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蟾毒灵的抗癌作用机制及组学研究进展

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摘要:癌症仍是全球主要公共卫生问题,因其难治性及高致死率成为严重威胁人类健康的疾病。中药及其有效成分在治疗恶性肿瘤方面已积累大量理论基础及实践经验。蟾毒灵是从中华大蟾蜍或黑眶蟾蜍皮肤中提取分离出的一种强心苷类化合物。现代研究证明,蟾毒灵对肝癌、肺癌、结直肠癌、乳腺癌等多种肿瘤具有广谱抗癌药理活性。其抗癌机制主要包括抑制肿瘤细胞增殖、侵袭与转移、血管生成、癌细胞干性,诱导凋亡和自噬,逆转耐药、增强化疗敏感性及免疫功能。组学技术的应用与发展为研究蟾毒灵抗肿瘤机制提供新的视野和策略。因此,本综述纳入最新研究文献,更新了蟾毒灵抗癌作用机制,并首次聚焦基因组学、转录组学、蛋白质组学及代谢组学技术在蟾毒灵调控恶性肿瘤发生发展中的作用机制,围绕相关机制及组学技术开展的中医药实验成果进行总结,旨在为后续更深入的机制研究及多组学的应用提供参考和借鉴。

关键词:蟾毒灵;抗癌;作用机制;组学技术;研究进展
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Research Progress of Anticancer Mechanism and Omics of Bufalin

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Abstract:Cancer is still a major public health problem in the world,and it has become a serious threat to human health due to its refractory and high fatality rate. Traditional Chinese Medicine and its active ingredients have accumulated a lot of theoretical basis and practical experience in the treatment of malignant tumors. Bufalin is a cardiac glycoside compound isolated from the skin of Zhonghua Dachanchu(*Bufo gargarizans*) or Heikuang Chanchu(*Bufo melanostictus*). Modern studies have proved that bufalin has broad-spectrum anti-cancer pharmacological activity against liver cancer,lung cancer,colorectal cancer,breast cancer and other tumors. Its anti-cancer mechanism mainly includes inhibition of tumor cell proliferation,invasion and metastasis,angiogenesis,cancer stem cancer,induction of apoptosis and autophagy,reversal of drug resistance,enhancement of chemotherapy sensitivity and immune function. The application and development of omics technology provide a new vision and strategy for studying the anti-tumor mechanism of bufalin. Therefore,this review included the latest research literature,updated the anti-cancer mechanism of bufalin,focused on the mechanism of genomics,transcriptomics,proteomics and metabolomics technology in the regulation of bufalin in the development of malignant tumors for the first time,and summarized the anti-cancer molecular mechanism of bufalin and the experimental results of traditional Chinese medicine based on related mechanisms and omics technology. The aim was to provide reference for further mechanism research and application of multiomics.

Keywords:bufalin;anti-cancer;mechanism of action;omics technology;research progress

恶性肿瘤作为全球第2大死亡原因,其发病率与病死率持续攀升[1]。尽管放化疗仍是主流治疗手段,但化学合成抗癌药普遍存在疗效局限、不良反应大及成本高昂等问题[2]。近年来,中药活性成分因具有抑制转移、逆转耐药、调节免疫等协同抗肿瘤作用而备受关注[3-4]。

蟾毒灵($C_{24}H_{34}O_4$,PubChem CID:9547215)作为华蟾素的关键活性成分,是从中华大蟾蜍或黑眶蟾蜍皮肤中提取的甾体类强心苷[5],其化学结构式见图1。蟾毒灵是临床经典抗癌中成药华蟾素中的关键抗癌活性成分,研究表明,该化合物通过阻滞细胞周期、抑制增殖信号、诱导凋亡/自噬等机制发挥广谱抗肿瘤作用,同时可抑制血管生成和转移进程,并具有逆转耐药、增强化疗敏感性的独特优势[6-7]。尽管存在溶解性差、治疗窗窄等瓶颈,但纳米递送技术的应用为提升其生物利用度、推动临床转化提供了新策略[8]。

随着高通量技术的突破,多组学整合分析已成为解析生命复杂系统的核心策略。该技术通过基因组、转录组、蛋白质组与代谢组学等协同解析,构建分子动态网络图谱,系统阐明生

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物调控机制[9]。在肿瘤研究中,多组学技术不仅推动精准诊疗体系构建,更为中药抗肿瘤机制研究提供全新范式:从分子互作网络层面揭示活性成分的多维调控效应[10]。近年来,国内外学者们利用组学技术探索蟾毒灵抗肿瘤机制,从组学层面阐明其治疗恶性肿瘤的作用机制和关键分子靶点,为其临床转化奠定理论基础[11]。本文综述蟾毒灵抗肿瘤分子机制及组学研究进展,旨在为深度开发提供科学依据。

