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• 综 述 •

三氧化二砷在实体瘤中的作用机制与递送技术研究进展

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Research Advances in Mechanisms of Action and Delivery Technologies of Arsenic Trioxide Against Solid Tumors

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Abstract: Arsenic trioxide (ATO) serves as a component of traditional Chinese medicine and a modern anticancer agent, demonstrating remarkable efficacy in the long-term treatment of acute promyelocytic leukemia. With increasing research into its application in solid tumors, ATO's diverse mechanisms of action and potential clinical value have attracted widespread attention. ATO can inhibit tumor cell proliferation by inducing various forms of cell death, such as apoptosis, autophagy, pyroptosis, necroptosis, and ferroptosis, as well as by regulating cell differentiation. Moreover, its modulatory effects on the tumor immune microenvironment provide a new aspectto its antitumor activity. Nevertheless, the clinical application of ATO in solid tumors faces challenges such as low bioavailability, inadequate targeting, and adverse effects. The development of nanocarriers and targeted delivery systems has emerged asa key strategy for enhancing the therapeutic efficacy of ATO. This review systematically summarizes the multiple mechanisms of action of ATO in solid tumors and recent advances in nanodelivery technologies, explores the potential of ATO-based combination therapies, and discusses future directions, aiming to provide a theoretical foundation and practical guidance for the clinical application of ATO in solid tumors.

Key words: Arsenic trioxide; Solid neoplasm; Nanoparticle; Immunotherapy; Combination therapy

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摘 要：三氧化二砷（ATO）有着传统中药成分和现代抗癌药物的双重身份，长期以来在急性早幼粒细胞白血病的治疗中疗效卓著。随着ATO在实体瘤治疗领域的研究逐渐增多，其多样化的作用机制及潜在的临床价值引起广泛关注。ATO能够通过诱导多种细胞死亡方式，如凋亡、自噬、焦亡、坏死性凋亡和铁死亡，从而影响肿瘤细胞增殖；也可通过调控分化来影响细胞命运。此外，ATO对肿瘤免疫微环境（TIME）的调节作用为其抗肿瘤效果提供了新的作用维度。尽管如此，ATO在实体瘤中的临床应用仍面临生物利用度低、靶向性不足及毒副作用等挑战。针对这些问题，纳米载体和靶向递送系统的开发已成为提升ATO治疗效果的重要策略。本文系统综述了ATO在实体瘤中的多重作用机制及其纳米递送技术的最新进展，探讨ATO联合治疗的潜力和未来发展方向，意在为ATO在实体瘤临床应用的转化提供理论基础和实践指导。

关键词：三氧化二砷；实体瘤；纳米递送；肿瘤免疫；联合治疗

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0 引言

三氧化二砷（Arsenic trioxide, ATO）俗称砒霜、鹤顶红，其药用历史最早可追溯至古代东西方传统医学。例如，雄黄（As_4S_4）经加热分解可生成ATO，传统医学认为其具有“解毒杀虫、祛痰截疟”之效，民间曾以其外用制剂治疗皮肤病，亦有少量内服用于疟疾和哮喘的尝试[1]。19世纪，西方

曾尝试低剂量ATO治疗白血病，但随着抗生素与化疗药物的兴起，ATO因“高毒性、低疗效”被正式医学弃用，仅作为毒物加以管控。20世纪70年代迎来重要转折。我国研究团队逐步揭示了ATO的分子作用机制，并证实其在治疗急性早幼粒细胞白血病（Acute promyelocytic leukemia, APL）中的卓越疗效。同期，美国食品药品监督管理局正式批准ATO注射液用于复发性或难治性APL的治疗，使其成为首个基于中国原创研究获批的抗癌药物[2]。然而，当试图将这一高效细胞毒剂拓展至实体瘤治疗时，却面临一系列显著的药学与毒理学瓶颈，包括快速肾清除、极短的血浆半衰期、对正常组织的严重毒性以及由此导致的低治疗指数[3]。这些因素极大地限制了ATO在实体瘤临床治疗中的广泛应用[4]。近年来，纳米医学的兴起为精准递送ATO、重塑其体内命运提供了革命性的策略。通过精密设计的纳米载体系统，能够显著增强ATO的生物相容性，赋予其主动或被动靶向能力，并最终提升其抗肿瘤疗效[3,5]。纳米技术不仅改善了ATO的生物利用度和靶向性，还增强了其抗肿瘤活性，并降低了系统毒性，实现了更安全、高效的药物递送和控释。

现有研究总结了ATO的抗癌机制，包括诱导肿瘤细胞凋亡、抑制肿瘤血管生成、调节细胞分化及重塑肿瘤免疫微环境（Tumor immune microenvironment, TIME）等，并强调了联合化疗的潜力价值。纳米载体的应用被认为是未来提升ATO实体瘤疗效的关键路径，亟须开展相关的临床前和临床研究，以实现高效、低毒的癌症治疗新策略。

1　ATO在实体瘤中的主体机制

1.1　ATO调控实体瘤细胞死亡的多重机制

1.1.1　诱导细胞凋亡　ATO通过多条细胞凋亡途径发挥抗肿瘤作用，其中线粒体途径和死亡受体途径的激活是其关键机制。ATO能够调控Bcl-2家族蛋白表达，降低Bcl-2/Bax比例，促使线粒体膜电位丧失，诱导细胞色素C释放进入细胞质，进而激活caspase级联反应，尤其是caspase-3、caspase-7等效应性半胱天冬酶，最终引发肿瘤细胞程序性死亡。例如，一项针对人脐静脉内皮细胞的研究发现，ATO处理后细胞活力显著下降，伴随Bcl-2/Bax比例降低及细胞凋亡率上升，并证实circRNA-0028171的表达调控参与了该过程[6]。在宫颈癌细胞中，ATO与Bcl-2家族抑制剂ABT-737联用可协同增强caspase-7活化、下调抗凋亡蛋白Mcl-1，进一步加剧线粒体膜电位的丧失，强化凋亡效应[7]。这些研究表明，ATO可通过调节线粒体膜通透性和促凋亡蛋白的表达，激活caspase依赖性的凋亡途径。

除线粒体途径外，ATO还可激活死亡受体介导的细胞凋亡信号。在APL细胞中，ATO可促进caspase-8活化，增强死亡受体的信号转导，进而激活下游效应性caspase，诱导细胞凋亡。此外，ATO诱导的凋亡伴随着细胞色素C从线粒体释放进入细胞质，进一步激活caspase级联反应，强化凋亡效应。此外，ATO可调控cofilin-1蛋白由细胞质向线粒体的转位，促进线粒体介导的细胞凋亡，这为揭示ATO诱导细胞凋亡的机制提供了新的分子靶点[8]。

