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靶向p53-MDM2信号轴的研究现状与挑战

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摘要 恶性肿瘤严重威胁人类健康, 尽管近年来肿瘤药物治疗取得了显著进展, 但仍存在响应率低、剂量限制性毒性以及耐药性等问题, 目前晚期肿瘤患者的五年生存率仍不理想, 因此亟需研发新的高效安全的靶向药物。p53-MDM2信号轴在肿瘤发生发展中起着重要作用, 靶向p53-MDM2信号轴以恢复p53蛋白的肿瘤抑制功能, 已成为肿瘤靶向治疗领域的研究热点。该文系统阐述p53-MDM2信号轴的分子调控机制, 全面综述靶向该通路在肿瘤治疗中的药物研究进展, 并深入分析和讨论临床转化过程中面临的挑战, 以期为肿瘤靶向治疗新策略提供参考。

关键词 p53; MDM2; 蛋白–蛋白相互作用; 肿瘤靶向治疗; 临床转化

Current Status and Challenges of Targeting the p53-MDM2 Axis

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Abstract Malignant tumors constitute a grave threat to human health. Although significant progress has been made in tumor pharmacotherapy in recent years, challenges including low response rates, dose-limiting toxicities, and drug resistance persist. What's worse, the five-year survival rate for patients with advanced tumors remains unsatisfactory. Therefore, it's necessary and urgent to develop novel, highly effective and safe targeted therapeutics. The p53-MDM2 axis plays a critical role in the regulation of tumorigenesis and progression. Targeting this axis to reinstate the tumor-suppressive function of p53 has emerged as a prominent direction in the field of cancer targeted therapy. This review systematically delineates the molecular mechanisms of the p53-MDM2 axis, summarizes the research advances in drugs targeting this pathway for cancer treatment, and critically analyzes the challenges encountered during clinical translation, aiming to offer insights for innovative strategies in cancer targeted therapy.

Keywords p53; MDM2; protein-protein interaction; cancer targeted therapy; clinical translation

恶性肿瘤是现代社会高发的致死性疾病之一, 严重威胁人类生命健康。目前临床常用的手术切除、化学治疗、放射治疗、靶向治疗及免疫治疗等肿瘤治疗手段, 虽在一定程度上改善了患者的生存预后, 但仍普遍存在疗效有限、毒副作用显著等问题, 因此亟需研发安全、高效的新型肿瘤治疗策略。

p53-鼠双微体2(murine double minute 2, MDM2)信号轴不仅在细胞正常的生理过程(包括DNA修复、周期阻滞、细胞凋亡、细胞衰老等)中发挥着关键作用, 还在肿瘤发生发展中发挥关键调控作用[1-3]。在约

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50%人类恶性肿瘤中存在*TP53*基因突变或缺失[4-6], 这些异常不仅使p53蛋白丧失肿瘤抑制功能, 还可能令突变型p53蛋白获得新的致癌活性[7]。作为p53最主要的负调节因子, 在生理状态下MDM2一方面通过泛素化修饰降解p53蛋白, 另一方面与p53直接结合阻断其与相关共激活因子的相互作用, 抑制p53转录活性, 从而维持细胞内p53的低水平状态[4,8-10]。然而, 在肉瘤和胶质瘤等多种肿瘤类型中, MDM2的扩增或过表达可显著下调p53表达, 导致p53功能受损, 这已成为肿瘤发生发展的关键因素[10-14]。因此, p53与MDM2形成的严格的负反馈环路在维持基因组稳定和细胞稳态方面发挥着至关重要的作用, 而靶向p53-MDM2信号轴以恢复p53的肿瘤抑制功能, 已成为当前肿瘤靶向治疗领域的研究热点。

目前靶向p53-MDM2信号轴在肿瘤治疗中已取得阶段性突破, 但是该领域仍存在诸多瓶颈, 包括药物客观缓解率有限、剂量限制性毒性以及原发性和获得性耐药等[15], 仍需探寻更有效、更安全的治疗策略。基于此, 本文系统阐述了p53-MDM2信号轴的相关分子机制, 总结分析了目前p53-MDM2信号轴靶向治疗的研究进展和面临的严峻挑战, 并对未来发展方向进行了展望, 以期为之后研发新型有效的抗肿瘤策略提供理论参考和研究思路。

1 p53-MDM2信号轴

1.1 p53和MDM2蛋白的结构和功能

*TP53*基因位于染色体17p13.1, 编码由393个氨基酸残基组成的p53蛋白; p53蛋白通常以四聚体形式结合DNA并启动靶基因转录[1]。p53蛋白包含5个不同的功能结构域, 分别是转录激活域、富含脯氨酸域、DNA结合域、四聚化域、C-端调节域[1]。p53蛋白的结构域与其功能息息相关, 其中DNA结合域是p53的核心识别区, 能够识别并结合特定DNA序列。作为一种关键的肿瘤抑制因子, p53被称为“基因的守护者”, 在维持细胞的稳态和基因组完整性方面发挥着重要的作用[16]。

MDM2属于原癌蛋白家族, 是一类定位于细胞核与细胞质的关键E3泛素连接酶。从蛋白结构层面分析, MDM2由491个氨基酸组成, 主要由4个区域构成, 分别是N-端的p53结合区、高度酸性区域、锌指结构区和C-端的RING(really interesting new gene)指结构域。其中C-端RING结构域是其发挥E3泛素连接酶催化活性的关键功能区域, 直接决定泛素分子转移效率与底物降解水平[10]。MDM2广泛参与DNA损伤应答、细胞周期调控等多种生理过程, 是维持细胞内p53信号稳态的核心负调控枢纽蛋白, 同时MDM2在肿瘤发生发展过程中发挥着重要的调控作用[17]。

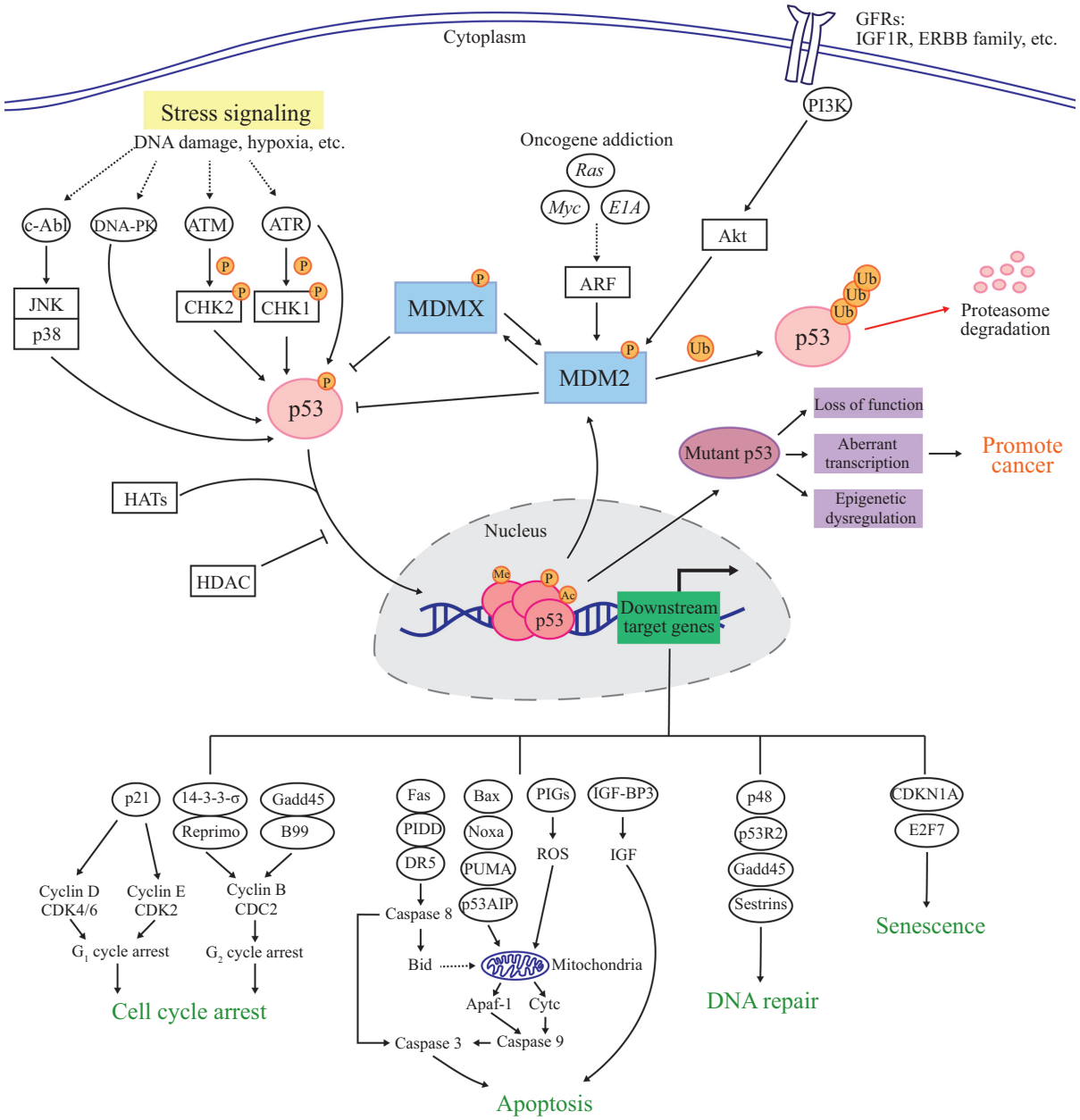
1.2 p53-MDM2信号轴的作用和机制

在正常的生理状态下, 细胞内p53蛋白的水平较低且受到严格调控[15]。p53-MDM2信号轴的机制如图1所示, 当细胞受到DNA损伤、缺氧或致癌基因激活等应激信号刺激时, 上游激酶包括ATM/ATR、CHK1/CHK2等被激活, 进而磷酸化修饰并活化p53蛋白。与此同时, 原癌基因异常表达可诱导关键肿瘤抑制因子ARF表达上调, ARF可直接抑制MDM2对p53的泛素化和降解功能, 进一步提高胞内p53蛋白含量。随即活化的p53启动其下游的靶基因转录调控, 其中p53-MDM2信号轴负反馈调节机制是维持细胞稳态的核心机制。活化的p53可特异性结合*MDM2*基因启动子区域, 显著促进*MDM2*的基因转录与翻译。新合成的MDM2通过其E3泛素连接酶活性将泛素分子标记到p53蛋白上, 使p53蛋白被蛋白酶体识别并降解, 进而在正常细胞中维持p53处于低水平状态。此外, MDM2可直接结合p53的N末端转录激活结构域, 阻断p53与靶基因启动子区域的结合, 从而抑制p53对细胞周期停滞和细胞凋亡相关靶基因[包括*TP21*、Bcl-2关联X蛋白(Bcl-2-associated X protein, *BAX*)等基因]的转录激活[10]。在负反馈机制中, MDM2常与MDMX协同作用, 共同增强对p53的降解和功能抑制, 还参与调控p53的核输出, 将p53从细胞核转移到细胞质, 进一步削弱p53的肿瘤抑制功能[15,18]。在某些肿瘤细胞中, 这种核输出作用被证实是MDM2调控p53活性的主要方式。由此可见, p53与MDM2通过蛋白互作、泛素化修饰、转录反馈及核质转运等多重分子机制, 共同维持p53信号通路的动态平衡。

除上述p53-MDM2信号轴负反馈调节外, 活化的p53蛋白可以通过诱导*TP21*等基因的表达, 抑制CDK1、CDK2和CDK4等细胞周期蛋白依赖性激酶的活性, 进而导致细胞周期停滞[1,19]。而当DNA损伤无法修复时, p53通过激活如*BAX*、Bcl-2结合组分3(Bcl-2 binding component 3, *BBC3*)等促凋亡基因, 触发细胞程序性死亡, 从而清除受损细胞, 防止肿

瘤发生。另外，p53可以触发细胞衰老机制，使受损细胞进入一种不可逆的生长停滞状态从而阻止受损细胞转化为癌细胞，这是一种重要的肿瘤抑制机制。p53可以通过调节细胞新陈代谢影响糖酵解和氧化磷酸化等代谢途径以适应细胞的能量需求和应激条件，也可以通过调控DNA修复和细胞周期检查点防止基因突变和染色体异常积累[16]。然而，若*TP53*基因发生突变，则可能导致*TP53*异常转录或p53蛋白的失活，甚至获得新的致癌功能，驱动细胞恶性转化。

总而言之，p53-MDM2信号轴并非简单的线性转导通路，而是包含多节点的复杂网络，任一节点的异常均会扰乱细胞稳态，诱发肿瘤恶性增殖，也为恶性肿瘤靶向药物研发与精准治疗提供了重要的分子靶点与理论依据。



P代表磷酸化; Ub代表泛素化; ARF为ADP-核糖基化因子; MDMX为MDM2同源蛋白; ATM/ATR和CHK1/CHK2为DNA损伤应答相关激酶。黑色箭头表示激活或转运, 红色箭头表示降解, T形线表示抑制, 虚线表示间接调控。

P represents phosphorylation; Ub represents ubiquitination; ARF is ADP-ribosylation factor; MDMX is MDM2 homolog protein; ATM/ATR and CHK1/CHK2 are DNA damage response-related kinases. Black arrows indicate activation or transport, red arrows indicate degradation, T-shaped lines indicate inhibition, and dashed lines indicate indirect regulation.