1 蟾毒灵抗肿瘤机制

1.1 蟾毒灵抑制肿瘤细胞增殖 蟾毒灵抑制肿瘤细胞增殖的机制主要涉及调控细胞增殖相关基因表达和阻滞细胞周期。LIU X 等[12]研究表明,蟾毒灵能够下调骨髓细胞瘤癌基因(Cellular Xyelocytomatosis oncogene,c-MYC)的表达,进而抑制胰腺癌细胞增殖,与调控缺氧诱导因子-1α(Hypoxia-inducible factor-1 alpha,HIF-1α)/基质细胞衍生因子-1(Stromal cell-derived factor-1,SDF-1)/CXC 趋化因子受体4(C-X-C chemokine receptor Type 4,CXCR 4)通路密切相关。SONG J C 等[13]发现蟾毒灵能抑制弥漫性大 B 细胞淋巴瘤的细胞增殖,且与剂量和时间呈正相关,每天腹腔注射 1.5 mg/kg 蟾毒灵可显著抑制皮下移植瘤生长,并通过调控 Ca^{2+}/核因子活化 T 细胞 1/c-MYC 轴发挥抗肿瘤活性。此外,蟾毒灵通过阻止 β-连环蛋白(β-Catenin)的核转位,下调上皮-间质转化(Epithelial-mesenchymal transition,EMT)标志物神经钙黏蛋白(N-Cadherin)和锌指 E-box 结合同源异型盒 1 基因(Zinc finger E-box binding homeobox 1,ZEB 1)表达,抑制结直肠癌(Colorectal cancer,CRC)类器官的增殖。在非小细胞肺癌中,蟾毒灵以剂量和时间依赖性方式降低受体酪氨酸激酶(Anexelekto,Axl)启动子的活性,抑制 A549 和 H460 细胞增殖[14]。此外,蟾毒灵通过抑制细胞周期蛋白依赖性激酶(Cyclin-dependent kinases,CDKs)表达,诱导多种肿瘤细胞周期停滞在 G2/M 期。在肾细胞癌中,蟾毒灵上调 p21 激活激酶 1(p21-activated kinase 1,PAK1)和 E-钙黏蛋白(E-Cadherin),下调 CDK1、细胞周期蛋白 B1(Cyclin B1)、N-Cadherin 和 HIF-1α,阻滞细胞周期于 G2/M 期[15]。在肝癌中,蟾毒灵能够诱导 G2/S 期及 G1/G0 期阻滞;在乳腺癌中,蟾毒灵调控细胞分裂周期 25A(Cell division cycle 25A,Cdc25A)和 Cdc25C 的表达和活性,阻滞细胞周期[16-17]。蟾毒灵通过调控表皮生长因子受体(Epidermal growth factor receptor,EGFR)/蛋白激酶 B(Protein kinase B,AKT)/胞外信号调节激酶(Extracellular signal-regulated Kinase,ERK)信号通路抑制卵巢癌细胞增殖[18],并通过抑制整合素亚基 β2(Integrin subunit Beta 2,ITGB 2)/局部黏着斑激酶(Focal adhesion kinase,FAK)信号通路降低细胞糖酵解,进而抑制细胞生长和增殖[19]。总体而言,蟾毒灵主要通过下调致癌基因、调节细胞周期相关蛋白的表达及调控相关信号通路来抑制肿瘤细胞增殖。

