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· 综 述 ·

CD39-CD73-腺苷通路在肝细胞癌免疫调控中的研究进展



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[摘要] 肝细胞癌 (hepatocellular carcinoma, HCC) 患者占原发性肝癌患者总数的 85%~90%。以切除术和肝移植术为代表的手术治疗疗效较好, 是目前 HCC 首选治疗方法, 患者治疗后 5 年生存率为 70%~80%。然而, HCC 的高复发率仍是目前肝癌治疗的难点。由于 HCC 存在异质性, 现有化疗药物和多激酶抑制剂疗效有限, 研究新的治疗策略至关重要。CD39-CD73-腺苷通路通过将促炎的细胞外三磷酸腺苷 (extracellular adenosine triphosphate, eATP) 转化为免疫抑制性腺苷, 在肝脏微环境中发挥调控作用。靶向该通路中的关键分子进行治疗有抗肿瘤效果。靶向 CD39-CD73-腺苷通路或以该通路为基础的联合治疗策略可能为 HCC 患者提供更有效的治疗选择。本文对 CD39-CD73-腺苷通路在 HCC 中的生物学效应及其免疫调控作用作一综述。

[关键词] 肝细胞癌; 免疫调控; CD39; CD73; 腺苷通路**[中图分类号]** R 735.7 **[文献标志码]** A

Research progress of CD39-CD73-adenosine pathway in immune regulation of hepatocellular carcinoma

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[Abstract] Hepatocellular carcinoma (HCC) patients accounts for 85%-90% of all primary liver cancer patients. Surgical treatment methods, represented by resection and liver transplantation, have relatively good efficacy and are currently the preferred treatment approaches for HCC, with a 5-year survival rate of 70%-80% after treatment. However, the high recurrence rate of HCC remains the greatest challenge in current liver cancer treatment. Due to the heterogeneity of HCC, the efficacy of current chemotherapy drugs and multi-kinase inhibitors is limited. It is crucial to explore new therapeutic strategies. The CD39-CD73-adenosine pathway plays a significant regulatory role in the liver microenvironment by converting pro-inflammatory extracellular adenosine triphosphate (eATP) into immunosuppressive adenosine. Targeting key molecules in this pathway for treatment has shown anti-tumor effects. Strategies of targeting the CD39-CD73-adenosine pathway and combined therapeutic strategies based on the CD39-CD73-adenosine pathway might offer more effective treatment options for HCC patients. This article reviews the biological effects and roles of the CD39-CD73-adenosine pathway in the immune regulation of HCC.

[Key Words] hepatocellular carcinoma; immune regulation; CD39; CD73; adenosine pathway

肝细胞癌 (hepatocellular carcinoma, HCC) 起源于肝实质细胞, 是主要的原发性肝癌类型 (85%~90%), 是终末期肝病患者的主要死亡原因之一^[1]。全球范围内, 肝癌发病率在所有肿瘤

中排名第六, 致死率排名第三^[2]。在我国, 肝癌的发病率在所有恶性肿瘤中排名第四、死亡率排名第三, 患者数占全球 50% 以上^[3]。以肝切除术和肝移植术为代表的手术治疗方式是目前肝癌的

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首选治疗方法^[4-5]。然而, HCC 的高复发率仍是目前肝癌治疗的最大难题。即使是单个肿瘤且最大径 ≤ 2 cm, 切除术后患者 5 年复发率也高达 70%^[6]。由于 HCC 基因、代谢和炎症存在异质性, 化疗药物(如顺铂、吉西他滨和多柔比星)和多激酶抑制剂(如一线索拉非尼、二线瑞戈非尼和乐伐替尼、三线卡波替尼)仅使少数患者总体生存期延长、生活质量稍提高^[7-14]。因此, 发掘复杂的细胞和分子免疫网络表征肝脏微环境是促进发展新的 HCC 治疗措施(包括免疫治疗)的重要基础^[8,15]。本文总结了 CD39-CD73-腺苷通路在 HCC 免疫调控中的作用。

1 CD39-CD73-腺苷通路的生物学意义

CD39-CD73-腺苷通路是一个复杂系统, 包括酶、转运蛋白和受体, 可调控具有促炎和免疫刺激作用的细胞外三磷酸腺苷(extracellular adenosine triphosphate, eATP)转换为免疫抑制性腺苷^[16-17]。eATP 作为一种损伤相关分子模式, 可与嘌呤能受体(P2 受体)结合, 启动信号级联反应, 诱导炎症反应^[18]。eATP 能被细胞表面的外核苷酸酶水解, 进而避免 ATP 诱导的病理效应。

CD39 和 CD73 为细胞外核苷酸酶, 能使 ATP 脱磷为二磷酸腺苷(adenosine diphosphate, ADP)、单磷酸腺苷(adenosine monophosphate, AMP)和腺苷, 从而维持细胞外环境中 ATP 和腺苷的平衡^[19-20]。除了外核苷酸酶, ATP 也可以通过碱性磷酸酶去磷酸化形成 ADP 和 AMP^[19]。