ATO可通过改变细胞内氧化还原状态，增强其诱导的凋亡效应并提升肿瘤细胞对ATO的敏感性。在结直肠癌（Colorectal cancer, CRC）等实体瘤中，ATO与抗坏血酸联合应用可显著抑制细胞增殖、促进凋亡，其机制可能与抗坏血酸减轻ATO诱导的过度氧化应激损伤、优化凋亡信号转导通路相关[9-10]。ATO诱导的细胞凋亡并非局限于特定的实体瘤类型。在肝细胞癌（Hepatocellular carcinoma, HCC）中，ATO显著下调抗凋亡蛋白Bcl-2的表达，上调促凋亡蛋白Bax和Caspase-3水平，促进细胞凋亡，并抑制细胞迁移和侵袭能力[11]。在神经母细胞瘤中，ATO除诱导细胞凋亡外，还可通过调控GPX4介导的铁死亡（Ferroptosis）途径，部分促进细胞死亡，提示其凋亡机制可能与铁死亡等新型程序性死亡方式存在交叉[12]。ATO联合多种化疗药物如吉西他滨（Gemcitabine, GEM）、顺铂（Cisplatin）、二氢青蒿素等，在急性髓系白血病（Acute myeloid leukemia, AML）及其他恶性肿瘤中也都显示出协同诱导凋亡的作用[9]。此外，天然化合物如厚朴酚与ATO联用，不仅可增强其诱导肿瘤细胞凋亡的效果，还能减轻ATO所致的心脏毒性，提示抗氧化辅助策略在提升ATO治疗效果及安全性方面具有重要价值[13]。

1.1.2　自噬与细胞命运调控　ATO诱导肿瘤细胞自噬的作用机制复杂且呈现双重性——既可促进细胞死亡也可能作为细胞保护机制，从而影响治疗效果。在HCC中，ATO通过抑制PI3K/AKT/mTOR信号通路解除对自噬的负向调控，同时激活caspase级联反应并调控Bcl-2家族蛋白的表达，最终诱导自噬性细胞死亡。此状态下，自噬表现为促凋亡机制，显著降低了肿瘤细胞存活率[14]。类似地，在微波消融（Microwave ablation, MWA）联合ATO治疗HCC的研究中发现，ATO诱导的自噬可增强肿瘤细胞死亡并阻断上皮-间质转化（Epithelial-mesen-

chymal transition, EMT），提示自噬的激活在此情境下对抑制肿瘤进展具有积极意义[15]。相反，在某些细胞模型中，ATO诱导的自噬也表现为细胞保护机制，帮助肿瘤细胞抵御氧化应激和毒性损伤。例如，在鸡肝细胞中，ATO诱导的自噬通过调节抗氧化能力降低细胞凋亡率，而抑制自噬则加重氧化应激和细胞死亡[10]。在巨噬细胞中，ATO通过活性氧（Reactive oxygen species, ROS）介导的TFEB核移位促进自噬，从而在一定程度上减轻ATO所致的细胞毒性损伤[16]。

ATO诱导的自噬调控在其抗血液肿瘤效应中亦发挥关键作用。在FLT3-ITD突变的AML细胞中，ATO通过诱导自噬实现对致癌突变蛋白FLT3-ITD的降解，从而发挥抗肿瘤效应。自噬抑制剂或关键自噬基因的干扰可逆转ATO介导的FLT3-ITD蛋白降解，表明自噬是ATO治疗AML的关键机制之一[17]。此外，在APL中，自噬不仅参与ATO诱导的细胞死亡，还可能协同促进分化治疗，提升整体治疗效果[18]。综上，ATO诱导的自噬具有细胞类型依赖性及功能双重性。深入理解其在不同肿瘤及微环境中的调控机制，有助于设计更为精准的联合治疗策略，在最大化杀伤肿瘤细胞的同时保护正常细胞。

1.1.3 焦亡、坏死性凋亡及铁死亡 焦亡、坏死性凋亡与铁死亡是炎性细胞死亡的主要形式。ATO通过激活以上多条炎性细胞死亡途径，增强肿瘤的免疫原性，启动更为强烈的抗肿瘤免疫反应[19]。CRISPR-Cas9基因编辑研究揭示，焦亡执行蛋白Gasdermin E的激活是ATO诱导焦亡的关键机制之一。在星状胶质母细胞瘤细胞中，ATO通过活化caspase-3介导GSDME裂解，促使细胞出现焦亡表现，包括细胞肿胀、膜泡形成及乳酸脱氢酶释放，最终抑制肿瘤生长[20]。此外，ATO诱导的氧化应激亦可激活坏死性凋亡途径。该通路的关键执行蛋白RIP3和MLKL的表达水平对ATO的抗肿瘤效果至关重要，缺失上述蛋白可显著削弱ATO相关疗法的预防和治疗效果[19,21]。

铁死亡是一种依赖于铁离子介导的脂质过氧化作用的细胞死亡方式。在HCC中，ATO处理可显著上调细胞内的活性氧和脂质过氧化产物水平，该效应可被铁死亡抑制剂逆转。机制研究表明，ATO通过转录抑制关键抗氧化酶GPX4的表达，从而瓦解细胞对铁死亡的防御能力[22]。值得注意的是，ATO在诱导铁死亡的同时亦激活了细胞的自我保护程序——NRF2信号通路，导致其下游靶基因HO-1和SLC7A11表达上调。而沉默NRF2可显著削弱细胞的抗氧化能力，从而增强ATO诱导的铁死亡和细胞毒性。这一发现揭示了NRF2信号在ATO敏感性中的双重角色——既是细胞应激的标志，也可能成为联合治疗的潜在靶点[22]。在神经母细胞瘤中，ATO诱导铁死亡的机制与HCC类似，GPX4仍是该过程的关键分子，但作用方式有所不同：ATO通过转录抑制降低GPX4蛋白水平，而非促进其泛素化降解。值得关注的是，ATO对视黄酸耐药的高危神经母细胞瘤细胞同样具有杀伤效应，铁螯合剂可逆转其作用，而铁补充剂则可增强其杀伤效果。这一发现为治疗难治性神经母细胞瘤提供了新的策略依据[23]。

1.2 调控细胞分化的机制

从细胞分化的角度审视，ATO抗肿瘤的核心机制之一在于其能逆转肿瘤细胞的分化阻滞，驱动其向正常或终末阶段分化。ATO与全反式维甲酸（All-trans retinoic acid, ATRA）联合治疗APL已成为标准方案，其疗效基石之一便是高效诱导白血病细胞分化。经典机制在于ATO靶向降解致癌融合蛋白PML、RARα，从而解除维甲酸（Retinoic acid, RA）信号通路的分化阻滞[24]。最新研究进一步揭示，ATO对于APL中罕见的TBLR1-RARα融合蛋白同样具有降解作用，通过酶解该融合蛋白恢复RA信号通路活性，显著增强线粒体caspase通路依赖的细胞凋亡和分化[25]。此外， ATO与ATRA联合处理可诱导APL细胞中靶基因RARβ启动子区域的DNA去甲基化，这种表观遗传重塑可能是联合疗法降低复发率的重要机制之一[26]。