1.2 蟾毒灵诱导肿瘤细胞凋亡 细胞凋亡是基因调控下有序地细胞死亡的过程,分为内源性和外源性途径。内源性凋亡途径,即线粒体途径,常由线粒体外膜损伤和促凋亡因子释放引起,如细胞因子剥夺、DNA 损伤、活性氧(Reactive oxygen species,ROS)过载、胞质 Ca^{2+} 过量及内质网应激等因素[20]。外源性途径则多由死亡受体及其配体激活。含半胱氨酸的胱天蛋白酶(Caspase)家族和 B 细胞淋巴瘤 2(B-cell lymphoma/leukemia-2,Bcl-2)家族蛋白在凋亡中起关键作用。其中 Caspase 控制线粒体介导的凋亡级联反应,Bcl-2 家族中的 Bcl-xl 和 Bcl-2 相关 X 蛋白(Bcl-2-associated X protein,Bax)在线粒体中维持平衡,防止细胞色素 c(Cytochrome c,Cyto c)和凋亡诱导因子(Apoptosis-inducing factor,AIF)释放到胞质中,避免 Caspase 激活引发凋亡[21]。蟾毒灵主要通过线粒体途径诱导细胞凋亡。QIAN L Q 等[22]报道称蟾毒灵抑制磷酸化间充质上皮转化受体的表达,影响髓细胞性白血病序列 1、E-Cadherin、基质金属蛋白酶 9(Matrix metalloproteinase-9,MMP-9)和 Snail 锌指蛋白等凋亡相关蛋白表达,诱导胆囊癌细胞凋亡,抑制增殖、迁移和侵袭,并阻滞细胞周期于 G2/M 期。研究[23-24]表明蟾毒灵降低 Bcl-2、Bcl-xl 等抗凋亡蛋白表达,增加促凋亡蛋白 Bax、Cyto c、AIF 表达,诱导舌癌和骨癌细胞凋亡。此外,联合使用蟾毒灵能增强药物诱导的细胞凋亡。耐药性是 5-氟尿嘧啶(5-Fluorouracil,5-FU)在结肠癌化疗中的挑战,DAI X Y 等[25]发现蟾毒灵与 5-FU 联用可降低 Bcl-2 等抗凋亡蛋白的表达,上调 Bax 和 Bcl-2 相关结合蛋白(Bcl-2 antagonist of cell death,Bad),通过线粒体途径增强 5-FU 对 CRC 的细胞毒性。ROS 过载与抗癌药物诱导的细胞死亡相关,蟾毒灵能降低 NCI-H292 细胞 ROS 和线粒体膜电位,KUO J Y 等[26]研究表明索拉非尼联合蟾毒灵通过激活 ROS、线粒体和 Caspase 信号通路增强凋亡。GU R Z 等[27]研究显示,蟾毒灵联合羟基喜树碱可增加 Bax、p53、程序性细胞死亡因子 4(Programmed cell death 4,PDCD4)和糖原合成酶-3β(Glycogen synthase kinase 3β,GSK-3β)的表达,降低 Bcl-xl 和 P-Akt 表达,激活抑癌基因,通过调控线粒体凋亡、磷脂酰肌醇 3-激酶(PI3K)/Akt/GSK-3β 和 p53 依赖性细胞凋亡信号通路增强对前列腺癌的抑制。最新研究报道[28-29],蟾毒灵纳米颗粒水凝胶通过靶向 Na^+/K^+-ATP 酶泵诱导 Ca^{2+} 超载,触发细胞凋亡。LI Y 等[30]研究发现,蟾毒灵上调 Cyto c 表达,裂解 Caspase-3,诱导氧化应激引起线粒体损伤,促进细胞凋亡。然而,蟾毒灵诱导的细胞凋亡不仅仅涉及线粒体途径。据 LINGHU H R 等[31]报道,蟾毒灵能通过上调肿瘤坏死因子、TNF 受体 1 和受体相互作用蛋白 1,诱导 Caspase-8 失活,促进坏死小体形成和坏死下垂,诱导凋亡发挥抗胶质细胞瘤作用。综上所述,蟾毒灵通过调控抗凋亡和促凋亡蛋白表达、激活 Caspase 级联反应、诱导 ROS 过载和线粒体损伤,以及触发死亡受体介导的凋亡途径,发挥抗肿瘤作用。

1.3 蟾毒灵调节细胞自噬 细胞自噬作为重要的细胞稳态调控机制,通过自噬体介导的降解过程参与生存和死亡的动态平衡。蟾毒灵能够通过上调微管相关蛋白 1A/1B-轻链 3-Ⅱ(LC3-Ⅱ)/LC 3-Ⅰ的比例诱导自噬。研究[32-33]表明,蟾毒灵增加 LC 3-Ⅰ向 LC 3-Ⅱ的转化,激活 Ca^{2+}/钙调素依赖性蛋白激酶 β(Ca^{2+}/Calmodulin-dependent protein kinase kinase β,CaMKKβ)/腺苷酸激活蛋白激酶(Adenosine monophosphate-activated protein kinase,AMPK)/B 细胞淋巴瘤-2 相互作用蛋白(Bcl-2 interacting protein,Beclin 1)信号通路,诱导细胞自噬。此外,在结肠癌[34]、乳腺癌[35]中观察到类似效果。蟾毒灵不仅能通过下调 P-AKT、Cyclin D1、MMP-2/9 和血管内皮生长因子(Vascular endothelial growth factor,VEGF)抑制增殖与血管生成,还能上调同源性磷酸酶-张力蛋白(Phosphatase and tensin homolog,PTEN)和 E-Cadherin 等调控自噬抑制肝癌[36]。胃癌模型进一步揭示其通过抑制 AKT/雷帕霉素靶蛋白(Mammalian target of rapamycin,mTOR)/p70 核糖体 S6 激酶(70 kDa ribosomal protein S6 Ki-

nase,p70S6 K)通路同时激活丝裂原活化蛋白激酶(Mitogen-activated protein kinase,MAPK)/ERK信号的双重调控机制诱导胃癌细胞的保护性自噬[37]。最新剂型研究表明[38],蟾毒灵纳米载体(BA-rMSNs)可通过激活mTOR信号调控脂肪吞噬过程抑制CRC进展。这些发现系统阐明了蟾毒灵通过影响自噬相关蛋白、调控AMPK、MAPK、PI3K/AKT、mTOR等信号通路等调控自噬网络实现抗肿瘤效应的分子机制。

