抗体偶联药物肿瘤渗透性的挑战与用药策略

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摘要: 抗体偶联药物 (antibody-drug conjugates, ADC) 是一类创新的强效抗癌药物, 它将单克隆抗体药物的高特异性和小分子毒素的高效杀伤作用通过连接子相连接, 有效提高肿瘤靶向性、减少毒副作用; 它作为肿瘤治疗领域极具潜力的创新疗法, 为癌症患者带来了新希望。然而, 肿瘤渗透性问题成为制约其疗效充分发挥的关键因素。本综述介绍了ADC的作用机制和结构优化策略, 分析肿瘤微环境中阻碍ADC渗透的复杂因素, 并探讨了提升ADC渗透性的用药策略。通过相关研究进展的系统梳理, 为推动ADC在肿瘤治疗中的进一步发展提供了理论依据与实践指导。

关键词: 抗体偶联药物; 肿瘤渗透性; 肿瘤微环境; 用药策略

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Challenges and dosing strategies for tumor penetration of antibody-drug conjugates

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Abstract: Antibody-drug conjugates (ADC) are a type of innovative and highly effective anti-cancer drugs. They connect the high specificity of monoclonal antibody drugs with the efficient killing ability of small molecule toxins through a linker, effectively enhancing tumor targeting and reducing toxic side effects. As a highly promising innovative therapy in the field of cancer treatment, ADC have brought new hope to cancer patients. However, the issue of tumor permeability has become a key factor restricting the full exertion of their efficacy. This review introduces the mechanism of action and structural optimization strategies of ADC, analyzes the complex factors that hinder the permeation of ADC in the tumor microenvironment, and discusses the drug administration strategies to improve ADC permeability. Through the systematic review of relevant research progress, it provides theoretical basis and practical guidance for promoting the further development of ADC in tumor treatment.

Key words: antibody-drug conjugate; tumor permeability; tumor microenvironment; drug administration strategy

抗体偶联药物作为肿瘤治疗领域的新兴力量, 融合了单克隆抗体的精准靶向性与小分子细胞毒性药物的强大杀伤力, 为癌症患者带来了新的希望。自2000年首个抗体偶联药物 (antibody-drug conjugates, ADC)[1]获批上市以来, ADC的研发呈蓬勃之势。目前, 全球已有19款ADC药物 (表1) 获批用于多种血液瘤和实体肿瘤的治疗。

ADC在治疗肿瘤上优势显著, 其抗体部分能特异性识别并结合肿瘤细胞抗原, 将有效载荷精准递送至肿瘤细胞, 提高杀伤减少正常细胞损害, 降低全身毒副作用[2]。ADC的靶向性和选择性在面对复杂多变的肿

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Table 1 List of approved of antibody-drug conjugates (ADC). GSK: GlaxoSmithKline; BCMA: B-cell maturation antigen; CD19: Cluster of differentiation 19; CD22: Cluster of differentiation 22; CD30: Cluster of differentiation 30; CD33: Cluster of differentiation 33; CD79B: Cluster of differentiation 79B; c-Met: Mesenchymal-epithelial transition factor; EGFR: Epidermal growth factor receptor; HER2: Human epidermal growth factor receptor 2; Trop-2: Tumor associated antigen 2; FRα: Folate receptor alpha; Nectin-4: Nectin cell adhesion molecule 4

Company	Generic name	Trade name	Target antigen	Indication	Frist approved
GSK	Belantamab mafodotin	Blenrep	BCMA	Multiple myeloma	2020.8
ADC Therapeutics	Loncastuximab tesirine	Zynlonta	CD19	Relapsed/refractory diffuse large B-cell lymphoma	2021.4
Pfizer	Inotuzumab ozogamicin	Besponsa	CD22	Acute lymphoblastic leukemia	2017.6
AstraZeneca	Moxetumomab pasudotox	Lumoxiti	CD22	Hairy cell leukemia	2018.9
Seagen & Takeda	Brentuximab vedotin	Adcetris	CD30	CD30-positive Hodgkin lymphoma and systemic anaplastic large cell lymphoma	2011.8
Pfizer	Gemtuzumab ozogamicin	Mylotarg	CD33	CD33-positive acute myeloid leukemia	2000.5
Genentech	Polatuzumab vedotin	Polivy	CD79B	Diffuse large B-cell lymphoma	2019.6
Abbvie	Telisotuzumab vedotin	Emrelis	cMet	c-Met over expressing non-small cell lung cancer	2025.5
Rakuten Medical	Cetuximab sarotalocan sodium	Akalux	EGFR	Unresectable locally advanced or recurrent head and neck cancer	2020.9
ImmunoGen	Mirvetuximab soravtansine	Elahere	FRα	FRα-positive platinum-resistant	2022.11
Genentech & Roche	Trastuzumab emtansine	Kadcyla	HER2	HER2-positive metastatic breast cancer	2013.2
Daiichi Sankyo	Trastuzumab deruxtecan	Enhertu	HER2	HER2-positive breast cancer	2019.12
RemeGen	Disitamab vedotin	Aidixi	HER2	The integration of a stomach/stomach esophagus adenocarcinoma, breast cancer, urothelial carcinoma	2021.6
Hengrui Pharmaceuticals	Trastuzumab rezetecan	Aiweida	HER2	HER2-mutant non-small cell lung cancer	2025.5
Astellas Pharma & Seagen	Enfortumab vedotin	Padcev	Nectin-4	Urothelial carcinoma	2019.12
Seagen	Tisotumab vedotin	Tivdak	Tissue factor	Recurrent/metastatic cervical cancer	2021.9
Gilead Sciences	Sacituzumab govitecan	Trodelvy	Trop-2	Metastatic triple-negative breast cancer	2020.4
Kelun-Biotech	Sacituzumab tirumotecan	Jiatailai	Trop-2	Metastatic triple-negative breast cancer	2024.11
AstraZeneca & Daiichi Sankyo	Datopotamab deruxtecan	Datroway	Trop-2	Unresectable/metastatic breast cancer	2024.12

瘤微环境时有望突破传统化疗局限, 实现精准有效治疗。

然而, ADC在临床应用中面临诸多挑战, 肿瘤渗透性是其面临的关键挑战之一。肿瘤微环境极为复杂, 致密细胞外基质[3]、异常血管结构[4]及高压间质液压[5]等因素, 构成了ADC深入肿瘤发挥疗效的屏障。本文将围绕ADC渗透性, 阐述屏障构成、阻碍机制、影响因素, 并探究解决方案, 展望研发策略, 为ADC领域发展提供参考。

