

恶性胸膜间皮瘤化疗抵抗机制研究进展

张利, 于杰, 陈瑜, 罗小迪, 汪继翠, 涂东

Research Progress on Molecular Mechanism Underlying Chemotherapy Resistance of Malignant Pleural Mesothelioma

ZHANG Li, YU Jie, CHEN Yu, LUO Xiaodi, WANG Jicui, TU Dong

Department of Cardiothoracic Surgery, the 920th Hospital of Joint Logistics Support Force, Kunming 650032, China

Corresponding Author: TU Dong, E-mail: 912836769@qq.com

Abstract: Malignant pleural mesothelioma (MPM) is a rare, highly aggressive, and lethal tumor with poor prognosis. Its survival period ranges from four months to one year, and the 5-year survival rate is only about 10%. MPM is highly resistant to chemotherapy, and conventional treatments such as cisplatin combined with pemetrexed or raltitrexed only have a certain effect in about 20% of patients. In recent years, with the continuous in-depth understanding of the genetic variation characteristics of MPM, some progress has been made in the molecular mechanism underlying the chemotherapy resistance of MPM. This article will summarize the research progress of the molecular mechanism underlying the chemotherapy resistance of MPM, including *BAP1* gene mutation, microRNA, *MTA1*-mediated DNA damage repair pathway, GATR-GITRL pathway, TGF α pathway, tumor stem cell, EGFR, and PTEN. The aim of this work is to provide a reference for exploring new therapeutic targets and combined treatment options for MPM.

Key words: Malignant pleural mesothelioma; Chemotherapy resistance; Molecular mechanism

Funding: Science and Technology Plan Project of Yunnan Province Science and Technology Department (No. 202101AY070001-303)

Competing interests: The authors declare that they have no competing interests.

摘 要: 恶性胸膜间皮瘤 (MPM) 是一种发病率不高, 但侵袭性强、预后差、致死率高的肿瘤, 生存期为4个月~1年, 5年生存率仅为10%左右。MPM具有很强的化疗抵抗性, 顺铂联合培美曲塞或者雷替曲塞的常规治疗只在20%左右患者中有一定的效果。近年来, 随着对MPM遗传特征研究的不断深入, 对MPM化疗抵抗分子机制的研究也取得一定进展。本文总结了近年来MPM化疗抵抗分子机制的研究进展, 包括*BAP1*基因突变、MicroRNA、*MTA1*介导的DNA损伤修复通路、GATR-GITRL通路、TGF α 通路、肿瘤干细胞、EGFR、PTEN等, 旨在为探索MPM新治疗靶点、新联合治疗方案提供参考。

关键词: 恶性胸膜间皮瘤; 化疗抵抗; 分子机制

中图分类号: R734.3

开放科学(资源服务)标识码(OSID):



0 引言

恶性胸膜间皮瘤 (malignant pleural mesothelioma, MPM) 是一种起源于胸膜间皮细胞恶性转化的原发肿瘤, 其发病率不高, 2020年全球新发病30 870例, 占全球恶性肿瘤的0.2%, 同时, 其造成

的死亡病例数为26 278例, 占全球恶性肿瘤死亡数的0.3%^[1]。尽管罹患率较低, 但MPM具有侵袭性强、预后差、致死率高的特点, 平均生存期为4个月~1年, 5年生存率仅为10%左右。导致MPM高致死率的主要原因之一是其极强的化疗耐药性, 目前常规疗法如顺铂联合培美曲塞或雷替曲塞只在少数患者中显示出一定效果。因此, 探究MPM耐药机制对于指导MPM治疗具有重要意义。近年来, 随着对恶性胸膜间皮瘤遗传特征的深入研究, MPM化疗耐药分子机制的探索也取得了一定进展, 包括基因突变、信号通路、MicroRNA和肿瘤干细胞等因素, 为MPM治疗开辟新途径发挥作用。未来, 通过研发能抑制MPM化疗耐药性的小分子化合