1.4 蟾毒灵增强免疫功能 在调节肿瘤免疫中,巨噬细胞的极化状态是当前抗肿瘤研究的热点。蟾毒灵作为新型免疫调节剂在肿瘤免疫治疗中展现出多靶点调控作用,其核心机制在于重塑肿瘤相关巨噬细胞极化状态。最新研究[39]发现,蟾毒灵通过激活核因子κB p65,抑制巨噬细胞抑制因子表达,下调M2型标志物,同时上调M1型标志物及IL-6、TNF-α等促炎因子,有效促进巨噬细胞向M1表型极化及M2表型逆转。在肝癌微环境调控中,该化合物不仅通过Wnt1/β-Catenin信号轴抑制肿瘤细胞增殖和恶性转化,还能协同增强抗PD-1抗体的治疗效果,这种协同效应源于其对肿瘤浸润性巨噬细胞表型重编程的调控,以及随之激活的核因子κB(Nuclear factor kappa-light-chain-enhancer of activated B cells,NF-κB)介导的T细胞免疫应答[40-41]。白血病模型进一步揭示其免疫增强机制:通过下调CD3/CD16/CD68等免疫调控分子,增强巨噬细胞吞噬功能,同时调节NK细胞表面受体平衡,形成多维度免疫激活网络[42-43]。总之,蟾毒灵通过调节巨噬细胞极化的核心节点,调控NF-κB、β-Catenin、Wnt1等关键信号通路,协同固有免疫与适应性免疫应答,最终实现抗肿瘤免疫增效的作用模式。

1.5 蟾毒灵减少血管生成、阻止侵袭与转移 血管生成是肿瘤细胞增殖、侵袭与转移的关键环节,抑制血管新生是肿瘤综合治疗的重要策略。肿瘤微环境(Tumor microenvironment,TME)是肿瘤血管生成条件之一。蟾毒灵通过多途径发挥显著的抗血管生成作用。WANG H J等[44]发现蟾毒灵可通过调控STAT3信号通路,下调血管内皮细胞(HUVEC)中VEGF等促血管生成基因的表达,从而抑制TME介导的血管生成。同时,多项研究[45-46]证实蟾毒灵能增强索拉非尼在HUVEC中的抗血管生成效应,二者联合通过靶向mTOR/VEGF、AKT/VEGF信号通路影响肿瘤血管微环境,发挥协同抗肝癌作用。

YUAN Z T等[47]研究显示,蟾毒灵能增强光敏剂mTHPC介导的光动力学疗法对CRC的治疗效果,主要通过抑制CRC中的类固醇受体共激活剂-3(Steroid receptor coactivator-3,SRC-3)/HIF-1α通路,从而缓解缺氧并抑制血管生成。

肿瘤侵袭与转移作为恶性肿瘤预后不良的核心因素,其关键机制涉及上皮间质转化(EMT)的调控。ZOU D等[48]研究以体内外实验证实蟾毒灵能经内皮型一氧化氮合酶(eNOS)/MAPK信号通路阻断EMT进程,从而抑制胃癌的腹膜播散。癌相关成纤维细胞(Cancer-associated fibroblasts,CAFs)促进肿瘤细胞EMT,研究显示蟾毒灵通过抑制STAT3途径可逆转CAFs介导的CRC侵袭转移[44]。在肝癌研究中,TONG Z W等[49]发现蟾毒灵通过下调转移关键调节因子SRC-1的表达,同时降低MMP-9活性,实现体内外转移的双重抑制。值得关注的是,蟾毒灵的转移抑制作用具有广谱特性,其在膀胱癌[50]、肺癌[51]等多种恶性肿瘤模型中均展现出显著的抗侵袭转移效应。