腺苷通路中, CD39 是一种膜蛋白, 作为限速酶以 Ca^{2+} 和 Mg^{2+} 依赖的方式水解 ATP 和 ADP, 产生 AMP^[21-23]。CD73 由 NT5E 基因编码, 是一种由糖基磷脂酰肌醇锚定的细胞膜同型二聚体, 相对分子质量为 70 000, 负责将细胞外 AMP 分解为腺苷^[16]。腺苷通过与 4 种 G 蛋白偶联腺苷受体结合发挥生物学功能。其中, 腺苷受体 A2A (adenosine receptor A2A, AA2AR) 通过活化蛋白激酶 A (PKA) 和 C 端 Src 激酶来抑制一系列免疫活化相关信号通路, 如 Src 家族酪氨酸激酶(LCK)、LCK 原癌基因、丝裂原激活蛋白激酶(MAPK)、

蛋白激酶 C 和丝氨酸/苏氨酸蛋白激酶(AKT), 从而发挥免疫抑制作用^[24-25]。

在炎症和缺氧条件下, CD39-CD73-腺苷通路的活化能作为一种负反馈机制, 防止免疫细胞持续活化导致的过度组织损伤^[16, 26-27]。CD39 和 CD73 水平在炎症条件下升高, 可在急性肝衰竭期间抑制肝脏炎症发展^[28-29]。然而, 在某些病理情况下, 该通路会产生超过腺苷脱氨酶(adenosine deaminase, ADA)水解能力上限的腺苷, 引起免疫抑制, 导致疾病发生发展^[30]。因此, CD39 和 CD73 被视为“免疫开关”。研究^[31-32]发现, CD39 和 CD73 过表达会促进 HCC 进展和转移, 并可作为不良预后的标志物。

2 CD39-CD73-腺苷通路中关键分子在 HCC 中的表达和功能

肿瘤进展与肿瘤微环境(tumor microenvironment, TME)密切相关, 免疫抑制微环境会减弱抗肿瘤免疫应答, 并促进肿瘤细胞的免疫逃逸^[33]。TME 中, 应激细胞和死细胞会释放 eATP, 而 eATP 是先天免疫和适应性免疫反应发生的重要信号^[34]。腺苷通过调节 A2AR 的下游信号转导, 抑制 CD4^+ 和 CD8^+ T 细胞的免疫反应^[35-36]。腺苷激活 AA2AR 可以抑制幼稚 T 细胞的增殖和分化, 导致 Th1 和 Th2 的分化抑制^[34]。此外, TME 中高水平的腺苷也会破坏 CD8^+ T 细胞的激活、扩增和细胞因子分泌, 抑制细胞毒性 T 细胞活性, 并干扰 NK 细胞的溶细胞活性^[37-38]。因此, CD39-CD73-腺苷轴对重塑免疫抑制 TME 起关键作用。

在 HCC 进展过程中, 肿瘤细胞释放的 eATP 通过 CD39 和 CD73 催化产生大量腺苷。腺苷与腺苷受体结合激活下游信号通路, 发挥免疫抑制作用^[39]。Cai 等^[31]和 Fu 等^[40]研究发现, HCC 中 CD39 过表达和 $\text{CD39}^+\text{Foxp3}^+\text{Treg}$ 细胞浸润分别是术后不良预后和术后复发的独立预测因素。 $\text{Foxp3}^+\text{Treg}$ 上 CD39 的表达可抑制 NK 细胞活性, 并促进肝转移瘤的生长^[41]。HCC 组织浸润 CD4^+ 和 CD8^+ T 细胞中 CD39 表达水平与 HCC 患者的总体生存率负相关^[42]。CD73 可作为临床 HCC 复发时间和总生存率的独立预后不良指

标^[43]。CD73 在 HCC 和肝硬化患者中显著增加,其表达与 HCC 总生存率负相关^[44]。CD73 通过上调 SOX9 表达并增强其蛋白稳定性来维持肿瘤干细胞特性,从而进一步促进 HCC 疾病进展^[45]。腺苷与 A2AR 结合并诱导 Rap1 介导的 P110 β 膜定位,激活 PI3K/AKT 信号,并上调 HCC 中表皮生长因子受体的表达,从而促进 HCC 的进展和转移^[32, 44]。A2BR 在 HCC 患者中高表达,其表达水平与 HCC 的肿瘤进展和患者的总体生存率负相关^[42, 46]。A3R 与 A2BR 类似,在 HCC 患者中高表达。A3R 能通过抑制腺苷酸环化酶和调节 MAPK 通路,影响大多数免疫细胞的功能和肿瘤细胞的增殖^[47]。

总之,CD39-CD73-腺苷通路在 TME 中通过免疫抑制机制在 HCC 的发展、侵袭迁移中起重要作用^[33]。CD39-CD73-腺苷通路中多个关键分子对 HCC 预后具有预测作用,可作为潜在预后评估标志物用于辅助评估患者 HCC 病情进展。

