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砷化合物抗肿瘤多药耐药性作用及作用机制研究进展

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摘要:目的 探讨砷化合物抗肿瘤多药耐药性(MDR)的作用及作用机制。方法 查阅相关文献,分别从细胞、分子、基因水平,以及相关通路阐述砷化合物抗肿瘤MDR的作用及作用机制。结果 三氧化二砷(ATO)联合维生素C、雄黄转化溶液(RST)均可抑制耐药性肿瘤细胞血管再生和转移;ATO、负载紫杉醇的亚砷酸钆纳米颗粒、ATO与阿霉素联用均可抑制耐药性肿瘤细胞侵袭和迁移;ATO、口服纳米硫化砷均可诱导肿瘤MDR细胞发生自噬。ATO、RTS、ATO-As₄O₆-顺铂的组合、白藜芦醇(RSV)和ATO联用,丁硫氨酸亚砷亚胺与ATO联用,As₄S₄均可抑制耐药相关蛋白的表达。ATO可抑制耐药酶谷胱甘肽S转移酶和DNA拓扑异构酶II的表达;ATO与阿霉素联用可下调Stathmin表达。ATO、ATO联合RSV,As₄S₄均可抑制凋亡控制基因表达;ATO、ATO联合RSV均可抑制核因子κB;RST可下调MDR1基因;载有砷的双重药物(阿霉素和ATO)纳米药物系统协同DNA损伤和干预DNA修复。ATO、亚砷酸、亚砷酸钠、加马布他汀和p38丝裂原活化蛋白激酶抑制剂SB203580均可激活膜受体酪氨酸蛋白激酶信号传导途径(RAS/RAF/MAPK);As₄S₄,As₄S₄和L-丁硫氨酸-(S,R)-亚磺酰亚胺联用,单用ATO或与磷脂酰肌醇激酶/蛋白激酶B(PI3K/AKT)信号通路抑制剂LY294002均可抑制PI3K-AKT信号通路;ATO可引发内质网应激反应;ATO可抑制Notch信号通路。结论 砷化合物能有效逆转肿瘤细胞的MDR,是极具潜力的抗肿瘤药物。

关键词:多药耐药性;肿瘤;砷化合物;作用机制

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Research Progress of Anti-Tumor Multidrug Resistance and Mechanism of Arsenic Compounds

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Abstract: Objective To investigate the anti-tumor multidrug resistance(MDR) of arsenic compounds and their mechanism. **Methods** The

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relevant literature was searched to explained the anti-tumor MDR of arsenic compounds and their mechanism from the cellular, molecular, gene level and related pathways. **Results** The combination of arsenic trioxide (ATO), vitamin C and realgar transformation solution (RST) could inhibit the angiogenesis and metastasis of drug-resistant tumor cells. ATO, hybrid paclitaxel-loaded arsenite nanoparticle (HPAN) and the combination of ATO and azithromycin could inhibit the invasion and migration of drug-resistant tumor cells. ATO and oral nano-arsenic sulfide ($ee-As_4S_4$) could induce autophagy in tumor MDR cells. The combination of ATO, RTs, ATO- As_4O_6 -cisplatin, the combination of resveratrol (RSV) and ATO, the combination of *L*-buthionine-sulfoximine and ATO, and As_4S_4 could inhibit the expression of drug resistance-related protein. ATO could inhibit the expression of drug-resistant enzyme glutathione S-transferase π and DNA topoisomerase II. The combination of ATO and adriamycin could down-regulate the expression of Stathmin. ATO, the combination of ATO and RSV, and As_4S_4 could inhibit the expression of apoptosis control apoptosis genes. ATO, the combination of ATO and RSV could inhibit nuclear factor- κ B. RST could down-regulate MDR1 gene. Nano dual-drug (azithromycin and ATO) delivery system containing arsenic could synergistically aggravate DNA damage and intervene DNA repair. ATO, arsenite, sodium arsenite, gambutatin and p38 mitogen-activated protein kinase (MAPK) inhibitor SB203580 could activate RAS/RAF/MAPK signaling pathway. As_4S_4 , the combination of As_4S_4 and *L*-butylthionine-(*S*, *R*)-sulfimide, ATO or the combination of ATO and phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) inhibitor LY294002 could inhibit the PI3K/AKT signaling pathway. ATO could induce endoplasmic reticulum stress response, and inhibit the Notch signaling pathway. **Conclusion** Arsenic compounds can effectively reverse the MDR of tumor cells, and they are potential anti-tumor drugs.

