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CD73抑制剂在肺癌免疫治疗中的研究进展

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摘 要

肺癌是全球发病率与死亡率最高的恶性肿瘤。免疫检查点阻断(Immune Checkpoint Blockade, ICB)已成为肺癌标准治疗方案之一，但大多数患者接受ICB时会出现原发或获得性耐药，这是制约治疗疗效与患者生存的关键瓶颈。研究证实，肿瘤免疫微环境抑制是ICB耐药的核心原因，CD73作为胞外腺苷生成的关键限速酶，可通过CD73-腺苷轴重塑免疫抑制微环境，且其在肺癌组织的高表达与疾病进展、复发及生存期缩短显著相关。因此，CD73抑制剂与ICB联用是解决该问题的重要方向。目前，CD73抑制剂主要分为单克隆抗体、小分子抑制剂及抗体偶联药物三类，临床研究显示，其与ICB合用可显著提升客观缓解率、改善耐药，与化疗构成的三联方案亦具良好前景，CD73与PD-L1共表达有望成为联合治疗疗效的潜在生物标志物。文章综述了CD73的生物学特性、抗肿瘤机制及肺癌临床研究进展，分析了相关生物标志物价值及临床挑战，以期为肺癌耐药的临床干预与基础研究提供参考。

关键词

CD73，CD73抑制剂，肺癌，免疫耐药，临床研究

Research Progress of CD73 Inhibitors in Lung Cancer Immunotherapy

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Abstract

Lung cancer is the malignant tumor with the highest incidence and mortality rates globally. Immune checkpoint blockade (ICB) has established itself as one of the standard treatment modalities for

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lung cancer. However, the majority of patients exhibit primary or acquired drug resistance after undergoing ICB, which poses the key bottleneck constraining treatment efficacy and patient survival. It has been established that the suppression of the tumor immune microenvironment is the core cause of ICB resistance. CD73, as the crucial rate-limiting enzyme for extracellular adenosine production, is capable of reshaping the immunosuppressive microenvironment via the CD73-adenosine axis. Its high expression in lung cancer tissues is significantly associated with disease progression, recurrence, and reduced survival. Therefore, the combination of a CD73 inhibitor with ICB is an important approach to address this issue. Currently, CD73 inhibitors are primarily classified into three categories: monoclonal antibodies, small-molecule inhibitors, and antibody-drug conjugates. Clinical studies have demonstrated that the combination of CD73 and ICB can significantly enhance the objective response rate and overcome drug resistance. Triple therapy incorporating CD73 inhibition with PD-L1 blockade and chemotherapy also demonstrates significant potential. This article reviews the biological characteristics, anti-tumor mechanism, and clinical research progress of CD73 in lung cancer, analyzes the value and clinical challenges of related biomarkers, with the aim of providing references for clinical intervention and basic research on lung cancer drug resistance.

Keywords

CD73, CD73 Inhibitor, Lung Cancer, Immune Drug Resistance, Clinical Research

1. 引言

肺癌是全球范围内发病率与死亡率均居首位的恶性肿瘤，严重威胁人类生命健康，其中非小细胞肺癌(Non-Small Cell Lung Cancer, NSCLC)约占所有肺癌病例的 80% [1] [2]。当前临床治疗中，化疗疗效仍存在明显局限，即便接受规范一线化疗，晚期肺癌患者的 5 年生存率也仅为 10%左右[3] [4]。近年来，免疫检查点抑制剂(Immune Checkpoint Inhibitor, ICIs)的临床应用为肺癌治疗带来了重要突破，赋予了晚期患者长期生存的希望；然而，该领域目前仍面临亟待突破的临床瓶颈：尽管已有程序性死亡受体 1 (Programmed Death 1, PD-1)及程序性死亡配体 1 (Programmed Death Ligand 1, PD-L1)等预测生物标志物，但 ICIs 治疗仍仅能使部分患者获益；同时，仍有 70%~80%的患者对 ICB 治疗无响应或出现获得性耐药[5] [6]。

