相关的糖皮质激素诱导[30], 同时也受色氨酸、胆固醇和前列腺素E_2的调节[31]。3种亚型IDO的表达部位和功能特点决定了不同的生理作用, 本文将聚焦于IDO1进行研究和探讨。

3 IDO1与脓毒症等感染性疾病

在对脓毒症患者血浆氨基酸浓度的研究中, 研究者发现了氨基酸代谢的改变与脓毒症患者的死亡率显

著相关[32]。研究表明, 脓毒症患者色氨酸代谢的显著改变与患者发生低血压、免疫和微血管功能障碍相关联[33]。而IDO1作为色氨酸代谢的限速酶, 也被报道和脓毒症的危险程度相关[34,35]。在一项关于83名成年脓毒症患者的研究中, 研究者发现死亡患者的IDO1活性高于幸存者, 且IDO1的活性与脓毒症分期、简化急性生理学评分和器官功能障碍系统严重程度评分相关, 并可预测脓毒症预后。

IDO1介导感染性疾病的发生和发展。在病毒感染方面, 对一项艾滋病 (human immunodeficiency virus, HIV) 患者血清研究中发现, IFN-γ和Kyn水平升高提示IDO1参与了T细胞功能的抑制[36]。在最近的一项临床试验中, 对HIV患者给予烟酸 (控制色氨酸的过度消耗) 和逆转录病毒治疗 (anti-retroviral therapy, ART) 后Kyn/Trp比值、$CD8^+$ T细胞亚群和炎症因子指标均没有得到改善[37], 这提示纠正色氨酸的耗竭对于恢复免疫调节和抗感染的作用具有一定的局限性。与之不同的是, 在先前的猴免疫缺陷病毒感染 (simian immunodeficiency virus, SIV) 的模型中, 采用IDO1抑制剂1-甲基色氨酸 (1-methyltryptophan, 1-MT) 结合ART治疗, 发现1-MT结合ART治疗增加了动物对ART治疗的敏感性, 使其血浆和淋巴结中的病毒水平显著降低, 而只用1-MT对Kyn/Trp比值及血浆病毒载量基本无影响, 于是研究者得出了1-MT与ART治疗在抗病毒方面具有协同作用[38]。对于细菌感染, Blumenthal等[39]用结核分枝杆菌感染小鼠后, 观测到巨噬细胞上IDO1表达增多, 但小鼠敲除IDO1后T细胞反应、细菌负荷量、肺部炎症反应及生存期均无显著改善。综上, 靶向IDO1治疗感染性疾病的有效性需要更多的研究去验证。

靶向IDO1能否治疗脓毒症等感染性疾病, 现在仍存在很大的争议。一方面, IDO1活性增强加速色氨酸的代谢, 抑制以色氨酸为必需氨基酸的病原微生物的复制[36], 同时产生的色氨酸代谢产物如Kyn等也被报道具有抗菌的作用[40], 这些证据表明抑制IDO1似乎是不利的。另一方面, IDO1的激活也会导致T细胞的耗竭, 从而导致感染的加重[41], 原因在于色氨酸是T细胞增殖所必需的氨基酸, IDO1可通过局部耗尽色氨酸来抑制T细胞清除细菌的作用, 同时色氨酸代谢产物如Kyn对T细胞具有毒性和促凋亡作用[42]。IDO1的活性除了在疾病感染期发挥作用外, 还可通过调节血压、线粒体损伤、微循环等影响主要器官的功能, 包括心脏、肾脏和中枢神经系统等[43-45] (图2)。

4 IDO1参与脓毒症的发病过程

脓毒症被认为是一种不平衡的免疫反应, 病原体逃避宿主的防御机制, 不断繁殖, 持续地刺激和损伤宿主细胞, 最终导致稳态无法恢复。在这种不平衡的反应中, 许多最初被激活以提供保护的免疫机制已经变