1 抗体偶联药物的作用机制及结构优化现状

1.1 作用机制

ADC的作用机制与其结构有关, 其通过抗体部分特异性地识别并结合肿瘤细胞表面的靶点抗原, 随后内吞进入细胞, 在细胞内连接子根据其特性发生断裂, 释放有效载荷发挥作用, 例如通过干扰DNA合成、抑制微管聚合、破坏细胞膜结构等多种途径, 诱导肿瘤细胞凋亡或死亡。因肿瘤细胞具有较高的通透性, 有效载荷扩散至邻近的肿瘤细胞发生凋亡, 这一现象称为旁观者效应。旁观者效应指其释放的有效载荷不仅能杀伤直接结合的靶细胞, 还能对周围未结合ADC的肿瘤细胞产生杀伤作用, 是ADC在靶抗原呈异质性表达的肿瘤中发挥药效的重要助力[6-8](图1)。

1.2 结构优化现状

ADC结构优化围绕单克隆抗体、连接子和有效载荷进行革新, 从早期提升靶向性与毒性适配性, 逐步向增强肿瘤穿透、降低脱靶毒性等需求演进, 为不同阶段ADC疗效提升奠定关键基础 (图2)。

1.2.1 单克隆抗体 在ADC结构设计中, 抗体类似于导弹导航仪的制导系统, 精准识别并结合癌细胞表面的特定抗原。理想的抗体须满足特定标准。第一, 高稳定性、低免疫原性, 其来源至关重要。抗体类型从鼠源性发展至人源化乃至全人源, 降低免疫原性, 提高耐受性和疗效[9,10]; 第二, 对特定抗原有明确特异性, 在肿瘤细胞中高表达, 在正常组织中低表达, 实现ADC在肿瘤细胞内有效积累而不伤害健康细胞。因此, 抗体识别肿瘤细胞表面靶抗原的能力至关重要[11]; 第三, 与抗原有适当亲和力及高效内化, 保证被靶细胞快速吸收[12]; 第四, 在血浆中有长半衰期, 如人源化或嵌合免疫球蛋白G (immunoglobulin G, IgG) 抗体, 尤其是IgG1, 常作ADC基础框架。一些抗体可抑制癌细胞, 通过

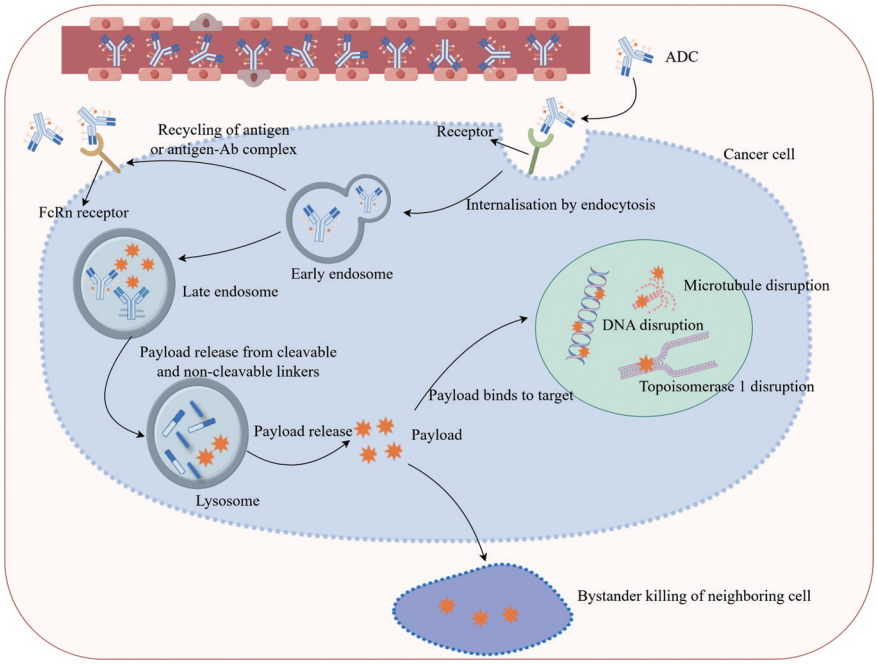
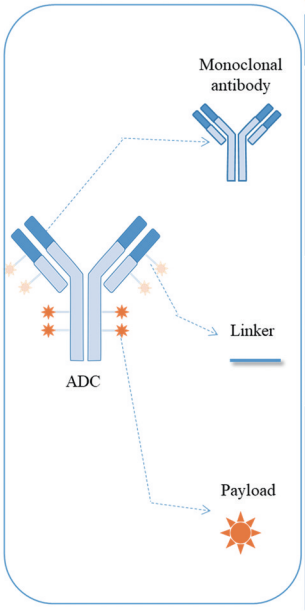


Figure 1 Mechanism action of antibody drug conjugates. FcRn: Neonatal Fc receptor. Figure drawn by Figdraw



First generation	Second generation	Third generation	Fourth generation
1. Murine or chimeric antibodies 2. High immunogenicity and short half-life 3. Low targeting ability, prone to cross-react with normal tissues	1. Humanized antibody 2. Reduce immunogenicity and prolong half-life 3. Enhance target antigen specificity	1. Fully human antibody 2. Optimize endocytosis efficiency 3. Target more solid tumor antigens	1. Bispecific antibodies/multi-epitope targeting 2. Antibody fragmentation to enhance tumor penetration 3. AI-assisted design of high-affinity antibodies
1. Non-lytic linker 2. Poor cyclic stability, prone to premature release of payload 3. No tumor microenvironment specificity	1. Cleavable linker 2. Enhanced cycle stability, but still with off-target release 3. Initiate adaptation to the tumor microenvironment	1. Highly stable cleavable linker 2. Enhanced responsiveness to tumor microenvironment 3. Site-specific coupling technology	1. Intelligent responsive linker 2. Self-degradable linker 3. Synergistically optimize pharmacokinetics with payload/antibody
1. Traditional chemotherapy drugs 2. High toxicity, narrow therapeutic window 3. No bystander effect 4. Easy to develop drug resistance	1. Highly toxic payload 2. The toxicity is lower compared to the first generation, and the therapeutic window has been expanded 3. Some of the payloads exhibit a weak bystander effect	1. New type of highly active payload 2. Strong bystander effect, addressing tumor heterogeneity 3. Controllable toxicity, further expansion of therapeutic window	1. Multi-mechanism load 2. Low immunogenicity load 3. Broad-spectrum killing load with adaptability to antigen heterogeneity