3 CD39-CD73-腺苷通路作为治疗靶点的进展

阻断 PD-1/PD-L1 和 CTLA-4 等肿瘤免疫疗法疗效显著,但仅使部分患者获益^[48-49]。实体肿瘤中坏死细胞大量释放 eATP,导致 CD39 和 CD73 在肿瘤细胞和浸润免疫细胞中高表达,而 AA2AR 在浸润免疫细胞中表达^[50-51]。CD39-CD73-腺苷通路通过积累腺苷,重塑 TME 中免疫抑制环境,削弱肿瘤免疫监视。因此,CD39-CD73-AA2AR 通路是目前肿瘤免疫治疗的热门潜在靶点。

靶向 CD39 的单克隆抗体能够抑制肿瘤细胞表面的 CD39 酶活性,并有效抑制转移^[52]。此外,抗 CD39/TGF- β 双特异性单克隆抗体 ES014,可同时抑制 TME 中这 2 种主要的免疫抑制分子(CD39 和 TGF- β)^[53]。小分子药物研究也进展迅速。AB680 是一种高效、可逆的 CD73 选择性抑制剂,在临床前研究中显示出良好的药代动力学特性,正在进行 I 期临床试验^[54]。鞣花酸因对正常细胞的毒性低,已被确定为 CD39 和 CD73 双重抑制剂的先导化合物^[55]。近年来,随着计算机技术和生物信息学的发展,虚拟

筛选技术(virtual screening, VS)逐渐成为药物研究的重要工具。根据 CD73 与 α,β -亚甲基-ADP 的结合方式,通过 VS 发现一系列新型有效的 CD73 小分子抑制剂。这些 CD73 候选抑制剂中,OP-5244 表现出效价高且口服生物利用度高的优势^[56]。

CD39-CD73-腺苷通路多靶点联合治疗也是临床研究重点。AZD4635 (5'-N-乙酰化腺苷)是一种口服高亲和力腺苷类似物,是 AA2AR 拮抗剂,在体外和体内诱导逆转 T 细胞抑制^[57]。靶向 AA2AR 和 CD73 的选择性抑制剂联合应用对肿瘤生长有协同抑制效果。此外,CD73 小分子抑制剂聚钨酸钠和 AZD4635 联合应用可以阻断腺苷通路,从而激活免疫细胞,增加 INF- γ 的产生,并减少 Treg 数量^[58]。以其他腺苷受体作为治疗靶点的研究也陆续被开展,如:CF102 作为一种 AA3R 激动剂,通过下调 NF- κ B 和 Wnt 信号转导通路诱导 HCC 细胞凋亡,发挥相应的抗炎和抗肿瘤作用,在治疗 HCC 的 I 期/II 期临床试验中显示出较高的安全性和良好的耐受性^[59]。另有研究^[60]显示,CD39-CD73-腺苷通路治疗靶点与其他现有疗法联用,可以增强 HCC 疗效。

CD39-CD73-AA2AR 通路抑制剂可以增强晚期实体肿瘤中免疫检查点抑制剂(immune checkpoint inhibitor, ICI)的疗效。高浓度 PT199 与抗 PD-1 单克隆抗体联合应用时可避免钩状效应。因此,PT199 与 PD-1 通路抑制剂联合应用有增强 PD-1 通路抑制剂抗肿瘤免疫活性的潜在作用,为肿瘤患者提供治疗新选择^[61]。联合应用小分子 CD39-CD73-AA2AR 抑制剂 CPI-444 与 atezolizumab (抗 PD-L1 单克隆抗体),相比单独应用 atezolizumab 可以诱导更持续的抗癌反应和更多细胞毒性 T 细胞浸润 TME^[62-63]。A2BR 阻断剂联合索拉非尼较单独应用索拉非尼延缓了 HCC 进展^[64]。

4 小 结

CD39-CD73-腺苷通路对 HCC 具有重要作用,是近年来 HCC 发病机制研究的热点。CD39-CD73-腺苷通路因在 TME 中产生腺苷导致免疫系

统抑制,成为肿瘤免疫治疗新靶点。针对 CD39-CD73-腺苷通路上的分子靶点进行药物筛选,目前已获得先导化合物和单克隆抗体。阻断抗体和小分子抑制剂靶向 CD39-CD73-AA2AR 通路表现出良好的抗肿瘤功效。

然而,腺苷作为重要的局部代谢产物,广泛分布于各组织器官。在肿瘤发生发展中,腺苷发挥的作用以及对全身各组织器官的影响仍停留在初步研究阶段。腺苷在不同 HCC 治疗手段中或可成为双刃剑,为 HCC 诊疗提供新思路。因此,深入研究 CD39-CD73-腺苷通路的生物学效应和其中的分子机制,对未来 HCC 诊疗具有重要意义。

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