收稿日期: 2024-02-07; 修回日期: 2024-03-29

基金项目: 云南省科技厅科技计划项目 (202101AY070001-303)

作者单位: 650032 昆明, 解放军联勤保障部队第920医院心胸外科

通信作者: 涂东 (1983-), 男, 硕士, 主任医师, 主要从事胸部肿瘤系统性诊疗相关研究, E-mail: 912836769@qq.com, ORCID: 0000-0002-5505-0924

作者简介: 张利 (1967-), 男, 本科, 副主任医师, 主要从事胸部肿瘤的临床及外科治疗研究, ORCID: 0000-0002-1432-3375

物，并与传统化疗药物联合应用，有望显著提升MPM的治疗效果，延长患者生存期。

1 MPM的流行病学、诊断及治疗

1.1 流行病学

在美国，从2003—2008年间，每年新发病例超过3 000例，预计2005—2050年间将有94 000例患者^[2-3]；在中国，根据2019年肿瘤登记年报，新发病例为682例，发病率约为0.86/100万；在欧洲，英国发病率最高，达到4.3/100万^[4]；芬兰最高时达到1.5/100万；挪威最高时达到1.7/100万^[5]。恶性胸膜间皮瘤发病率呈现明显的地域差异性，这主要与不同国家石棉的生产和使用量有关，研究证实MPM的发病主要与石棉暴露有关，80%MPM患者曾暴露于石棉^[6]，尽管多个国家和地区已严禁石棉的开采、生产和应用，但MPM全球发病率仍在逐年稳步上升^[7]。

1.2 症状及诊断

MPM主要临床症状有胸腔积液、胸膜增厚，患者常在胸后外侧下部出现非胸膜炎性胸痛^[8]；约40%患者会出现呼吸困难症状，但仅有10%患者出现咳嗽；大约30%患者会出现发热、疲惫、体重减轻等症状；很少有患者出现急性呼吸困难和胸痛^[9]。目前，MPM的诊断主要结合临床表征、影像学及病理学，影像学检测主要包括CT、PET-CT等。CT可以检测胸膜是否出现弥漫性增厚、是否有胸腔积液等可疑症状，其中胸腔积液在95%的患者中检出；研究表明CT检测出的MPM肿瘤体积对于肿瘤分类更精确，也是评估总体生存率的独立预测因子^[10-12]。PET-CT常用于检测是否有远端转移^[13-14]；多个血清或组织标志物可用于MPM的诊断，如间皮素（mesothelin）、腓骨蛋白3（fibulin-3）、骨调素（osteopontin）和透明质酸（hyaluronan）等^[15-18]。miR-143、miR-210、miR-200c等microRNA在胸腔积液细胞中的表达也是常用的分子标记^[19]；外周血DNA甲基化水平可用于检测石棉暴露者MPM的早期发展阶段^[20]。

1.3 治疗

目前，MPM的治疗手段主要包括手术切除、放疗、化疗及免疫治疗等。手术切除包括胸膜切除术和胸膜外全肺切除术^[21]，其中胸膜切除术表现出较低的死亡率和并发症，较胸膜外全肺切除术死亡率降低了3.9%，并发症降低了34.1%^[22]。2021年6月，CTLA-4抑制剂伊匹木单抗联合PD-1抑制剂纳武利尤单抗获批用于不可手术切除的、初治的非上皮样恶性胸膜间皮瘤成人患者，是国内首个且目前