Key words: multidrug resistance; tumor; arsenic compounds; mechanism

多药耐药性(MDR)是指肿瘤细胞对一种抗肿瘤药物出现耐药性的同时,对其他多种结构不同、作用靶位不同的抗肿瘤药物也有耐药性。随着肿瘤化学治疗(简称化疗)药物在临床的广泛应用,抗肿瘤药物肿瘤耐药性问题也越来越突出,已成为化疗失败的重要原因^[1]。目前的治疗手段包括采用西药类抗肿瘤MDR药物维拉帕米、他莫昔芬、环孢素A等^[2-3],中药类抗肿瘤MDR药物三七总皂苷、白藜芦醇(RSV)、甲基莲心碱、雄黄等^[4],纳米载体药物和光动力治疗等。但抗肿瘤MDR的西药类药物毒副作用较大,不宜长期应用,且部分药物价格昂贵,限制了临床的广泛应用。研究发现,砷化合物包括有机砷化合物、三氧化二砷(ATO)、五氧化二砷、砷酸、亚砷酸、亚砷酸钠($NaAsO_2$)、硫化砷、三硫化二砷、雄黄等治疗肿瘤疗效显著,且能逆转肿瘤MDR。现对近年来砷化合物对肿瘤MDR的作用及作用机制研究进展综述如下。

1 在细胞水平对肿瘤MDR的作用及作用机制

1.1 抑制耐药性肿瘤细胞血管再生和转移

肿瘤组织依靠新生血管维持自身的营养供应,抑制肿瘤血管生成可最大限度达到“饿死肿瘤”的目的。蒋碧佳等^[5]用ATO联合维生素C对人耐药肺腺癌裸鼠移植瘤模型进行干预,发现ATO能抑制耐药性肺癌移植瘤血管内皮生长因子(VEGF)的表达,促进细胞凋亡。LIANG等^[6]研究发现,3.2 μ mol/L的ATO可显著抑制MDR白血病(K562/AO2)细胞的增殖,并下调K562/AO2细胞中VEGF的表达水平,逆转K562/AO2细胞的MDR。SONG等^[7]通过免疫组织化学染色法和藻酸盐包

封的肿瘤细胞测定法发现,雄黄转化溶液(RTS)抑制VEGF诱导的VEGFR₂和下游蛋白激酶[胞外信号调节激酶(ERK)、黏着斑激酶(FAK)、非受体酪氨酸激酶C(SRC)]的磷酸化,阻断了血管生成作用。

1.2 抑制耐药性肿瘤细胞侵袭和转移

ATO对耐药人上皮性卵巢癌细胞系(3AO/CDDP)细胞的生长抑制率呈剂量和时间依赖性,较低浓度的ATO可干扰细胞进入S/G₂期,较高浓度可选择性地诱导S期细胞凋亡,抑制3AO/CDDP的增殖和转移^[8]。陈飞研^[9]通过引入负载紫杉醇的亚砷酸钆纳米颗粒(HPAN)来克服紫杉醇的MDR。其中,紫杉醇与亚砷酸钆纳米颗粒形成棒状混合簇,由内源性无机磷酸盐促使HPAN结构崩塌,释放出紫杉醇和ATO。HPAN对耐紫杉醇的人结直肠癌细胞系(HCT166)体内抗癌试验证明,HPAN对异种移植小鼠模型中的抗性肿瘤作用优于原始紫杉醇或等剂量紫杉醇和ATO的混合物。ATO与阿霉素(ADM)联合可下调磷酸化促分裂原活化蛋白激酶(MAPK)1和 β 联蛋白(β -catenin),上调磷酸化MAPK8和上皮钙黏素,抑制耐阿霉素的人骨肉瘤(MG63/dox)细胞迁移和侵袭^[10]。

1.3 诱导肿瘤MDR细胞发生自噬

自噬可防止应激时有毒或致癌的蛋白质和细胞器积累,抑制细胞癌变。肿瘤一旦形成,自噬可为癌细胞提供更丰富的营养,促进肿瘤生长,避免药物或辐射损伤,产生耐药性^[11]。研究表明,增强自噬组织蛋白(Beclin-1)凋亡途径是克服抗癌药物耐药性的有效方法^[12]。CHENG等^[13]研究发现,ATO可作为白血病K562及其耐药株

K562/ADM 细胞中自噬的有效诱导剂,提高 K562/ADM 细胞 Beclin-1 的表达水平,降低凋亡基因 B 细胞淋巴瘤 2 (Bcl-2) mRNA 及蛋白表达水平,促进自噬细胞死亡。口服纳米硫化砷($ee-As_4S_4$)作用慢性粒细胞白血病(CML)患者骨髓中的 K562, K562/AO2 和原代细胞,发现 $ee-As_4S_4$ 可通过下调细胞内活性氧(ROS)和低氧诱导因子 1α 的水平诱导上述细胞自噬^[14]。