图1　p53-MDM2信号轴机制示意图

Fig.1　Schematic diagram of the p53-MDM2 signaling axis

2 靶向p53-MDM2信号轴的研究进展

p53蛋白的失活几乎是所有人类恶性肿瘤的关键特征, 这主要通过两种机制介导, 即*TP53*基因突变与MDM2的扩增或过表达[10]。p53-MDM2信号轴在多种常见肿瘤中的表达特征与异常状态见表1。研究表明*TP53*基因突变多为错义突变, 集中于DNA结合结构域, 不仅能干扰野生型p53的功能, 还可以促进肿瘤的侵袭、转移等, 并与患者不良预后密切相关[20]。相比之下, 在*TP53*基因未突变的肿瘤中, p53功能的失活主要归因于MDM2的异常高表达。在多种实体瘤如肉瘤、胶质母细胞瘤、乳腺癌等中, *MDM2*基因扩增已被证实是诱导肿瘤恶性发生的重要因素[21]。因此, 精准靶向p53-MDM2信号轴以恢复肿瘤细胞内野生型p53功能, 已成为抗肿瘤靶向新药研发领域极具前景的前沿研究方向。

2.1 突变型p53靶向策略

长期以来, 由于p53靶点的不可成药和传统药物难以恢复此类蛋白正常功能的原因, 突变型p53靶向治疗长期停滞不前。然而, 近年来围绕突变型p53功能修复的策略取得了突破性进展, 主要聚焦于突变p53激活、突变p53降解、合成致死、基因治疗四类机制。

2.1.1 突变p53激活 依据蛋白空间结构变异特征, *TP53*基因突变主要分为两大类, 结构性突变和接触性突变[22]。结构性突变主要通过改变p53蛋白的三维结构, 导致其热稳定性增加和构象异常进而失活, 例如Y220C和R175H位点突变[22-24]。接触性突变则通过影响p53与DNA的结合能力, 从而减弱其肿瘤抑制活性。其中结构性突变p53的稳定化是当前靶向药物攻坚的核心突破口, 这类药物通过小分子精准靶向突变空腔、填补疏水缺陷从而稳定蛋白的天然折叠状态, 高效恢复突变p53野生型生物学功能, 该策略具备良好的应用转化价值和临床转化前景。

APR-246(Eprenetapopt)作为首个进入临床后期阶段的突变p53靶向再激活剂, 其本质是一种前药, 在体内生理环境下迅速代谢为小分子亚甲基奎宁环酮(methylene quinuclidinone, MQ)。MQ能够与错误折叠的p53蛋白核心内的特定半胱氨酸残基共价结合, 从而诱导错误折叠的p53蛋白恢复正确的折叠构象并重新获得转录活性, 激活下游靶基因如*TP21*、*BAX*和*PUMA*, 最终诱导细胞周期停滞和细胞凋亡发生[20]。

大量临床前研究数据充分验证了APR-246的广谱抗肿瘤潜力与良好的安全性特征。在体外细胞系和体内异种移植模型中, APR-246能显著诱导携带R175H、Y220C等多种结构性热点突变的肺癌、肝癌、血液肿瘤细胞的凋亡, 而对表达野生型p53的正常组织细胞无明显毒副作用, 药物安全窗口宽泛[20-21]。目前APR-246的研发聚焦于*TP53*突变型高危骨髓增生异常综合征和复发难治急性髓系白血病患者, 多项I/II期临床试验表明, APR-246与去甲基化药物阿扎胞苷联用具有显著的协同效应[20,25]。一项国际多中心联合II期临床试验分析汇总了100例接受APR-246联合阿扎胞苷治疗的*TP53*突变型高危骨髓增生异常综合征和急性髓系白血病患者的意向性治疗数据, 结果显示该联合方案的总体缓解率达69%, 其中完全缓解率为41%, 中位总生存期为11.8个月, 远优于历史对照[20]。这些研究成果推动了III期临床试验(NCT03745716)的开展, 然而结果最终未达到预期。综上, APR-246虽在III期遭遇瓶颈, 但其作为先驱者, 为后续更具突变特异性和更高效力的p53再激活剂研发提供了重要经验。

表1 p53-MDM2信号轴在常见肿瘤中表达水平

Table 1 Expression levels of the p53-MDM2 axis in common cancers

常见肿瘤 Common cancers	*TP53*突变频率 *TP53* mutation frequency	MDM2扩增频率 MDM2 amplification frequency	主要p53-MDM2信号轴变化 Major alterations of the p53-MDM2 axis
Triple-negative breast cancer	~80%	Rare	*TP53* inactivation mutation
High-grade serous ovarian carcinoma	~96%	Rare	*TP53* mutation (containing Y220C)
Liposarcoma	~10%	>90%	MDM2 amplification
Glioblastoma	~30%	10%-15%	Both exist simultaneously
Osteosarcoma	20%-30%	~10%	Both have a certain proportion
Colorectal cancer	40%-50%	Rare	*TP53* mutation
Non-small cell lung cancer	50%-60%	~5%	*TP53* mutation as the main type
Chronic lymphocytic leukemia	10%-40%	Rare	17p deletion/*TP53* mutation

Rezatapopt(PC14586), 针对 *TP53* Y220C突变开发的Rezatapopt是一种新型、口服生物可利用的小分子结构校正剂, 该药物可选择性结合p53 Y220C突变蛋白, 并以高亲和力、非共价方式嵌入Y220C空腔, 通过疏水填充与氢键网络重构, 显著提升突变蛋白的整体热力学稳定性, 从而恢复p53野生型构象和转录活性。临床前研究已充分验证了其机制特异性和抗肿瘤效力[26]。在多种携带 *TP53* Y220C突变的实体瘤和血液肿瘤模型中, Rezatapopt均能选择性地杀伤突变细胞, 而对野生型p53细胞无显著影响。尤其是在急性髓系白血病临床模型中, Rezatapopt能够特异性地靶向 *TP53* Y220C突变型急性髓性白血病细胞, 并剂量依赖性地诱导细胞凋亡和显著增强细胞周期阻滞作用[26-27]。

在临床转化方面, Rezatapopt同样进展迅速且成果显著。一项针对携带*TP53* Y220C突变的晚期实体瘤患者首次I期临床研究发表于2026年2月 *The New England Journal of Medicine*, 结果显示患者的客观缓解率随着Rezatapopt剂量的增加而提高, 部分患者实现肿瘤持续退缩, 且药物具有良好的安全性和耐受性[28]。目前正在进行的II期注册性临床试验数据进一步展现了该药物优异的临床价值。这些成果为Rezatapopt靶向 *TP53* Y220C突变抗肿瘤治疗提供了坚实的临床依据, 标志着突变型 *TP53*靶向治疗领域取得里程碑式突破。然而, 随着耐药机制相关研究的不断深入, 研究人员对治疗后患者的肿瘤样本进行了深度测序分析, 发现病灶中 *TP53*基因可发生二次顺式突变, 大幅降低Rezatapopt疗效[29-30]。总而言之, Rezatapopt的研发和临床试验为*TP53* Y220C突变患者带来了切实的希望, 为p53“不可成药”难题提供了关键性临床概念验证, 但其仍面临耐药性这一难题, 后续仍需深入研究, 完善耐药应对策略。

2.1.2 突变p53降解 靶向突变p53的降解是当前肿瘤精准治疗中极具前景的研究方向之一。在一些肿瘤中, 突变型p53的稳定性往往高于野生型p53, 并且突变型p53积累受到多种机制的调控, 其中分子伴侣特别是热休克蛋白90(heat shock protein 90, HSP90)和脱乙酰化酶6(histone deacetylase 6, HDAC6)扮演着关键角色[22]。

HSP90是一种关键的分子伴侣, 负责维持多种靶蛋白的正确折叠、稳定性和功能, 包括构象不稳定的突变型p53[22]。在生理条件下, HSP90通过N-端ATP活性口袋结合突变型p53, 阻止其被泛素–白酶体系统降解, 从而促进突变型p53的累积并持续驱动肿瘤恶性进展[22]。而HSP90抑制剂可竞争性结合HSP90蛋白N-端ATP活性口袋, 阻断ATP酶循环, 直接破坏HSP90与突变型p53之间的保护性结合复合物[31]。失去分子伴侣保护的突变型p53暴露大量疏水区域, 被内源性E3泛素连接酶识别, 最终经由26S蛋白酶体降解, 显著下调突变型p53蛋白表达, 抑制肿瘤恶性增殖[22,32]。

经典代表药物Tanespimycin(简称17-AAG)作为全球首个进入临床试验的HSP90抑制剂, 大量的临床前研究已证实了17-AAG在多种癌症模型中的广谱抗肿瘤活性[33-34]。淋巴瘤模型研究证实, 17-AAG可同步下调Akt、Cyclin D1等多重促癌蛋白表达, 有效阻断肿瘤的恶性发生发展[35]。同时, 17-AAG在多种妇科恶性肿瘤细胞如子宫内膜癌、卵巢癌等中也具有显著的细胞毒活性, 该效应与其靶向多条常见致癌通路密切相关[36]。更重要的是, 体外机制实验进一步验证, 17-AAG可高效诱导多株p53突变肿瘤细胞内突变蛋白降解, 部分恢复残余野生型p53活性, 协同提高肿瘤细胞对化疗药物的敏感性, 为克服化疗耐药提供了新的策略[37]。然而, 尽管17-AAG在临床前研究中展现出巨大的广谱抗肿瘤潜力, 其临床开发却因显著的毒性问题而受到严重限制。

HDAC6主要定位于细胞质, 可通过稳定HSP90分子伴侣复合体间接保护突变型p53不被降解, HDAC6是另一种稳定突变型p53的关键调控蛋白[38]。HDAC抑制剂可特异性阻断HDAC6酶活性, 干扰HSP90复合物的正常组装过程, 间接降低突变型p53结构稳定性[39]。除此之外, HDAC抑制剂可提高突变型p53乙酰化水平, 促进其核输出, 干扰其致癌功能, 双重促进突变型p53泛素化降解, 有效逆转突变p53介导的化疗和靶向治疗的多重耐药性[39]。

Vorinostat作为首个获FDA批准的HDAC抑制剂, 其获批主要基于在皮肤T细胞淋巴瘤中的显著疗效。在两项关键II期临床试验中, 对于接受过至少两种全身性治疗后疾病仍出现进展、持续或复发的患者, 口服Vorinostat(400 mg, 每日一次)客观缓解率达到约30%, 部分患者可获得持久的完全缓解, 且Vorinostat具备良好的安全性和有效性, 充分证明了其在皮肤T细胞淋巴瘤中的临床价值[40-41]。此外, Vorinostat在霍奇金淋巴瘤、多发性骨髓瘤及非小细

胞肺癌等恶性肿瘤中也进行了探索研究。在一项针对复发/难治性霍奇金淋巴瘤的I/II期临床试验中, 发现Vorinostat联合mTOR抑制剂西罗莫司具有协同抗肿瘤效应[42]。在实体瘤治疗领域, 也已有I期临床试验探索Vorinostat与抗血管生成药物帕唑帕尼或蛋白酶体抑制剂伊沙佐米的联合方案[43]。这些研究为克服*TP53*突变相关耐药提供了坚实的理论基础与广阔的临床转化前景。

2.1.3 合成致死 合成致死的核心定义为细胞内两个基因或信号通路中任意一个单独发生功能缺失、抑制或异常表达时, 细胞仍可存活, 但二者同时功能受阻会引发细胞严重损伤或死亡[4]。该模式不依赖传统化疗杀伤机制, 仅精准针对肿瘤特有的基因缺陷, 特异性高、脱靶毒性低、耐药风险低, 契合现代低毒高效抗肿瘤药物研发的核心需求。野生型p53是G_1/S期DNA损伤检查点核心调控枢纽, 突变型p53肿瘤细胞G_1期检查点功能缺失, 转而依赖G_2/M期检查点进行DNA修复, 且对复制应激的耐受性增强。因此, 靶向G_2/M期关键调控因子或复制应激反应通路可在p53突变细胞中诱发合成致死。

WEE1抑制剂。WEE1激酶通过磷酸化CDK1 Tyr15位点阻滞细胞向有丝分裂过渡, WEE1激酶是G_2/M检查点的关键分子。这种依赖关系构成了合成致死的理想靶点, 也是WEE1抑制剂发挥作用的机制基础。在突变型p53肿瘤细胞中, WEE1抑制剂通过特异性阻断WEE1的激酶活性, 解除其对CDK1的抑制作用, 诱发DNA双链损伤大量累积, 进而导致细胞死亡。WEE1抑制剂Adavosertib正是基于这一原理设计的代表性药物。

Adavosertib是一种口服有效的WEE1高选择性小分子抑制剂, 大量临床前研究证实Adavosertib在卵巢癌、结直肠癌、胶质母细胞瘤等多种实体瘤模型中具有显著的抗肿瘤活性, 并有效增强多种DNA损伤剂和放疗对肿瘤细胞的杀伤效应[44-46]。更重要的是, AT富集序列相互作用结构域5A(AT-rich interaction domain 5A, ARID5A)是SWI/SNS染色质重塑复合物的核心抑癌成分, 在约9%的结直肠癌中发生突变, 近期研究发现同时携带*ARID5A*和*TP53*双突变的结直肠癌对WEE1抑制表现出超常敏感性[47-48]。这一发现不仅从机制上深化了对合成致死网络复杂性的理解, 更为临床试验中精准筛选最可能获益的患者群体(即*TP53*/*ARID5A*共突变人群)提供了明确、可检测的分子依据。在临床转化方面, Adavosertib同样取得了显著进展。在一项针对*TP53*突变型铂类耐药卵巢癌的II期临床研究中, Adavosertib联合卡铂的方案显示出良好的安全性和有效性, 疗效显著[49]。这验证了WEE1抑制剂在特定分子背景下通过合成致死抗肿瘤的可行性, 为p53突变肿瘤的精准治疗提供了新思路。

PARP抑制剂。聚腺苷二磷酸–核糖聚合酶(poly ADP-ribose polymerase, PARP)是细胞内DNA单链碱基切除修复过程中的核心限速酶。细胞受到应激信号刺激时, PARP尤其是PARP1能够迅速识别单链断裂, 并通过催化NAD^+转化为聚ADP-核糖链, 对自身及周围蛋白进行PAR化修饰, 进而维持基因组稳定。突变型p53肿瘤细胞中普遍伴随同源重组修复固有缺陷, DNA双链损伤无法自主修复, 高度依赖PARP代偿维持基因组稳态。而PARP抑制剂通过抑制PARP酶活性, 同时将PARP固定结合在DNA单链断裂处, 干扰DNA损伤修复。该机制不仅是PARP抑制剂临床应用的基石, 且已被广泛用于多种恶性肿瘤的治疗, 尤其对于存在同源重组修复缺陷的BRCA1/2突变肿瘤细胞, 该策略可发挥显著的杀伤作用。临床实践也已充分证实, PARP抑制剂作为一线或复发后维持治疗的有效预测生物标志物, 显著延长了患者的无进展生存期[50-51]。

然而, p53的缺失本身可以驱动一种独立的耐药机制。研究表明, p53缺失可以通过稳定复制叉、激活替代性非同源末端连接等多种途径帮助癌细胞逃避PARP抑制剂诱导的死亡[52]。p53的这种双重性使其成为PARP抑制剂疗效与耐药动态演变的关键因素。为了拓展PARP抑制剂的应用边界, 研究者们正积极探索创新的联合治疗策略。一个极具前景的方向是利用患者来源的肿瘤类器官模型进行精准药敏测试。已有研究明确显示p53突变乳腺癌类器官对PARP抑制剂Talazoparib与替莫唑胺的联合治疗表现出显著的协同敏感性, 而野生型p53类器官则不敏感, 表明该联合方案具有良好的靶向特异性[53]。这一发现为临床精准筛选受益人群提供了强有力的实验依据。更为重要的是, 针对非BRCA突变的p53突变型肿瘤, 新的合成致死靶点正在被发掘。近期研究发现, DNA2核酸酶作为DNA复制和修复过程中的关键调控因子, 其抑制剂可在p53突变型细胞中诱导出一种独特的合成致死效应, 与PARP抑制剂产

生协同抗肿瘤活性，为PARP抑制剂的应用拓展至非*BRCA*突变的p53突变型肿瘤提供了新的思路[54]。综上所述，PARP抑制剂在p53突变型肿瘤中的应用是一个动态演进的过程，未来仍需深入探究不同p53突变亚型对PARP抑制剂反应的异质性，并结合类器官药敏平台和新型合成致死靶点，开发出更为精准和高效的个体化联合治疗方案。

2.1.4 基因治疗 基因治疗作为现代医学中一种革命性治疗策略，通过修正、替换或调控细胞内的遗传物质，从分子根源上干预疾病的发生与发展。在肿瘤学领域，*TP53*作为重要的肿瘤抑制基因，也是基因治疗的重要靶点。

*TP53*基因替换疗法是一种经典的基因增补策略，主要是通过病毒载体将外源性野生型*TP53*基因精准导入突变p53肿瘤细胞内，恢复*TP53*转录调控功能，从而重新激活下游靶基因，抑制肿瘤生长增殖。