Figure 2 Summary of the fourth generation innovation of ADC

多机制触发其死亡, 包括与ADC中的免疫效应细胞结合, 以及通过抗体依赖等过程触发抗肿瘤免疫细胞介导的细胞毒性 (antibody-dependent cell-mediated cytotoxicity, ADCC)、补体依赖性细胞毒性 (complement-dependent cytotoxicity, CDC)、抗体依赖性细胞介导的吞噬作用 (antibody-dependent cellular phagocytosis, ADCP)[13,14], 以及对肿瘤细胞信号通路和T细胞免疫调节功能的干扰[15]。但越来越多研究表明将完整IgG用于实体癌治疗存疑, 其大小是关键局限之一[16]。ADC中常用的IgG1分子质量大, 达到150 kDa, 阻碍ADC在肿瘤中的分布, 影响其药代动力学与疗效。小分子抗体片段 [如抗原结合片段 (fragment antigen-binding, Fab)、单链可变片段 (single-chain variable fragment, ScFv)、小免疫蛋白等, 分子质量10～50 kDa] 因穿透力强成为研究焦点[17]。例如Muchekehu等[18]研究发现, 与IgG相比, Fab片段更能深入肿瘤。例如, 一种人源

化 Fab 片段 (ABC3315) 可以增强 MMAE-ADC 的治疗选择性及治疗窗口期, 降低脱靶毒性, 但不降低抗肿瘤疗效[19]。与传统 ADC 相比, 基于小分子抗体片段构建的 ADC 在肿瘤组织分布更均匀, 可有效到达远离血管的肿瘤细胞区域。尽管小分子抗体片段 ADC 在稳定性、半衰期等面临挑战, 如 ScFv 易聚集、纳米抗体在体内清除较快等, 但通过合理的分子工程改造, 如引入稳定化突变、与白蛋白等长效载体融合, 有望克服这些问题, 推动其临床应用进程[20-22]。

较低的靶抗原结合亲和力有助于 ADC 更深地渗透到肿瘤组织中, 如 Tsumura 等[23]构建了 3 种不同程度亲和力抗组织因子 (tissue factor, TF) 的 ADC: 低亲和力的 1084-ADC、中等亲和力的 444-ADC 和高亲和力的 1849-ADC。在 BxPC3 小鼠肿瘤模型中, 3 种亲和力不同的抗 TF ADC 对小型肿瘤的抗肿瘤作用一致; 在较大的 BxPC3 肿瘤上, 1084-ADC 比 1849-ADC 抗肿瘤活性更高。且 1084-ADC 在整个肿瘤组织均有分布, 而 1849-ADC 仅聚集在肿瘤血管附近。该研究表明抗体的选择优化在 ADC 设计中至关重要, 可有力推动新型 ADC 的研发, 为肿瘤治疗开拓更多可能性。

1.2.2 连接子 在 ADC 结构设计中, 连接子能稳定连接抗体与有效载荷, 起关键纽带作用, 为 ADC 发挥功效奠定基础; 理想连接子需在到达靶细胞前维持分子稳定, 进入细胞后能高效释放有效载荷。因此, 连接子结构是扩大治疗范围、增强 ADC 疗效的关键因素。

常见的 ADC 连接子分为可切割与不可切割两类。可切割连接子对细胞内环境敏感, 经细胞内降解、代谢和解离释放有效载荷。在血液中表现出稳定性, 但在低 pH 值、溶酶体中富含蛋白酶或谷胱甘肽浓度升高的环境中迅速分解并释放其活性化合物; 不可切割连接子的血浆稳定性强于可切割连接子, 因其高稳定性和良好安全性, 能抑制脱靶毒性, 拓宽治疗范围[24-27]。但不可切割连接子由于依赖细胞内化后才能发生降解激活, 且释放的分解代谢产物通透性较差, 不能发挥旁观者效应, 适应症受限等原因, 目前大部分 ADC 常用的还是可切割连接子[28]。

第一代 ADC 如吉妥珠单抗奥佐米星 (gemtuzumab ozogamicin), 使用早期腙类连接子, 稳定性差, 致使有效载荷在体循环中提前快速释放, 在未抵达目标组织前就发挥作用[27]; 第二代 ADC 采用更稳定的化学连接子, 分为可裂解 [如维布妥昔单抗 (brentuximab vedotin) 中的二肽连接子] 和不可裂解 [如恩美曲妥珠单抗 (trastuzumab emtansine, T-DM1) 中的硫醚连接子] 两类, 确保 ADC 在血液中的稳定性, 减少药物的过早释放; 但仍存在异质抗体–药物比 (drug-antibody ratio, DAR)、高 DAR 药物清除过快、脱靶毒性和耐药等问题[29]; 第三代 ADC 能响应肿瘤微环境中常见的酸性 pH、特定酶等条件, 结合光、热等内源性或外源性刺激实现药物释放, 提高药物释放的精准性与有效性。还可调节连接子亲疏水性改善 ADC 水溶性和药代动力学特性, 减少药物在非靶组织分布, 提升治疗指数[23,30,31]。以德曲妥珠单抗 (trastuzumab deruxtecan, T-DXd) 为例, 其为蛋白酶可切割的马来酰亚胺四肽连接子, 能精准递送有效载荷 (DXd) 至肿瘤细胞中, 最大程度减少在正常细胞中的暴露; 在多种人表皮生长因子受体 (human epidermal growth factor receptor 2, HER2) 阳性实体瘤中展现出良好抗肿瘤活性, 已获 FDA (Food and Drug Administration) 批准用于乳腺癌、胃癌等治疗[32]。第四代 ADC 采用位点特异性可裂解连接子和新型偶联技术, 在血液循环中保持高度稳定, 抵达肿瘤微环境后响应特定刺激精准释放有效载荷, 提升疗效与安全性。以 CRB-701 为例, 其为组织蛋白酶 B 响应型连接子, 使其在血浆稳定性延长, 且显著降低传统 nectin 细胞黏附分子-4 (nectin cell adhesion molecule 4, Nectin-4) ADC [如恩诺单抗 (enfortumab vedotin)] 的剂量限制性毒性, 且在晚期 Nectin-4 阳性实体瘤患者中显示出良好的抗肿瘤活性和良好的耐受性[33]。因此, 新型连接子的发展优化将为 ADC 设计开拓新方向, 进一步拓展肿瘤治疗领域的范围。