肿瘤微环境(Tumor Microenvironment, TME)的免疫抑制状态是导致 ICB 疗法耐药的关键机制之一[7]。肿瘤和抗肿瘤疗法会促使大量三磷酸腺苷(Adenosine Triphosphate, ATP)释放到细胞外空间，随后由 CD39 水解成单磷酸腺苷(Adenosine Monophosphate, AMP)，再由 CD73 水解生成腺苷(Adenosine, ADO)。ADO 通过其四种受体(A1、A2A、A2B 和 A3)直接抑制效应免疫细胞功能并促进免疫抑制细胞扩增[8] [9]。其中，CD73 作为催化 AMP 转化为 ADO 的关键限速酶，在建立免疫抑制性 TME 中发挥着核心作用[10]。同时，CD73 高表达还与治疗耐药相关，因此将免疫检查点抑制剂与 CD73 抑制剂联合应用，有望为肺癌治疗开辟新的途径。

CD73 (又称胞外-5'-核苷酸酶，由 NT5E 基因编码)是肿瘤微环境中胞外腺苷生成的关键限速酶，高效催化 AMP 脱磷酸生成腺苷。多项研究证实，CD73 在肺癌细胞、调节性 T 细胞(Regulatory T Cell, Treg)、髓系来源抑制细胞(Myeloid-Derived Suppressor Cell, MDSC)、肿瘤相关巨噬细胞(Tumor-Associated Macrophage, TAM)中均呈异常高表达[11]-[14]。其通过 CD73-腺苷轴诱导 T 细胞耗竭、促进免疫抑制细胞浸润，参与肺癌的免疫逃逸过程，同时与 PD-1/PD-L1 通路形成正反馈，介导 ICB 耐药[6]。基于此，CD73 抑制

剂的研发应运而生，其通过阻断 CD73 酶活性、降低胞外腺苷水平、重塑肿瘤免疫微环境、恢复 T 细胞抗肿瘤功能，为肺癌治疗提供了新的思路。本文系统综述 CD73 的生物学特性、抗肿瘤作用机制、代表性药物在肺癌中的临床研究进展，深入分析相关生物标志物及临床应用面临的挑战，为肺癌的临床治疗与基础研究提供参考依据。

2. CD73 的生物学特性及其介导肿瘤免疫抑制的作用机制

2.1. CD73 的生物学特性

CD73 蛋白是一种糖基磷脂酰肌醇锚定的 70 千道尔顿分子的细胞膜结合酶，由胞外结构域、跨膜区及胞质尾组成，其 C 端的丝氨酸 523 负责 CD73 与质膜的结合[15] [16]。CD73 存在膜结合型和可溶性两种形式，其中膜结合型 CD73 是主要的功能形式，可溶性 CD73 由膜结合型 CD73 裂解产生，同样具有酶活性，可在血液中循环，参与全身免疫抑制[17]。

在正常的生理状态下，CD73 作为机体免疫调控网络中的重要分子，其表达具有高度的组织特异性与细胞靶向性，主要定位于血管内皮细胞及淋巴细胞表面，是维持机体生理平衡的关键调控因子。而在肺癌等恶性肿瘤中，CD73 的表达水平显著升高，其表达部位主要包括肺癌细胞表面、肿瘤微环境中的免疫抑制细胞及血管内皮细胞。CD73 的表达受缺氧、炎症因子、肿瘤微环境代谢异常等多种因素调控，其中组织缺氧是诱导 CD73 高表达的核心诱因；同时，CD73 高表达又可进一步加剧肿瘤局部缺氧与代谢抑制，形成促进肿瘤进展的恶性循环[11] [16]。

2.2. CD73 介导肿瘤免疫抑制的核心机制

CD73 通过催化 AMP 生成腺苷，激活腺苷介导的免疫抑制通路，进而参与肿瘤的免疫逃逸。

2.2.1. T 细胞耗竭

T 细胞作为适应性免疫系统的关键效应细胞，通过识别特定抗原来提供针对病原体的长期防御。CD73 将胞外 AMP 催化生成大量 ADO；而肿瘤微环境中高浓度的 ADO 可进一步激活 A_2A 受体，提高细胞内环磷酸腺苷水平，进而抑制 PI3K/Akt [18]、ERK [19]等促 T 细胞活化信号通路的激活；ADO 诱导 T 细胞表面 PD-1、T 细胞免疫球蛋白黏蛋白 3 (T Cell Immunoglobulin and Mucin Domain-Containing Protein 3, TIM-3)、淋巴细胞活化基因 3 (Lymphocyte Activation Gene 3, LAG-3)等耗竭标志物异常高表达，损害 T 细胞受体介导的信号传导及白细胞介素-2 受体介导的信号转导过程[20]。上述信号通路的异常干扰，可显著影响 T 细胞的关键功能，包括细胞增殖、迁移能力、细胞毒性效应及细胞因子的分泌，最终导致 T 细胞功能障碍[21] [22]。