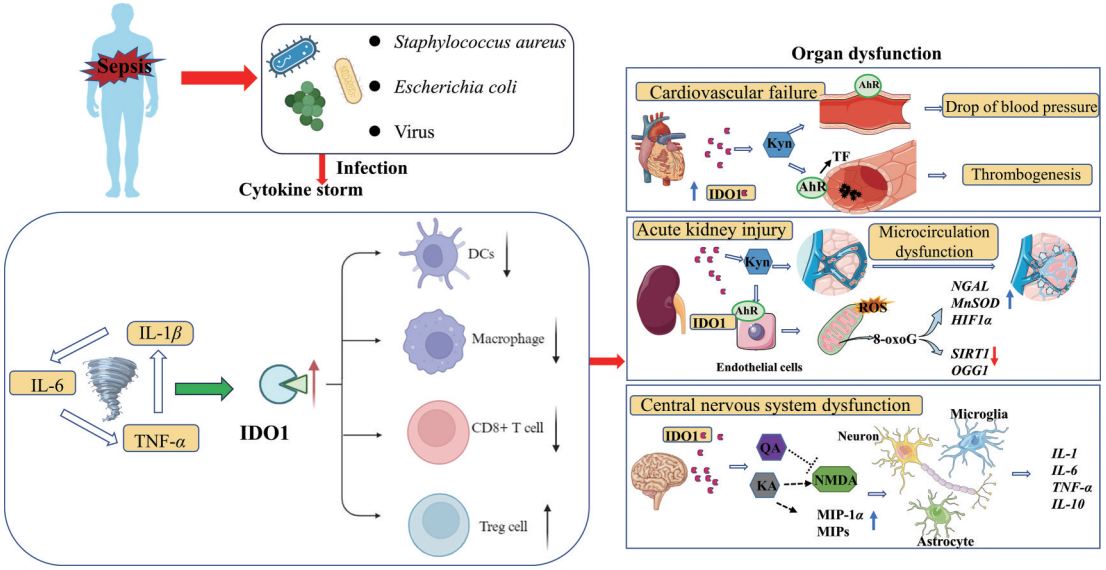

Figure 2 Schematic diagram of IDO1 involvement in the pathogenesis of sepsis. Viruses and other pathogenic microorganisms invade the body, causing severe inflammatory reaction, which leads to the increase of IDO1 enzyme activity. The activity of IDO1 increased and the number and function of all kinds of immune cells were changed. At the same time, the increase of IDO1 activity in peripheral organs can mediate vascular thrombosis, endothelial cell dysfunction and cognitive impairment through the IDO1-AhR axis. TF: Tissue factor; 8-oxoG: 8-Hydroxyguanine; NGAL: Neutrophil gelatinase-associated lipocalin; MnSOD: Manganese superoxide dismutase; HIF1*α*: Hypoxia-inducible factor 1*α*; SIRT1: Sirtuin 1; OGG1: 8-Oxoguanine glycosylase; NMDA: *N*-Methyl-*D*-aspartic acid; MIP1*α*: Macrophage inflammatory protein-1*α*; MIPs: Macrophage inflammatory proteins; AhR: Aryl hydrocarbon receptor

得有害, 脓毒症患者的宿主反应同时出现炎症和免疫抑制的迹象, 部分涉及不同的细胞类型和器官系统[46]。而IDO1在脓毒症中被炎症信号诱导高表达, 控制T细胞反应, 参与了脓毒症的发生和发展[47-49]。

4.1 IDO1参与脓毒症急性期炎症反应 当脓毒症发生时, 免疫系统通过识别微生物表达的病原体相关分子模式来监测病原体, 诱导初始免疫反应, 促进免疫细胞的激活和细胞因子的产生[46]。IDO1被免疫微环境中的INF-γ和其他细胞因子强烈激活[50]。树突状细胞和巨噬细胞上的IDO1激活后可通过一般性调控阻遏蛋白激酶2 (general control nonderepressible 2, GCN2)途径产生白细胞介素-10 (interleukin-10, IL-10)、转化生长因子-β (transforming growth factor-beta, TGF-β)等抗炎细胞因子[51]。在肾上皮细胞中, IDO1/GCN2途径通过诱导自噬来限制组织损伤[52,53]。同时, IDO1也可以通过激活芳香烃受体 (aryl hydrocarbon receptor, AhR)来控制局部和全身免疫应答。犬尿氨酸可以通过激活幼稚T细胞的AhR, 来促进其向调节性T细胞(regulatory T cell, Treg)的分化, 参与维持免疫耐受性。同时, Treg可以通过刺激巨噬细胞分泌抗炎细胞因子来促进炎症的消退[53]。