1.2.3 有效载荷 有效载荷是 ADC 的发挥药效的关键部分, 为实现最佳肿瘤抑制, 它要满足以下要求: ① 低免疫原性, 优选的是非免疫原性细胞毒性药物在血液循环时应表现出稳定性和无毒性, 同时在纳摩尔浓度下具有高效力[34]; ② 高细胞毒性, 有效载荷应在最低纳摩尔浓度下表现出最大的细胞毒性, 并在肿瘤细胞中精准释放[35]; ③ 在水环境中足够的抗体溶解度, 进入细胞的有效载荷需要在水缓冲溶液中溶解, 以便偶联; ④ 适宜的脂溶性和半衰期, 这一属性允许可控的旁观者效应[36]。临床测试的 ADC 常用的有效载荷可分为 3 组: 微管抑制剂、DNA 损伤剂和拓扑异构酶抑制剂[37]。

除了传统的有效载荷外, 越来越多具有新机制的有效载荷正被纳入 ADC 设计。例如, 小分子免疫调节剂开始应用于新型 ADC 的开发, 这些药物也被称为免疫刺激抗体偶联物 (immunostimulatory antibody conjugates, ISACs)。ISACs 结合抗体靶向的精准性和基于小分子调节先天及适应性免疫系统的能力, 在多种肿瘤模型中显示出肿瘤消退和长期抗肿瘤免疫的潜力[38]; 各种非细胞毒性有效载荷, 如甾体、糖皮质激素、寡核苷酸等, 可以与抗体偶联形成 ADC, 从而发挥其

作用[39,40]。例如, Hobson 等[41]在慢性关节炎小鼠模型中发现, 将糖皮质激素受体调节剂 (glucocorticoid receptor modulator, GRM) ABBV-3373 作为载荷与人类抗肿瘤坏死因子 (tumor necrosis factor, TNF) 抗体结合比具有相同 GRM 载荷的抗体和同型对照更有效。未来可利用类固醇和糖皮质激素作为有效载荷, 通过免疫调节和炎症抑制等机制发挥 ADC 的抗癌作用。

有效载荷的多样化有望扩大 ADC 的适应症治疗范围, 包括未受益于靶向治疗的肿瘤, 这是 ADC 研究的一个重要方向。更深入地研究其协同效应, 可能会为治疗具有肿瘤异质性和耐药性的难治性癌症的开辟新方法。

总的来说, 双特异性抗体偶联药物融合双特异性抗体与 ADC 技术的新型治疗药物, 是第四代 ADC 技术革新的重要突破; 其通过同时靶向细胞表面两个不同抗原或表位, 强化靶向精准性与穿透性。例如埃万妥单抗 (anivantamab) 可同时结合表皮生长因子受体 (epidermal growth factor receptor, EGFR) 和细胞间质上皮转化因子 (mesenchymal-epithelial transition factor, cMET) 两个非重叠靶点, 增强与肿瘤细胞的结合广度与信号阻断效率, 配合其独特的 Fc 端介导的受体聚集、内化和 ADCC 效应, 在抑制关键驱动信号通路同时诱导免疫细胞杀伤, 对 EGFR 经典突变、MET 外显子 14 跳跃突变患者等有显著疗效, 有效弥补传统单靶点 ADC 的不足, 拓宽了 ADC 的临床应用空间[42]。

2 影响 ADC 肿瘤渗透的因素

结构优化赋予 ADC 更精准的“分子武器”, 但这些优势在进入体内后将直面肿瘤微环境 (如血管异常、间质高压等) 的筛选。这要求结构优化策略预判其在实体瘤中的递送轨迹, 唯有将 ADC 的“智能导航”、精准释放等特性与微环境改造相结合, 方能突破当前疗效瓶颈。

2.1 肿瘤微环境

肿瘤微环境 (tumor microenvironment, TME) 是一个复杂的生态系统, 由肿瘤细胞、间质细胞 (如成纤维细胞、内皮细胞等)、免疫细胞 (如巨噬细胞、自然杀伤细胞等) 及各种因子和代谢产物共同组成[43](图 3), 这些成分间相互作用、相互影响, 既利于肿瘤细胞生长、增殖和转移, 也阻碍 ADC 的渗透与杀伤。

肿瘤相关成纤维细胞 (cancer-associated fibroblasts, CAFs) 是肿瘤微环境中关键间质细胞成分, 其可分泌大量细胞外基质成分促进肿瘤间质的致密化, 对 ADC 的扩散形成物理障碍。此外, 还分泌多种生长因子 [如转化生长因子-β (transforming growth factor-β, TGF-β)、表皮生长因子 (epidermal growth factor, EGF) 等] 和趋化因子 [如 C-X-C 基序趋化因子配体 12 (C-X-C motif chemokine ligand 12, CXCL12) 等] 来刺激肿瘤细胞的增殖迁移, 调节肿瘤血管生成, 间接影响 ADC 的递送[44,45]。同时, 部分由 CAFs 分泌的因子能诱导肿瘤细胞产生耐药表型, 降低 ADC 对肿瘤细胞的敏感性。

免疫细胞在肿瘤微环境中的作用具有两面性。一方面, 肿瘤浸润的免疫细胞, 如巨噬细胞、髓源性抑制细胞等, 在肿瘤细胞分泌的细胞因子作用下常呈现免疫抑制表型, 通过分泌免疫抑制性介质 [如白细胞介素-10 (interleukin-10, IL-10)、TGF-β等], 抑制机体免疫系统对肿瘤细胞的杀伤作用, 使得肿瘤细胞得以逃脱