此外，ADO 还可调控 $CD4^+$ T 细胞亚群分化及功能：不仅显著抑制 $CD4^+$ T 细胞炎症因子分泌[23]，而且诱导幼稚 $CD4^+$ T 细胞偏离 Th1 型分化，促进 Treg 增殖活化[24]。Treg 作为免疫抑制细胞，可通过分泌白细胞介素 10 (Interleukin-10, IL-10)、转化生长因子 β (Transforming Growth Factor-β, TGF-β)等细胞因子进一步抑制效应 T 细胞功能，同时肿瘤微环境中 Treg 异常分泌的腺苷，还可通过自分泌/旁分泌形成正向调控环路，持续强化免疫抑制状态[25]。值得注意的是，T 细胞 CD73 高表达可促进外腺苷生成，通过旁分泌及全身循环参与免疫抑制，与 Treg 协同维持肿瘤免疫逃逸[26]。

2.2.2. 重塑免疫抑制微环境

TME 的免疫抑制状态是肿瘤进展的重要基础，而 CD73-腺苷轴作为调控该状态的关键通路，可通过多种途径促进免疫抑制细胞的浸润和活化，进而参与肿瘤的发生发展。TME 中产生的腺苷可与单核细胞、树突状细胞(Dendritic Cell, DC)、MDSCs、Tregs 及巨噬细胞表面的 A_2R 结合，进而调控这些细胞的分化

与功能[27]。腺苷可通过招募 MDSC、Treg、TAM 等免疫抑制细胞向肿瘤组织浸润，MDSC 与 Treg 可通过细胞接触依赖及非依赖方式，直接抑制 $CD8^+$效应 T 细胞与辅助性 T 细胞的增殖、活化及细胞毒活性；TAM 可分泌 IL-10、TGF-β 等抗炎细胞因子进一步加重免疫抑制[27] [28]。同时腺苷还可显著抑制 DC 的成熟进程，下调其表面共刺激分子与主要组织相容性复合体II类分子的表达，降低 DC 对抗原的加工与呈递效率，阻碍 T 细胞的活化[29]，诱导形成稳固且有利于肿瘤生长的免疫抑制性微环境。上述多重效应相互协同、逐级放大，最终在肿瘤组织内部诱导形成稳定、强效且高度免疫抑制的微环境，为肿瘤细胞的免疫逃逸、持续增殖及远处转移提供了有利条件。

2.2.3. 调控肿瘤代谢与血管生成，间接促进肺癌免疫逃逸

CD73 不仅通过直接调控免疫细胞功能介导免疫抑制，还可通过影响肿瘤代谢与血管生成，间接推动免疫逃逸，如图 1 所示。CD73 催化生成的腺苷可加剧肿瘤局部缺氧状态，而缺氧又可进一步诱导 CD73 高表达，形成恶性循环[30]。缺氧环境不仅会抑制效应 T 细胞的功能，还会促进肺癌细胞的无氧糖酵解，导致肿瘤微环境中乳酸等代谢产物堆积，进一步抑制免疫细胞浸润与活化[31]。此外，腺苷可通过激活血管内皮细胞表面的 A2B 受体，促进肿瘤新生血管生成，为肿瘤细胞的增殖、侵袭和转移提供营养支持，同时新生血管的异常结构也会阻碍免疫细胞进入肿瘤组织，削弱抗肿瘤免疫应答[11]。