色氨酸代谢控制炎症的重要作用通常体现在炎症时期IDO1活性的改变。在特发性肺部炎症中, 肺上皮细胞和肺泡巨噬细胞产生的犬尿氨酸通过AhR途径抑制肺上皮细胞的炎症活动。组蛋白脱乙酰酶抑制剂促进IDO1的表达, 从而起到改善特发性肺部炎症的作用[54], 其原因可能在于犬尿氨酸等代谢产物的累积发挥了抗炎作用。但是, 在盲肠结扎穿刺法 (cecum ligation and puncture, CLP)诱导的脓毒症相关性脑病(sepsis-associated encephalopathy, SAE)小鼠模型中, CLP组小鼠IDO活性增加, 与小鼠血浆和海马中TNF-α、IL-1β和IL-6水平正相关; 与CLP对照组相比, 1-MT处理降低了CLP组的TNF-α、IL-1β和IL-6水平, 其原因可能在于抑制IDO1后改善了免疫抑制, 从而促进了细菌清除, 减少了机体炎症[55]。在LPS诱导的脓毒症肾损伤小鼠模型中, 研究者发现敲除IDO1或1-MT预处理降低了模型小鼠血清或肾脏中的炎症因子和氧化应激状态, 经过分析发现其发挥作用是通过负反馈调节TLR/NF-κB信号通路实现的[56]。因此, 靶向炎症介质的响应因子IDO1, 可以调节脓毒症期间炎症反应, 但是由于IDO1参与免疫反应机制的复杂性, 其有效性目前争议仍比较大。

4.2 IDO1参与脓毒症后期免疫抑制 IDO1作为炎症响应因子, 在限制机体过度炎症反应中也起着至关重要的作用。IDO通过催化色氨酸代谢作为免疫反应的主要抑制剂。IDO1活性的增加将导致两个结果: 色氨酸的耗竭和犬尿氨酸等代谢产物的累积, 而两者都可导致T细胞的活化和免疫状态的改变[30]。研究表明, IDO主要通过两种途径改变免疫反应: ① IDO激活色氨酸代谢途径导致色氨酸水平降低, 抑制哺乳动物雷帕霉素 (mammalian target of rapamycin, mTOR)激酶途径和激活氨基酸敏感的GCN2激酶途径, 最终促进T细胞无反应性, 同时导致T细胞向Treg转化而导致免疫抑制。一方面, 色氨酸的耗竭导致未带电的色氨酸转移核糖核酸 (transfer ribonucleic acid, tRNAs)的积累。随后, tRNAs的增加诱导GCN2的表达增多。GCN2通过磷酸化翻译起始因子2α (phosphorylation of eukaryotic initiation factor-2α, eIF2α)来响应氨基酸匮乏[30], 控制蛋白质合成, 导致细胞周期停滞或细胞凋亡[29,57]; 另一方面, mTOR激酶途径的抑制可破坏树突状细胞的成熟和功能, 并抑制T细胞增殖[58]。IDO激活导致的mTOR和GCN2通路的应答, 最终促进$CD8^+$ T细胞无反应性; ② Kyn等代谢产物的累积也可以通过直接作用或者结合AhR间接发挥作用来影响免疫细胞[31]。AhR是一种配体门控转录因子, 可被Kyn激活, 并介导广泛的免疫调节作用, IDO与AhR结合后可降低树突状细胞免疫原性, 同时促进Treg细胞转化, 产生免疫抑制作用。因此, 色氨酸代谢途径广泛影响免疫细胞的增殖和功能[59] (图3)。

靶向IDO1可以改善脓毒症期间的免疫抑制。许多脓毒症危重症患者在度过急性炎症期之后进入持续的全身免疫抑制状态, 也称为脓毒症相关性免疫抑制。在此期间, 淋巴细胞和树突状细胞凋亡的增加, 免疫抑制细胞Treg增多[33,60]。一些研究者认为, 脓毒症中的大多数死亡与无法根除原发感染或继发感染有关。再入院诊断以感染最多见, 11.9%患者因脓毒症、肺炎、尿路或皮肤或软组织感染再次入院[6,61]。重症监护患者出院后1年观察到持续性免疫紊乱, 提示脓毒症损伤后存在长期免疫抑制[62], 因此通过靶向IDO1、程序性死亡受体-1 (programmed cell death protein 1, PD-1)等免疫检查点增强免疫, 改善脓毒症后期免疫抑制可能有效改善脓毒症患者的预后。在盲肠结扎致小鼠脓毒症动物模型中, 程序性死亡受体配体-1 (programmed cell death-ligand 1, PD-L1)阻断能显著提高CLP小鼠的存活率。抗PD-L1抗体可防止脓毒症诱导的淋巴细胞耗损, 增加TNF-α和IL-6[63]。在一项关于脓毒症的二次打击模型中, 研究者采用CLP后的两种不同感染模型诱导小鼠真菌败血症, 之后给予抗PD-1和抗细胞毒T淋巴细胞相关抗原4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4)治疗, 对原发性和继发