今又生(Gendicine)是全球首个获批的癌症基因治疗产品，于2003年获得中国国家药品监督管理局批准，专门用于头颈部鳞状细胞癌的治疗[55]。该药物采用重组人5型腺病毒作为载体，携带完整的野生型*TP53*基因，其临床应用模式主要为瘤内注射，并辅以放疗。一项包含69例头颈部鳞状细胞癌患者的随机对照临床试验显示，接受Gendicine联合放疗组患者的完全缓解率和客观缓解率显著高于单纯放疗组，且未观察到严重的系统性不良反应，证实了其良好的安全性和协同放疗增敏效应[56]。这种局部高浓度的p53蛋白表达水平能够有效提高p53缺失的肿瘤细胞的放疗敏感性，为局部晚期、无法手术切除的实体瘤患者提供了重要的微创治疗选择[57]。然而，由于基于腺病毒的递送系统固有的局限性，包括腺病毒递送系统的强烈免疫原性、非肿瘤组织的转导效应和表达持续时间有限性，Gendicine的应用仅局限于局部治疗。总而言之，Gendicine不仅验证了*TP53*基因替换疗法的可行性，也为后续更安全、高效、广谱的基因治疗策略奠定了坚实基础。

CRISPR-Cas9基因编辑技术是一种更为精准和持久的修复策略，利用Cas9核酸酶在特异性向导RNA的指引下，精准识别并切割位于靶基因的高频热点突变位点，如*TP53*基因DNA结合域的高频热点突变位点R175H、R248Q和R273H等，进而激活细胞自身高保真的同源定向修复通路，以共递送的野生型DNA供体模板为参照，精确修正突变碱基为野生型序列，从基因层面恢复内源性p53的正常结构与功能[58]。

CRISPR-p53的应用策略需根据肿瘤中p53失活的具体机制进行差异化设计。在针对以*TP53*基因突变为主要失活机制的如头颈部鳞状细胞癌或肺癌等肿瘤中，直接编辑修复突变基因；在人乳头瘤病毒阳性的宫颈癌中，p53功能丧失主要源于病毒E6蛋白介导的泛素–蛋白酶体降解，研究人员创新性地开发了基于催化失活Cas9(dCas9)的CRISPR激活系统，通过dCas9与强效转录激活结构域融合，靶向*TP53*基因启动子区域，显著上调内源性野生型*TP53* mRNA及p53蛋白的表达水平，从而诱导癌细胞凋亡[59]。截至2026年，CRISPR-p53疗法仍处于临床转化的早期阶段，少数进入I期临床试验阶段，主要探索两大方向：一是体外编辑策略，即从患者体内分离T细胞并在体外利用CRISPR-Cas9敲除*TP53*基因，以增强其在恶劣肿瘤微环境中的持久性和抗肿瘤活性；二是开发体内递送系统，直接在患者体内靶向编辑肿瘤组织中的*TP53*基因[60-61]。然而，该技术的实际应用仍面临递送效率、脱靶效应和体内安全性等诸多挑战，目前尚未有任何关于CRISPR-p53疗法的II期或III期临床试验数据公布，其临床价值仍有待大规模、长期随访数据的验证。

综合前文各节所述，近年来突变型p53的靶向策略已取得显著进展，展现出重要的科研价值与广阔的临床转化前景，但仍面临诸多严峻挑战，有待进一步深入研究，表2和表3分别为突变型p53靶向策略的相关药物及其临床研究进展。

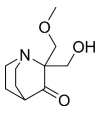
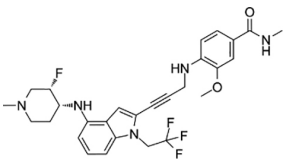
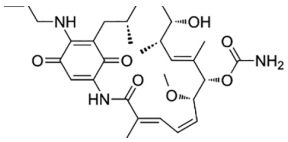
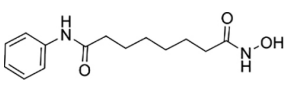
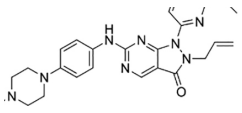
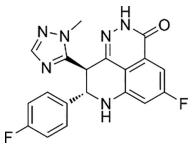
2.2 MDM2靶向策略

临床研究证实，超过50%的人类恶性肿瘤虽保留野生型*TP53*基因，但却通过MDM2的异常扩增、转录上调或蛋白高表达间接抑制p53的功能[4]。因此，精准靶向MDM2，阻断p53-MDM2信号轴，已成为肿瘤精准靶向治疗的核心热门方向。

2.2.1 靶向MDM2的小分子抑制剂 MDM2抑制剂作为目前恢复内源性野生型p53活性的核心治疗策略，其作用机制是竞争性结合MDM2表面的p53结合口袋，阻断p53与MDM2的结合，恢复p53转录活性和下游靶基因功能。目前，至少13款p53与MDM2相互作用抑制剂已进入临床试验阶段，主要针对实体瘤和血液肿瘤等癌症适应证开展研究[62]。临床研究初步验证了靶向p53-MDM2信号轴的抗肿瘤可行性，

表2 突变型p53靶向策略

Table 2 Mutant p53 targeting strategies

小分子抑制剂 Small-molecule inhibitor	来源 Source	结构 Structure	特点 Characteristics
APR-246	Quinuclidinone-derived reactivator		A first-in-class small molecule designed to restore wild-type p53 function, which covalently modifies cysteine residues in mutant p53 to facilitate refolding, thereby re-establishing the wild-type conformation and transcriptional activity of p53. Additionally, it targets thioredoxin reductase 1 to disrupt cellular redox homeostasis
Rezatapopt	Carbazole-fluoropiperidine derivative		Rezatapopt selectively binds to the surface cavity of *TP53* Y220C mutant, stabilizes the p53 protein structure, and restores its tumor-suppressive function. In mouse tumor models harboring the *TP53* Y220C mutation, it exhibits significant tumor-inhibitory and regression effects
17-AAG	Ansamycin antibiotic		A potent HSP90 inhibitor with substantially higher affinity for HSP90 in tumor cells than in normal cells. It effectively diminishes the viability of tumors carrying mutant p53, induces the degradation of mutant p53, and partially restores wild-type p53 function
Vorinostat	Hydroxamic acid derivative		An orally active, potent inhibitor targeting HDAC1, HDAC2, HDAC3, HDAC6, HDAC7, and class IV HDACs. It downregulates the expression of mutant p53 and promotes its ubiquitination, thereby reducing the protein level of mutant p53
Adavosertib	Pyrazolopyrimidinone derivative		An orally efficacious WEE1 kinase inhibitor. By inhibiting the G_2/M checkpoint, it triggers synthetic lethality in tumors with p53 functional defects (mutation or deletion), leading to the accumulation of DNA damage and subsequent cell death
Talazoparib	Benzimidazole derivative		A highly potent, orally active PARP1/2 inhibitor with robust PARP-trapping activity. It exerts potent cytotoxic effects on tumors with BRCA mutations or HRD (homologous recombination deficiency) and is frequently used in combination with chemotherapy or other targeted agents
Gendicine	Recombinant p53 adenoviral vector	/	The world's first commercially approved gene therapy drug. It delivers exogenous wild-type *TP53* gene into tumor cells via an adenoviral vector to reconstitute the tumor-suppressive function of p53

/: 基因治疗药物, 不适用化学结构式。

/: gene therapy drugs do not apply to chemical structural formulas.

但该类药物的临床应用仍面临剂量限制性毒性及耐药性等挑战。以下介绍了一些常见的MDM2小分子抑制剂, 表4和表5分别为相关MDM2小分子抑制剂及其临床研究进展。

Nutlins。Nutlin家族是首个被系统开发并广泛应用于体内外研究的MDM2抑制剂, 核心机制为通过卤素取代苯环模拟p53转录激活域的3个关键疏水残基(Phe19、Trp23、Leu26), 高选择性结合MDM2表面的p53疏水口袋, 竞争性阻断p53-MDM2信号轴[63]。该家族主要包括Nutlin-1、Nutlin-2与Nutlin-3, 其中Nutlin-3(活性对映体为Nutlin-3a)活性最强、应用最广, 在临床前研究中显示出显著的抗肿瘤活性[20]。体外实验显示, Nutlin-3a可显著诱导p53野生型肿瘤细胞凋亡与周期阻滞, 而体内研究表明Nutlin-3可有效抑制白血病、肉瘤及多种实体瘤异种移植瘤生长, 且具有良好的耐受性[64-66]。然而, Nutlin家族存在代谢稳定性差、口服生物利用度低、体内半衰期短及高剂量下胃肠道毒性明显等缺陷, 限制了其直接临床转化, 其仅作为工具化合物广泛用于p53-MDM2信号轴机制研究与药物筛选模型构建[63]。

RG7112与RG7388(国际通用名为Idasanutlin)。为克服Nutlin的药代动力学缺陷, Roche公司开发了

表3 突变型p53靶向策略的药物临床试验进展

Table 3 Clinical research progress of drugs targeting the mutant p53

药物名称 Drug name	靶点/机制 Target/mechanism	适应症 Indications	临床试验阶段 (截至2026年5月) Clinical trial phase (as of May 2026)	试验编号/备注 Clinical trial identifier/notes
APR-246	Mutant p53 reactivator	Myelodysplastic syndromes, acute myeloid leukemia, and solid tumors harboring *TP53* mutations	Phase I/II	NCT03072043; NCT03588078; NCT04419389
Rezatapopt	Selective reactivator of *TP53* Y220C mutant	Solid and hematologic malignancies harboring the *TP53* Y220C mutation	Phase I/II	NCT04585750
17-AAG	HSP90 inhibitor that indirectly destabilizes mutant p53	*TP53*-mutant solid tumors and hematologic malignancies	Phase I/II	Early-phase exploratory clinical trials
Vorinostat	HDAC inhibitor that modulates p53 expression and function	Advanced solid tumors with *TP53* mutations and cutaneous T-cell lymphoma	Phase I/II	NCT00091559; NCT04308330
Adavosertib	WEE1 inhibitor that targets the DNA damage response and repair pathway	*TP53*-mutant solid tumors, including ovarian cancer	Phase II/III	NCT01357161; NCT01164995; NCT03284385
Talazoparib	PARP inhibitor that induces synthetic lethality	*BRCA1/2*-mutant or homologous recombination-deficient tumors; synthetic-lethal strategies are also being investigated in *TP53*-mutant settings	Phase III	NCT01945775
Gendicine	Recombinant p53-expressing adenoviral vector for gene therapy	*TP53*-deficient head and neck squamous cell carcinoma	Approved in China in 2003	NMPA-approved; first-in-world *TP53* gene therapy product

首个进入临床试验的MDM2抑制剂RG7112。其核心结构为顺式咪唑啉衍生物, 通过甲基化修饰提高代谢稳定性与口服生物利用度。早期I期临床试验纳入晚期实体瘤与血液系统恶性肿瘤患者, 结果显示RG7112单药具有一定的抗肿瘤活性, 尤其在脂肪肉瘤与急性髓系白血病患者中观察到部分缓解, 但存在显著血液学与胃肠道毒性, 且单药客观缓解率低[67]。为进一步优化药效与药代动力学特征, 在此基础上开发的第二代衍生物RG7388, 其对MDM2的结合活性较RG7112提高约3倍, 口服生物利用度达80%, 且具备良好的药代动力学特征[67]。II期临床试验显示, RG7388单药或与阿糖胞苷联用在急性髓系白血病患者治疗中展现出更好的疗效与耐受性, 但III期临床试验未达到总生存期改善的主要终点, 疗效有限且耐药易发仍是其临床应用的主要障碍[68]。

Navtemadlin(AMG-232/KRT-232)。Navtemadlin作为新一代哌啶酮骨架MDM2高选择性小分子抑制剂, 代表了靶向p53-MDM2信号轴治疗策略在结构优化与临床转化方面取得的重要进展之一。其主要机制是通过模拟p53蛋白N-端α螺旋上Phe19、Trp23和Leu26 3个关键疏水残基的空间构象, 特异性结合MDM2蛋白N-端的深疏水口袋, 从而有效阻断p53与MDM2结合。因此, Navtemadlin较早期Nutlin类化合物具有更高选择性和更优化的药代性质, 还可与多种药物联用从而有效规避初代药物非特异性毒性缺陷[20]。

临床前及早期临床研究充分证实了Navtemadlin单药的强大生物学活性。在*TP53*为野生型且MDM2过表达的多种恶性肿瘤模型(如胶质瘤和子宫内膜癌)中, Navtemadlin能够有效激活内源性p53通路, 诱导下游靶基因的表达, 从而实现对肿瘤细胞增殖的强力抑制和促凋亡效应[69-70]。更为重要的是, Navtemadlin展现出卓越的联合治疗潜力。有研究证实Navtemadlin与放疗联用可显著增强对黑色素瘤的抑制效果, 且不会导致骨髓抑制或影响肿瘤浸润淋巴细胞, 提示其良好的联合治疗潜力[71]。与此同时, Navtemadlin通过与不同作用机制的药物联用, 可以产生显著的协同抗肿瘤效应, 并有效克服单药治疗易产生的耐药性问题。III期BOREAS试验比较了Navtemadlin单药与最佳可用疗法在JAK抑制剂经治的复发/难治性*TP53*野生型骨髓纤维化

表4 MDM2靶向小分子抑制剂

Table 4 Small molecule inhibitors targeting the MDM2

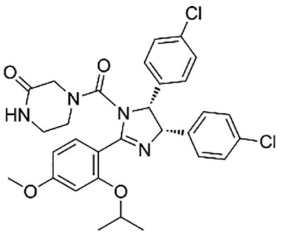
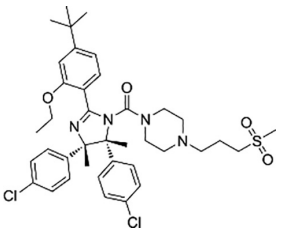
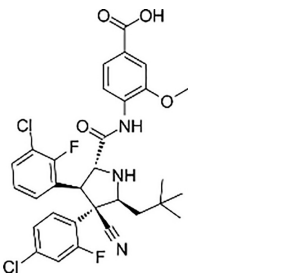
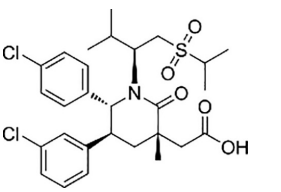
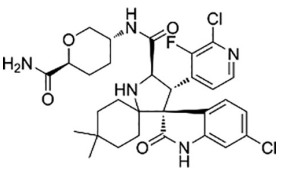
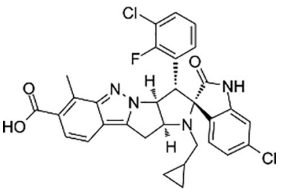
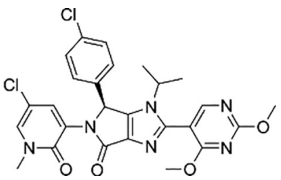
小分子抑制剂 Small-molecule inhibitor	来源 Source	结构 Structure	特点 Characteristics
Nutlin-3a	*Cis*-imidazoline analogue		An MDM2 inhibitor that binds MDM2 with an IC_{50} of 9×10^{-8} mol/L, disrupts the p53-MDM2 signaling axis, and stabilizes p53, thereby inducing autophagy and apoptosis. It exhibits >10-fold selectivity over tumor cells harboring mutant or deleted p53
RG7112	Imidazoline analogue		An MDM2 inhibitor that binds MDM2 with an IC_{50} of 1.8×10^{-8} mol/L. It is approximately fourfold more potent than Nutlin-3a and exhibits favorable selectivity for tumor cells expressing wild-type p53
RG7388	Methoxy-substituted pyrrolidine compound		An MDM2 inhibitor that binds MDM2 with an IC_{50} of 6×10^{-9} mol/L^{-1}
Navtemadlin	Piperidin-2-one-based scaffold		An MDM2 inhibitor that binds MDM2 with varying IC_{50} values across different tumor cell lines. In addition to mimicking the interactions of the p53 residues Phe19, Trp23, and Leu26 with MDM2, it forms additional hydrophobic interactions
Milademetan	Spiro-oxindole compound		A selective, orally bioavailable MDM2 inhibitor that induces G_1 cell-cycle arrest, cellular senescence, and apoptosis. It is being investigated for the treatment of acute myeloid leukemia and solid tumors
Brigimadlin	Spiro-oxindole compound		An orally bioavailable MDM2 inhibitor that prevents MDM2-mediated negative regulation of p53
Siremadlin	Pyrrolidine-imidazolone derivative		A potent and selective inhibitor of the MDM2-p53 interaction. Its primary mechanism involves blocking MDM2-mediated negative regulation of p53, thereby restoring wild-type p53 tumor-suppressive signaling