1.6 蟾毒灵逆转耐药,增强化疗敏感性 肿瘤耐药性是化疗失败和癌症病死的主要因素。当前越来越多研究表明蟾毒灵能有效逆转肿瘤多药耐药并增强化疗药物敏感性。蟾毒灵通过泛素特异性肽酶36(Ubiquitin specific peptidase 36,USP36)/c-Myc通路抑制卵巢癌对顺铂的耐药性,并通过抑制ITGB2/FAK信号通路,降低癌细胞的糖酵解,增强顺铂效果[19,52]。在乳腺癌中,蟾毒灵可抑制ATP结合盒亚家族B成员1表达,增加多西他赛在耐药细胞中的积累,提高其敏感性[53]。LIU X D等[54]研究表明蟾毒灵通过受体相互作用蛋白激酶1/ROS介导的途径诱导坏死,有效杀伤三阴性乳腺癌耐药细胞株。在结肠癌中,蟾毒灵靶向SRC-3蛋白调节M2型巨噬细胞的极化,增强奥沙利铂的抗肿瘤效果[55]。在肺癌中,蟾毒灵能够促进耐药细胞对奥希替尼的敏感性[56]。此外,蟾毒灵纳米颗粒可减轻化疗心脏毒性,并提高胰腺癌对吉西他滨和5-FU等药的敏感性[57-58]。

1.7 蟾毒灵抑制癌细胞干性 癌细胞干性指肿瘤细胞中具有干细胞特性的亚群,具备未分化、自我更新的能力及高度致瘤性[59]。现代研究已鉴定出肿瘤干细胞的表面标志物,如CD133、CD44、Lgr5等。蟾毒灵通过抑制球状体形成,降低干细胞相关蛋白SRY-box转录因子2(SRY-box transcription factor 2,SOX2)、八聚体结合转录因子4(Octamer-binding transcription factor 4,OCT4)及干性标志物表达,抑制乳腺癌[17,60]、结直肠癌[61]、胆囊癌[22]的干细胞特性。此外,肿瘤细胞的高干细胞性可诱导多药耐药。ZHAN Y P等研究[62]发现,蟾毒灵能通过调节CD133/NF-κB/MDR 1通路逆转CRC多重耐药性。以上研究凸显了蟾毒灵在抑制癌细胞干性方面的潜力。蟾毒灵的主要抗癌作用机制见插页XXXI图1。

2 组学技术在蟾毒灵抗肿瘤机制中的应用研究

2.1 基因组学

基因组学是研究基因组结构、功能、进化及相互作用的学科,涉及高通量测序(NGS)、全基因组测序(WGS)、CRISPR/Cas9基因编辑等技术[63],在揭示蟾毒灵抗肿瘤机制方面发挥重要作用。NGS分析[64]发现,蟾毒灵通过调控细胞周期和凋亡通路发挥抗肝癌作用,其中钙蛋白酶表达显著上调。基因芯片研究进一步证实,蟾毒灵可诱导HL-60和K562细胞凋亡,并调控4296个特征表达基因(2185个上调,2111个下调),涉及转录调控、非编码RNA代谢和DNA修复等过程[65-66]。表观遗传学研究揭示,蟾毒灵通过调控DNA甲基化(DNMT1、DNMT3a、DNMT3b)和组蛋白修饰影响基因表达,其中Wilm肿瘤1(Wilms´tumor 1,WT1)基因甲基化水平的上调与白血病细胞增殖抑制和凋亡诱导密切相关,此外,蟾毒灵还可通过上调miR-155-5p水平增强其化学预防效果[67-68]。综上,基因组学技术阐明了蟾毒灵主要通过调控细胞周期进程和诱导细胞凋亡发挥抗肿瘤作用,尤其在血液系统恶性肿瘤研究中取得显著进展。

2.2 转录组学

转录组学是研究细胞中基因转录的情况及转录调控规律的学科,主要分析RNA水平上的基因表达情况[69],涉及(Messenger RNA,mRNA)和非编码RNA(Non-coding RNA,ncRNA),如微小RNA(MicroRNA,miRNA)、长链非编码RNA(Long non-coding RNA,lncRNA)、环状非编码RNA(Circular RNA,circRNA)。在肿瘤学领域,miRNA的调控作用备受关注[70]。蟾毒灵通过靶向特定miRNA(如miR-155-5p[68]、miR-221[71]、miR-298[72])调控下游基因表达,诱导癌细胞凋

亡。SUN X C 等[73]研究证实上调 miR-3129 能抑制卵巢癌细胞增殖并增强蟾毒灵的化疗敏感性。CHANG Y W 等[74]研究显示,蟾毒灵靶向 miR-148a 调节 DNMT1 和 p27 可抑制骨肉瘤干细胞特性和侵袭性。此外,蟾毒灵通过调控 lncRNA 影响肝癌干细胞特性[75],抑制 SRC-1/XIST/miR-152/Kruppel 样因子 4(Kruppel-like factor 4,KLF4)信号轴可阻断胶质母细胞瘤(Glioblastoma multiforme,GBM)的增殖和球体形成能力[76],上调 circRNA(如 circ_0046264)则可抑制 NSCLC 细胞的增殖、侵袭和迁移[77]。目前,转录组学在蟾毒灵抗肿瘤作用机制的研究较少,主要运用 RNA 测序技术探索其靶向特定 miRNA 调控下游基因的机制。进而实现诱导凋亡、抑制增殖和肿瘤干性、逆转耐药等抗癌效果。