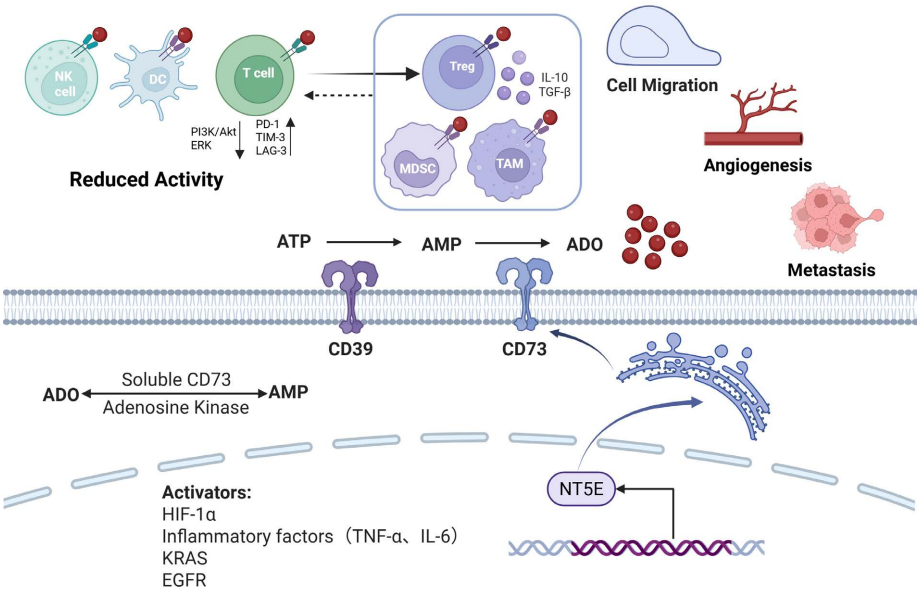

Figure 1. Mechanistic diagram of CD73-mediated tumor immune suppression
图 1. CD73 介导肿瘤免疫抑制的核心机制图

3. CD73 抑制剂代表性药物及治疗肺癌临床进展

NT5E 在肺癌组织中较正常肺上皮细胞显著高表达[14]，与其编码产物 CD73 在 NSCLC 中高表达的特征一致[32]-[35]。肿瘤细胞表面 CD73 的高表达水平与疾病进展、治疗后复发风险升高及患者生存期缩短均存在显著相关性[27] [30]。

基于 CD73 在肺癌发生发展中的关键作用，靶向该分子的抑制剂已成为肺癌治疗的重要研究方向。CD73 抑制剂的核心作用为阻断 CD73-腺苷轴、减少胞外腺苷、重塑肿瘤免疫微环境、逆转 T 细胞耗竭、克服 ICB 耐药。目前，CD73 抑制剂主要分为抗体类、口服小分子抑制剂类及抗体偶联药物(ADC)类三类，其中抗体类是目前临床研发最成熟、推进最快的类型，口服小分子抑制剂凭借其便捷性成为新兴研

发方向，ADC 类处于前沿探索阶段。

3.1. 抗体类 CD73 抑制剂

抗体类 CD73 抑制剂可通过抗体依赖的细胞毒性、补体依赖的细胞毒性杀伤 CD73 的肿瘤细胞及免疫抑制细胞[36]。该类药物与 PD-1/PD-L1 抑制剂联用可通过双重阻断免疫抑制通路，逆转 T 细胞耗竭、重塑免疫微环境，有效克服 ICB 耐药，是目前临床研发的主流策略[37]。

3.1.1. Uliledlimab

Uliledlimab (TJ004309)是天境生物自主研发的一款差异化单克隆抗体，通过非底物竞争的方式结合 CD73 的 C 端表位，可有效规避传统单抗的“钩状效应”，从而强效抑制 CD73 酶活性[37] [38]。其 I 期临床试验中，含 NSCLC 在内的患者客观缓解率(Objective Response Rate, ORR)达 23%，疾病控制率(Disease Control Rate, DCR)为 46%[39]。该药物联合特瑞普利单抗(Toripalimab，PD-1 抗体)治疗一线 NSCLC 的 Ib/II 期临床试验[38]显示，ORR 为 31.3%，DCR 为 79.2%；其中 CD73 高表达患者的 ORR 达 50%~53%，PD-L1 阳性且 CD73 高表达患者的 ORR 高达 57.1%~63%，显著高于单药治疗疗效，且安全性良好，未出现严重不良反应[40]-[42]。该药物已获得中国国家药品监督管理局药品审评中心突破性治疗认定，其 II/III 期临床试验已完成入组[43]。