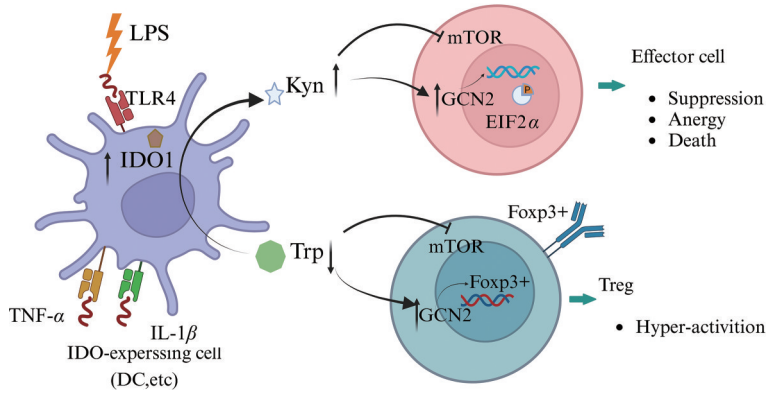

Figure 3 Enhanced IDO1 enzyme activity leads to exhaustion of T cells, which in turn suppresses immune system function. Foxp3: Forkhead box P3; EIF2α: Eukaryotic initiation factor-2α

性真菌性败血症的生存率均有显著疗效。两种抗体均可逆转败血症诱导的IFN-γ抑制, 并增加抗原呈递细胞上II类组织相容性抗原的表达, 促进细菌的清除[64]。在CLP致小鼠腹膜炎型脓毒症模型中, 敲除IDO1小鼠表现出中性粒细胞和单核细胞向腹膜腔内募集增加, 血液中细菌数量减少。因此, 敲除IDO1在脓毒症的宿主保护中起到了有益的作用[65]。

4.3 IDO1参与脓毒症低血压的调节 低血压是人和小鼠脓毒症的常见并发症, 脓毒症时发生的系统性炎症会导致血压急剧下降或低血压, 进而导致器官功能障碍和死亡[43], 而IDO1可通过产生犬尿氨酸等血管松弛因子来参与调节血管压力[45]。机体发生炎症反应时, IFN-γ、TNF-α等炎性因子大量释放, 导致IDO1的激活[26], 内皮细胞产生大量Kyn[44]。Kyn的增加通过激活腺苷酸环化酶 (adenylyl cyclase, AC) 可溶性鸟苷酸环化酶通路 (guanylate cyclase, GC) 介导血管舒张, 从而引起炎症期间血压下降[43,45]。脓毒症发生时调节血压的另一个重要因子是一氧化氮 (nitrous oxide, NO)。一方面, IDO1活性的增加会引起一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 活性的增加, 从而促进NO产生, 加剧微血管反应性的失调。另一方面, IDO1活性增加造成的3-羟基邻氨基苯甲酸 (3-hydroxyanthranilic acid, 3-HAA) 增多和NO的蓄积抑制IDO1的酶活性及下游代谢产物的生成, 形成负反馈机制[66]。脓毒症时IDO1活性的增加可能通过犬尿氨酸直接降低血管压力, 也可以通过影响NO来间接调节血管张力。因此, IDO1参与脓毒症中血压的调节 (图4)。

靶向IDO1可能改善脓毒症期间低血压。研究表明, 小鼠体内IDO1的激活与感染性休克期间患者的低血压和对肌力调节药物的需求相关。在脓毒症模型小鼠中, 采用1-MT抑制IDO1酶, 可能防止内毒素血症