2.3 蛋白质组学 蛋白组学研究生物体中全部蛋白质的组成、结构、功能和动态变化规律,涉及蛋白质的分离、鉴定、定量和相互作用网络分析[78]。由于蟾毒灵抗癌机制不完全体现在基因表达层面,而蛋白作为基因的最终产物,为探究其抗癌机制提供重要视角。在多发性骨髓瘤(Multiple myeloma,MM)中,通过蛋白质组芯片技术鉴定出 HSP90 ATPase 活性激活因子 1(Activator of HSP90 ATPase activity 1,AHSA1)为蟾毒灵的靶点,该蛋白在 MM 患者中表达升高,与疾病复发和预后不良相关,且 AHSA1 被证实为介导 MM 细胞增殖和蛋白酶抑制剂耐药的新靶点。

PAN L J 等[79]通过类似方法发现,蟾毒灵在神经母细胞瘤中作用于线粒体内膜的电子传递链(Electron transport chain,ETC),通过破坏 ETC 诱导线粒体依赖性凋亡。CHEN G 等[80]通过人类蛋白组微阵列、生物信息学及分子对接技术筛选出蟾毒灵治疗胃癌的潜在蛋白靶点双功能凋亡调节因子(Bifunctional apoptosis regulator,BFAR),并发现其通过下调 BFAR 蛋白抑制 PI3K/AKT/mTOR 信号通路,抑制胃癌生长和转移。ZHANG D M 等[81]采用 ITRAQ 和无标记蛋白质组学分析蟾毒灵对肺癌 A549 细胞的影响,鉴定出 4799 个蛋白质,其中 45 个差异表达显著,表明蟾毒灵通过影响氧化应激和调控基因表达发挥抗癌作用,纤连蛋白相关通路是其关键作用途径。此外,多项研究[82-84]显示,蟾毒灵诱导细胞凋亡与下调热休克蛋白 27(Heat shock protein 27,Hsp27)密切相关。蛋白组学在蟾毒灵抗肿瘤机制研究中的主要思路是通过获取差异表达蛋白,筛选并鉴定蛋白靶点,并进行功能和通路分析。

2.4 代谢组学 代谢组学利用核磁共振(NMR)、液相色谱-质谱(LC-MS)、气相色谱-质谱(GC-MS)等技术,结合大数据分析,研究生物体内代谢物的定性和定量变化[85],揭示蟾毒灵对肿瘤细胞代谢的影响,筛选潜在生物标志物,阐明其多靶点、多途径的抗肿瘤机制。SHI S L 等[86]通过非靶向代谢组学发现,蟾毒灵可调节肺腺癌(Lung adenocarcinoma,LUAD)裸鼠的脂质代谢,特别是花生四烯酸途径,筛选出 66 种差异代谢物。HUANG C J 等[87]结合转录组学和代谢组学,揭示蟾毒灵通过调控 ATP1A1/CA2 轴和甾醇调节元件结合蛋白 1(Sterol regulatory element-binding protein 1,SREBP-1)/脂肪酸合成酶(Fatty acid synthase,FASN)/乙酰辅酶 A 羧化酶(ATP citrate lyase,ACLY)信号通路抑制肝癌。LI Y 等[30]利用 DARTS-PAGE、LC-MS/MS 和分子对接等技术鉴定出膜联蛋白 A2(Annexin A2,ANXA2)和动力相关蛋白 1(Dynamin-related protein 1,DRP 1)是蟾毒灵诱导 GBM 细胞凋亡的作用靶点。脂质组学作为代谢组学的分支,专注于内源性脂质的动态变化,对细胞膜稳定性和能量供应至关重要[88]。ZHANG J H 等[89]通过 LC-MS 和质谱成像发现蟾毒灵和华蟾毒精通过干预鞘脂代谢和甘油磷脂代谢,触发凋亡并破坏生物膜,发挥协