3.1.2. Oleclumab

Oleclumab (MEDI9447)是阿斯利康研发的人源化单克隆抗体[44]。其 I 期临床试验[45]显示，在 NSCLC 患者中，6 个月无进展生存期(Progression-Free Survival, PFS)率为 16.0%，ORR 为 9.5%，DCR 约为 40%~50%，虽疗效有限，但安全性良好，为后续联合治疗提供了基础[46]。该药联合度伐利尤单抗(Durvalumab，PD-L1 抗体)治疗不可切除III期 NSCLC 临床研究[47]显示，联合治疗组的 ORR 为 35.0%，显著高于度伐利尤单抗单药组的 23.9%，疾病进展/死亡风险降低 41%，且安全性与单药组相当[48]。此外，一项针对可切除 IIa~IIIb 期 NSCLC 的临床试验[49]评估了 Oleclumab 联合度伐利尤单抗及铂类双药化疗的三联方案[49]，结果显示该方案在治疗人群中的病理完全缓解率为 20.3%，主要病理缓解率为 41.9%，且未观察到新增毒性[50]。基于上述结果，该联合方案已成为III期不可切除 NSCLC 放化疗后巩固治疗的潜在新方案，相关 III 期临床试验正在进一步验证[51]。

3.1.3. 其他在研抗体

全球多款 CD73 靶向单克隆抗体处于不同研发阶段，均以与 ICIs 联用为核心研究方向。Mavrostobart (PT199)联合抗 PD-1 单抗或化疗治疗晚期实体瘤的 I/II 期研究显示出良好的安全性和初步抗肿瘤活性[52] [53]；Sym024 为双表位抗 CD73 抗体，可进一步降低“钩状效应”并提升抑制效果，目前处于 I 期临床阶段[54] [55]。国内研发方面，加科思药业 JAB-BX102、信达生物 IBI325 等均处于 I/II 期临床，主要评估与 PD-1 抑制剂联用的安全性及疗效；康方生物 AK137 为全球首个进入临床的 CD73/LAG-3 双抗，可同时靶向两条核心免疫抑制通路，为多靶点联合治疗提供新方向[56] [61] [62]。多款抗体药物的研发信息见表 1。

3.2. 小分子 CD73 抑制剂

小分子 CD73 抑制剂以口服给药、组织分布广、肿瘤穿透性强为核心优势，可穿透多种组织屏障发挥作用[63]。

德琪医药研发的 ATG-037 是目前研发进展最快的口服小分子 CD73 抑制剂，可强效抑制 CD73 酶活性，无“钩状效应”，组织穿透性强，降低胞外腺苷水平[64]。其联合帕博利珠单抗(Pembrolizumab, PD-1 抗体)治疗 ICB 耐药 NSCLC 的 I/Ib 期研究[65]显示，ORR 为 21.4%，DCR 为 71.4%，部分患者实现长

期疾病控制(≥6 个月)，安全性良好，为 ICB 耐药患者提供了新的治疗选择[64]。鉴于抗血管生成药物可改善肿瘤微环境缺氧并下调 CD73 表达，与 CD73 抑制剂存在协同作用，ATG-037 的 II 期临床试验正探索联合君实 JS207 (PD-1/VEGF 双抗)的 CD73+PD-1+VEGF 三重阻断策略的疗效[64]。

目前，以肺癌为核心适应症的 CD73 小分子抑制剂已初步显现出潜在的治疗价值与应用前景，多款在研药物见表 2。

Table 1. Research status of CD73 antibody and related clinical studies in lung cancer
表 1. CD73 抗体药物研发现状及肺癌相关临床研究进展