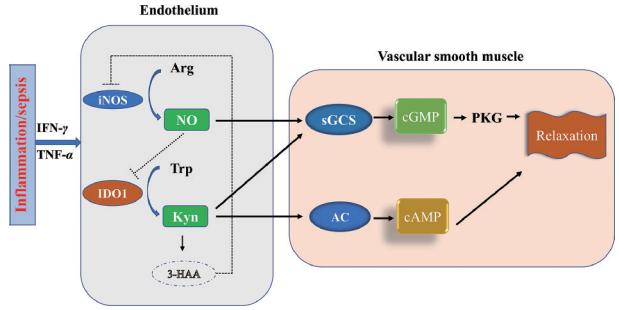

Figure 4 Schematic diagram of the regulation of blood pressure by IDO1. iNOS: Inducible nitric oxide synthase; Arg: *L*-Arginine; sGC: Soluble guanylate cyclase; AC: Adenylyl cyclase; cGMP: Cyclic guanosine monophosphate; cAMP: Cyclic adenosine monophosphate; PKG: Protein kinase G

中低血压和死亡的发生[44]。在伯氏疟原虫的感染中发现IDO1活性增强, 而在给予1-MT后可以使小鼠收缩压恢复至正常, 说明IDO1参与了疟原虫感染引起的低血压。且研究者发现感染对*IDO1*$^{-/-}$小鼠的色氨酸和犬尿氨酸的血浆浓度、血压没有显著性影响, 再次证明了IDO1参与了脓毒症期间低血压反应。研究者随后建立LPS诱导的脓毒症模型, 肾脏中IDO1 mRNA表达在LPS注射后2 h被诱导, 并在LPS注射后5～10 h达到最高水平。IDO1抑制或敲除均可以改善脓毒症并发的低血压。添加犬尿氨酸可以使预收缩的猪冠状动脉舒张, 而施加1-MT可以逆转血管舒张[45]。以上研究结果均提示, 抑制IDO1为脓毒症低血压的治疗提供了一种新的思路。

4.4 IDO1参与其他环节的调节 由IDO1介导的色氨酸代谢除了影响免疫反应/炎症反应、血压调节等主要环节外, 还可以通过诱发其他旁路参与疾病的发生过程, 如认知障碍、内皮功能障碍等。据报道, 色氨酸代谢产物中3-HAA和喹啉酸 (quinolinic acid, QA) 具有神经毒性, 而犬尿喹啉酸 (kynurenic acid, KA) 则具

有神经保护作用[67]。有研究发现, IDO1介导SAE模型小鼠的认知障碍。外周注射IDO1的代谢产物犬尿氨酸, 可以诱发认知障碍的缺陷。然而, 用IDO1抑制剂1-MT治疗的小鼠可以改善CLP诱导的小鼠的运动迟缓和焦虑样行为, 使小鼠免受脓毒症引起的认知障碍的影响。因此, IDO1依赖的神经毒性犬尿氨酸代谢是导致脓毒症所致认知障碍的关键因素, 并可能成为治疗SAE的新靶点, 为靶向IDO1治疗脓毒症提供了更多的思路[55]。此外, IDO1及其相关通路介导晚期动脉粥样硬化免疫炎症反应, Kyn、3-HAA和QA浓度与终末期肾病患者的炎症、氧化应激、内皮功能障碍和颈动脉内膜−中膜厚度值呈正相关。在一项针对普通人群的大型队列研究中发现, IDO活性与颈动脉内膜/中膜厚度相关, 反映了24～39岁女性动脉粥样硬化的早期特点[68]。动脉粥样硬化小鼠的淋巴组织浆细胞样树突状细胞 (plasmacytoid dendritic cells, pDCs) 中IDO1的表达阻断了其对T细胞促增殖作用, 提示pDCs通过抑制T细胞增殖并以IDO1依赖的方式在动脉粥样硬化中发挥保护作用[69]。

5 IDO1抑制剂治疗脓毒症的临床前研究进展及总结

关于靶向IDO1治疗感染性疾病及脓毒症的药物基本处于理论研究或临床前研究阶段, 暂时没有药物进入临床研究。本文总结了近5年IDO1抑制剂治疗脓毒症临床前研究进展情况[56,70-72] (表1)。结合现有研究来看, 作为炎症反应的下游响应因子, IDO1在脓毒症中的升高是必然的, 但靶向IDO1能否治疗脓毒症仍有很大的不确定性。一方面, 目前关于IDO1抑制剂治疗脓毒症的文献支持较少; 另一方面, 由于脓毒症发病机制的复杂性和色氨酸代谢产物的多样性, IDO1参与脓毒症中的机制复杂多变, 在不同的动物模型表现不一样的生理作用, 在炎症的不同阶段表现不同的生物学效应, 在不同的细胞表现不同的功能。