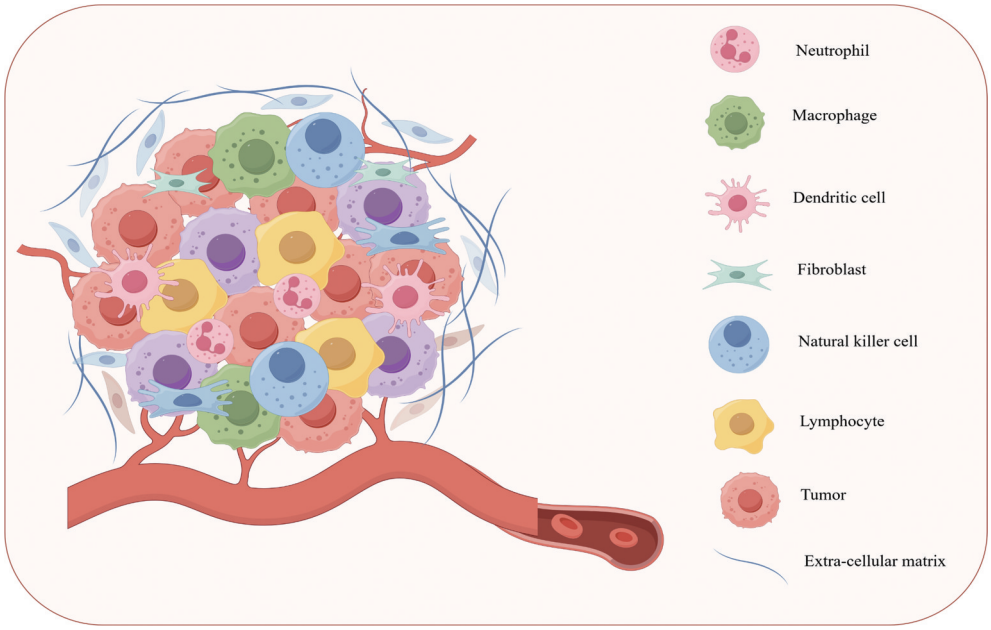


Figure 3 Schematic diagram of tumor microenvironment. Figure drawn by Figdraw

免疫监视, 间接降低了ADC联合免疫治疗的协同效应; 另一方面, 免疫细胞分泌的一些炎性因子 [如肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、干扰素-γ (interferon-γ, IFN-γ) 等], 在一定程度上可能具有抗肿瘤活性, 但也会使肿瘤微环境的炎性状态改变, 影响ADC的稳定性与活性, 甚至促进肿瘤细胞的耐药性产生[46,47]。

细胞外基质 (extra-cellular matrix, ECM) 是肿瘤微环境的主要组成部分, 也是药物深入肿瘤组织的物理和生物障碍。其胶原蛋白等生物大分子的合成与降解失衡, 导致ECM过度沉积、交联, 使肿瘤间质变得异常致密[48]。这种结构通过狭小孔隙、紧密的纤维排列限制ADC的扩散, 使其仅在肿瘤边缘积累; 同时增加流体阻力, 阻碍药物对流运输, 降低向深部渗透的速率, 影响整体分布[49]。

肿瘤微环境中的代谢异常也是影响ADC疗效的重要因素。肿瘤细胞的快速增殖导致其呈现低糖、低氧、高乳酸等代谢特征。低糖、低氧环境可诱导肿瘤细胞适应性改变, 如上调糖酵解相关酶的表达, 改变细胞表面抗原表达、内吞机制及耐药相关蛋白的表达, 降低ADC的靶向性与杀伤效果。高乳酸化的微环境会影响ADC连接子的稳定性与释放, 还通过激活相关信号通路促进肿瘤细胞的存活、增殖与迁移, 进一步对抗ADC的治疗作用[46,50]。

2.2 高间质压力

肿瘤组织内的高间质压力主要源于肿瘤细胞快速增殖、ECM大量合成及液体分泌与排泄的失衡[5,51]。肿瘤细胞不断分裂增殖, 占据越来越多的空间并持续分泌ECM成分使间质变得致密。此外, 血管通透性异常导致大量液体渗出并积聚在间质中, 且缺乏正常的淋巴引流系统来有效清除这些多余液体, 从而使得间质压力不断升高[52]。这会挤压药物扩散路径, 阻碍ADC向肿瘤深部渗透使其局限于边缘, 限制整体杀伤效果。

2.3 肿瘤血管系统异常

正常血管呈规则的分支状结构, 内皮细胞排列整齐, 基底膜完整且连续。而肿瘤新生血管则是迂曲、扩张、分支不规则, 内皮细胞间隙较大且连接不紧密, 基底膜也常常不完整或缺失[53,54]。肿瘤细胞的快速增殖迫使血管分离, 降低血管密度并产生远离血管 (> 100 μm) 的细胞, 增加了药物分子与血管内皮细胞碰撞并渗出的难度; 肿瘤血管结构紊乱导致血流缓慢及分布不均, 延缓ADC到达肿瘤的速率、增加其被代谢清除的风险, 又使渗出的药物易局部积聚引发毒性、阻碍后续渗透[55]; 内皮细胞间隙大虽理论上利于药物渗出, 却血流不稳定难以形成有效浓度梯度, 不利于药物向肿瘤深部扩散[49]。此外, 由于结合位点屏障 (binding site barrier, BSB) 的作用使ADC在血管附近的肿瘤细胞上快速结合和内吞, 被过度消耗, 无法触及远端肿瘤细胞, 进而影响对肿瘤整体的杀伤效果[56](图4)。

2.4 肿瘤细胞异质性

肿瘤细胞存在异质性, 同一肿瘤内不同肿瘤细胞在基因型、表型及生物学行为差异显著。其中, 表面抗原表达异质性是影响ADC疗效的核心因素之一[57]。ADC需靶向肿瘤细胞表面特异性高表达抗原, 但实际肿瘤中并非所有肿瘤细胞均高表达该抗原。部分肿瘤细胞因基因变异、表观遗传修饰或微环境因素, 致使靶抗原表达下调或缺失, 使ADC无法有效结合形成治疗“盲区”。如HER2阳性乳腺癌, 疾病进展与治疗会使部分肿瘤细胞HER2表达动态改变, 出现低表达或阴