代表药物	研发企业	临床阶段	肺癌相关研究
TJ004309 (Uliledlimab)	天境生物(I-Mab Biopharma)	II/III 期	联合 PD-1 抑制剂治疗 PD-L1 阳性、CD73 高表达 NSCLC [38]
MEDI9447 (Oleclumab)	MedImmune/阿斯利康(AstraZeneca)	II/III 期	联合 PD-L1 抑制剂治疗 NSCLC [45]
PT199 (Mavrostobart)	凡恩世制药(Phanes Therapeutics)	I/II 期	联合 PD-1 抑制剂治疗含 NSCLC 在内的晚期实体瘤[52]
BMS-986179	百时美施贵宝(Bristol Myers Squibb, BMS)	I/II 期	联合 PD-1 抑制剂治疗包括 NSCLC 在内的晚期实体瘤[57]
CPI-006	Corvus Pharmaceutical	I/II 期	联合 ICIs 治疗包括 NSCLC 在内的晚期实体瘤[58]
IPH5301	Innate Pharma	I 期	晚期实体瘤，覆盖 NSCLC [59]
NZV930	诺华(Novartis)	I 期	晚期实体瘤，覆盖 NSCLC [60]
JAB-BX102	加科思药业	I/IIa 期	联合 PD-1 抗体治疗含 NSCLC 等晚期实体瘤[61]
IBI325	信达生物	I/II 期	联合 PD-1 抗体治疗含 NSCLC 等晚期实体瘤[62]
AK119	康方生物	Ib/II 期	与 PD-1/VEGF 双特异性抗体的联合疗法治疗含 NSCLC 晚期实体瘤[62]
Sym024	Symphogen	I 期	联合 PD-1 抗体治疗 PD-L1 高表达晚期 NSCLC [55]

Table 2. Research status of CD73 small-molecule and related clinical studies in lung cancer
表 2. CD73 小分子药物研发现状及肺癌相关临床研究进展

代表药物	研发企业	临床阶段	肺癌相关研究
ATG-037	德琪医药	I/II 期	ICB 耐药实体瘤，覆盖 NSCLC [65]
LY3475070	礼来制药(Lilly Pharma)	I 期	实体瘤，覆盖 NSCLC [66]
ABSK-051	和誉医药	I 期	实体瘤，覆盖 NSCLC [67]

3.3. 抗体偶联药物(ADC)类 CD73 抑制剂

CD73-ADC 兼具单克隆抗体的靶向性与细胞毒药物的杀伤作用，可通过特异性结合 CD73 高表达肿瘤细胞并定向递送细胞毒药物，兼具靶向性强、全身毒性低的优势[68] [69]。

Hu001-MMAE 为首个靶向 CD73 的 ADC 药物，由抗 CD73 单抗与细胞毒药物 MMAE (单甲基澳瑞他汀 E)偶联而成。体外及体内研究均显示其对 NSCLC 具有显著抑制作用，可有效抑制肿瘤细胞增殖，同时重塑肿瘤免疫微环境、逆转 T 细胞耗竭[68]。目前，全球进入临床阶段的 CD73-ADC 药物主要有两款，分别为 BB-1709 和 HB0052，二者均处于 I 期临床试验阶段[70] [71]。这类创新型 ADC 药物有望为

CD73 高表达、ICB 耐药的肺癌患者提供新的治疗选择，相关研发信息见表 3。

Table 3. Research status of ADC drugs and related clinical studies in lung cancer
表 3. ADC 药物研发现状及肺癌相关临床研究进展

代表药物	研发企业	临床阶段	肺癌相关研究
BB-1709	百力司康	I 期	实体瘤，覆盖肺癌[70]
HB0052	华奥泰生物	I 期	实体瘤，覆盖肺癌[71]

3.4. 三类 CD73 抑制剂的特性对比与临床应用前景

三类 CD73 抑制剂均以阻断 CD73-腺苷轴为核心作用机制，通过抑制 CD73 酶活性减少胞外腺苷生成、重塑肿瘤免疫微环境，发挥抗肿瘤作用，但在作用特点、药理学特性、临床应用及研发局限方面存在显著差异。

单克隆抗体可通过 ADCC/CDC 效应靶向杀伤靶细胞，兼具高靶向性与长半衰期[36]，是临床研发最成熟的类型，适用于 CD73/PD-L1 共表达的不可切除III期、晚期 NSCLC 一线治疗，联合 ICIs 或化疗的疗效与安全性均获验证[51]。但其存在组织穿透性弱、部分药物存在“钩状效应”、仅能静脉输注的局限，需通过抗体结构优化、探索便捷给药剂型改进不足。