ATO在实体肿瘤中分化调节作用机制多样，且常与促凋亡效应协同发挥抗肿瘤作用[27]。在分化型甲状腺癌中，ATO处理能诱导肿瘤细胞分化，表现为碘摄取能力增强，同时抑制细胞增殖并促进凋亡。该分化诱导作用部分源于其对PI3K-Akt信号通路的抑制，从而解除该通路对细胞分化的阻滞[28]。在神经母细胞瘤这一胚胎源性实体瘤中，ATO能够克服RA耐药，诱导细胞分化。其机制涉及对表观遗传调控器的干预：ATO可下调组蛋白甲基转移酶EZH2的表达，解除其对分化关键基因HoxC9启动子的抑制，重新激活HoxC9的表达，最终驱动RA耐药的肿瘤细胞走向分化和凋亡[29]。在乳腺癌模型中，ATO与植物源性分化诱导剂cotylenin A联用，可协同抑制MCF-7细胞增殖与MDA-MB-231细胞侵袭能力，该效应与caspase-7活化及生存素（survivin）表达下调有关[30]。此外，ATO对肿瘤微环境（Tumor microenvironment, TME）中的间充质干细

胞的分化平衡具有调节作用，能够促进其成骨分化而抑制成脂分化，这种对骨髓微环境的调控可能间接影响肿瘤生长[31]。值得注意的是，ATO对分化过程的影响具有双重性，也可能干扰正常的发育分化程序。研究显示，临床相关浓度的ATO会阻碍人诱导多能干细胞向心肌细胞的分化，并引起细胞周期停滞和DNA损伤，揭示了其在抗癌治疗中潜在的发育毒性风险[32]。同样，在鼠胚胎干细胞向心肌细胞分化的模型中，ATO会破坏中胚层承诺、心肌细胞特异性基因表达及肌节蛋白的正常组装，导致心肌细胞功能受损[33]。

综上所述，尽管ATO在实体肿瘤中可通过直接诱导肿瘤细胞分化、调控表观遗传状态、影响TME等多种机制发挥抗肿瘤作用，但其对正常组织分化的潜在干扰也是治疗中需权衡的重要方面[27]。

1.3　ATO调节TIME的机制

1.3.1　免疫细胞激活与肿瘤免疫监视　免疫细胞在肿瘤免疫监视中发挥着关键作用。ATO可通过诱导免疫原性细胞死亡（Immunogenic cell death, ICD）有效激活免疫系统，从而促进抗肿瘤免疫反应。ATO诱导的ICD特征性表现为释放多种危险相关分子模式（DAMPs），包括细胞表面暴露的钙网蛋白、高迁移率族蛋白B1、ATP及INF-β等。这些信号分子能够促进树突状细胞的成熟及抗原交叉呈递，进一步激活$CD8^+$ T细胞和NK细胞，增强肿瘤特异性$CD8^+$ T细胞的浸润和效应功能。在HCC模型中，ATO通过ROS/内质网应激通路激发ICD，释放DAMPs促进树突状细胞成熟，显著改善TIME的免疫状态，增强$CD8^+$ T细胞的抗肿瘤活性[34]。

ATO在诱导ICD的基础上，还能直接调节免疫细胞功能。研究显示，ATO可通过调控免疫细胞间的相互作用，激活T细胞免疫反应。在骨髓增生异常综合征（Myelodysplastic syndromes, MDS）小鼠模型中，ATO通过促进外周血、脾脏和肝脏中T细胞的激活，平衡免疫抑制与免疫激活状态，从而提升机体免疫功能[35]。然而，ATO对B细胞功能的影响较为复杂，有研究报道，ATO可抑制外周B细胞活化及表面抗体表达，提示其在体外可能削弱体液免疫应答[36]。总体而言，ATO通过调节T细胞亚群的活化状态，促进抗肿瘤免疫监视，在实体瘤治疗中仍具有重要作用。

1.3.2　免疫逃逸机制的抑制　ATO主要通过调控肿瘤相关巨噬细胞（Tumor-associated macrophages, TAMs）的极化方向及抑制免疫抑制因子的表达，逆转肿瘤免疫“冷”微环境，促进其向免疫“热”状态转化，从而有效抑制肿瘤的免疫逃逸[37]。在肺腺癌模型中，ATO能够显著抑制TAMs向M2型极化，进而削弱其免疫抑制功能。据研究显示，ATO通过阻断Notch信号通路中的Jagged1和Notch1的表达，破坏肿瘤细胞与TAMs之间的正反馈环路，从而抑制M2型TAMs分泌免疫抑制因子CCL2、IL-1β及TGF-β1。该调控效应不仅抑制了肺腺癌细胞的增殖、迁移、侵袭及EMT进程，还在小鼠异种移植模型中显著降低肿瘤生长速率及M2样TAMs在肿瘤组织中的浸润密度。提示ATO通过重塑TIME发挥抗肿瘤作用[38]。

2　ATO在实体瘤中的响应规律

2.1　固有及获得性耐药机制

ATO的耐药机制复杂，涉及遗传突变、代谢重塑及细胞死亡通路调控等多个层面。除罕见的PML-RARα融合基因突变外，新近研究发现，未发生重排的野生型PML等位基因若发生点突变，亦可干扰ATO对致癌蛋白PML-RARα的靶向降解，导致耐药[39]。此外，在ATO耐药的APL细胞中，耐药表型与显著的代谢重编程密切相关，表现为对线粒体呼吸的依赖性增强。值得注意的是，此类代谢适应性改变并不依赖于已知的耐药相关基因突变，提示其作为一种独立的耐药机制存在[40]。在胰腺导管腺癌等实体瘤中，谷胱甘肽S-转移酶Theta 2（GSTT2）的高表达可通过负向调控铁死亡通路介导ATO耐药。该研究揭示了实体瘤微环境下ATO耐药的独特分子基础，也为联合靶向铁死亡通路提供了潜在干预策略[41]。

2.2　疗效与氧化应激水平密切相关

ATO抗肿瘤效应的核心机制之一在于其能够扰乱细胞内氧化还原平衡，通过诱导ROS生成和铁死亡来杀伤肿瘤细胞。研究证实，GSTT2通过调控下游蛋白表达来抑制ATO诱导的脂质过氧化与铁死亡，直接影响细胞对ATO的敏感性[41]。为突破氧化应激耐受屏障，联合用药放大氧化应激已成为增强ATO疗效的重要策略。例如，在慢性移植物抗宿主病模型中，ATO与氯化铜联用可通过类芬顿反应显著提升氧化应激水平，从而在降低ATO剂量的条件下达到同等治疗效果[42]。

2.3　以ATO为基础的联合治疗是核心策略

在APL治疗中，ATO联合ATRA已成为标准一线方案。在此背景下，诸多联合方案应运而生，见表1。临床研究进一步优化治疗方案，证实以ATO为基础的方案在巩固治疗中可替代或减少传统化疗