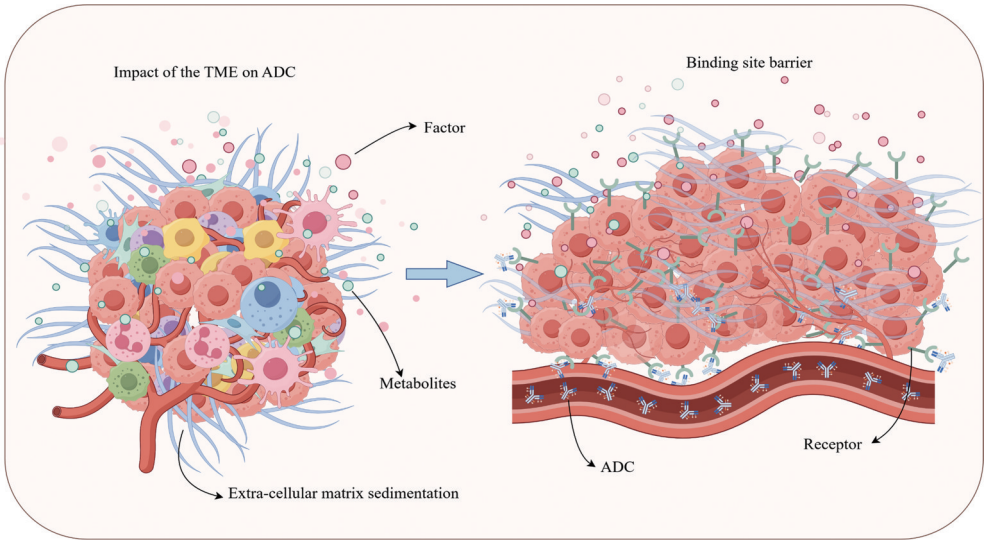


Figure 4 Impact of the tumor microenvironment on ADC. TME: Tumor microenvironment. Figure drawn by Figdraw

性细胞亚群, 致使ADC无法识别结合, 降低疗效[58]。

肿瘤细胞耐药机制的多样性是ADC治疗面临的重大挑战。肿瘤细胞可经多种途径产生耐药性[37,59-61], 主要与以下机制相关: ① 靶抗原下调、表达缺失或基因突变, 致使ADC与肿瘤细胞结合减少或无法结合; ② 内化途径缺失, 阻碍ADC内吞与转运; ③ 溶酶体蛋白水解、酸化功能降低或转运蛋白功能缺失, 抑制接头裂解及有效载荷在肿瘤细胞内的释放; ④ 胞浆因子如polo样激酶1 (polo-like kinase 1, PLK1) 活化、细胞周期蛋白如视网膜母细胞瘤蛋白1 (retino-blastoma 1, RB1) 缺失, 分别导致有丝分裂受阻、细胞周期停滞; ⑤ 肿瘤细胞中ABC转运蛋白上调, 使有效载荷被直接转运排出等。这些耐药机制使肿瘤细胞得以逃避ADC杀伤, 导致治疗失败或肿瘤复发。

3 ADC用药策略

由于ADC种类日益丰富, 其应用策略已从单药治疗拓展至与其他治疗手段的联合, 旨在协同增效、克服耐药性并扩大受益群体, 具体策略分类如表2[62-72]。

3.1 ADC联合化疗

ADC联合化疗体现出协同增效潜力, 为解决ADC渗透性难题提供新思路。许多化疗药物为DNA损伤剂, 如抗代谢物、铂基化合物和拓扑异构酶抑制剂等, 能与含靶向G2/M期的微管抑制剂有效载荷的ADC有效联合使用。如卡铂与anetumab ravtansine及luveltamab tazevibulin的有效联合用药在临床前得到证实[62,63]。此外, 化疗药物还能改变肿瘤细胞生物学特性, 间接促进ADC摄取与作用。部分化疗药物可上调肿瘤细胞表面靶抗原表达, 增加ADC结合位点。如吉西他滨与T-DM1联合治疗腺导管腺癌, 吉西他滨处理后胰腺癌细胞表面HER2抗原表达上调, 使T-DM1与肿瘤细胞结合更高效, 协同杀伤肿瘤细胞, 增强抗癌效果[64,73]。

ADC联合化疗在临床中也显示出好的生存效益。如本妥昔单抗被FDA批准与环磷酰胺 + 多柔比星 + 泼尼松联合用于先前未治疗 (初级治疗) 的系统性间变性大细胞淋巴瘤或其他CD30 (cluster of differentiation 30) 阳性外周T细胞淋巴瘤的一线治疗[65,74]。同时, 本妥昔单抗被批准与环磷酰胺 + 长春新碱 + 达卡巴嗪联合用于一线治疗先前未治疗的 (原发性) III期或IV期经典型霍奇金淋巴瘤[66]。2023年在德国霍奇金研究组上公布了III期HD21研究的中期分析结果, 结果表明BrECADD (本妥昔单抗、依托泊苷、环磷酰胺、多柔比星、达卡巴嗪、地塞米松) 与EBEACOPP (博来霉素、依托泊苷、多柔比星、环磷酰胺、长春新碱、甲苄肼) 的非劣效性。EBEACOPP (n = 740) 或BRECADD (n = 742) 治疗晚期霍奇金淋巴瘤的无进展生存期 (progression-free survival, PFS) 分别为92.3%和94.9%[75]。该结果表明多药联合治疗已成为大多数癌症的标准治疗方法。

然而, 在ADC与化疗联合应用时, 还需考量多种机制, 如给药时间、联合毒性叠加、剂量限制毒性、细胞周期相互作用及有效载荷对表面抗原表达的调节等[76]。如以HER2阳性转移性乳腺癌 (metastatic breast cancer, mBC) 患者为对象, 对比卡培他滨和T-DM1联合治疗与T-DM1单药治疗的疗效及安全性研究显示, 联合治疗未显著提升患者的客观缓解率 (objective response rate, ORR), 且联合治疗组不良事件发生率更高[77]。因此, 有必要深入筛选ADC联合化疗方案来克服毒性叠加问题, 阐明其疗效提升机制, 为药物研发提供有价值的见解。