唯一获批的双免联合疗法。CheckMate-743研究结果显示，双免联合疗法显著延长患者的中位生存时间，与化疗相比，患者的中位生存时间从14.1个月延长到18.1个月，三年生存率从15%提高到23%，三年无进展生存率为14% vs. 1%^[23-24]。顺铂或卡铂等铂类药物联合叶酸拮抗物（培美曲塞或雷替曲塞）的一线治疗方案比单独使用铂类具有更好的整体生存率，延长生存期3个月，中位进展时间2个月，且对上皮样亚型具有最好的疗效^[25]。在此基础上，加上贝伐单抗，可以进一步延长生存期2.7个月，因此建议将顺铂、培美曲塞联合贝伐单抗作为MPM一线治疗方案^[26-28]。二线化疗方案涉及到的药物有吉西他滨、长春花碱、长春瑞滨及蒽环类药物^[29-30]。MPM的免疫疗法包括肿瘤疫苗、树突状细胞疗法、嵌合抗原受体T细胞（CAR-T）等，目前已开展了多项临床试验，并取得了一定进展^[31-33]。尽管如此，仍迫切需要探索新的治疗靶点和治疗方案。

2 MPM耐药相关基因及机制研究

由于MPM具有较强的药物抗性，导致MPM患者中位总生存期仍不足1年，五年存活率只有10%左右。因此研究MPM化疗药物抵抗的分子机制可能有助于开发新的治疗手段。如图1所示，当患者吸入的石棉纤维、自然纤维、人工纤维等危险物体到达患者胸膜后，刺激胸膜间皮细胞发生炎症反应或基因改变，从而发生恶性转化形成肿瘤；化疗、双免联合疗法等治疗具有一定的疗效，但由于MPM的超强耐药性，使得患者总体生存率仍未得到有效提高。本文总结了近年来MPM化疗抵抗分子机制的研究进展。主要包括*BAP1*基因突变、microRNA（包括miR-15a、miR-16、miR-34a、miR-379、miR-411）、DNA损伤修复通路、TGF α 通路、肿瘤干细胞、EGFR、PTEN以及其他的基因或者信号通路，见表1。

2.1 *BAP1*基因

BAP1（BRCA1 associated protein 1）属于去泛素化酶C-端水解酶超家族，在与BRCA1相关的DNA修复复合物中被发现，主要发挥去泛素化酶功能^[48-49]，在多个肿瘤中失活，包括黑色素瘤、肾癌、胆管癌等^[50]。在约60%的MPM中存在缺失或者突变造成的*BAP1*蛋白丢失^[51]，不直接影响患者生存期，而是影响患者对化疗药物的敏感度^[52]。Oehl等研究发现，*BAP1*突变或者缺失的患者对顺铂类化疗药物抗性更强，*BAP1*通过抑制化疗药物诱导

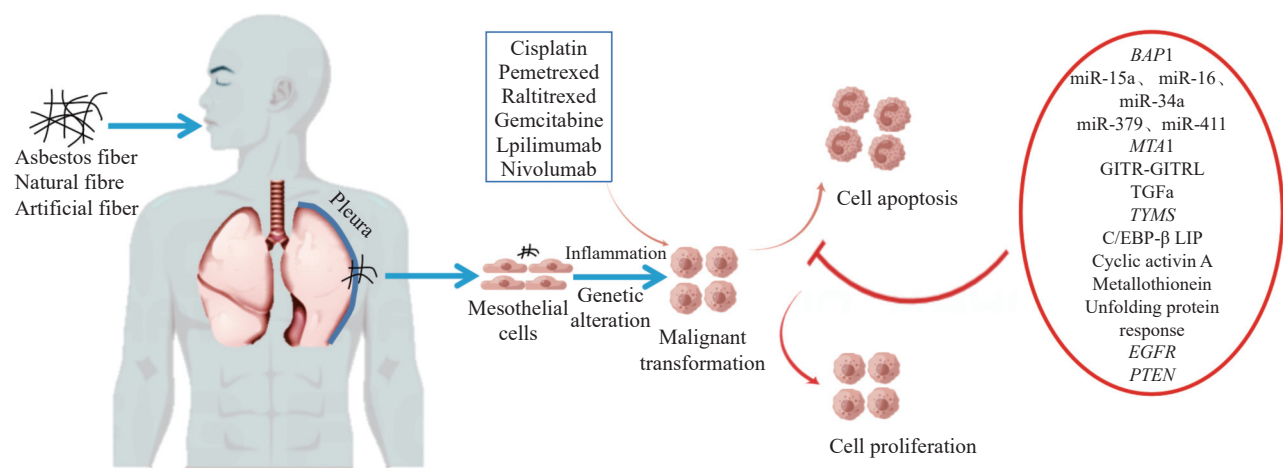


图 1 MPM化疗抵抗的分子机制模式图^[7]
Figure 1 Molecular mechanism pattern of chemotherapy resistance of malignant pleural mesothelioma^[7]