药物，其长期疗效不劣于传统化疗方案，且血液学毒性更低[43]。为克服ATO耐药，联合靶向线粒体呼吸的药物（mitocans）可有效逆转APL细胞的耐药表型，为耐药复发患者提供了新的治疗选择[40]。在实体瘤领域，ATO联合免疫治疗显示出协同增效潜力。如胰腺癌中，低剂量ATO可通过抑制TME中胰腺星状细胞的活化，重塑细胞外基质屏障，从而显著增强抗PD-L1免疫检查点抑制剂的疗效[44]。这一发现为ATO在免疫“冷”肿瘤中的应用开辟了新路径。

表 1　砷剂在不同实体瘤中的给药方式、联合用药方案及作用机制

Table 1　Administration routes, combination therapy regimens, and mechanisms of action of arsenic agents in different solid tumors

Malignancies	Intervention	Experimental subjects	Treatment conditions	Mechanism	Ref.
Pancreatic cancer	ATO + GEM	MIA PaCa-2, PANC-1 cells; Mouse model	ATO: 0.5, 1.5 μmol/L, 1 mg/kg; GEM: 100 mg/kg	Inhibits the TIMP1/PI3K/AKT/mTOR signaling pathway	[55-56]
	ATO + aPD-L1	PANC-1, hPSCs; Mouse model	ATO: 1 μmol/L, 0.5 mg/kg; aPD-L1: 200 μg	Downregulates the expression of LOXL3	[44]
Cholangiocarcinoma	ATO	RBE, HCCC-9810 cells	ATO:2 μmol/L	Reverses chemoresistance via the ATO/miR-885-5p/MTPN axis	[57]
Hepatocellular carcinoma	ATO + 5-Fu + Cisplatin	Huh7, Hep3B cells; Mouse model	ATO: 3 μmol/L, 5 mg/kg; 5-Fu: 0–75 μmol/L, 10 mg/kg; Cisplatin: 0–75 μmol/L, 10 mg/kg	Synergistically inhibits the LIF/JAK1/STAT3 and NF-κB signaling pathways	[58]
	ATO	H22, Hepa1-6, Huh7, MHCC97H, Hep G2, Hep 3B cells; Mouse model	ATO: 0.5–1 μg/ml, 3 mg/kg	Induces mitochondrial damage and activates the cGAS-STING-IFN signaling pathway	[54]
	ATO + ISL	HepG2, Hep3B, THLE-2 cells; Mouse model	ATO: 10 μmol/L, 1.5 mg/kg; ISL: 15 μmol/L, 10 mg/kg	Activates the apoptotic pathway and inhibits the PI3K/Akt/mTOR signaling pathway	[55-56]
	ATO	Hep3B, Huh7.5.1, HCCLM3, PLC, SMMC-7 721 cells; Mouse model	ATO: 3.6 μmol/L; 1 mg/kg	Targeting the SRF/MCM7 complex to suppress MCM7 expression	[59]
Neuroblastoma	ATO	Patients	ATO: 0.16 mg/kg/d	Inhibits the HH-Gli pathway, downregulates MYCN expression and P-glycoprotein	[60]
	ATO	SK-N-AS, SH-SY5Y cells	ATO: 8, 10, 20 μmol/L	Induces ferroptosis	[23]
	ATO	Patients	ATO: 0.18 mg/kg/d	Enhances chemotherapy efficacy, reverses drug resistance, restores tumor suppressor gene function	[61]
Ovarian cancer	ATO + As_4O_6	SKOV3ip1, HeyA8 cells	ATO: 0.01–100 μmol/L; As4O6: 0.01–100 μmol/L	Induces G_2/M phase cell cycle arrest	[62-63]
	ATO	Patients	ATO: 10–15 mg/d	Induces apoptosis and ferroptosis; modulates oxidative stress and ICD	[64]
	ATO + Olaparib	A2780-CIS, SKOV3-CIS cells; Mouse model	ATO: 3 μmol/L, 2.5 mg/kg；Olaparib: 50/250 μmol/L, 50 mg/kg	Induces apoptosis; triggers ferroptosis via the AMPKα-SCD1 pathway	[65]
	ATO + GSK458	JHOC5, TOV21G cells; Mouse model	ATO: 0.1–1 μmol/L, 5 mg/kg; GSK458: 0.01–0.5 μmol/L, 2 mg/kg	Inhibits the PI3K/AKT/mTOR pathway; induces DNA damage and autophagy	[55,66]
Laryngeal cancer	ATO	TU212, TU686, AMC-HN-8 cells; Mouse model	ATO: 2 μmol/L; 0.8, 1 mg/kg	Upregulates hsa-miR-573, which targets and suppresses DYNAP, thereby blocking the PI3K/AKT signaling pathway	[67]

续表 1　砷剂在不同实体瘤中的给药方式、联合用药方案及作用机制

Table 1 (Continued)　Administration routes, combination therapy regimens, and mechanisms of action of arsenic agents in different solid tumors

Malignancies	Intervention	Experimental subjects	Treatment conditions	Mechanism	Ref.
Oral cancer	ATO + MWA	Cal-27, SCC15 cells; Mouse model	ATO: 5 mg/kg/d	Upregulates HSPA6 expression	[68]
Breast cancer	ATO + CP; ATO + CY	BT-20, MDA-MB-231 cells	ATO: 3 μmol/L; CP: 5 000 μmol/L; CY: 500 μmol/L	Enhances sensitivity to apoptosis	[69-70]
	ATO	MCF-7, MDA-MB-231 cells	ATO: 1–100 μmol/L	Involves crosstalk between the AhR and Notch pathways, combined with mitochondrial dysfunction and oxidative stress imbalance	[71]
	As_4O_6	EO771, 4T1, Hs578T, MDA-MB-231 cells; Mouse model	As_4O_6: 0–5 μmol/L; 4 mg/(kg·d)	Induces pyroptosis via the mitochondrial ROS-caspase-3/GSDME axis and inhibits mitochondrial STAT3 phosphorylation	[72]
Lung adenocarcinoma	ATO	LLC, RAW264.7, HEK-293T cells; Mouse model	ATO: 2–16 μmol/L; 5.0 mg/kg	Targets the Notch signaling pathway, inhibits M2-type TAM polarization, thereby remodeling the TME	[71,38]
	ATO + VPA	NCI-H460, NCI-H1299 cells; Mouse model	ATO: 0–10 μmol/L; VPA: 0–10 mmol/L; Combination: ATO 5 mg/kg + VPA400 mg/kg	Induces G_2/M phase cell cycle arrest and caspase-dependent apoptosis	[62-63]
	ATO	A549 cells	ATO:0–20 μmol/L	Inhibits the NF-κB/ABCG2 signaling pathway	[73]
	ATO	NCI-H1299 cells; Mouse model	ATO:16 μmol/L; 2–4 mg/kg	Blocks the Nrf2-IL-33 pathway, thereby inhibiting angiogenesis	[74-75]
	ATO	NCI-H69, LLC cells; Mouse model	ATO:2.5–5.0 mg/(kg·d)	Upregulates DSCR1, blocking the Cn-NFAT signaling pathway	[76]
Cervical cancer	ATO + CsA	Caski, SiHa cells	ATO: 2 μmol/L; CsA: 5–10 μmol/L	Induces autophagy-dependent cell death	[77]
Prostate cancer	ATO+Flutamide	LNCaP，PC3 cells	ATO:0–10 μmol/L；Flutamide:0–20 μmol/L	Inhibits EMT (via downregulation of SNAIL) and induces apoptosis (via upregulation of P53)	[78]
	ATO + Simvastatin	LNCaP, PC3 cells	ATO: 5–8 μmol/L; Simvastatin: 8–12 μmol/L	Upregulates pro-apoptotic and tumor suppressor factors (BAX, P53, PTEN) and downregulates anti-apoptotic Bcl-2, leading to concurrent proliferation inhibition and anti-angiogenesis	[79]
Renal cell carcinoma	ATO + Cisplatin	HuH-7, HK-2 cells	ATO: 2.5–10 μmol/L; Cisplatin: 15, 25 μmol/L	Inhibits WIP1 and induces microtubule depolymerization	[80]
Bladder cancer	ATO + BCG	5 637, DCs cells; Mouse model	ATO:30 μmol/L,30 μmol/L; BCG:300 mg/L, 600 mg/L (0.2 ml)	Blocks the IER3:Nrf2 signaling pathway	[75]
Glioblastoma	ATO + VIS + TMZ	GUO, U138MG, U251MG cells; Mouse model	ATO: 1 μmol/L, 3 μmol/L, 2.5 μg/(kg·d); VIS: 20 μmol/L, 50 μmol/L, 25 mg/(kg·d); TMZ:300 μmol/L, 1 000 μmol/L, 10 mg/(kg·d)	Inhibits the Hedgehog signaling pathway; induces apoptosis and DNA damage	[70]