表5 临床阶段的p53-MDM2信号轴靶向药物

Table 5 Clinical-stage p53-MDM2 axis-targeted agents

药物名称 Drug name	主要靶点/机制 Primary target/ mechanism	临床试验阶段 Clinical trial phase	适应症 Indications	试验编号/备注 Clinical trial identifier/notes	关键临床结果/限制性 Key clinical findings/limitations
Nutlin-3a	MDM2	Preclinical	A prototype tool compound extensively investigated in preclinical studies	Used exclusively for mechanistic studies	Demonstrated antitumor activity across multiple *TP53*-wild-type tumor models. However, its clinical development is limited by poor metabolic stability, low oral bioavailability, a short *in vivo* half-life, and pronounced gastrointestinal toxicity at high doses
RG7112	MDM2	Phase I	Hematologic malignancies	NCT00623870	Demonstrated antitumor activity; however, it was associated with substantial hematologic and gastrointestinal toxicities, and its objective response rate as monotherapy was low
RG7388	MDM2	Phase I, phase III	Acute myeloid leukemia and acute lymphoblastic leukemia	NCT02407080; NCT02545283 (the phase III trial was terminated after failing to meet its primary overall-survival endpoint)	RG7388, administered either as monotherapy or in combination with cytarabine, demonstrated favorable efficacy and tolerability in patients with acute myeloid leukemia. However, the phase III trial failed to meet its primary endpoint of improved overall survival, and its efficacy was limited, with drug resistance remaining a concern
Navtemadlin	MDM2	Phase I, phase Ib, phase III	Myelofibrosis, acute myeloid leukemia, glioblastoma, endometrial cancer, and other malignancies	NCT03662126 (phase III, BOREAS); NCT06479135 (phase III, POIESIS); NCT05797831 (phase II/III)	Compared with earlier Nutlin-class compounds, navtemadlin exhibits greater selectivity and more favorable pharmacokinetic properties. It outperformed the best available therapy on endpoints such as SVR35 and TSS50. Nevertheless, gastrointestinal toxicity and thrombocytopenia remain important adverse events, and its efficacy as monotherapy is limited
Milademetan	MDM2	Phase II, phase III	MDM2-amplified solid tumors, acute myeloid leukemia, and myelodysplastic syndromes	NCT05012397; NCT04979442 (terminated)	Demonstrated some antitumor activity, although the overall durability of response was limited. The phase III MANTRA study failed to meet its primary progression-free-survival endpoint in previously treated patients with dedifferentiated liposarcoma
Brigimadlin	MDM2	Phase I, phase III	Dedifferentiated liposarcoma, biliary tract cancer, pancreatic cancer, and other solid tumors	NCT03964233; NCT06058793 (phase III, brightline-4)	Early studies demonstrated promising antitumor activity. However, the findings of subsequent pivotal studies and the current development status of the program warrant cautious interpretation
Siremadlin	MDM2	Phase I/II	Acute myeloid leukemia, myelodysplastic syndromes, and liposarcoma	NCT03940352 (combination therapy, phase I/II)	Demonstrated preliminary activity and an evaluable safety profile across different dosing regimens. However, further development in acute myeloid leukemia and other hematologic malignancies has been constrained by hematologic toxicity and dose-limiting adverse events. Development as monotherapy has been discontinued, with subsequent efforts shifting toward combination therapy

患者中的疗效与安全性，结果显示Navtemadlin在SVR35和TSS50等终点上优于最佳可用疗法，但在临床上仍有胃肠道毒性和血小板减少等不良反应，其临床疗效需结合给药方案、毒性等因素进行综合评价[72]。值得注意的是，Navtemadlin联合芦可替尼用于JAK抑制剂初治MF患者的III期POIESIS研

究(NCT06479135)正在积极招募中, 计划入组600例患者, 预计2028年完成。该研究采用双主要终点设计, 若取得成功, 将确立Navtemadlin作为首个获批的MDM2抑制剂在骨髓纤维化一线治疗中的标准地位。鉴于其突出的临床价值, Navtemadlin已获得FDA的快速通道认定, 有望成为该领域首个成功商业化的药物, 为MDM2依赖型恶性肿瘤患者带来新的希望。

Milademetan(DS-3032b/Rain-32)是一种基于二氢异喹啉酮骨架的新一代口服MDM2小分子抑制剂, 在化学结构创新、临床适应症精准定位及给药策略优化方面均体现了该领域的重要进展。该药物的临床开发主要聚焦于*TP53*野生型且MDM2扩增的实体瘤以及FLT3-ITD突变的急性髓系白血病。最新II期临床研究结果显示, 在MDM2扩增且*TP53*野生型的晚期实体瘤患者中, Milademetan具有一定的抗肿瘤活性, 但总体疗效有限, 仍需依赖分子分层和联合策略进一步增加获益[73]。一项在日本进行的Ib/II期研究也显示, Milademetan治疗后患者的肿瘤出现显著缩小, 且肿瘤缩小程度与MDM2拷贝数呈正相关[74]。然而, III期MANTRA研究在经治去分化脂肪肉瘤患者中未能达到主要无进展生存期终点, 提示该药在DDLPS中的单药疗效并不充分。在血液系统恶性肿瘤领域, 一项I期研究显示Milademetan单药及其与阿扎胞苷联用在复发/难治性急性髓系白血病或高危骨髓增生异常综合征患者中具有可管理的安全性和一定的协同潜力[75]。综上所述, Milademetan仍可作为MDM2扩增/TP53野生型肿瘤精准治疗的重要探索方向, 但其临床价值需要更明确的患者筛选和联合治疗证据支持。

Brigimadlin(BI 907828为早期研发编号)是由Boehringer Ingelheim International GmbH开发的口服MDM2抑制剂, 化学结构属于二氢异喹啉酮类, 具有不同于Nutlin类的新颖骨架。其临床研究主要聚焦于*MDM2*基因扩增且*TP53*为野生型的肿瘤。一项I期试验显示, Brigimadlin在MDM2扩增的去分化脂肪肉瘤及多种*TP53*野生型实体瘤中具有抗肿瘤活性信号[76]。此外, 一项I期亚组分析重点评估了Brigimadlin在晚期胆道癌患者中的疗效, 结果证实其在MDM2扩增的胆道癌中展现出抗肿瘤活性, 值得进一步研究[77]。随着研究的不断深入, 一项关键II/III期Brightline-1试验结果显示, 在晚期去分化脂肪肉瘤患者中, Brigimadlin的中位无进展生存期显著优于标准一线化疗药物多柔比星, 且客观缓解率增加[78]。然而, Brightline-1研究最终未能达到主要终点, 且Boehringer Ingelheim International GmbH已决定停止对Brigimadlin的进一步开发或至少终止部分后续项目。总而言之, Brigimadlin早期显示较强活性, 但后续关键研究结果和项目开发状态需谨慎解读。

Siremadlin(HDM201为早期研发编号)是Novartis AG开发的第二代口服、高选择性p53-MDM2小分子抑制剂, 是第一代MDM2抑制剂RG7112之后具有更高选择性与药代动力学优化的重要候选药物。一项在*TP53*野生型晚期实体癌或血液系统癌症患者中进行的剂量递增研究明确了Siremadlin在不同给药方案下的安全性与初步活性, 但也显示在急性髓系白血病等血液肿瘤中的进一步研发受到血液学毒性和剂量限制性不良反应的制约[79]。在联合治疗方面, 近期的一项Ib期剂量递增研究表明, Siremadlin与CDK4/6抑制剂Ribociclib联用在MDM2和CDK4共扩增的去分化脂肪肉瘤中表现出良好的抗肿瘤活性和可控的毒性, 为其精准治疗定位提供了概念验证, 成为该药物临床开发中的标志性进展[80]。此外, 近期的临床前研究通过大规模药物组合筛选, 发现Siremadlin与PARP抑制剂Olaparib的联用, 在p53野生型横纹肌肉瘤模型中具有强效的协同抗肿瘤作用, 揭示了p53激活与DNA修复缺陷之间的合成致死关系。尽管前景广阔, Siremadlin的临床应用仍面临挑战, 如剂量限制性毒性、耐药性等, 未来仍需进一步深入研究。

2.2.2 蛋白水解靶向嵌合体技术 蛋白水解靶向嵌合体(proteolysis targeting chimeras, PROTAC)是一种新兴的治疗方式, 如图2所示, PROTAC通过机体自身泛素–蛋白酶体系统募集E3泛素连接酶, 选择性地靶向降解相关目的蛋白, 从而可能调节传统小分子难以靶向的“不可成药”靶点[11,81-82]。PROTAC是一类双功能嵌合分子, 通常一个配体招募E3泛素连接酶, 另一个配体招募并结合目的蛋白[83-85]。与传统的小分子抑制剂不同, PROTAC具备催化降解、低剂量起效、循环反复利用等独特优势, 更重要的是, 可突破MDM2自身负反馈代偿环路, 作用更为持久彻底[86-88]。

MD-224是一种基于PROTAC技术开发的代表性高活性小分子MDM2降解剂, 其研发代表了靶向p53肿瘤治疗的重要突破[89]。该化合物由密歇根大学王

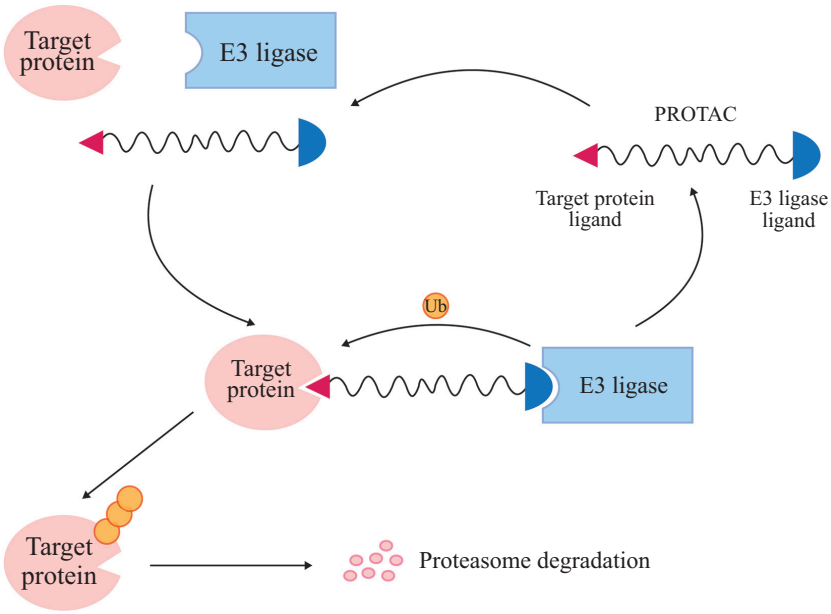


图2 PROTAC作用机制示意图

Fig.2 Schematic diagram of the mechanism of PROTAC

少萌教授团队[89]设计合成，并在多项研究中被证实能够有效诱导MDM2蛋白的快速降解，从而激活野生型p53肿瘤抑制功能，在多种白血病模型中实现完全且持久的肿瘤消退。更重要的是，在急性髓系白血病的原代细胞和患者来源的异种移植小鼠模型中，MD-224同样表现出强大的抗肿瘤活性[90]。这些结果有力地证明了MDM2降解策略在治疗*TP53*野生型白血病中的巨大潜力。然而后续研究发现，经简单的结构修饰后的MD-224可能将转变为一种分子胶，提示PROTAC的设计仍需依赖严谨的机制验证[90]。尽管MD-224尚未进入临床试验阶段，但它为后续更优化的MD-265和MD-4251等口服生物可利用的MDM2降解剂奠定了基础，在单次给药后即可诱导肿瘤完全消退，显示出更强的临床转化前景[91-92]。KT-253也是一种新型、高效且高选择性的双功能MDM2蛋白降解剂，并且是首个进入I期临床试验的MDM2降解剂，是该领域从基础研究向临床转化迈出的关键[93]。这项针对实体瘤、淋巴瘤、高级别骨髓恶性肿瘤和急性淋巴细胞白血病的I期临床试验早期数据显示，KT-253可有效激活p53，并已在患者体内观察到靶蛋白降解的证据，其有望成为一种全新的、更具潜力的治疗选择。

另外，YX-02-030作为一种靶向MDM2的PROTAC降解剂，主要用于治疗p53失活的三阴性乳腺癌，它能同时高亲和力地结合MDM2蛋白和VHL，形成MDM2-YX-02-030-VHL三元复合物，使得MDM2被蛋白酶体识别并降解。有研究表明，在p53突变的三阴性乳腺癌细胞中，MDM2被降解后p53家族成员尤其可促进TAp73蛋白稳定和激活，进而上调*BAX*、*NOXA*、*PUMA*等一系列促凋亡基因的表达，启动细胞凋亡[94-95]。目前YX-02-030的研究尚处于临床前阶段，已在细胞和动物模型上取得了积极结果。例如，在携带三阴性乳腺癌细胞的小鼠异种移植模型中，YX-02-030治疗能显著抑制肿瘤生长、延长小鼠生存期，并在肿瘤组织中检测到MDM2蛋白的缺失和凋亡标志物的增加[94]。

尽管前景广阔，但PROTAC技术在临床转化过程中仍面临诸多挑战。首先PROTAC分子量通常较大(>700 Da)，水溶性低，往往导致口服生物利用度低；其次PROTAC的高极性表面限制了分子的渗透性，导致其细胞膜渗透性差；更重要的是，细胞内较高浓度的PROTAC倾向于形成靶蛋白–降解剂的二元复合物，产生钩状效应(hook effect)，从而降低靶蛋白的降解活性，并阻碍其体内剂量的合理设计。另外，E3泛素连接酶的选择是PROTAC设计中的关键环节。人类基因组编码超过600种E3连接酶，但目前在PROTAC开发中被广泛利用的仅有少数几种，主要包括MDM2、CRBN、VHL等，表6列举了这三种适配E3连接酶及其优缺点。现有E3连接酶配体的局限性也是当前PROTAC技术的瓶颈之一。目前全

表6 PROTAC适配E3连接酶及其优缺点

Table 6 E3 ligase recruiters used in PROTAC and their advantages and disadvantages

E3连接酶元件 E3 ligase component	优点 Advantages	缺点 Disadvantages
MDM2	High tumor specificity and preferential expression in tumor cells, enabling synergistic tumor targeting	Basal MDM2 expression in normal hematopoietic cells may be aberrantly activated by exogenous PROTACs, potentially causing hematologic toxicities such as myelosuppression and hematopoietic stem cell apoptosis
CRBN	Broad tissue distribution and a diverse substrate repertoire, making it well suited for the development of PROTACs targeting hematologic malignancies	May induce dose-limiting adverse events, including thrombocytopenia and neurotoxicity, resulting in a narrow therapeutic window
VHL	Relatively high specificity and a low risk of off-target effects, making it suitable for the development of targeted protein degradation strategies against solid tumors	Its relatively low intracellular abundance may result in insufficient PROTAC-mediated degradation and reduced therapeutic efficacy