脓毒症是重症医学科常见的危重症, 每年有上百万人发病, 病死率很高, 是重症监护患者死亡的主要原因之一。以早期目标导向治疗为基础的《拯救脓毒症运动指南》推出后, 脓毒症患者的病死率明显改善, 但目前病死率仍然高达25%[73]。脓毒症患者处于急性炎症反应期时, IDO1介导的Trp代谢的Kyn通路被激活, 犬尿氨酸等代谢产物参与免疫反应、炎症和兴奋性神经传递, 进一步扭转了免疫平衡, 造成了脓毒症后期的免疫抑制。从临床角度来看, 血浆Trp降低和KP比值升高是临床不良结果的重要预测指标。因此, 扭转IDO1介导的色氨酸代谢异常可能会改善脓毒症及其器官损害。

本文讨论了色氨酸代谢途径激活参与控制炎症的分子机制, 重点描述了IDO1途径的局部效应。本课题讨论了IDO1在脓毒症中的可能作用, 并提出IDO1是治疗感染性脓毒症的潜在治疗靶点, 它可以通过调节炎症、增强免疫和改善循环来提高生存率, 为脓毒症的治疗提供了新的思路。由于IDO参与了脓毒症发病过程的各个阶段, 因此通过靶向IDO可以对脓毒症的全过程 [早期急性炎症期、中期器官损伤期 (低压) 和缓解期 (免疫抑制期)] 进行调控, 可能会弥补现有治疗药物功能单一、疗效不佳的现状。

由于IDO1在脓毒症急性炎症期发挥的作用较为复杂, 临床研究数据匮乏, 通过靶向IDO1能否治疗脓毒症也存在着较大的争议, 靶向IDO1治疗脓毒症药物的开发也面临巨大的挑战。未来研究将进一步明确IDO1在脓毒症不同阶段 [早期急性炎症期、中期器官损伤期 (低压) 和缓解期 (免疫抑制期)] 异常免疫反应炎症中的调控特点, 阐明IDO1分别调控免疫细胞功能活性的分子病理机制, 揭示其介导的KP异常代谢与自

Table 1 Preclinical research of IDO1 inhibitors. CMI: 3-[(4-Chlorophenyl)selanyl]-1-methyl-1*H*-indole; GM-CSF: Granulocyte-macrophage colony-stimulating factor; CLP: Cecum ligation and puncture; LPS: Lipopolysaccharides; IAS: Intra-abdominal sepsis

Drug	Candidate model disease	Treatment	Result
Navoximod	CLP or LPS induced sepsis	Navoximod was administered 100 and 200 mg·kg^{-1} orally before and after CLP or LPS treatment, respectively	Inhibiting IDO1 activity can alleviate the IAS-induced muscle wasting
1-MT	LPS induced sepsis kidney injury	Mice were injected intraperitoneally with 10 mg·kg^{-1} 1-MT	Blockade of IDO attenuates LPS-induced kidney injury by inhibiting TLR4/NF-κB signaling
Indoximod	CLP induced sepsis	The inhibitor was administered intracerebroventricularly at 0 and 6 h after the CLP surgery	The inhibition of IDO prevented memory impairment and avoided the changes in energetic metabolism that was triggered by sepsis
GM-CSF	LPS induced sepsis	GM-CSF was administered (30 μg·kg^{-1}, i.p.) 30 min before LPS injection	GM-CSF could exert antidepressant effects through IDO downregulation in a model for acute inflammation-induced depression
CMI	LPS induced sepsis	CMI was administered (1 mg·kg^{-1}, i.g.) after LPS injection	CMI modulated the expression of IDO and can ameliorate depression- and anxiogenic-like behavior

身免疫紊乱的关系, 为脓毒症等感染性疾病的药物研发提供有效分子靶标, 以期弥补目前临床治疗药物的不足。

作者贡献: 赵晓迪和马铖延完成了文献收集及论文初稿撰写; 张森是文章的构思者并进行修改和定稿; 陈晓光提供了指导性意见; 王雨辰和崔华清共同参与了文章的撰写及修改。

利益冲突: 所有作者均声明没有利益冲突。

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