Notes: ATO: arsenic trioxide; GEM: Gemcitabine; 5-Fu: 5-Fluorouracil; ISL: Isoliquiritigenin; MWA: microwave ablation; CP: Carboplatin; CY: Cyclophosphamide; TAM: Tumor-associated macrophage; VPA: Valproic acid; CsA: Cyclosporin A; Cn: Calcineurin; BCG: Bacillus Calmette-Guérin; VIS: Vismodegib; TMZ: Temozolomide.

2.4 ATO具有激发抗肿瘤免疫反应的潜力

ATO预处理的肿瘤细胞可作为有效的全细胞疫苗，其免疫原性源于ATO能同时激活坏死性凋亡和铁死亡等多重炎性细胞死亡途径，导致大量免疫刺激性危险信号分子释放。该疫苗的抗肿瘤效力依赖于特定的细胞死亡执行蛋白，并与PD-1阻断剂具有协同增效作用[19]。此外，用于递送ATO的肿瘤源性微囊泡（TMVs）本身也能因其携带的肿瘤抗原，可在递送药物的同时引发免疫反应，进一步增强抗肿瘤免疫监视[45]。

2.5 纳米递送系统可显著改善疗效指数

纳米递送系统是改善ATO靶向性、疗效及安全性的重要策略。研究者构建的多功能纳米颗粒可实现ATO与靶向自噬关键基因Beclin 1的DNAzyme共同递送。该体系在肿瘤细胞内通过抑制自噬流，将细胞死亡模式由凋亡转向更具免疫原性的焦亡，从而显著增强抗肿瘤效应并激发免疫应答[5]。利用生物源性载体（如经靶向肽修饰的肿瘤微囊泡）递送ATO，也能提高药物在肿瘤部位的富集浓度[45]。研究还发现，白蛋白偶联的ATO（HSA-ATO）在肿瘤细胞内的转运效率与MUC4基因状态相关。这一发现为基于生物标志物的精准纳米递送提供了新思路，推动了ATO个体化治疗的发展[46]。

3 ATO临床转化的主要瓶颈与挑战

3.1 不利的药代动力学特性

游离的ATO在体内面临快速肾脏清除和短血浆半衰期，导致其在抵达实体瘤组织之前便被系统清除，生物利用度低下[3]。这种快速的清除限制了药物在肿瘤部位的累积，是其在实体瘤中疗效不佳的关键原因之一。

3.2 严重的系统毒性

ATO缺乏对肿瘤细胞与正常细胞的选择性识别能力，对心脏、肝脏等高代谢器官可造成显著损害，构成了剂量限制性毒性瓶颈[3-4,43]。例如，ATO可诱导心肌纤维化和内皮-间质转化，导致心脏结构与功能损伤[10]；也能引起肝细胞氧化应激、自噬流紊乱和细胞凋亡，诱发肝损伤[47]。这些毒性反应与ATO的全身分布特性直接相关，极大地限制了其治疗窗口。

3.3 药物耐药性与治疗失败

耐药性的产生是ATO临床应用中，尤其是复发患者面临的重大挑战。其耐药机制具有多样性：一方面，肿瘤细胞可通过代谢重编程等非遗传机制获得对ATO及ATRA的交叉耐药，这种适应性改变涉及糖酵解和线粒体呼吸等多条通路[40]；另一方面，遗传性突变，特别是ATO直接作用靶点——PML蛋白或其致癌融合蛋白PML::RARα中PML结构域的突变，是导致临床耐药和疾病复发的明确机制。值得关注的是，耐药突变甚至可发生于未发生重排的野生型*PML*等位基因，通过蛋白质相互作用干扰ATO对致癌蛋白的降解，这提示了更复杂的耐药网络[48]。肿瘤细胞还可通过激活氧化应激应答和炎症通路（如TLR4信号通路）来适应ATO的细胞毒性压力，最终致使治疗失败[49]。

3.4 给药方式局限性

现有给药方式的局限性也给长期治疗带来负担。现行的静脉输注要求患者频繁住院，影响了治疗依从性与生活质量。尽管口服ATO制剂的开发为改善给药便利性带来了希望[39,50]，但如何确保其在不同患者群体中的生物利用度、稳定疗效与可靠的安全性，仍需进一步探索。

4 联合治疗策略

4.1 联合化疗与放疗

ATO能够与顺铂、紫杉醇（Paclitaxel, PTX）、吉西他滨（GEM）等化疗药物产生协同抗肿瘤效应。在卵巢癌的临床试验中，ATO联合顺铂和PTX的序贯化疗方案取得了良好的疗效（客观缓解率达到42%，疾病控制率高达85%，且患者的无进展生存期显著延长），表明ATO联合化疗对耐药和复发性实体瘤具有潜在的治疗优势，且毒性反应在可控范围内[51]。从分子机制角度分析，ATO与化疗药物的协同作用主要通过增强细胞内ROS生成，促进肿瘤细胞的凋亡和程序性细胞死亡，进而提高化疗药物的细胞毒性[9-10]。

联合放疗方面，ATO作为放疗增敏剂的潜力也被广泛探讨。研究表明，ATO能够通过调节肿瘤细胞的信号转导通路，增强放射线诱导的DNA损伤和细胞凋亡，从而提高局部肿瘤的控制率。例如，ATO与PTX及表皮生长因子受体抑制剂联合应用于乳腺癌细胞系时，联合放疗显著提升了细胞死亡率，相关凋亡基因Bax表达上调，抗凋亡基因Bcl-2表达下调，提示ATO能够发挥放疗增敏作用[52]。此外，ATO联合微波热疗等局部治疗手段也被证实能够通过协同诱导肿瘤细胞线粒体损伤和凋亡，提高放疗疗效[53]。