表 1 MPM化疗抵抗的基因及分子机制汇总表
Table 1 Summary of genes and molecular mechanisms underlying chemotherapy resistance of MPM

Genes or pathways	Gene status	Resistant drug	Molecular mechanism	Reference
<i>BAP1</i>	Mutation or deletion	Cisplatin	BAP1-HCF1-E2F1	Oehl, <i>et al</i> ^[34]
	Mutation or deletion	Gemcitabine	Inhibit DNA damage	Guazzelli, <i>et al</i> ^[35]
miR-15a, miR-16, miR-34a	Down-regulated	Cisplatin, Gemcitabine, Vinorelbine	Inhibit BCL-2	Williams, <i>et al</i> ^[36]
miR-379, miR-411	Down-regulated	Cisplatin, Pemetrexed	Regulate IL-8	Yamamoto, <i>et al</i> ^[37]
<i>MTA1</i>	Up-regulated	Cisplatin	Inhibit ATR-Chk1 signal	Xu, <i>et al</i> ^[38]
GTR-GITRL	Up-regulated	Cisplatin	Inhibit cell apoptosis	Chan, <i>et al</i> ^[39]
TGFa	Up-regulated	Adriamycin valproic acid	Inhibit cell apoptosis	Staumont, <i>et al</i> ^[40]
<i>TYMS</i>	Up-regulated	Pemetrexed	Up-regulated Deoxythymidylic acid	Sato, <i>et al</i> ^[41]
C/EBP-β LIP	Ubiquitination degradation	Cisplatin	Inhibit CHOP/TRB3/caspase	Kopecka, <i>et al</i> ^[42]
Circulating Activin A	Up-regulated	Cisplatin	Inhibit cell apoptosis	Paajanen, <i>et al</i> ^[43]
Metallothionein	Up-regulated	Cisplatin	Inhibit cell apoptosis	Borchert, <i>et al</i> ^[44]
Unfolding protein response	Induced expression	Cisplatin	Activate PERK/eIF2α/ATF4	Xu, <i>et al</i> ^[45]
EGFR	Up-regulated	Cetuximab	COX-2/PGE2	Cortese, <i>et al</i> ^[46]
PTEN	Down-regulated	Gefitinib Erlotinib	PI3K/AKT/mTOR	Bronte, <i>et al</i> ^[47]

的细胞凋亡及转录调节BAP1-HCF1-E2F1信号轴来抑制药物敏感度^[34]。Guazzelli等发现*BAP1*突变或者缺失的细胞对吉西他滨药物更敏感，*BAP1*主要是通过抑制吉西他滨诱导的双链断裂DNA损伤来抑制细胞对吉西他滨的敏感度^[35]。因此*BAP1*的状态可以作为MPM患者化疗效果的指标，并指导临床化疗方案的选择。

2.2 MicroRNA

MicroRNA（miRNA）是一类18~24 nt的非编码RNA，通过结合靶基因mRNA 3'-UTR来转录后调控基因表达，被证实在肿瘤中发挥重要功能。目前已发现多个miRNA与MPM的诊断、预后及治疗