表 1 基于组学技术的蟾毒灵抗癌机制研究进展

组学技术	肿瘤类型	主要作用机制
基因组学	肝癌[64]	钙蛋白酶↑,诱导 PLC/PRF/5 细胞凋亡
	急性白血病[65]	细胞周期蛋白 CDKN 2B,CDKN 2D↑;促凋亡基因 TXNIP、CTSB、BID↑;抗凋亡基因 GADD 45、MST 4、IGBP 1↓;AP-1 和 NF-κB↑,诱导 HL-60 细胞凋亡
	慢性髓系白血病[66]	2185 个基因↑,2111 个基因↓;转录调控、非编码 RNA 代谢和 DNA 修复;靶点 BMI 1↓,诱导 K562 细胞凋亡
	红细胞白血病[67]	WT1↓,DNMT3a↑,DNMT3b↑ 抑制 HEL 细胞增殖,细胞周期停滞于 G0/G1 期,诱导凋亡
	乳腺癌[68]	miR-155-5p↑,DNMT1↓,DNMT3a↓;诱导 MDA-MB-231 和 MCF-7/ADR TNBC 细胞系细胞凋亡,增强蟾毒灵化疗敏感性
转录组学	卵巢癌[73]	miR-3129↑,CD44↓,抑制 SK-0 V-3 和 CAOV-3 细胞增殖,逆转耐药
	骨肉瘤[74]	miR-148↑,DNMT1↓,P27↓,抑制 CSCs 干性 miR-221↓,BB3↑,抑制 U-2 OS 和 Saos-2 细胞增殖,诱导凋亡
	肝癌[75]	调控 lncRNA,抑制癌细胞干性
	胶质母细胞瘤[76]	抑制 SRC-1/XIST/miR-152/ KLF4 信号轴;抑制细胞增殖和癌细胞干性
	非小细胞肺癌[77]	circ_0046264↑/miR-522-3p↓;抑制 A549 and H460 细胞增殖、侵袭与转移
	胃癌[72]	miR-298↓,靶基因 BAX↑ 抑制 MGC 803 和 SGC 7901 细胞增殖,诱导凋亡
蛋白组学	神经母细胞瘤[79]	ETC↓,ROS↑,诱导凋亡
	胃癌[80]	靶点 BFAR↓,PI3K/AKT/mTOR↓;抑制 MKN-45、HGC-27 细胞增殖与转移
	肺癌[81]	鉴定出 4799 个蛋白质,其中 45 个蛋白差异表达,调控氧化应激、基因表达调控及纤连蛋白通路,抑制 A549 细胞增殖,侵袭与转移
	骨肉瘤[82-84]	24 个差异表达蛋白,Hsp27↓,Cyto c、p-AKT、NF-κB p65↓,抑制增殖、诱导凋亡
代谢组学	胶质瘤[30]	靶点 ANXA2,DRP 1,诱导 U251 细胞凋亡
	肺腺癌[86]	筛选出 66 种差异代谢物,调控花生四烯酸途径;靶点 AKT 1、STAT 3、EGFR、CASP 3 和 SRC;调控 PI3K/AKT、FoxO1、MAPK/ERK,抑制 A549 细胞增殖,诱导凋亡
	肝细胞癌[87]	调控 ATP1A1/CA2 轴,SREBP-1/FASN/ACLY 信号通路↓ 抑制增殖和转移,调控脂质代谢
	肝癌[89-90](蟾毒灵和华蟾毒精联合)	调控鞘脂代谢、甘油磷脂代谢,诱导细胞凋亡;影响蛋氨酸代谢、脂质代谢和氨基酸代谢,阻断 HepG2 细胞周期,诱导凋亡

同抗癌作用。另一研究[90]结合代谢组学和脂质组学,发现这两种化合物影响蛋氨酸代谢、脂质代谢、能量代谢和氨基酸代谢等途径,诱导凋亡并阻断细胞周期,协同发挥抗肿瘤作用。总体而言,代谢组学在蟾毒灵抗癌研究中主要采用非靶向代谢组学,部分结合转录组学或脂质组学,揭示其通过调节脂质代谢等途径,参与多种生物学过程和信号通路,发挥抗癌作用。基于组学技术的蟾毒灵抗癌机制的研究进展具体内容详见表 1。

3 总结与展望

蟾毒灵作为一种具有多靶点特性的天然抗肿瘤药物,在肺癌、乳腺癌、胃癌等实体肿瘤中展现出显著疗效。其作用机制涉及抑制肿瘤增殖转移、诱导凋亡自噬、调节免疫微环境、逆转耐药及抑制肿瘤干细胞活性等多个层面。近年来,组学技术的应用为解析蟾毒灵的抗癌机制提供了新视角,从动态性、整体性、系统性的角度阐明其作用机制中的基因、转录本、蛋白质、代谢物等差异生物标志物及其互作网络,为精准化、客观化地揭示蟾毒灵抗肿瘤作用提供了科学依据。