4.2 联合免疫疗法的潜力

ATO与肿瘤疫苗和免疫检查点抑制剂的联合应用，可以通过多种机制相互协同，增强抗肿瘤免疫

反应，从而达到协同增效的治疗效果。一项针对HCC的研究表明，ATO通过诱导肿瘤细胞线粒体损伤及mtDNA释放，激活cGAS-STING-IFN通路，增强肿瘤细胞的免疫原性，并促进$CD8^+$ T细胞的浸润和活化[54]。然而，ATO在激活免疫系统的同时，也可能诱发肿瘤细胞的适应性抵抗，上调PD-L1表达便是其中一种关键的免疫逃逸反馈机制[19]。这并非意味着ATO单纯地促进免疫逃逸，而是揭示了一个动态过程：ATO在杀伤肿瘤细胞、暴露肿瘤抗原并募集T细胞的同时，也触发了TME中的免疫抑制检查点作为“刹车”信号。因此，观察到的PD-L1上调，更可能是免疫激活后的反馈性抑制现象，而非ATO的直接促癌作用。反之，这是否也在暗示联合抗PD-1免疫检查点抑制剂可能进一步增强ATO的抗肿瘤免疫效应，实现更优的治疗效果。

正是基于上述免疫激活与反馈抑制并存的复杂性，精心设计的联合策略能够将潜在的拮抗效应转化为强大的协同治疗窗口。核心思路是：利用ATO诱导ICD和T细胞浸润，同时使用免疫检查点抑制剂阻断随之诱发的抑制信号，从而将“热”但被抑制的TME转化为有效的抗肿瘤免疫应答场域。研究证实，PD-1阻断剂能够与ATO预处理的全细胞疫苗协同增效，通过增强局部IFN-γ的产生，显著提升治疗效果[19]。在胰腺癌这种典型的“冷肿瘤”中，低剂量ATO通过抑制胰腺星状细胞（PSCs）活化、下调LOXL3表达来重塑细胞外基质，从而显著增加肿瘤内$CD8^+$ T细胞的浸润；在此基础上联合抗PD-L1治疗，可产生显著的协同抗肿瘤效应[44]。这证实了ATO能够改善免疫微环境，为检查点抑制剂的有效浸润与功能发挥创造必要前提。

5　ATO纳米递送系统及靶向策略

5.1　ATO前沿进展与多维性能

当前，ATO纳米递送系统的研究在全球范围内持续深入，其焦点已从基础的药物包封转向功能集成与机制创新。国际前沿研究致力于构建诊疗一体化平台，例如开发含锰的脂质体，其在高效装载并响应性释放ATO的同时，释放的Mn^{2+}可作为磁共振成像造影剂，实现治疗过程的可视化监测[48,81]。同时，运用系统生物学方法（如金属蛋白质组学）揭示了ATO的新靶点与作用路径，例如其可通过靶向热休克蛋白60（Hsp60）诱导p53和生存素蛋白降解[82]。在临床转化方面，推动口服ATO制剂的研发是重要方向，多项研究证实其与静脉制剂具有生物等效性，有望提升治疗的便利性[83-84,50]。

国内研究同样活跃，注重通过纳米设计实现协同治疗与解决临床瓶颈。例如，开发能共递送ATO与靶向自噬基因Beclin-1的DNAzyme的纳米组装体，通过将细胞死亡方式从凋亡转向焦亡来增强抗肿瘤免疫应答[5]。此外，通过构建全面的ATO相关数据库（ATOdb），系统整合其靶点、疗效及联合用药数据，为机制研究与药物重定位提供了重要资源[1]。

这些创新研究不仅拓展了ATO的作用边界，也催生了设计学各异的纳米载体平台，主要包括脂质体、高分子聚合物纳米粒、无机纳米材料及混合系统。为系统评估这些载体技术在推动ATO临床转化中的潜力与局限，以下从载药效率、稳定性、体内代谢及临床转化潜力四个核心维度进行对比分析，见表2。

5.2　核心作用机制

ATO纳米递送系统的核心作用在于，通过纳米尺度的工程化设计，系统性重塑ATO的体内命运、作用位点及治疗模式，将其从一种具有严重系统毒性的传统药物转化为可实现精准、高效及协同治疗的智能制剂[3]，从而为不同类型的实体瘤提供差异化和精准化的靶向策略方案（见表3）。其机制原理主要涵盖以下四个逐级深入的层面。

5.2.1　药代动力学的系统性重塑　纳米递送系统首要解决的是游离ATO快速肾脏清除、半衰期短导致的肿瘤部位暴露不足，以及全身毒性问题[3]。纳米载体通过包封ATO，有效延长了其在血液循环中的时间，并减少正常组织对其非特异性摄取，为利用实体瘤的EPR效应在肿瘤部位富集创造了条件[85]。更为极致的策略是局部递送，例如将载有ATO微晶的聚合物微球用于肝动脉化疗栓塞，可实现药物在肿瘤血管内的长期滞留与缓释，从而在极大提高局部疗效的同时，将全身毒性降至最低[86]。

5.2.2　微环境响应与亚细胞精准递送　在细胞水平上，纳米系统通过智能响应释放机制，实现了对ATO作用的精确时空控制。许多载体被设计为对TME（如弱酸性pH）敏感，例如pH敏感的砷-锰复合物脂质体可在肿瘤部位特异性解离，实现药物的爆发性释放[81]。此外，低强度超声等外部刺激也可与ATO纳米系统联用，以增强其抗肿瘤效果[39]。系统生物学研究进一步揭示了ATO作用的关键分子靶点，例如其可与Hsp60结合，导致p53和生存素蛋白降解——这为通过纳米靶向递送增强该通路的作用提供了理论依据[82]。