3.2 ADC联合放疗

放疗作为局部治疗手段, 在肿瘤治疗中具有重要地位, 可对肿瘤细胞表面抗原表达, 肿瘤微环境进行调节等[45], 与ADC联用产生潜在协同效应, 提高疗效。

放疗通过激活核因子κB (nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB) 和I型干扰素反应通路来诱导促炎细胞因子的表达, 增加肿瘤中的炎症, 使肿瘤血管通透性短暂增加, 利于抗体从血管渗出进入肿瘤组织[78]。先前的研究发现, 在剂量高于400 cGy的照射后24 h, 肿瘤的血管通透性显著增加, 导致辐射后抗体摄取增加[67]。此外, 有研究表明, 放疗上调肿瘤细胞表面抗原表达[79], 可提升ADC靶向结合效率。同时, 放疗不仅直接作用于肿瘤细胞, 还以复杂动态的方式影响TME。越来越多的研究表明放疗和TME之间的相互作用可用于增强由脉管系统和间质改变介导的纳米颗粒和脂质体制剂的积累和瘤内分布, 并对缺氧、间质液压力、固体组织压力, 以及骨髓源性髓样细胞的募集和活化[78,80]。总之, 放疗联合ADC存在多种潜在协同效益和潜在机制需在临床前和临床阶段进行探索。多项临床试验证实放疗与ADC联合治疗的有效性。但值得注意的是, 靶向HER2的T-DM1与脑放疗同时使用时, 增加了放射性坏死的风险, 这可能是神经胶质细胞也表达HER2, 增加了不良反应风险[81]。同时, 放疗甚至还能引起器官特异性效应, 如肺和心脏毒性等。ADC联合放疗治疗缺乏可靠的临床数据, 导致人们对某些联合治疗方法的特定不良反应及最终毒性和安全性权衡的关注。ADC与放疗联合使用的安全性和有效性需要大规模临床研究来评估, 相信在不久的将来会有更多ADC联合放疗的组合取得成功[82]。

Table 2 Comparison table of efficacy of combined administration. T/C: Treatment/Control; T-DM1: Trastuzumab emtansine; GEM: Gemcitabine; mPFS: Median progression-free survival; ORR: Objective response rate; CR: Complete response; ICIs: Immune checkpoint inhibitors; PD-L1: Programmed cell death-ligand 1

Category	Drug	Partner drug	Treatment setting	Efficacy	Ref.
ADC + chemotherapy	Anetumab ravtansine	Carboplatin	Mesothelin-expressing human ovarian cancer models	Combined treatment: T/C = 0.15; anetumab ravtansine: T/C = 0.51; carboplatin: T/C = 0.32	[62]
	Luveltamab tazevibulin	Carboplatin	Ovarian cancer models	combined treatment: T/C = 43%; monotherapy: T/C = 20%	[63]
	T-DM1	GEM	Pancreatic ductal adenocarcinoma cells	The binding of T-DM1 to MIA PaCa-2 cells treated with GEM was higher than that to untreated MIA PaCa-2 cells. GEM and T-DM1 exhibited synergistic cytotoxic effects on MIA PaCa-2 cells *in vitro*. After GEM treatment, cells in the G2/M phase of the cell cycle were retained, and the HER2 expression level was higher	[64]
	Brentuximab vedotin	Cyclophosphamide + doxorubicin + prednisone	Pediatric anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas	Monotherapy: mPFS was 4.8 months; combined treatment: mPFS was 48.2 months, improvement in overall survival	[65]
	Brentuximab vedotin	Cyclophosphamide + vincristine + dacarbazine	Front-line treatment for newly diagnosed advanced Hodgkin lymphoma (stage III−IV)	Monotherapy: ORR 74%; CR 34%; combined treatment: ORR 86%; CR 73%	[66]
ADC + radiotherapy	Monoclonal antibodies targeting colorectal adenocarcinoma antigens	Ionizing radiation	Colorectal adenocarcinoma	Compared with the control values, when the irradiation dose was higher than 400 cGy, the vascular permeability of the tumor significantly increased 24 hours after irradiation, while the vascular volume decreased	[67]
	T-DM1	Stereotactic radiosurgery/ whole-brain radiation therapy	HER2+ breast cancer patients with brain metastases	Monotherapy: mPFS was 5.5 months; combined treatment: mPFS was 6.1 months, and the treatment was well tolerated, with no unexpected toxicities, treatment delays or dose reductions	[68]
	T-DM1	Conformal radiation therapy	Patients with HER2-positive early-stage breast cancer who still have invasive lesions in the breast or axilla after receiving neoadjuvant therapy	The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group	[69]
ADC + ICIs	T-DM1	Atezolizumab	PD-L1-positive subset in HER2-positive breast cancer	The mPFS for the combined group was 8.5 months, while that for the control group was 4.1 months	[70]
	Brentuximab vedotin	Nivolumab	Relapsed/refractory Hodgkin lymphoma	Monotherapy: ORR 75%; CR 34%; combined treatment: ORR 85%; CR 67%; the 3-year PFS 77%; the 3-year overall survival rate 93%	[71]
ADC + molecular targeted drugs	IMGN853	Bevacizumab	Ovarian cancer models	Neither bevacizumab nor IMGN853 drugs induced sustained tumor growth inhibition or tumor regression. However, the combination of IMGN853 and bevacizumab resulted in strong tumor regression in all animals	[63]
	T-DM1	Trastuzumab	NCI-N87 tumor mouse model	Co-administration of trastuzumab with a fixed dose of T-DM1 at 3∶1 and 8∶1 ratios dramatically improved ADC tumor penetration and resulted in twice the improvement in median survival compared to T-DM1 alone	[72]

3.3 ADC联合免疫检查点抑制剂

ADC可通过诱导免疫原性细胞死亡 (immunogenic cell death, ICD)、ADCC和树突状细胞活化与肿瘤和免疫细胞相互作用, 通过与免疫治疗联合提供潜在的协同作用[76]。ADC可诱导肿瘤特异性适应性免疫, 增加T细胞浸润到肿瘤微环境中, 而免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 可使枯竭的T细胞恢复活力, 增强抗肿瘤免疫反应[83,84]。有研究表明, 接受T-DM1短期术前治疗的乳腺癌患者配对样本中肿瘤浸润T细胞的数量和密度显著增加[32]。

截至目前, 已公开发表的评估ADC和ICIs联合的随机试验是KATE2试验。KATE2 II期试验中T-DM1 + 阿替利珠单抗 (atezolizumab) 与T-DM1 + 安慰剂在既往接受过曲妥珠单抗和紫杉醇类药物治疗的HER2阳性局部晚期或转移性乳腺癌患者中的疗效和安全性[70]显示, 联合治疗组未能改善患者的PFS, 且不良事件增加。但在程序性死亡配体1 (programmed cell death ligand 1, PD-L1) 阳性亚组中, 联合治疗组的中位无进展生存期 (median progression-free survival, mPFS) 比对照组长4.4个月。表明T-DM1联合阿替利珠单抗在PD-L1阳性和HER2阳性mBC患者中有潜在益处。基于此, III期KATE3临床试验对相关亚组 (PD-L1和HER2阳性mBC) 进行了广泛的样本分析, 以进一步研究HER2-ADC联合阿替利珠单抗的有效性和安全性。