当前研究仍存在以下关键问题亟待突破:1)转录组学研究需加强基于 RNA - seq 和高通量测序的差异表达 RNA 筛选及功能验证[91];2)基因组学研究应从差异基因筛选向靶点机制验证深化;3)现有单一组学研究需向多组学整合联合应用转变,筛选抗癌靶点,优化药理和药效学研究对蟾毒灵抗癌机制的明确具有重要意义;4)海量组学数据的解析需引入机器学习及深度学习等 AI 技术[92],建立智能分析平台;5)现有研究过度依赖体外及动物模型,其结论与人体实际效果尚存在差异,仍需开展规范化临床试验验证其临床转化潜力,尤其需重视基于多组学技术筛选的生物标志物在人体中的动态验证,建立“分子机制 - 临床表型”的可靠关联。

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蟾毒灵的抗癌作用机制及组学研究进展

（正文见 125－131 页）

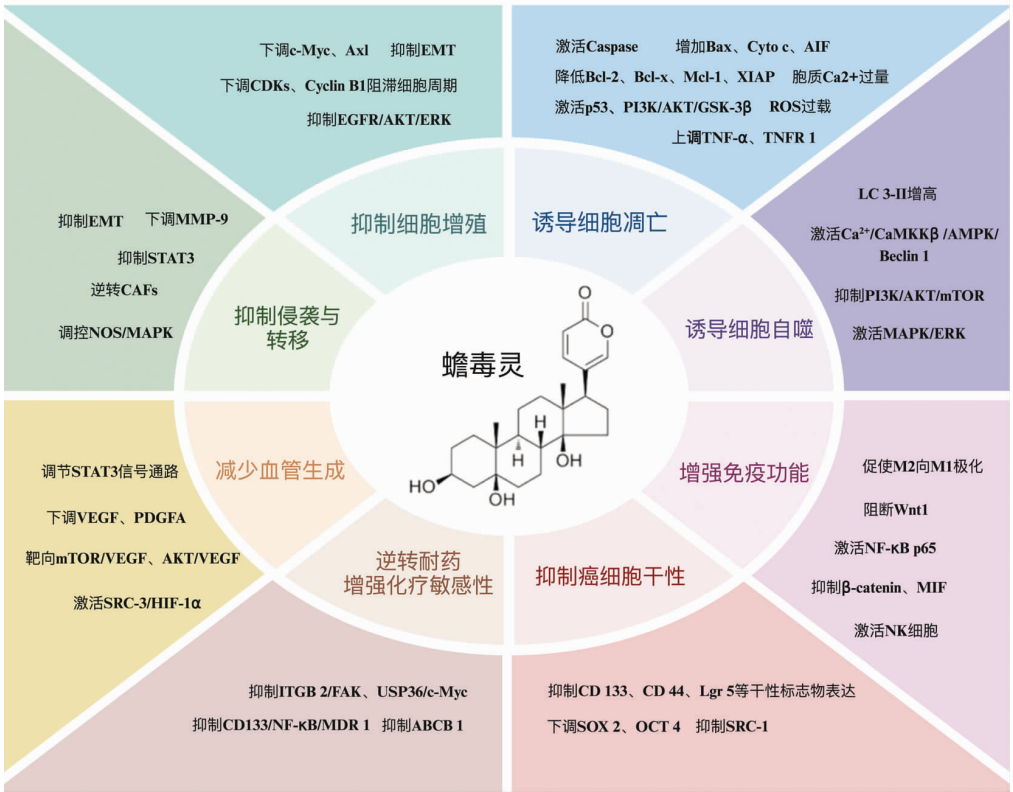


图 1　蟾毒灵的主要抗肿瘤机制

不同炮制方法对厚朴化学成分和药理作用的影响研究

（正文见 211－216 页）

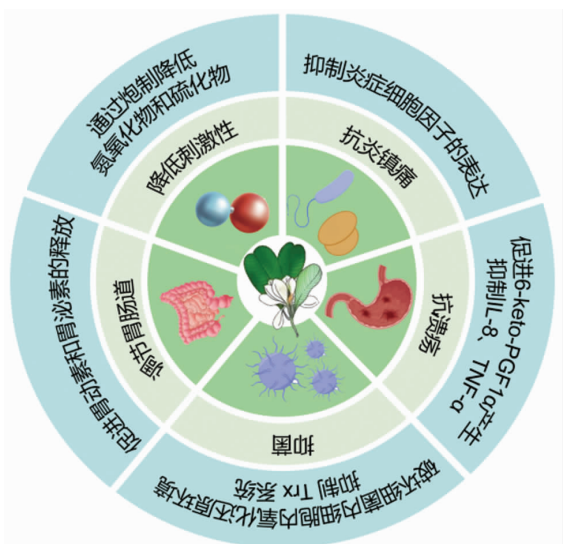


图 2　厚朴的药理作用及其作用机制