5.2.3　多功能协同治疗范式的建立　纳米平台能够

表 2 三氧化二砷主要纳米递送载体核心性能差异

Table 2 Core performance differences of main ATO nanodelivery carriers

Characteristics	Liposomes	Polymer nanoparticles	Inorganic nanomaterials	Others/Hybrid carriers
Drug loading efficiency	Remote loading via ion gradient enables high encapsulation efficiency (>80%)[81,85]	Strategies such as encapsulating ATO microcrystals enable extremely high drug loading capacity (e.g., 40.1%)[86]	It can form stable inorganic complexes to achieve effective loading[81]	Encapsulation is achieved via ion pairing and molecular self-assembly, enabling co-loading of multiple active ingredients[5]
Stability	Sustained drug release can be stably achieved; some designs possess pH-responsive release capability to the TME[81]	It can provide sustained drug release with excellent stability	The inorganic framework structure is robust; it can be designed to be responsive to the TME (e.g., pH) for controlled release[48, 81]	Endogenous albumin is used as a stabilizer, featuring favorable biocompatibility; it can disintegrate in specific microenvironments for precise drug release
In vivo metabolism	Significantly prolongs the blood circulation time of ATO, increases tumor accumulation via the enhanced permeability and retention (EPR) effect[85]; local high-concentration drug delivery can be achieved[86]	It achieves long-term retention in tumor-localized blood vessels, significantly increasing local drug concentration and reducing systemic exposure[86]	Improves the nonspecific distribution of drugs and prolongs in vivo circulation[81]; some materials also possess magnetic resonance imaging (MRI) functionality, enabling theranostics integration[48, 81]	Leveraging natural molecules with high biocompatibility and intelligent design, it exhibits a promising safety profile and synergistic therapeutic efficacy
Clinical translation potential	With a relatively mature technical platform, it is one of the most in-depth studied nano-drug carriers with the longest clinical application history[47]	PLGA has been approved as a pharmaceutical excipient, featuring favorable biodegradability, a solid safety record, and a robust foundation for clinical translation	It exhibits significant potential in constructing multifunctional nano-platforms integrating targeting, therapy, and diagnosis	Leveraging natural molecules with high biocompatibility and intelligent design, it exhibits a promising safety profile and synergistic therapeutic efficacy
Main challenges and limitations	Issues such as process stability in large-scale production, high cost, and potential immunogenicity[47]; there may be a risk of drug leakage during long-term storage	It lacks active targeting capability during systemic intravenous administration, resulting in limited tumor enrichment efficiency[3]; batch-to-batch consistency of drug release rate is a production bottleneck	There is a lack of long-term in vivo biosafety data; the metabolic clearance mechanism is unclear, with risks of long-term accumulation and potential toxicity of metal ions[48]	It imposes extremely high requirements on production processes and quality control; there are batch-to-batch variations in homogeneity and stability during large-scale production

整合多种治疗模式，实现超越单纯化疗的协同增效。一种重要策略是整合化学动力学治疗。通过共递送ATO与锰离子（Mn^{2+}），后者在肿瘤细胞内可催化类芬顿反应产生活性氧，与ATO的化疗作用协同杀伤肿瘤；同时，Mn^{2+}还可作为磁共振成像造影剂，实现诊疗一体化[48,81]。另一前沿策略涉及对细胞死亡程序的调控。例如，共递送ATO和靶向自噬基因Beclin-1的DNAzyme，可通过抑制自噬将ATO诱导的细胞死亡方式从凋亡转向焦亡，后者能触发更强的抗肿瘤免疫响应，从而实现化疗与免疫治疗的协同效应[5]。

5.2.4 基于耐药机制创新的联合治疗新策略 纳米递送系统为克服ATO耐药提供了新思路。研究发现，ATO耐药与细胞代谢重编程密切相关，耐药细胞可能转而依赖线粒体呼吸功能。这提示，利用纳米载体共递送ATO与靶向线粒体呼吸的抑制剂，是

表 3　三氧化二砷在不同实体瘤中的纳米递送系统及靶向策略

Table 3　3Nanodelivery systems and targeting strategies of arsenic trioxide in different solid tumors

Malignancies	Nanodelivery	Intervention	Experimental subjects	Treatment conditions	Mechanism	Ref.
Colorectal cancer	Sav-ATO NPs, Sav-D-VC NPs	ATO+D-VC	HCT116, SW620 cells	ATO:7.5 μmol/L; D-VC:1.5 mmol/L	Targeting mitochondria to synergistically disrupt redox homeostasis and selectively induce apoptosis in CRC cells	[87]
Ovarian cancer	AMGNPs@SKOV3	ATO	SKOV3 cell; Mouse model	ATO: 0–25 μmol/L, 1 mg/kg	pH-responsive drug release for precise targeting of the TME	[88]
Liver cancer	As-MnZnS$_x$ NRs	$Na_2HAsO_4·7H_2O$	HepG2, RAW264.7, BMDCs; Mouse model	As: 3 mg/kg; Mn: 10 mg/kg	Synergistic activation of the cGAS-STING pathway by Mn^{2+} and H_2S	[89]
	ZnAs@SiO_2NPs	ATO	MHCC97L, Hep3b cells; Mouse model	ATO: 5 μmol/L	Modulating the SHP-1/JAK2/STAT3 pathway to simultaneously target CSCstemness and the EMT process	[90]
	DCA-CS-PEG-FA-NAC	ATO	HepG2，293T cells；Mouse model	ATO: 0.1-10 μmol/L	Targeted delivery - intelligent release - dual anticancer synergistic	[91]
Cervical cancer	Liposome	ATO	HeLa, HT-3, KB, A549 cells	ATO: 5-18 μmol/L	Folate receptor-mediated active targeting combined with EPR-based passive targeting	[92]
Prostate cancer	NLP-RGD	ATO, Cur	PC3 cell	ATO: 7.5–22.5 μg/ml Cur: 3.4–50 μg/ml	Inhibiting NF-κB and angiogenesis; inducing ROS generation and activating the caspase cascade; upregulating FOXO3a and PTEN	[93]
Glioblastoma	Sp-Exo/AI	ATO+ IR780	GL261, U87MG cells; Mouse model	ATO: 0.1 μg/ml, 1 mg/kg; IR780: 0.3 μg/ml, 2.5 mg/kg	Ferroptosis-induced disruption of ROS homeostasis-TME remodeling - Immune activation	[94]
Melanoma	AP-CHAL	ATO	B16, MEF cells	ATO: 0.1–10 μmol/L, 10 mg/kg	AS1411 binding to NCLto activate nucleolin-dependent macropinocytosis	[95]
Breast cancer	FPL-PMSNs	ATO+ PTX	MCF-7, HUVECs, Mouse model	ATO: 0–35 μmol/L, 1 mg/kg; PTX: 0.5 mg/kg	Enhancing targeted delivery and tumor penetration, activating apoptotic pathways, and reversing MDR	[96]

Notes: Sav-ATO NPs: Savinase-coated nanoparticles loaded with ATO; D-VC: D-vitamin C; AMGNPs@SKOV3: SKOV3 cell membrane-coated arsenic-manganese and enzyme nanoparticles; As-MnZnS$_x$ NRs: Arsenic prodrug-loaded bimetallic sulfide MnZnS$_x$ nanorods; CSC: Cancer stem cell; DCA-CS-PEG-FA-NAC: (deoxycholic acid)-chitosan-(polyethylene glycol)-folate-(N-acetyl-L-cysteine); NLP-RGD: Arginine-glycine-aspartic-decorated nanoliposome; Cur: Curcumin; Sp-Exo/AI: Homologous magnetic targeted immune vesicles; IR780: IR780 iodide; AP-CHAL: AS1411 aptamer-functionalized CHA-loaded liposomes; NCL: Nucleolin; FPL-PMSNs: F56 peptide-PAA- PSL-coated mesoporous silica nanoparticles; MDR: Multidrug resistance.