小分子抑制剂可同时作用于膜结合型与可溶性 CD73，实现全身腺苷阻断，且口服便捷、肿瘤穿透性强[37]，成为 ICB 耐药 NSCLC 的治疗优选，适合肿瘤组织致密、CD73 高表达的晚期患者，与抗血管生成药物/ICIs 的联合策略前景良好[64]。但此类药物靶向特异性低、脱靶风险高、体内半衰期短，需开发高选择性制剂、优化缓释剂型以提升临床价值。

ADC 类药物融合靶向性与细胞毒性，对 CD73 高表达 ICB 耐药肺癌具有特异性杀伤作用，全身毒性低[68]，为精准治疗的前沿方向，但目前仅处于 I 期临床阶段，存在研发制备难度高、连接子稳定性与药物释放效率难把控、临床证据不足的问题，需进一步优化偶联工艺并开展大样本临床研究。

综合来看，三类药物在作用机制、应用场景、获益人群上形成互补，临床应基于患者 CD73 表达水平、肿瘤组织特征及治疗阶段进行分层选择：单克隆抗体用于一线主流治疗，小分子抑制剂用于 ICB 耐药后治疗，ADC 类药物待临床证据完善后，用于 CD73 高表达且对前两者无响应的晚期患者，通过三类药物的优势互补与分层应用，最大化提升肺癌患者临床获益。

4. CD73 抑制剂临床应用的生物标志物研究

生物标志物的筛选和应用，是实现 CD73 抑制剂精准治疗的关键，可用于筛选优势获益人群、预测治疗疗效、监测病情进展。多项研究表明，肿瘤组织中 CD73 高表达与非小细胞肺癌患者病理分级、肿瘤浸润、淋巴结转移及预后不良密切相关[72]-[75]，其中 CD73 与 PD-1/PD-L1 的表达相关性备受关注[76] [77]。在经表皮生长因子受体酪氨酸激酶抑制剂治疗后产生耐药的非小细胞肺癌中，PD-L1 和 CD73 的表达均会升高[78] [79]。既往研究表明，CD73 的表达水平可作为免疫检查点抑制剂疗效的预测指标，在 NSCLC 中 CD73 高表达与患者对免疫检查点抑制剂治疗的更佳应答相关[80]。

临床试验的结果表明，CD73 与 PD-L1 的共表达或可作为预测 CD73 抑制剂联合免疫检查点抑制剂治疗疗效的潜在生物标志物[42] [81]。一项纳入 19 例晚期 NSCLC 患者的研究中，Uliledlimab 联合特瑞普利单抗的临床疗效与肿瘤 CD73 表达显著相关：5 例部分缓解患者中 4 例为 CD73 高表达，9 例病情稳定患者中 4 例为 CD73 高表达[42]。另一项研究中也得出了相似的结论：在度伐利尤单抗联合 Oleclumab 的治疗组中，患者基线时 CD73 表达水平越高，术后残留的肿瘤细胞越少，病理缓解效果也更优[81]。

但上述研究证据仍存在局限，未来需开展大样本随机对照研究以进一步明确联合治疗的获益人群。通过免疫细胞比例检测、免疫活性分子检测、肿瘤细胞与免疫细胞表面分子表达检测及肿瘤突变负荷检测等方法对肿瘤微环境组分进行精准检测，并结合蛋白质组学、基因组学、单细胞测序、二代测序等技术手段，将有助于进一步明确此类潜在生物标志物，从而指导联合治疗策略应用于更合适的人群，实现最优的临床获益。

5. 结论

CD73-腺苷轴是肺癌免疫抑制和 T 细胞耗竭的核心调控通路，CD73 抑制剂通过阻断该轴、重塑免疫微环境、逆转 T 细胞耗竭、克服 ICB 耐药，在肺癌免疫治疗中展现出明确的临床价值。目前，CD73 抑制剂已进入临床快速发展阶段，单克隆抗体联合 PD-1/PD-L1 抑制剂是主流方案，口服小分子抑制剂和 ADC 类药物逐步崛起，多项关键临床试验正在推进中。尽管 CD73 抑制剂在肺癌治疗中仍面临疗效异质性、安全性、耐药机制不明确等挑战，但随着研究的不断深入、药物研发的不断优化及联合治疗策略的不断完善，CD73 抑制剂有望成为肺癌精准免疫治疗的核心靶点之一，为不同类型的肺癌患者提供个体化的治疗方案，改善患者的生存质量，延长生存期。

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