球范围内针对新型难成药靶点的大多数PROTAC分子仍处于临床前评估阶段, 未来突破有赖于分子理化性质的优化、适配E3连接酶的筛选以及递送系统的创新改造, 从而为PROTAC的临床转化提供切实可行的策略。

2.2.3 *核酸药物* 核酸药物凭借序列特异性高、靶向精准、研发周期短等优势, 成为调控MDM2表达的新型治疗手段, 用于调控MDM2表达的核酸干预形式包括主要包括小干扰RNA(small interfering RNA, siRNA)、反义寡核苷酸(antisense oligonucleotides, ASO)和环状RNA(circular RNA, circRNA), 展现了作为新兴治疗策略的巨大潜力[96-98]。核酸药物可直接在转录水平调控*MDM2* mRNA表达, 从源头降低MDM2蛋白合成量, 稳定p53蛋白并重启抑癌通路, 为MDM2扩增型耐药肿瘤提供新型干预策略。

siRNA特异性地识别、结合*MDM2*的mRNA并诱导其降解, 阻断MDM2蛋白表达, 抑制肿瘤细胞恶性增殖[96,99]。体外实验证实, 针对*MDM2*的siRNA显示出显著的肿瘤细胞生长抑制效果, 这为临床应用提供了理论基础, 有研究表明靶向*MDM2*的siRNA显著下调骨肉瘤细胞中MDM2表达, 激活p53, 从而有效抑制肿瘤细胞的增殖并诱导细胞凋亡[98]。ASO是一类能够与*MDM2*的mRNA以序列特异性的方式结合的单链寡核苷酸[100], 可诱导RNase H降解mRNA-ASO异源双链或直接阻滞核糖体翻译等, 有效降低MDM2蛋白表达水平, 稳定p53蛋白表达量, 在化疗耐药肿瘤模型中表现出良好应用潜力[100-102]。circRNA是一种共价闭合的环状分子, 结构稳定、不易被核酸酶降解, 而这种稳定性是circMDM2作为基因调控因子和潜在治疗靶点的关键优势, 为肿瘤治疗提供了新的思路和策略[103-106]。有研究表明, circMDM2在多种肿瘤类型中可通过影响MDM2表达调控, 促进肿瘤细胞的增殖和存活, 同时可能影响p53通路应激反应[107-108]。

由于高度的序列特异性, 核酸药物能够高效精确靶向*MDM2* mRNA, 减少脱靶效应。对因MDM2过表达而对传统化疗产生耐药性的肿瘤患者, 核酸药物可以通过直接降低MDM2蛋白水平来克服这种耐药机制。但是目前核酸药物普遍存在体内递送困难、易被核酸酶降解、免疫原性偏高等瓶颈, 仍需优化载体系统以推进临床转化。

2.3 联合治疗策略

由于p53-MDM2信号轴的复杂性和肿瘤异质性, 单一靶向治疗往往难以实现持久临床获益。联合治疗策略已成为这一领域的重要发展方向。根据联合用药的作用机制, 靶向p53-MDM2信号轴的联合治疗策略主要包括与化疗药物、与其他可协同靶点抑制剂、与免疫检查点抑制剂等联合治疗策略。

2.3.1 *与化疗药物联用增强DNA损伤* 化疗药物可直接诱导DNA双链断裂与复制应激, 激活肿瘤DNA损伤应答, 但肿瘤细胞常代偿性上调MDM2, 加速活化p53的降解, 从而获得对化疗药物的耐药性。基于此, MDM2抑制剂与化疗药物的联合应用具有协同抗肿瘤的理论基础: 一方面, 化疗药物上游诱导广泛DNA损伤, 激活ATM/ATR应激激酶, 进而激活p53-MDM2信号轴; 另一方面, MDM2抑制剂同步阻断MDM2介导的p53泛素化降解, 防止p53被应

激代偿清除，持续高水平活化p53，进一步放大DNA损伤信号，彻底损伤肿瘤细胞DNA修复能力，强制启动细胞周期阻滞与线粒体凋亡。

APR-246作为首创p53再激活小分子，可靶向细胞氧化还原平衡，在共价修饰突变型p53肿瘤细胞中诱导凋亡和铁死亡发生。两项平行II期临床试验(NCT03072043和NCT03588078)为APR-246联合阿扎胞苷方案的有效性提供了强有力的证据，结果汇总分析100例*TP53*突变高危骨髓增生异常综合征及急性髓系白血病伴骨髓增生异常相关改变的患者，总体缓解率达69%，完全缓解率为41%，CR中位持续时间10.2个月，中位OS为11.8个月，耐受性良好。但是，后续的III期随机对照试验(NCT03745716)未能达到其主要终点，即未能证明APR-246联合阿扎胞苷在总生存期上优于单用阿扎胞苷，提示该联合可能仅对特定亚群有效[25]。除此之外，一项临床试验(NCT03107780)显示，Navtemadlin单药在复发胶质母细胞瘤患者中仅可诱导部分肿瘤细胞死亡，其中位无进展生存期仅为3.1个月。当其与替莫唑胺联用时可显著增强细胞凋亡反应，且不影响正常骨髓细胞，后者仅发生可逆性生长停滞，提示联合治疗可在不额外增加血液学毒性的前提下提升疗效[69]。机制研究进一步揭示，少突胶质细胞分化相关基因的上调是介导Navtemadlin耐药的新机制，而在治疗失败后的复发肿瘤中并未出现新的*TP53*失活突变，表明存在非经典的耐药通路[69]。

上述研究表明，靶向p53-MDM2信号轴的化合物与化疗药物联合应用，在多种临床前模型及早期临床试验中展现出协同增强的抗肿瘤活性，提示该联合策略具有进一步临床转化的潜力。然而，部分III期研究未达到预设终点，提示仍需通过精准的患者筛选以及优化联合方案来验证其临床可行性，从而为未来的肿瘤治疗提供可靠的策略选择。

2.3.2 *与其他可协同靶点抑制剂联用实现合成致死* 肿瘤发生发展过程中伴随多条代偿性通路异常激活，单一阻断p53-MDM2信号轴易触发旁路信号代偿激活，从而限制疗效并导致获得性耐药。而基于合成致死原理的多通路协同阻断策略，成为提升MDM2抑制剂抗肿瘤效力、增强肿瘤细胞特异性杀伤的关键发展方向。

MDM2高表达肿瘤常伴随CDK4通路异常激活，共同驱动细胞周期快速进展。MDM2抑制剂激活p53，进而阻滞细胞周期进程，CDK4/6抑制剂同步抑制CDK通路，双重阻断细胞周期G_1/S期转换，协同抑制肿瘤增殖。有临床研究(NCT02343172和NCT04116541)显示，Siremadlin联合CDK4/6抑制剂已在MDM2扩增脂肪肉瘤中取得良好的临床效果[80]。另外，联合WEE1、PARP等DNA修复检查点抑制剂是协同抗肿瘤的有效策略。肿瘤细胞依赖G_2/M检查点与PARP介导修复通路代偿存活，MDM2抑制剂通过p53依赖性诱导强化DNA损伤蓄积，同WEE1或PARP抑制剂联合作用发挥更强效的合成致死效应。最新研究显示，在*TP53*野生型横纹肌肉瘤模型中，Siremadlin与PARP抑制剂Olaparib的组合筛选被证实具有高度协同的抗肿瘤活性，能显著促进DNA双链断裂并诱导细胞死亡。总而言之，此类靶向联合方案特异性强、副作用可控，为精准个体化治疗提供了极具前景的策略选择。

2.3.3 *与免疫检查点抑制剂联用重塑肿瘤微环境* 近年来研究发现，p53不仅调控细胞凋亡，还广泛参与肿瘤免疫微环境重塑，调控程序性死亡配体、炎症因子及趋化因子表达，介导肿瘤免疫逃逸。MDM2抑制剂激活p53后，可上调肿瘤细胞表面MHC-I分子表达、促进趋化因子分泌、增加肿瘤微环境内$CD8^+$杀伤性T细胞浸润，同时下调免疫抑制因子表达，显著提升肿瘤免疫治疗敏感性[108]。

免疫治疗已成为肿瘤治疗领域的一项突破性进展，尤其是程序性死亡受体1(programmed death receptor 1, PD-1)抑制剂在激活T细胞依赖的抗肿瘤免疫反应方面显示出显著的疗效[109-110]。MDM2抑制剂联合PD-1/PD-L1免疫检查点抑制剂使用可协同解除肿瘤免疫抑制微环境，增强机体全身性抗肿瘤免疫应答，抑制肿瘤远处转移与复发[111]。一项I期临床试验(NCT03964233)显示，Brigimadlin联合免疫检查点抑制剂不仅能有效诱导MDM2扩增的脂肪肉瘤细胞凋亡，还能显著促进肿瘤细胞表面MHC-I的表达，并促进T细胞向肿瘤核心区域的浸润；更重要的是，Brigimadlin联合免疫检查点抑制剂可协同促进T细胞活化，并增强抗肿瘤免疫应答[111-112]。此外，APG-115通过激活肿瘤微环境中免疫细胞的p53，实现巨噬细胞M2向M1重编程，增强T细胞活化，上调肿瘤细胞PD-L1。这一机制为APG-115与PD-1抑制剂联合应用提供了理论基础，其协同效应不依赖于

肿瘤细胞自身的p53状态[113]。因此, PD-1抑制剂与靶向p53-MDM2轴的联合策略, 在克服免疫逃逸方面展现出重要的临床转化潜力[111]。

综合前文各节所述, 联合治疗策略通过多机制、多靶点的协同作用, 在增强抗肿瘤疗效、降低毒性反应、延缓耐药发生及扩大适用人群等方面具有显著优势, 是推动靶向p53-MDM2信号轴策略从基础研究走向临床实践的关键路径, 展现出重要的科研价值与广阔的临床转化前景。然而, 最佳联合策略的确定及适用患者群体的识别, 仍有赖于严格的分子分层策略及大型随机对照试验的进一步验证。表7归纳总结了上述靶向p53-MDM2信号轴的联合治疗策略。

3 在肿瘤治疗中靶向p53-MDM2信号轴的挑战

在肿瘤治疗中靶向p53-MDM2信号轴的治疗策略虽已取得重要进展, 但相关靶向药物在临床转化阶段仍面临严峻挑战, 严重制约了其大规模临床普及与长期安全应用。

3.1 肿瘤固有生物学限制

靶向p53-MDM2信号轴的有效性严格依赖于肿瘤细胞携带*TP53*野生型基因且伴有MDM2扩增或过表达。然而, 约50%的人类恶性肿瘤携带*TP53*基因的体细胞突变, 这些突变通常导致p53蛋白功能部分或全部丧失, 甚至可能获得新的致癌功能, 不同的突变位点和构象可能对小分子抑制剂的敏感性产生显著影响[7,114-115]。与此同时, 临床肿瘤患者存在高度异质性, 多数晚期肿瘤伴随*TP53*突变、缺失或功能失活, 部分肿瘤存在MDMX共扩增、p53旁路抑制通路异常激活等代偿特征, 因此无论单药还是联合疗效均有限。此外, 原发灶与转移灶之间, 以及治疗过程中肿瘤亚克隆的动态演变所导致的基因表达异质性, 使得联合疗效难以稳定, 无法实现广谱抗肿瘤应用。

3.2 剂量限制性血液毒性

MDM2抑制剂通过稳定野生型p53, 在肿瘤细胞中恢复抑癌功能, 但同样可在正常造血祖细胞和巨核细胞谱系中激活p53-p21轴, 从而抑制巨核细胞分化、多倍体化和前血小板形成, 并诱导造血干/祖细胞凋亡。因此, MDM2抑制剂在临床应用中普遍伴随显著的血液学毒性, 如血小板减少症, 其机制主要涉及巨核细胞生成的全过程抑制、骨髓微环境中广泛造血祖细胞损伤以及造血干细胞区的凋亡与克隆选择3个层面。

首先, p53激活抑制巨核细胞分化。巨核细胞的正常生成是血小板形成的前提。MDM2抑制剂通过稳定p53, 在巨核细胞发育的早期阶段即可诱导$CD34^+$造血祖细胞向巨核系分化的能力受损。体外研究显示, RG7112处理后巨核细胞集落形成单位减少约40%, 同时超过三分之二的巨核前体细胞发生凋亡[116]。在巨核细胞发育的晚期阶段, MDM2抑制剂通过p53-p21轴抑制巨核细胞的多倍体化和前血小板形成, 导致成熟巨核细胞数量减少、血小板释放障碍[117]。其次, p53介导的骨髓造血抑制。MDM2抑制剂诱导的p53激活并非仅选择性地影响巨核系, 而是广泛抑制红系、髓系及巨核系等多条造血谱系。动物实验及临床试验均证实, Nutlin、RG7112、Navtemadlin等药物在引起血小板减少的同时, 常伴有中性粒细胞数量减少及轻度贫血症状, 提示其对骨髓造血的抑制是全系性的。一项涵盖10种MDM2抑制剂共18项临床研究的系统综述指出, 血细胞减少是该类药物最为普遍的剂量限制性毒性[118]。最后, p53诱导造血干细胞凋亡与克隆性造血。更为根本的是, MDM2抑制剂对最原始的造血干细胞室也具有直接毒性。p53的激活可在造血干/祖细胞中诱导凋亡, 导致治疗相关的持续性血细胞数量减少。一篇2025年发表于*NPJ Precision Oncology*的病例报道显示, 部分患者在停药后仍出现长期全血细胞数量减少, 其外周血及骨髓中可检测到多达20种不同的*TP53*致病突变, 提示MDM2抑制剂可驱动*TP53*突变的克隆性造血, 这一现象可能增加继发性髓系恶性肿瘤的长期风险, 因此对长期用药的安全性提出更高要求[119]。

上述机制在多个进入临床试验的MDM2抑制剂中得到了反复验证。比如, 在Navtemadlin的一项I期实体瘤/多发性骨髓瘤试验中, 39例剂量递增队列中有3例患者出现剂量限制性毒性[118]。为平衡抗肿瘤疗效与血液学毒性, 间歇性给药及脉冲式给药已成为MDM2抑制剂临床开发中的主流策略。但仍需通过新药开发、联合支持治疗及精准患者筛选等策略进一步突破, 以推动该类靶向药物从概念验证走向真正的临床获益。