一种有潜力的逆转耐药策略[40]。此外，对耐药机制的深入解析——如发现复发患者的耐药突变可能位于未重排的PML等位基因而非PML-RARα融合基因中——强调了全面筛查对于设计对策的重要性，也

为纳米系统实施基于特定基因型的精准联合用药提供了明确方向[50]。

综上所述，ATO纳米递送系统的核心机制是一个多级联动的过程：始于对药物体内分布的系统性重编程，进阶于在靶部位的智能响应释放与分子靶点精准作用，并最终通过整合多种治疗模态及针对耐药机制的联合策略，实现协同增效与疗效最大化[3,5,81]。这些机制共同构成了纳米技术赋能传统药物、拓展其治疗疆界的科学基础。

5.3 纳米制剂的临床转化现状

尽管ATO纳米递送系统在临床前研究中展现出克服其原有缺陷的巨大潜力，但其真正的临床转化仍处于探索阶段，而开发长效与靶向制剂是解决其生物利用度低和靶向性不足的核心策略[3-4]。在临床转化方面，目前进入临床研究阶段的主要是口服ATO制剂——这本身可视为一种改善患者用药便利性的递送方式创新。一项名为“ALLG APML5”的试验评估了新型口服ATO胶囊在APL患者巩固治疗中的表现，证实该口服制剂与静脉ATO具有生物等效性，且安全性相似，为患者提供了一种更便捷的选择[39]。另一项Ⅰ期研究也验证了口服ATO（SY-2101）与静脉制剂在活性成分砷浓度上的生物等效性[50]。这些研究进展表明，ATO的剂型改进正在向临床推进。然而，针对实体瘤的复杂纳米递送系统（如功能化脂质体、聚合物纳米粒等）的临床转化仍面临显著瓶颈。这些挑战主要包括：严格的规模化生产工艺与质量控制要求[3]，以及对新型纳米材料长期生物安全性和体内代谢命运的担忧[4,53]。尽管临床前研究结果令人鼓舞，但要将这些多功能纳米系统成功应用于实体瘤患者，仍需系统性的临床试验来最终验证其疗效与安全性优势[3-4]。

5.4 纳米制剂改进与优化

针对ATO生物利用度低和靶向性不足的问题，其根源在于药物在体内被快速清除以及难以有效渗透并富集于肿瘤组织[3]。为此，研究人员设计了多种长效制剂以实现药物的可控持续释放或局部滞留。一个典型范例是用于肝动脉化疗栓塞（Transarterial chemoembolization, TACE）的载ATO微晶的PLGA微球。该制剂的原理是：通过微粉化技术形成高密度的ATO微晶，再利用溶剂交换法稳定，最后用PLGA包裹。这种设计实现了高达40.1%的药物负载。其长效化机制在于，PLGA作为可生物降解的聚合物外壳，在体内缓慢降解，从而持续释放其内部的ATO微晶，使得药物能够在HCC病灶局部长时间维持有效浓度。这种通过局部给药（如TACE）结合缓释载体的策略，从根本上避免了药物的全身快速清除，实现了极高的肿瘤局部暴露和极低的全身毒性，在HCC模型中显示出显著的抗肿瘤效果[86]。除局部给药系统外，全身给药的长效策略也有探索。例如，采用醋酸铜梯度法制备的ATO脂质体，在体外表现出超过72小时的持续释放特性[97]；而脂质体包被的LP@MnAsx 则在生理环境中稳定，并在TME的弱酸性条件下响应性释放药物，延长了作用时间[98]。这些长效化设计共同的目标是改变ATO的药代动力学，通过延缓释放或局部滞留来增加药物在肿瘤部位的累积时间和总量，从而克服其快速清除的短板。然而，大部分的纳米递送研究工作仍囿于材料构建、体外表征及细胞水平的功能测试，涉及动物体内药效、安全性评价或临床试验的研究十分有限，距离成熟的临床转化仍有关键环节需要突破[87]。

5.5 ATO长期用药的毒性管理

ATO的毒副作用累积规律表现为：长期使用ATO，其心、肾、肝等器官毒性呈进行性加重趋势，并与累积剂量相关[40]。其机制涉及慢性病理过程，例如通过诱导内皮—间质转化导致心脏纤维化，或通过促进PML蛋白SUMO化驱动肝脏纤维化[10]。核心调整策略包括两个方面：一是基于风险分层的优化方案，如对低/中危白血病患者采用ATO联合疗法以减少传统化疗，从而降低叠加毒性[99-100]；二是基于联合治疗的减毒策略，如与线粒体靶向药物联用以克服耐药，避免盲目增量[40]。

在解毒或保护性干预方面，直接的特异性解毒剂研发较少，但针对器官毒性的保护剂研究已取得进展，主要聚焦于天然产物[100]。例如，薯蓣皂苷（Diosgenin）可通过上调GR表达抑制IL-6，从而阻断ATO诱导的EndMT，缓解心脏纤维化[10]；单宁酸（Tannic acid）能通过激活Nrf2抗氧化通路并抑制NF-κB炎症通路，减轻ATO引起的肾脏氧化应激和细胞凋亡[101]；黄芪多糖可通过抑制JNK和p38信号通路减轻ATO对骨髓间充质干细胞的损伤[102]；而双醋瑞因和甲基阿魏酸可通过抗炎和抗氧化作用缓解ATO肝毒性[103]。

6 展望

尽管现有文献报道了ATO与基因编辑、溶瘤病毒等新兴技术联合应用的临床前或临床研究尚不充分，但基于ATO已知的作用机制及当前纳米递送与联合治疗的研究趋势，其与新兴疗法结合具有显著的潜力。ATO可通过诱导独特的细胞死亡方式（如

凋亡、焦亡）和释放肿瘤相关抗原，从而激发抗肿瘤免疫应答。这一特性为其与免疫治疗（如免疫检查点抑制剂）的联合奠定了理论基础，二者协同有望克服肿瘤免疫抑制微环境，实现“免疫增敏”效应。同时，ATO纳米载体可作为多功能平台，理论上能够共载溶瘤病毒或基因编辑工具，实现时空同步的“化疗—免疫—基因”多模式协同治疗。

在个体化医疗背景下，基于患者基因特征研发ATO精准给药方案已成为明确方向。研究揭示，ATO的疗效与耐药性与特定基因突变密切相关。例如，ATO能够通过结合一个隐秘的变构位点，有效“拯救”并恢复结构性突变p53蛋白的转录活性与抑癌功能。此外，鉴于ATO的直接作用靶点PML及其融合基因PML::RARα的突变是导致临床耐药的关键机制，对肿瘤组织进行突变谱筛查可作为预测ATO疗效、筛选优势获益人群重要生物标志物。值得注意的是，耐药突变不仅发生于融合基因，也可能出现在未重排的野生型等位基因中。因此，未来的精准给药方案研发需依赖于全面的基因分型，建立包括PML、p53等关键基因在内的突变图谱与ATO敏感性抑或耐药性的关联数据库，从而指导临床用药决策与剂量调整。

利益冲突声明：

所有作者均声明不存在利益冲突。

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