有关^[53-54]。研究表明microRNA的表达与肿瘤耐药紧密相关^[55]。Williams等发现miR-15a、miR-16、miR-34a等在MPM中低表达，使MPM细胞耐受顺铂、吉西他滨、长春瑞滨等化疗药物，上调miR-15a和miR-16的表达可以逆转细胞对顺铂、吉西他滨、长春瑞滨的耐受，表达miR-34a可以逆转细胞对顺铂和长春瑞滨的耐受；表达上述miRNA可以抑制BCL-2的表达，并促进药物诱导的细胞凋亡^[36]。Yamamoto等发现miR-379和miR-411通过介导IL-18的表达来调控MPM细胞对药物的敏感度^[37]。上述研究表明，靶向miR-15a、miR-16、miR-34a、miR-379和miR-411等miRNA或许可以为MPM患者的治

疗带来新的机会。

2.3 转移相关基因1

转移相关基因1 (metastasis-associated gene 1, MTA1) 是核小体重塑和组蛋白去乙酰化复合物的的重要组成部分, 在多个肿瘤中高表达, 与肿瘤的发生、转移及化疗抵抗密切相关, 研究证实MTA1的表达与乳腺癌、鼻咽癌及宫颈癌等肿瘤的药物抵抗相关^[56-58]。Xu等前期研究发现MTA1在MPM中高表达, 并与MPM的形成及转移相关^[59]; 他们进一步研究还发现MTA1通过抑制ATR-Chk1调控的DNA损伤修复促进MPM细胞对顺铂的抵抗^[38]。这些研究表明, MTA1或许可以作为克服MPM化疗抗性的新治疗靶点。

2.4 GTR-GITRL通路

GTR (glucocorticoid-induced TNFR-related protein) 属于TNF (tumor necrosis factor) 家族, GITRL是其配体, 激活GTR可以抑制肿瘤生长、延长生存期^[60]; 放化疗可以诱导GTR表达, 并促进小鼠间皮瘤放化疗抵抗^[61]。一项涉及73例患者的研究发现, 放化疗诱导的GTR表达与肉瘤样亚型患者预后负相关, GTR-GITRL通路通过抑制细胞凋亡促进MPM药物抵抗^[39]。阻断GTR-GITRL通路可能是非上皮样间皮瘤的新治疗靶点。

2.5 TGF α 通路

TGF α (transforming growth factor alpha) 是EGFR (epidermal growth factor receptor) 的配体, 可以激活细胞增殖、分化和发育相关的信号通路, 因此在多个肿瘤中发挥重要作用。Staumont等研究发现, TGF α 在对化疗药物不敏感的细胞中高表达, RNAi抑制TGF α 可以显著提高化疗药物诱导的细胞凋亡^[40]。因此靶向TGF α 可能是MPM治疗新策略。

2.6 肿瘤干细胞

肿瘤干细胞 (cancer stem cells, CSC) 是肿瘤中的一小类细胞群, 具有自我更新和增殖能力, 被认为是肿瘤发生发展、转移、复发和药物抵抗的关键^[62]。Cortes-dericks等利用CSC标记CD133、Bmi-1、uPAR和ABCG2, 从MPM细胞系中分离肿瘤干细胞, 然后检测该类细胞群对药物的敏感度, 发现Bmi-1⁺、uPAR⁺和ABCG2⁺细胞对顺铂和培美曲塞表现出不同的药物抗性, 而CD133⁺细胞在正常间皮细胞和MPM细胞中均表现出药物抗性^[63]。

2.7 EGFR

EGFR在50%MPM患者中高表达, 这使靶向EGFR治疗MPM成为可能, 但结果却显示, 靶向EGFR的抑制剂Gefitinib、Erlotinib和单抗Cetuximab

等均没有显著的治疗效果^[64]。可能的分子机制是EGFR的表达激活MAPK通路, 进一步上调COX-2和PGE2的表达; COX-2和PGE2反过来进一步激活EGFR, 促进肿瘤细胞增殖、迁移, 从而使细胞获得抵抗能力^[65]。因此, 同时使用EGFR和COX-2抑制剂或许可作为MPM的治疗方案。