虽然KATE2研究的结果令人失望, 但ADC联合ICIs在各种肿瘤中的临床探索仍在进行中。在DS8201-A-U105 (NCT03523572) 一项Ib期研究, 旨在探索T-DXd联合纳武利尤单抗治疗HER2表达晚期尿路上皮癌 (urothelial carcinoma, UC) 患者的疗效。队列3 (先前化疗失败的HER2 IHC 3+/2+ 晚期UC患者, n = 30) 的客观缓解率为36.7% (完全缓解率为13.3%), 疾病控制率为76.6%, 中位客观缓解率为13.1个月, 中位无进展生存期和中位总生存期分别为6.9和11.0个月[85]。因此, T-DXd联合ICIs在HER2高表达的UC患者中显示出良好的抗肿瘤活性。目前, FDA已批准ICIs帕博利珠单抗 (pembrolizumab) 联合ADC恩诺单抗用于不符合顺铂化疗条件的局部晚期或转移性UC患者的一线治疗。

此外, 其他癌症, 包括宫颈癌、霍奇金淋巴瘤等, 在联合使用抗程序性细胞死亡蛋白1 (programmed cell death 1, PD-1) 抗体和针对特定标记物 (如滋养层细胞表面抗原-2、CD30) 的ADC治疗时, 也显示出令人鼓舞的结果[76]。目前仍有多项临床试验正在探索和研究ADC与ICIs联合试验也在持续推进[86], 还需重点关注其相互作用, 有望为更多肿瘤患者带来生存希望。

3.4 ADC联合分子靶向药物

分子靶向药物 [单克隆抗体、酪氨酸激酶抑制剂 (tyrosine kinase inhibitor, TKIs) 和抗血管生成药物] 与ADC协同作用涉及机制包括改善肿瘤内药物传递、调节肿瘤细胞表面抗原表达、克服肿瘤内异质性和耐药、合成致死性等[81]。目前已确定有两种屏障会影响ADC的递送过程, 分别为物理屏障 (血液−肿瘤屏障) 和生理屏障 (BSB)。在血液−肿瘤屏障微环境中, 实体瘤中存在的血管由许多未成熟且无组织的血管组成, 导致血流不畅和缺氧[87]。同时, 高间质压使肿瘤血管塌陷, 从而限制了ADC从血液到肿瘤间质液的对流运输[5]。改变肿瘤血管系统的主要方法包括使用抗血管内皮生长因子抗体 (如贝伐单抗) 等药物调节血管生成和血管孔隙度。研究证实, 在临床前上皮性卵巢癌荷瘤小鼠模型中, IMGN853 (FRα-ADC) 联合贝伐单抗可增强贝伐单抗体内药效, 破坏肿瘤微血管系统, 发挥抗肿瘤活性[63]。在BSB中抗体紧密结合血管周围的肿瘤细胞, 无法有效扩散至肿瘤组织内部, 限制高亲和力抗体的疗效[88]。研究表明, 抗原表达升高和抗原快速内化, 以及肿瘤摄取迟缓和治疗性抗体间质扩散缓慢, 导致抗体渗透到肿瘤的能力较差; ADC联合裸抗是克服BSB的一种策略, 如Cilliers等[72]在NCI-N87肿瘤小鼠模型中, 对比T-DM1单独给药与和曲妥珠单抗联合给药的情况, 发现联合给药显著提升T-DM1在肿瘤中的穿透性, 使其能渗透至血管周围区域以外更远的肿瘤区域, 且分布更均匀。

在批准上市的19种ADC中, T-DM1联合靶向药物的有效性和安全性证据最多。在一项Ib期试验评估了T-DM1和HER2-TKI、图卡替尼的联合治疗中, 虽然这种联合疗法耐受性良好, 但常伴有胃肠道和肝脏毒性。特别是, 37%的患者经历了至少一次临床显著不良事件, 56%的患者需要停图卡替尼[89]。在复发性上皮性卵巢癌、输卵管癌或原发性腹膜癌患者 (n = 94) 接受索米妥昔单抗 (mirvetuximab soravtansine) 与贝伐单抗治疗中, ORR为44%, mPFS为8.2个月。与治疗相关的不良反应与单一药物治疗一致, 如视力模糊 (57%)、腹泻 (54%) 和恶心 (51%), 其中大多数为低级别不良反应[90]。ADC联合分子靶向药物使用已在多项研究中获益, 随着研究的深入, 联合给药方案的优化可提高疗效并降低不良反应, 为更多肿瘤患者带来更好的治疗效果和生存获益。

4 结语与展望

ADC作为新兴的肿瘤治疗手段, 为癌症患者带来新希望。但肿瘤渗透性难题限制了其在实体瘤中的应用。肿瘤间质的致密、血管异常、细胞异质性和复杂微

环境共同阻碍ADC深入肿瘤, 导致药物蓄积不足, 难以杀伤全部癌细胞。为攻克该难题, 已从多维度探索并取得一定成果。药物设计上通过结构优化提升ADC的肿瘤穿透性与靶向释放能力; 同时采用联合治疗策略, 将ADC与化疗、放疗等相结合来改善肿瘤微环境、增强免疫激活, 提高抗癌效果。

随着个体化ADC用药策略是当下临床治疗的重要发展方向, 可通过全面的生物标志物检测, 如精准测定肿瘤细胞表面靶抗原的表达与异质性、深入分析肿瘤微环境特征、评估患者的药物代谢基因多态性等, 可为患者定制最适宜的ADC治疗方案。例如, 对HER2表达较低但HER3过表达的患者选择双特异性ADC可能比单一HER2靶向ADC疗效更佳; 而对药物代谢酶基因存在特定突变的患者, 例如CYP450酶系相关基因的突变检测, 需要根据其代谢能力调整ADC的给药剂量与频次, 确保药物在体内既能发挥最佳疗效, 又不会因药物蓄积导致严重不良反应。

人工智能 (artificial intelligence, AI) 技术正深度融入ADC药物设计流程。随着深度学习算法的优化, AI将具备更强大的能力, 从海量数据库中精准筛选出最具潜力的有效载荷、连接子及抗体结构。通过构建高精度虚拟模型, 模拟不同结构的ADC在体内的药代动力学、药效学过程, 提前预测药物的疗效与潜在毒性。它们使ADC的发展进入一个更加智能化和系统化的时代, 为攻克ADC渗透性难题, 提升癌症治疗水平、改善患者预后、为抗癌事业注入动力具有深远意义, 有望让更多患者受益。

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