3.3 原发与获得性耐药

肿瘤细胞对MDM2抑制剂的耐药机制复杂, 主

表7 靶向p53-MDM2信号轴的联合治疗策略

Table 7 Combined therapeutic strategies targeting the p53-MDM2 axis

联合治疗策略 Combination strategy	靶点/通路 Target/pathway	代表性药物组合 Representative drug combination	作用机制和临床研究进展 Mechanism of action and clinical progress
Combination chemotherapy	Hypomethylating agents	APR-246+Azacitidine	APR-246 is a first-in-class small-molecule p53 reactivator that modulates cellular redox homeostasis and induces apoptosis and ferroptosis in tumor cells through covalent modification of mutant p53. A pooled analysis of two phase II trials included 100 patients with *TP53*-mutated high-risk myelodysplastic syndromes or acute myeloid leukemia with myelodysplasia-related changes. The overall response rate was 69%, with a complete remission rate of 41%, a median duration of complete remission of 10.2 months, and a median overall survival of 11.8 months. The combination was well tolerated
Combination chemotherapy	DNA-damaging agents	Navtemadlin+Cytarabine	Relief of MDM2-mediated inhibition of p53 potentiates the p53 signaling induced by DNA-damaging chemotherapy and drives tumor cells toward apoptosis. A clinical study showed that navtemadlin monotherapy induced death in only a subset of tumor cells, whereas its combination with cytarabine markedly enhanced apoptosis without affecting normal bone marrow cells. Upregulation of oligodendrocyte differentiation has been proposed as a mechanism of drug tolerance or resistance
Combination with inhibitors targeting complementary pathways	CDK4/6 inhibitors	Siremadlin+Ribociclib	The combination of Siremadlin and Ribociclib simultaneously blocks the p53-MDM2 signaling axis and the CDK4/6 pathway, thereby synergistically suppressing tumor proliferation. Clinical studies (NCT02343172 and NCT04116541) have demonstrated promising clinical activity for siremadlin combined with CDK4/6 inhibition in MDM2-amplified liposarcoma
Combination with inhibitors targeting complementary pathways	PARP inhibitors	Siremadlin+Olaparib	Combination screening of 22 agents identified marked synergistic activity. Among the combinations examined, Siremadlin plus Olaparib significantly increased DNA damage and induced cell death in *TP53*-wild-type rhabdomyosarcoma models. The proposed mechanism involves concurrent inhibition of MDM2 and PARP, resulting in dual disruption of the DNA-damage response and synergistic induction of cell death in tumors harboring wild-type p53
Combination with immune checkpoint inhibitors	Immune checkpoint inhibitors	Brigimadlin+Ezabenlimab	Combining an MDM2 inhibitor with a PD-1/PD-L1 immune checkpoint inhibitor can synergistically reverse the immunosuppressive tumor microenvironment, enhance systemic antitumor immune responses, and suppress distant metastasis and recurrence. Brigimadlin combined with an immune checkpoint inhibitor has entered phase I clinical evaluation. The results showed that this combination not only effectively induced apoptosis in MDM2-amplified liposarcoma cells but also significantly increased MHC class I expression on the tumor-cell surface and promoted T-cell infiltration into the tumor core
Combination with immune checkpoint inhibitors	Immune checkpoint inhibitors	APG-115+an immune checkpoint inhibitor	By activating p53 in immune cells within the tumor microenvironment, APG-115 promotes macrophage reprogramming from the M2 to the M1 phenotype, enhances T-cell activation, and upregulates PD-L1 expression in tumor cells. It synergizes with PD-1 inhibition to enhance antitumor immunity, and this effect is independent of the intrinsic p53 status of the tumor. A phase Ib/II clinical trial involving patients with metastatic or advanced solid tumors has been initiated (NCT03611868)

要分为原发性与获得性耐药两方面。原发性耐药主要源于*TP53*突变状态。MDM2抑制剂通过阻断p53与MDM2结合来稳定并激活p53, 其疗效严格依赖于肿瘤细胞携带野生型*TP53*基因。约50%的人类恶性肿瘤存在*TP53*体细胞突变, 这些患者对MDM2抑制剂存在天然的原发性耐药。

获得性耐药机制更为复杂, 主要包括*TP53*获得性新突变的克隆选择、MDMX代偿性过表达和旁路信号通路激活。长期暴露于MDM2抑制剂可诱导*TP53*野生型细胞出现携带*TP53*突变的耐药亚克隆[120]。在Siremadlin耐药模型中, 54%的复发肿瘤出现Trp53获得性功能缺失突变[121]。MDMX过表达可在MDM2被抑制时代偿性抑制p53, 转座子筛选发现, MDMX功能获得性改变是Siremadlin获得性耐药的核心机制之一[121]。此外, 耐药肿瘤中常出现Bcl-xL过表达及ΔNTrp63/ΔNTrp73上调, 拮抗p53功能; *MDM2*基因扩增可直接绕过药物阻断[121]。

肿瘤微环境中的细胞和因子也可能参与耐药性的形成, 影响靶向治疗的效果。一项研究结果显示, 在野生型p53肺腺癌中, MDM2/MDMX过表达通过抑制p53活性促进肿瘤细胞的增殖, 进而影响肿瘤微环境中免疫细胞的功能, 最终导致免疫逃逸[122]。综上, MDM2抑制剂的耐药机制涉及*TP53*突变、MDMX代偿及旁路激活等, 深入理解这些机制并开发联合策略, 是推动该类药物从概念验证走向临床获益的关键。

3.4 药代动力学与药物递送瓶颈

MDM2抑制剂多为口服小分子, 半衰期偏短、体内清除较快, 在体内的代谢稳定性、口服生物利用度及肿瘤组织渗透效率尚不理想。虽然RG7388等第二代药物在药代动力学方面较RG7112有所提升, 但临床试验中仍需通过间歇性给药方案来平衡血药浓度与血液学毒性, 给药策略的复杂性增加了临床实施的难度[123]。此外, MDM2抑制剂难以有效透过血脑屏障, 限制了其在胶质母细胞瘤等颅内肿瘤中的应用[124]。

3.5 临床精准分层与疗效预判的困难

现阶段临床筛选主要依赖*TP53*状态和MDM2扩增这两个单一生物标志物, 但这远不足以全面反映肿瘤的复杂性, 缺乏高效、便捷、可普及的伴随诊断生物标志物体系, 无法精准预判患者是否适合p53-MDM2联合治疗[125]。一旦肿瘤细胞通过激活旁路代偿通路或富集肿瘤干细胞来产生继发性耐药, 缺乏动态监测疗效与早期预警耐药的实时分子标志物, 临床往往无法及时察觉并调整治疗方案, 从而错失最佳干预时机, 并给患者带来不必要的经济和身体负担。因此, 急切需要开发更精准的伴随诊断体系及动态监测耐药发生的分子标志物。

4 展望

经过多年的靶点验证、化合物筛选及临床试验探索, 针对p53-MDM2信号轴的药物研发已积累了大量经验与教训。该领域正处于从“概念验证”向“临床转化”过渡的关键时期, 众多III期研究的阴性结果及剂量限制性毒性难题深刻揭示了传统MDM2小分子抑制剂的固有局限。人工智能驱动的药物研发、靶向蛋白降解技术、免疫联合疗法及基于*TP53*分型的精准医疗构成了该领域重要的4个研究方向。

4.1 人工智能驱动的药物研发

传统MDM2抑制剂的研发高度依赖高通量筛选及基于结构的药物设计, 该过程周期长、成本高, 且易出现选择性差、毒性偏大、成药性不佳等问题, 严重制约新药迭代效率。人工智能的介入正在从以下方面重塑MDM2抑制剂的研发模式。首先, 机器学习优化虚拟筛选的准确性。在一项2025至2026年的研究中, 研究者建立了一套以机器学习为基础的结构虚拟筛选框架, 其通过蛋白质–配体扩展连接性指纹结合随机森林和支持向量机模型, 在MDM2抑制剂识别中展现出优于传统打分函数的预测性能, 可显著降低假阳性率[126]。其次, 多尺度药物重定位发掘新化学实体。药物重定位策略可从已上市或临床阶段化合物中发现MDM2抑制剂。一项研究借助选择性清洗算法, 从超过24 000种临床测试分子中筛选出两种1型大麻素受体拮抗剂以及他汀类药物阿托伐他汀, 作为靶向MDM2的重定位候选药物, 其对MDM2的预测结合亲和力与Navtemadlin相当, 部分化合物还可作用于MDM4和Bcl-2以协同促进p53功能恢复[127]。最后, AI驱动的多靶点协同抑制剂被发现。2026年发表的研究通过整合机器学习QSAR模型与分子模拟管道, 首次从真菌代谢组中筛选出了多种具有MDM2和CDK4双重高亲和力的新型先导化合物, 为p53/Rb通路共失调的肿瘤治疗提供了理论可行的双靶点干预策略[128]。

4.2 靶向蛋白质的降解疗法

传统MDM2小分子抑制剂通过阻断p53与MDM2蛋白相互作用来稳定p53, 但易受肿瘤代偿通路干扰, 且患者长期用药易产生耐药。PROTAC通过同时结合目的蛋白和E3泛素连接酶, 诱导靶蛋白经泛素–蛋白酶体系统降解, 可从根本上打破这一限制。MD-4251是首个口服有效的MDM2降解剂, 在RS4;11细胞(人源B细胞前体急性淋巴细胞白血病的

经典研究模型)中的半数降解浓度为0.2 nmol/L, 2 h内最大降解率达96%, 单次给药即可诱导肿瘤持续消退[91]。KT-253作为进入临床试验的MDM2降解剂, 其半数降解浓度达亚纳摩尔级, 阻断了急性p53-MDM2信号轴负反馈调节环路, 在急性髓系白血病异种移植模型中表现出强抗白血病活性, 充分彰显了PROTAC技术在克服耐药及负反馈调节中的变革性潜力[129]。

4.3 联合免疫疗法

传统MDM2抑制剂的疗效严格限定于*TP53*野生型肿瘤。然而, 中山大学肿瘤防治中心的研究突破了这一限制: MDM2抑制剂APG-115可通过激活肿瘤微环境中免疫细胞的野生型p53, 实现巨噬细胞M2向M1的重编程, 增强T细胞活化并上调肿瘤细胞PD-L1表达, 与PD-1抑制剂协同增强抗肿瘤免疫, 且该效应独立于肿瘤自身的p53状态[113]。这一发现使得MDM2抑制剂联合免疫检查点抑制剂可惠及p53突变型肿瘤患者。与此同时, 一项Ib/II期研究进一步验证了上述策略的临床可行性。其结果显示, 在23例可评估的晚期腺样囊性癌患者中, APG-115联合PD-1抑制剂特瑞普利单抗的客观缓解率达13%, 疾病控制率达100%; 在恶性外周神经鞘瘤、去分化脂肪肉瘤及胆道癌等多种实体瘤中也观察到初步抗肿瘤活性[130]。目前, MDM2抑制剂联合免疫治疗的临床策略正从多个药物管线并行推进。

4.4 基于*TP53*突变的精准医疗

未来的诊疗体系必须超越简单的*TP53*野生型与突变型二分法, 走向多组学整合的精细分层。临床前研究证实, *TP53*突变等位基因频率与MDM2抑制剂的敏感性呈明确负相关, 提示药物研发需将突变异质性纳入考虑[125]。另外, R175H、R248Q、R273H三大热点突变约占所有p53错义突变的35%, 研究已发现, R273H突变患者对Bcl-2抑制剂Venetoclax的敏感性提升3倍, 但伴随化疗耐药性升高, 提示需基于突变功能进行伴随诊断[131]。此外, 2026年发表于*Cell Reports*的泛癌研究对45 259份肿瘤样本进行了基因突变频率分析, 将样本分为*TP53*高突变组、伴随突变组和非突变组三类, 绘制了52种癌症中47个突变信号通路网络, 明确了精准医学的两大核心策略——单点突变特异性靶向与多点突变广谱适配性靶向, 为p53通路药物的精准患者筛选奠定了系统性的理论基础[132]。

5 结论

p53-MDM2信号轴作为肿瘤发生发展中的关键节点, 靶向p53-MDM2信号轴已成为肿瘤治疗的重要研究方向。靶向p53-MDM2信号轴的策略主要有靶向突变型p53、靶向MDM2及联合治疗, 近年来这三种肿瘤治疗策略均取得了显著进展。直接靶向突变p53领域实现里程碑突破, Rezatapopt通过特异性结合p53 Y220C突变蛋白表面裂隙恢复其转录功能, I期试验显示客观缓解率达20%, 实现了p53这一“不可成药”靶点的药理重激活。在靶向MDM2领域, Navtemadlin等传统小分子抑制剂已进入关键临床研究阶段, 但Milademetan、Brigimadlin等药物的关键研究结果提示该策略仍受到疗效不确定、剂量限制性毒性和项目开发风险的限制。尤为值得关注的是, PROTAC技术正在加速临床转化, 如MD-4251、KT-253、YX-02-030等通过诱导MDM2蛋白降解而非阻断互作来规避p53-MDM2负反馈环路的代偿性上调, 突破传统抑制剂的耐药瓶颈, 且初步临床未观察到血小板减少, 但其长期安全性和血液学毒性仍需临床持续验证。在联合治疗领域, 靶向p53-MDM2信号轴与化疗药物、其他可协同靶点抑制剂、免疫检查点抑制剂等的联用在临床试验中也展现出较好的协同抗肿瘤效果。表8对上述三类靶向策略进行了比较, 三类策略各具特点, 共同推动p53靶向治疗走向精准化与临床转化。

然而, 靶向p53-MDM2信号轴的临床转化仍存在诸多瓶颈, 包括肿瘤本身异质性、剂量限制性毒性、原发与获得性耐药等。总之, 靶向p53-MDM2信号轴的肿瘤治疗是一个极具前景但充满挑战的领域, 其巨大的潜力仍在推动研究人员不断探索新的解决方案。未来的研究方向包括: 人工智能(AI)驱动的药物研发, 机器学习与生成式AI已成功应用于MDM2抑制剂的结构优化与从头设计, 显著缩短了药物研发周期并拓宽了化学空间; PROTAC降解技术, MD-4251、KT-253等MDM2降解剂通过彻底清除MDM2蛋白, 从机制层面破解了传统抑制剂的代偿性耐药困局, 部分已进入I期临床试验; 免疫联合疗法, MDM2抑制剂联合PD-1抑制剂或靶向药物在临床前及早期临床研究中展现出了跨越p53突变状态的协同抗肿瘤活性, 扩展了MDM2抑制剂的适用人群; 基于*TP53*分型的精准医疗, 将*TP53*突变按功能分型进行精细分层, 可为疗效预判和患者筛选提

表8 靶向p53-MDM2信号轴的三大策略的比较

Table 8 Comparison of three major strategies targeting the p53-MDM2 axis

治疗策略 Therapeutic strategy	靶向突变型p53 Mutant p53 targeting	靶向MDM2 MDM2 targeting	联合治疗 Combination therapy
Core mechanism of action	Restore the wild-type transcriptional function of the mutant p53	Disrupt the p53-MDM2 interaction and relieve negative regulation, thereby activating the p53 pathway in *TP53*-wild-type cells	Target multiple pathways to achieve mechanistic complementarity and synergistic effects
Primary applicability	Tumors harboring specific p53 mutations, such as Y220C, which occurs in approximately 1% of solid tumors	*TP53*-wild-type tumors with MDM2 overexpression or amplification, including liposarcoma, myelofibrosis, and certain acute myeloid leukemias and solid tumors	The widest range of applicability, encompassing *TP53*-wild-type tumors and some tumors harboring *TP53* mutations
Key advantages	Fundamentally reverse p53 loss of function and restore its intrinsic tumor-suppressive activity; overcome the traditionally “undruggable” nature of p53 and provides precision therapies for specific mutations	Broad-spectrum applicability, broadly applicable to *TP53*-wild-type tumors; agents can be administered orally, and their clinical development is relatively advanced	Provide mechanistic complementarity, enhance antitumor activity through synergistic effects, reduce the dose-limiting toxicities associated with monotherapy, and delay the development of resistance
Major toxicities	Predominantly anemia, including grade≥3 hematologic toxicity, nausea, vomiting, and elevated transaminase levels	Pronounced dose-limiting hematologic toxicity and gastrointestinal toxicities, including nausea, diarrhea, and vomiting	The toxicity profile depends on the specific combination regimen; dosing strategies must be optimized to avoid additive toxicity
Mechanisms of resistance	Heterogeneity among different mutation types makes it difficult for a single agent to target multiple mutations	The p53-MDM2 negative-feedback loop, activation of p53-independent bypass pathways, and clonal selection	Resistance mechanisms are more complex overall, although the emergence of resistance may be delayed through multi-target coverage
Limitations	The overall population likely to benefit is limited, generalizability is poor, and drug delivery remains challenging	Dose-limiting hematologic toxicity, diverse resistance mechanisms, and short-lived and inconsistent clinical responses. Several phase III trials have failed to meet their endpoints	The optimal dose combinations, treatment sequences, and drug-drug interactions require systematic investigation. Tumor heterogeneity results in substantial variability in treatment responses, and the mechanisms of resistance are more complex

供更加精准的分子导航。多学科交叉研究将不断克服现有障碍, 提高靶向治疗在肿瘤临床中的应用效果, 为患者带来更多生存获益。

参考文献 (References)

[1] Babamohamadi M, Babaei E, Ahmed Salih B, et al. Recent findings on the role of wild-type and mutant p53 in cancer development and therapy [J]. Frontiers in Molecular Biosciences, 2022, 9: 903075.