2.8 PTEN

在MPM患者中, 普遍存在PTEN基因缺失的情况, 研究表明PTEN基因表达下调或缺失使患者的预后更差。PTEN的丢失激活PI3K/AKT/mTOR通路, 提升肿瘤细胞增殖和迁移能力, 从而对靶向EGFR的抑制剂Gefitinib、Erlotinib或者单抗Cetuximab治疗产生抵抗。

2.9 其他

Sato等发现胸苷酸合成酶基因TYMS在培美曲塞抵抗的细胞中高表达, 敲低TYMS可以显著增加细胞对培美曲塞的敏感度, TYMS通过上调脱氧胸苷酸 (dTTP) 水平降低细胞对培美曲塞的敏感度, 因此dTTP水平可以作为预测MPM患者疗效的指标^[41]。Kopecka等发现C/EBP- β LIP (CAAT/enhancer binding protein- β LIP) 在顺铂耐受的细胞中被泛素化降解, 过表达C/EBP- β LIP可以激活CHOP/TRB3/caspase 3通路, 促进细胞凋亡^[42]。Paa-janen等发现循环激活素A (circulating activin A) 在MPM患者血清中明显升高, 降低MPM患者对铂类药物的反应^[43]。Borchert等发现金属硫蛋白 (metallothioneins) 的表达也能促进MPM患者的顺铂耐受, 抑制金属硫蛋白表达增加MPM细胞对顺铂的敏感度^[44]。Xu等发现内质网应激诱导的非折叠反应可以促进化疗抵抗的MPM细胞凋亡^[45]。

3 总结与展望

恶性胸膜间皮瘤是一种职业病, 多与石棉暴露相关, 虽然发病率不高, 但全球发病率仍逐年上升。MPM是一种致命的、高侵袭性的、预后差的胸部肿瘤, 患者总生存期不足1年。MPM具有很强的化疗抵抗, 顺铂联合培美曲塞或者雷替曲塞的常规治疗只在20%左右患者中有一定的效果。近年来对MPM化疗抵抗分子机制的研究取得了一定进展。对MPM的治疗提供新的思路、新的靶点及新的联合治疗方案, 如靶向激活BAP1, 靶向抑制MTA1, 过表达miR-15a、miR-16、miR-34a、miR-379和miR-411等miRNA, 靶向ATR-CHK1、靶向抑制GTR-GITRL、TGF α 等信号通路, 过表达C/EBP- β LIP等均可能是MPM的治疗新策略。

在患者接受化疗之前, 如果可以根据基因的状态、表达水平等制定出最适合的化疗方案, 将大大提高患者化疗疗效。本文中总结的多个基因或者蛋白的表达水平均可作为MPM患者化疗疗效预测指标, 如*BAP1*的状态、miR-15a、miR-16、miR-34a的表达水平、*TYMS*的表达及dTMP、C/EBP- β LIP的水平, 及血清中循环激活素A的水平等。精准的治疗方案将产生最大的疗效, 上述基因或蛋白的表达可以指导临床化疗方案的制定。

尽管MPM具有很强的化疗抗性, 目前的系统化疗方案疗效甚微, 但新的治疗手段不断出现, 如肿瘤疫苗、树突状细胞疗法、嵌合抗原受体T细胞(CAR-T)等, 目前已开展了多项临床试验, 并取得一定的进展^[44-46], 传统化疗结合新型免疫疗法, 或许会是未来MPM治疗的主要方案。

同时, MPM化疗抵抗机制研究的不断深入也为MPM治疗提供了新的治疗策略, 如果能研发出能够抑制MPM化疗抵抗的小分子抑制或者激活剂, 联合传统的化疗药物, 相信可以大大提高MPM的治疗效果, 延长患者的生存期。

利益冲突声明:

所有作者均声明不存在利益冲突。

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[编辑校对：安凤]

作者贡献：

张 利：资料收集、论文构思及撰写

于杰、陈瑜、罗小迪、汪继翠：论文修改及校对

涂 东：论文整体构思和审校