[2] Marei H E, Althani A, Afifi N, et al. p53 signaling in cancer progression and therapy [J]. Cancer Cell International, 2021, 21(1): 703.

[3] Olivos D J, Mayo L D. Emerging non-canonical functions and regulation by p53: p53 and stemness [J]. International Journal of Molecular Sciences, 2016, 17(12): 1982.

[4] Yao Y M, Zhang Q, Li Z, et al. MDM2: current research status and prospects of tumor treatment [J]. Cancer Cell International, 2024, 24(1): 170.

[5] Hu J H, Cao J S, Topatana W, et al. Targeting mutant p53 for cancer therapy: direct and indirect strategies [J]. Journal of Hematology & Oncology, 2021, 14(1): 157.

[6] Huang J. Current developments of targeting the p53 signaling pathway for cancer treatment [J]. Pharmacology & Therapeutics, 2021, 220: 107720.

[7] Chen X H, Zhang T T, Su W, et al. Mutant p53 in cancer: from molecular mechanism to therapeutic modulation [J]. Cell Death & Disease, 2022, 13(11): 974.

[8] Nag S, Qin J, Srivenugopal K S, et al. The MDM2-p53 pathway revisited [J]. Journal of Biomedical Research, 2013, 27(4): 254-271.

[9] Ramli I, Cheriet T, Posadino A M, et al. Modulating the p53-MDM2 pathway: the therapeutic potential of natural compounds in cancer treatment [J]. Excli Journal, 2024, 23: 1397-1439.

[10] Sun S Y, Crago A. MDM2 implications for potential molecular pathogenic therapies of soft-tissue tumors [J]. Journal of Clinical Medicine, 2023, 12(11): 3638.

[11] Li H W, Cai X H, Yang X Y, et al. An overview of PROTACs targeting MDM2 as a novel approach for cancer therapy [J]. Eu-

ropean Journal of Medicinal Chemistry, 2024, 272: 116506.
[12] Timmerman D M, Remmers T L, Hillenius S, et al. Mechanisms of TP53 pathway inactivation in embryonic and somatic cells-relevance for understanding (germ cell) tumorigenesis [J]. International Journal of Molecular Sciences, 2021, 22(10): 5377.
[13] Thoenen E, Curl A, Iwakuma T. TP53 in bone and soft tissue sarcomas [J]. Pharmacology & Therapeutics, 2019, 202: 149-164.
[14] Abdullazade S, Behrens H M, Krüger S, et al. MDM2 amplification is rare in gastric cancer [J]. Virchows Archiv, 2023, 483(6): 795-807.
[15] Zhu H H, Gao H, Ji Y Y, et al. Targeting p53-MDM2 interaction by small-molecule inhibitors: learning from MDM2 inhibitors in clinical trials [J]. Journal of Hematology & Oncology, 2022, 15(1): 91.
[16] Wang H L, Guo M, Wei H D, et al. Targeting p53 pathways: mechanisms, structures, and advances in therapy [J]. Signal Transduction and Targeted Therapy, 2023, 8(1): 92.
[17] Nomura K, Klejnot M, Kowalczyk D, et al. Structural analysis of MDM2 RING separates degradation from regulation of p53 transcription activity [J]. Nature Structural & Molecular Biology, 2017, 24(7): 578-587.
[18] Li X, Gohain N, Chen S, et al. Design of ultrahigh-affinity and dual-specificity peptide antagonists of MDM2 and MDMX for P53 activation and tumor suppression [J]. Acta Pharmaceutica Sinica B, 2021, 11(9): 2655-2669.
[19] Abuetabh Y, Wu H H, Chai C, et al. DNA damage response revisited: the p53 family and its regulators provide endless cancer therapy opportunities [J]. Experimental & Molecular Medicine, 2022, 54(10): 1658-1669.
[20] Peuget S, Zhou X, Selivanova G. Translating p53-based therapies for cancer into the clinic [J]. Nature Reviews Cancer, 2024, 24(3): 192-215.
[21] Brown D W, Beatty P H, Lewis J D. Molecular targeting of the most functionally complex gene in precision oncology: p53 [J]. Cancers, 2022, 14(21): 5176.
[22] Wang J J, Liu W J, Zhang L Q, et al. Targeting mutant p53 stabilization for cancer therapy [J]. Frontiers in Pharmacology, 2023, 14: 1215995.
[23] Lemos C, Schulze L, Weiske J, et al. Identification of small molecules that modulate mutant p53 condensation [J]. iScience, 2020, 23(9): 101517.
[24] Joerger A C, Bauer M R, Wilcken R, et al. Exploiting transient protein states for the design of small-molecule stabilizers of mutant p53 [J]. Structure, 2015, 23(12): 2246-2255.
[25] Zawacka J E. p53 biology and reactivation for improved therapy in MDS and AML [J]. Biomarker Research, 2024, 12(1): 34.
[26] Dumbrava E E, Johnson M L, Tolcher A W, et al. First-in-human study of PC14586, a small molecule structural corrector of Y220C mutant p53, in patients with advanced solid tumors harboring a TP53 Y220C mutation [J]. Journal of Clinical Oncology, 2022, 40 (S16): 3003.
[27] Carter B Z, Mak P Y, Ke B, et al. Selective targeting of TP53-Y220C mutant AML by PC14586 results in TP53 wild-type conformation and synergistical apoptosis induction by concomitant inhibition of Xpo-1, MDM2, or Bcl-2 [J]. Blood, 2023, 142(S1): 2261.
[28] Poh A. Glimmers of hope for targeting p53 [J]. Cancer Discovery, 2022, 12(8): Of5.
[29] Fece de La Cruz F, Varkaris A, Patel P S, et al. Acquired on-target alterations drive clinical resistance to p53-Y220C reactivators [J]. Cancer Discovery, 2026, 16(4): 677-685.
[30] Liu Y Q, Gu W. The moving target: *cis*-mutation–driven resistance to p53-Y220C reactivator [J]. Cancer Discovery, 2026, 16(4): 620-622.
[31] Choi S H, Cho S Y, Park S Y, et al. Post-translational regulation of proto-oncogene ZBTB7A expression by p53 status in cancer cells: HSP90-dependent stabilization *vs*. p53-KLHL20-ubiquitin proteasomal degradation [J]. Biochimica et Biophysica Acta-Gene Regulatory Mechanisms, 2023, 1866(2): 194931.
[32] Liu Y J, Li C Y, Liu H W, et al. Combination therapy involving HSP90 inhibitors for combating cancer: an overview of clinical and preclinical progress [J]. Archives of Pharmacal Research, 2024, 47(5): 442-464.
[33] Martinho M S, Nancarrow D J, Lawrence T S, et al. Chaperones and ubiquitin ligases balance mutant p53 protein stability in esophageal and other digestive cancers [J]. Cellular and Molecular Gastroenterology and Hepatology, 2021, 11(2): 449-464.
[34] Duffy M J, Tang M, Rajaram S, et al. Targeting mutant p53 for cancer treatment: moving closer to clinical use? [J]. Cancers, 2022, 14(18): 4499.
[35] Miller J J, Gaiddon C, Storr T. A balancing act: using small molecules for therapeutic intervention of the p53 pathway in cancer [J]. Chemical Society Reviews, 2020, 49(19): 6995-7014.
[36] Georgakis G V, Li Y, Younes A. The heat shock protein 90 inhibitor 17-AAG induces cell cycle arrest and apoptosis in mantle cell lymphoma cell lines by depleting cyclin D1, Akt, Bid and activating caspase 9 [J]. British Journal of Haematology, 2006, 135(1): 68-71.
[37] Gossett D R, Bradley M S, Jin X, et al. 17-allyamino-17-demethoxygeldanamycin and 17-NN-dimethyl ethylene diamine-geldanamycin have cytotoxic activity against multiple gynecologic cancer cell types [J]. Gynecologic Oncology, 2005, 96(2): 381-388.
[38] Wang Y L, Wu W, Su Y N, et al. Buxus alkaloid compound destabilizes mutant p53 through inhibition of the HSF1 chaperone axis [J]. Phytomedicine, 2020, 68: 153187.
[39] Zheng Y C, Kang H Q, Wang B, et al. Curriculum vitae of HDAC6 in solid tumors [J]. International Journal of Biological Macromolecules, 2023, 230: 123219.
[40] Roszkowska K A, Piecuch A, Sady M, et al. Gain of function (GOF) mutant p53 in cancer-current therapeutic approaches [J]. International Journal of Molecular Sciences, 2022, 23(21): 13243.
[41] Olsen E A, Kim Y H, Kuzel T M, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma [J]. Journal of Clinical Oncology, 2007, 25(21): 3109-3115.
[42] Duvic M, Talpur R, Ni X, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL) [J]. Blood, 2007, 109(1): 31-39.
[43] Janku F, Park H, Call S G, et al. Safety and efficacy of vorinostat plus sirolimus or everolimus in patients with relapsed refractory hodgkin lymphoma [J]. Clinical Cancer Research, 2020, 26(21): 5579-5587.

[44] Wang Y, Janku F, Piha-Paul S, et al. Phase I studies of vorinostat with ixazomib or pazopanib imply a role of antiangiogenesis-based therapy for TP53 mutant malignancies [J]. Scientific Reports, 2020, 10(1): 3080.

[45] Matheson C J, Backos D S, Reigan P. Targeting WEE1 kinase in cancer [J]. Trends in Pharmacological Sciences, 2016, 37(10): 872-881.

[46] Kong A, Mehanna H. WEE1 inhibitor: clinical development [J]. Current Oncology Reports, 2021, 23(9): 107.

[47] Ariyoshi M, Yuge R, Kitadai Y, et al. WEE1 inhibitor adavosertib exerts antitumor effects on colorectal cancer, especially in cases with p53 mutations [J]. Cancers, 2024, 16(18): 3214.

[48] Zhang C, Zhu Y J, Ai L Y, et al. Targeting WEE1 in ARID1A/TP53 concurrent mutant colorectal cancer by exploiting R-loop accumulation and DNA repair deficiencies [J]. Advanced Science, 2026, 13(9): e12074.

[49] Zhang C, Peng K, Liu Q, et al. Abstract 2908: WEE1 as a therapeutic target in TP53 and ARID1A concurrent mutant colorectal cancers [J]. Cancer Research, 2025, 85(S1): 2908.

[50] Embaby A, Kutzera J, Geenen J J, et al. WEE1 inhibitor adavosertib in combination with carboplatin in advanced TP53 mutated ovarian cancer: a biomarker-enriched phase II study [J]. Gynecologic Oncology, 2023, 174: 239-246.

[51] Baradács I, Teutsch B, Váradi A, et al. PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials [J]. Journal of Ovarian Research, 2024, 17(1): 53.

[52] Mus'ab Theeb M, Aws Khalid A, Mahmoud Taysir M, et al. Safety and efficacy of Rucaparib in the treatment of ovarian cancer and patients with BRCA mutation: a systematic review and meta-analysis of phase III randomized clinical trials [J]. Expert Review of Anticancer Therapy, 2024, 24(1/2): 71-79.

[53] Dilmac S, Ozpolat B. Mechanisms of PARP-inhibitor-resistance in BRCA-mutated breast cancer and new therapeutic approaches [J]. Cancers, 2023, 15(14): 3573.

[54] Florencia P, Gu X, Galina F K, et al. Patient-derived tumor organoids with p53 mutations, and not wild-type p53, are sensitive to synergistic combination PARP inhibitor treatment [J]. Cancer Letters, 2024, 584: 216608.

[55] Folly-Kossi H, Graves J D, Garan L A W, et al. DNA2 nuclease inhibition confers synthetic lethality in cancers with mutant p53 and synergizes with PARP inhibitors [J]. Cancer Research Communications, 2023, 3(10): 2096-2112.

[56] Li Q, Li G Q, Li P P, et al. Twenty years of Gendicine® rAd-p53 cancer gene therapy: the first-in-class human cancer gene therapy in the era of personalized oncology [J]. Genes & Diseases, 2024, 11(4): 101155.

[57] 张珊文, 肖绍文, 刘长清, 等. 头颈鳞癌基因治疗结合放射治疗的临床研究[J]. 中华肿瘤杂志, 2005, 27(7): 426-428.
Zhang S W, Xiao S W, Liu C Q, et al. Clinical study of gene therapy combined with radiotherapy for head and neck squamous cell carcinoma [J]. Chinese Journal of Oncology, 2005, 27(7): 426-428.

[58] Zhang W W, Li L, Li D, et al. The first approved gene therapy product for cancer ad-p53 (Gendicine): 12 years in the clinic [J]. Human Gene Therapy, 2018, 29(2): 160-179.

[59] Yang Zhou J, Suwan K, Hajitou A. Initial steps for the development of a phage-mediated gene replacement therapy using CRISPR-Cas9 technology [J]. Journal of Clinical Medicine, 2020, 9(5): 1474.

[60] Idres Y M, Lai A J, Mcmillan N A J, et al. Hyperactivation of p53 using CRISPRa kills human papillomavirus-driven cervical cancer cells [J]. Virus Genes, 2023, 59(2): 312-316.

[61] Enache O M, Rendo V, Abdusamad M, et al. Cas9 activates the p53 pathway and selects for p53-inactivating mutations [J]. Nature Genetics, 2020, 52(7): 662-668.

[62] Matano M, Date S, Shimokawa M, et al. Modeling colorectal cancer using CRISPR-Cas9-mediated engineering of human intestinal organoids [J]. Nature Medicine, 2015, 21(3): 256-262.

[63] 张佳怡, 杨振宇, 陈晓芳. MDM2-p53相互作用抑制剂的研究进展和临床现状[J]. 药学进展, 2025, 49(8): 612-620.
Zhang J Y, Yang Z Y, Chen X F. Recent advances and clinical status of MDM2-p53 interaction inhibitors [J]. Progress in Pharmaceutical Sciences, 2025, 49(8): 612-620.

[64] Haronikova L, Bonczek O, Zatloukalova P, et al. Resistance mechanisms to inhibitors of p53-MDM2 interactions in cancer therapy: can we overcome them? [J]. Cellular & Molecular Biology Letters, 2021, 26(1): 53.

[65] Drakos E, Singh R R, Rassidakis G Z, et al. Activation of the p53 pathway by the MDM2 inhibitor nutlin-3a overcomes BCL2 overexpression in a preclinical model of diffuse large B-cell lymphoma associated with t(14;18)(q32;q21) [J]. Leukemia, 2011, 25(5): 856-867.

[66] Wang B, Fang L M, Zhao H, et al. MDM2 inhibitor Nutlin-3a suppresses proliferation and promotes apoptosis in osteosarcoma cells [J]. Acta Biochimica et Biophysica Sinica, 2012, 44(8): 685-691.

[67] Pishas K I, Al-Ejeh F, Zinonos I, et al. Nutlin-3a is a potential therapeutic for ewing sarcoma [J]. Clinical Cancer Research, 2011, 17(3): 494-504.

[68] Ding Q, Zhang Z, Liu J J, et al. Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development [J]. Journal of Medicinal Chemistry, 2013, 56(14): 5979-5983.

[69] Montesinos P, Beckermann B M, Catalani O, et al. MIRROS: a randomized, placebo-controlled, Phase III trial of cytarabine±idasanutlin in relapsed or refractory acute myeloid leukemia [J]. Future Oncology, 2020, 16(13): 807-815.

[70] Rendo V, Lee E Q, Bossi C, et al. A window-of-opportunity trial reveals mechanisms of response and resistance to navtemadlin in patients with recurrent glioblastoma [J]. Science Translational Medicine, 2025, 17(786): eadn6274.

[71] Concin N, Giorgi U, Van Gorp T, et al. #84 Trial in progress: a phase 2/3 study of navtemadlin as maintenance therapy in patients with advanced or recurrent endometrial cancer (EC) who responded to chemotherapy (ENGOT-En21 and GOG-3089) [J]. International Journal of Gynecological Cancer, 2023, 33: A408.

[72] Ingelshed K, Spiegelberg D, Kannan P, et al. The MDM2 inhibitor Navtemadlin arrests mouse melanoma growth *in vivo* and potentiates radiotherapy [J]. Cancer Research Communications, 2022, 2(9): 1075-1088.

[73] Verstovsek S, Al-Ali H K, Mascarenhas J, et al. BOREAS: a global, phase III study of the MDM2 inhibitor navtemadlin (KRT-232) in relapsed/refractory myelofibrosis [J]. Future Oncology, 2022, 18(2): 139-148.

[74] Dumbrava E E, Chen C T, Cote G M, et al. Abstract B034: a phase 2 basket study of the oral MDM2 inhibitor milademetan for MDM2-amplified advanced solid tumors (MANTRA-2) [J]. Molecular Cancer Therapeutics, 2023, 22(S12): B034.

[75] Koyama T, Shimizu T, Kojima Y, et al. Clinical activity and exploratory resistance mechanism of milademetan, an MDM2 inhibitor, in intimal sarcoma with MDM2 amplification: an open-label phase Ib/II study [J]. Cancer Discovery, 2023, 13(8): 1814-1825.

[76] Dinardo C D, Olin R, Wang E S, et al. Phase 1 dose escalation study of the MDM2 inhibitor milademetan as monotherapy and in combination with azacitidine in patients with myeloid malignancies [J]. Cancer Medicine, 2024, 13(14): e70028.

[77] Lorusso P, Yamamoto N, Patel M R, et al. The MDM2-p53 antagonist Brigimadlin (BI 907828) in patients with advanced or metastatic solid tumors: results of a phase Ia, first-in-human, dose-escalation study [J]. Cancer Discovery, 2023, 13(8): 1802-1813.

[78] Neldemo I, Gausi K, Sarr C, et al. Exposure-tumour growth inhibition modelling of brigimadlin using phase I solid tumour data to support phase II dose selection [J]. British Journal of Clinical Pharmacology, 2025, 91(7): 2080-2089.

[79] Schöffski P, Lahmar M, Lucarelli A, et al. Brightline-1: phase II/III trial of the MDM2-p53 antagonist BI 907828 versus doxorubicin in patients with advanced DDLPS [J]. Future Oncology, 2023, 19(9): 621-629.

[80] Stein E M, Deangelo D J, Chromik J, et al. Results from a first-in-human phase I study of Siremadlin (HDM201) in patients with advanced wild-type TP53 solid tumors and acute leukemia [J]. Clinical Cancer Research, 2022, 28(5): 870-881.

[81] Abdul Razak A R, Bauer S, Suarez C, et al. Co-targeting of MDM2 and CDK4/6 with Siremadlin and Ribociclib for the treatment of patients with well-differentiated or dedifferentiated liposarcoma: results from a proof-of-concept, phase Ib study [J]. Clinical Cancer Research, 2022, 28(6): 1087-1097.

[82] Peuget S, Selivanova G. MDM2-PROTAC versus MDM2 inhibitors: beyond p53 reactivation [J]. Cancer Discovery, 2023, 13(5): 1043-1045.

[83] Han X, Wei W Y, Sun Y. PROTAC degraders with ligands recruiting MDM2 E3 ubiquitin ligase: an updated perspective [J]. Acta Materia Medica, 2022, 1(2): 244-259.

[84] Li X, Song Y C. Proteolysis-targeting chimera (PROTAC) for targeted protein degradation and cancer therapy [J]. Journal of Hematology & Oncology, 2020, 13(1): 50.

[85] Liu Y L, Zhang X, Chen X Y, et al. Proteolysis-targeting chimera (PROTAC) nanomedicines toward cancer treatment: from synthesis to therapeutic delivery [J]. Biomaterials, 2026, 325: 123621.

[86] Han X, Sun Y. PROTACs: a novel strategy for cancer drug discovery and development [J]. MedComm, 2023, 4(3): e290.

[87] He Y T, Liao T Z, Wang X E, et al. Application of proteolysis targeting chimeric (PROTAC) technology in protein regulation and drug development [J]. Bioorganic Chemistry, 2025, 164: 108846.

[88] Sincere N I, Anand K, Ashique S, et al. PROTACs: emerging targeted protein degradation approaches for advanced druggable strategies [J]. Molecules, 2023, 28(10): 4011.

[89] Li Y B, Yang J L, Aguilar A, et al. Discovery of MD-224 as a first-in-class, highly potent, and efficacious proteolysis targeting chimera murine double minute 2 degrader capable of achieving complete and durable tumor regression [J]. Journal of Medicinal Chemistry. 2019, 62 (2), 448-466.

[90] Kandarpa M, Peterson L F, Potu H, et al. Activity of PROTAC MDM2 degrader in primary leukemia cells and PDX models [J]. Leukemia, 2026, 40(5): 918-924.

[91] Yang J, Li Y, Aguilar A, et al. Simple structural modifications converting a bona fide MDM2 PROTAC degrader into a molecular glue molecule: a cautionary tale in the design of PROTAC degraders [J]. Journal of Medicinal Chemistry, 2019, 62(21): 9471-9487.

[92] Acharyya R K, Huang L, Aguilar A, et al. MD-4251: a first-in-class oral MDM2 degrader inducing complete tumor regression with single-dose administration [J]. Journal of Medicinal Chemistry, 2025, 68(13): 13249-13267.

[93] Aguilar A, Yang J, Li Y, et al. Discovery of MD-265: a potent MDM2 degrader that achieves complete tumor regression and improves long-term survival of mice with leukemia [J]. Journal of Medicinal Chemistry, 2024, 67(21): 19503-19518.

[94] Adams C M, Mitra R, Xiao Y, et al. Targeted MDM2 degradation reveals a new vulnerability for p53-inactivated triple-negative breast cancer [J]. Cancer Discovery, 2023, 13(5): 1210-1229.

[95] He Y H, Li W, Lü D W, et al. Inhibition of USP7 activity selectively eliminates senescent cells in part via restoration of p53 activity [J]. Aging Cell, 2020, 19(3): e13117.

[96] Peng B, Jayasinghe M K, Le A H, et al. Designing nucleic acid-based therapeutics for cancer treatment: updates on the state of the art [J]. Molecular Therapy, 2026, 34(1): 68-96.

[97] Wang B, Wu S Z, Liu J, et al. Development of selective small molecule MDM2 degraders based on nutlin [J]. European Journal of Medicinal Chemistry, 2019, 176: 476-491.

[98] Li C T, Su R, Wang X Y, et al. Discovery of the oncogenic MDM2, a direct binding target of berberine and a potential therapeutic, in multiple myeloma [J]. Functional & Integrative Genomics, 2022, 22(5): 1031-1041.

[99] Lu T L, Huang G J, Lu T J, et al. Hispolon from Phellinus linteus has antiproliferative effects via MDM2-recruited ERK1/2 activity in breast and bladder cancer cells [J]. Food and Chemical Toxicology, 2009, 47(8): 2013-2021.

[100] Ramasamy T, Ruttala H B, Munusamy S, et al. Nano drug delivery systems for antisense oligonucleotides (ASO) therapeutics [J]. Journal of Controlled Release, 2022, 352: 861-878.

[101] Wang W S, Hu Y Z. Small molecule agents targeting the p53-MDM2 pathway for cancer therapy [J]. Medicinal Research Reviews, 2012, 32(6): 1159-1196.

[102] Murray J K, Gellman S H. Targeting protein-protein interactions: lessons from p53/MDM2 [J]. Biopolymers, 2007, 88(5): 657-686.

[103] Saleem A, Khan M U, Zahid T, et al. Biological role and regulation of circular RNA as an emerging biomarker and potential therapeutic target for cancer [J]. Molecular Biology Reports, 2024, 51(1): 296.

[104] Li W, Liu J Q, Chen M, et al. Circular RNA in cancer development and immune regulation [J]. Journal of Cellular and Molecular Medicine, 2022, 26(6): 1785-1798.

[105] Sun X Y, Zhao X Y, Xu Y, et al. Potential therapeutic strategy

for cancer: multi-dimensional cross-talk between circRNAs and parental genes [J]. Cancer Letters, 2024, 588: 216794.

[106] Farhadi E, Khomeijani-farahani M, Nikbakhsh R, et al. The potential role of circular RNAs in regulating p53 in different types of cancers [J]. Pathology-Research and Practice, 2024, 261: 155488.

[107] Zheng Z, Ma X Z, Li H F. Circular RNA circMDM2 accelerates the glycolysis of oral squamous cell carcinoma by targeting miR-532-3p/HK2 [J]. Journal of Cellular and Molecular Medicine, 2020, 24(13): 7531-7537.

[108] Chaudhary R, Muys B R, Grammatikakis I, et al. A circular RNA from the MDM2 locus controls cell cycle progression by suppressing p53 levels [J]. Molecular and Cellular Biology, 2020, 40(9): e00433-19.

[109] Tak E, Kim J, Han K. Abstract A056: Therapeutic evaluation of Brigimadlin and anti-PD-1 in a PBMC-co-culture model of patient-derived liposarcoma organoids [J]. Molecular Cancer Therapeutics, 2025, 24 (S10): A056.

[110] Brummer T, Zeiser R. The role of the MDM2/p53 axis in antitumor immune responses [J]. Blood, 2024, 143(26): 2701-2709.

[111] Alaseem A M. Advancements in MDM2 inhibition: clinical and pre-clinical investigations of combination therapeutic regimens [J]. Saudi Pharmaceutical Journal, 2023, 31(10): 101790.

[112] Zeng Q R, Zeng S C, Dai X F, et al. MDM2 inhibitors in cancer immunotherapy: current status and perspective [J]. Genes & Diseases, 2024, 11(6): 101279.

[113] Fang D D, Tang Q, Kong Y, et al. MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment [J]. Journal for ImmunoTherapy of Cancer, 2019, 7(1): 327.

[114] Pervushin N V, Nilov D K, Pushkarev S V, et al. BH3-mimetics or DNA-damaging agents in combination with RG7388 overcome p53 mutation-induced resistance to MDM2 inhibition [J]. Apoptosis, 2024, 29(11): 2197-2213.

[115] Wang Z, Strasser A, Kelly G L. Should mutant TP53 be targeted for cancer therapy? [J]. Cell Death and Differentiation, 2022, 29(5): 911-920.

[116] Camelia I R, Goar M, Kelli G, et al. Activation of p53 by the MDM2 inhibitor RG7112 impairs thrombopoiesis [J]. Experimental Hematology, 2014, 42(2): 137-145.e5.

[117] Fuhrken P G, Apostolidis P A, Lindsey S, et al. Tumor suppressor protein p53 regulates megakaryocytic polyploidization and apoptosis [J]. Journal of Biological Chemistry, 2008, 283(23): 15589-15600.

[118] Gluck W L, Gounder M M, Frank R, et al. Phase 1 study of the MDM2 inhibitor AMG 232 in patients with advanced P53 wild-type solid tumors or multiple myeloma [J]. Investigational New Drugs, 2020, 38(3): 831-843.

[119] Khanna V, Eslami G, Reyes R, et al. MDM2 inhibition is associated with the emergence of TP53-altered clonal hematopoiesis [J]. NPJ Precision Oncology, 2025, 9(1): 34.

[120] James A M, Matilde Y F, Stefano R, et al. TP53 gene status can promote sensitivity and resistance to chemotherapeutic drugs and small molecule signal transduction inhibitors [J]. Advances in Biological Regulation, 2025, 95: 101073.

[121] Chapeau E A, Gembarska A, Durand E Y, et al. Resistance mechanisms to TP53-MDM2 inhibition identified by *in vivo* piggyBac transposon mutagenesis screen in an $Arf^{-/-}$ mouse model [J]. Proceedings of the National Academy of Sciences of the United States of America, 2017, 114(12): 3151-3156.

[122] Wong S, Xu L, You W M, et al. Bionic power play: dual-targeting MDMX/MDM2 to reboot p53 to beat lung adenocarcinoma's immune tricks [J]. International Journal of Nanomedicine, 2025, 20: 9885-9897.

[123] Italiano A, Miller W H Jr, Blay J Y, et al. Phase I study of daily and weekly regimens of the orally administered MDM2 antagonist idasanutlin in patients with advanced tumors [J]. Investigational New Drugs, 2021, 39(6): 1587-1597.

[124] Vaubel R A, Zhang W, Oh J H, et al. Preclinical modeling of navtemadlin pharmacokinetics, pharmacodynamics, and efficacy in IDH-wild-type glioblastoma [J]. Clinical Cancer Research, 2025, 31(17): 3771-3786.

[125] Ishizawa J, Nakamaru K, Seki T, et al. Predictive gene signatures determine tumor sensitivity to MDM2 inhibition [J]. Cancer Research, 2018, 78(10): 2721-2731.

[126] Castillo Tarazona M Y, Miscione G P. Enhancing structure-based virtual screening of MDM2-p53 inhibitors: a benchmark of machine learning vs. traditional docking scoring functions [J]. Frontiers in Drug Discovery, 2026, 5: 1731262.

[127] Akmal M F, Wong M W. Selective cleaning enhances machine learning accuracy for drug repurposing: multiscale discovery of MDM2 inhibitors [J]. Molecules, 2025, 30(14): 2981.

[128] Prince Danan B, Dickson A, Lawrence Kwame N, et al. Dual-targeting MDM2 and CDK4: an integrated machine learning and molecular Simulation pipeline identifies novel fungal metabolites for cancers with co-dysregulated p53 and Rb pathways [J]. In Silico Research in Biomedicine, 2026, 2: 100340.

[129] Chutake Y K, Mayo M F, Dumont N, et al. KT-253, a novel MDM2 degrader and p53 stabilizer, has superior potency and efficacy than MDM2 small-molecule inhibitors [J]. Molecular Cancer Therapeutics, 2025, 24(4): 497-510.

[130] Guo Y, Li N, Zhang X, et al. A phase 2 study of novel MDM2 inhibitor alrizomadlin (APG-115) with or without toripalimab in patients (pts) with advanced adenoid cystic carcinoma (ACC) or other solid tumors [J]. Journal of Clinical Oncology, 2025, 43(S16): 6102.

[131] Urrutia S, Wong T N, Link D C. A clinical guide to TP53 mutations in myeloid neoplasms [J]. Blood, 2025, 146(18): 2157-2167.

[132] Ma F Y, Dong Z G. TP53-based tripartite classification reveals three distinct mutation patterns across pan-cancer [J]. Cell Reports, 2026, 45(5): 117337.