2 在分子水平对肿瘤 MDR 的作用及作用机制

2.1 抑制耐药相关蛋白表达

糖蛋白(P-gp)过表达是引起细胞多药耐药的主要原因^[15]。研究表明,ATO 孵育 K562/AO2 细胞 48 h 和 72 h 后,3.2 $\mu\text{mol/L}$ ATO 可显著降低 K562/AO2 细胞中 P-gp 的表达水平^[6],且 P-gp 的下调有助于降低 ATO 对抗 ADM 胃癌细胞的耐药性^[16]。1 $\mu\text{mol/L}$ ATO 处理 K562/RA 细胞 4 d 后,P-gp 的表达水平下降,荧光强度降低。提示 ATO 可通过抑制 P-gp 的表达减弱对药物的消除作用,延长 K562/D 细胞内药物的释放时间^[17]。王欣^[18]发现,RST 具有更强的靶向性,可快速、有效蓄积在耐药白血病细胞中,显著降低 K562/ADM 细胞中 P-gp 的表达水平。ATO, As_4O_6 与顺铂的组合可在耐紫杉醇的癌细胞系中产生协同作用,通过诱导切割型半胱氨酸天冬氨酸蛋白水解酶(cleaved caspase)3 的表达,抑制对紫杉醇耐药的卵巢癌细胞系的细胞生长,并诱导其凋亡^[19]。

ATO 通过下调多药耐药关联蛋白(MRP)1 的表达水平,降低膜转运蛋白活性,导致细胞内药物蓄积,抑制膀胱癌细胞(BIU-87)中 P-gp 和 MRP1 的表达,最终逆转肿瘤细胞的耐药抗药性^[20]。RSV 和 ATO 联合治疗耐阿霉素的 K562 白血病细胞,发现联合用药主要降低 P-gp, MRP1 和 B 细胞受体(BCR)耐药相关蛋白,抑制耐药白血病细胞的生长^[21]。丁硫氨酸亚砷亚胺(BSO)与 ATO 联用可通过抑制 MRP1 及其编码基因 mRNA 的表达诱导 K562/ADM 细胞凋亡^[22]。靶蛋白 SET 的表达和功能调控在对视黄酸具有抗药性的急性早幼粒细胞白血病(APL)中有潜在的治疗作用。TIAN 等^[23]研究发现, As_4S_4 诱导的凋亡伴随抗维甲酸急性早幼粒细胞白血病细胞(NB_4-R_1)中 SET 基因的 mRNA 和蛋白表达水平降低。

2.2 抑制耐药酶谷胱甘肽 S 转移酶(GST- π)和 Topo-II 表达

GST- π 是 GST 家族中关系最密切的 II 期解毒酶,主要作用包括催化药物降解,促进药物代谢,降低抗肿瘤药物的细胞毒性,其表达水平与肿瘤耐药性成正比^[24]。

DNA 拓扑异构酶(Topo) II 是人体内重要的核酸酶,参与 DNA 转录、翻译、复制、染色体分离等遗传过程,主要发生在 S-G₂/M 期。ZHAO 等^[25]研究表明,ATO 可促进耐药肿瘤细胞中 Topo-II 表达,抑制 GST- π 表达,0.8 $\mu\text{mol/L}$ 的 ATO 可通过抑制 P-gp 来提高耐阿霉素胃癌细胞(SGC7901/ADR)对 ADM 的敏感性,抑制 GST- π 表达,并增加阿霉素在 SGC7901/ADR 细胞中的积累,部分逆转 SGC7901/ADR 细胞对阿霉素的耐药性^[26]。

2.3 下调血清微管解聚蛋白(Stathmin)表达

Stathmin 作为一种新的肿瘤标志物,有多种生物学功能,与多个系统的肿瘤都有关联,并呈现高表达^[27]。ATO 与 ADM 联用通过下调 Stathmin 而逆转 MG63/dox 对阿霉素的耐药性^[28]。

3 在基因水平对肿瘤 MDR 的作用及作用机制

3.1 抑制凋亡控制基因表达

LI 等^[29]研究发现,ATO 可下调凋亡抑制蛋白生存素(Survivin)的表达水平,抑制癌细胞多药耐药性。ZAKI DIZAJI 等^[30]分析了不同阶段(诊断、缓解和复发)的 50 份外周血和 19 份骨髓样品中 Survivin 基因的表达水平,发现 ATO 抑制了 Survivin 基因的表达。同时,ATO 联合 RSV 干预 K562/RA 白血病细胞,协同抑制了 Bcl-2、核转录因子 κB (NF- κB)和 p53 的表达,增强了耐药性白血病细胞对细胞凋亡的敏感性^[21]。WANG 等^[31]研究发现, As_4S_4 通过阻断细胞周期 S 期和 G₂/M 期 NB_4-R_1 细胞发挥细胞毒性作用。流式细胞术检测结果发现,随着 As_4S_4 诱导 NB_4-R_1 细胞在 S 期和 G₂/M 期的积累, As_4S_4 通过 Bcl-2 和 BAX 的改变、Caspase-3 的激活诱导细胞凋亡。2 $\mu\text{mol/L}$ ATO 可下调 Bcl-2 的表达水平,选择性抑制对顺铂耐药上皮性卵巢癌细胞(CI80-13S)的生长,并诱导细胞凋亡^[32]。

3.2 抑制 NF- κB

NF- κB 是一种多功能的转录因子,参与调控免疫炎症、细胞增殖、分化和凋亡;也是肿瘤细胞转移和耐药性的关键调节因子。因此,控制 NF- κB 的活性将为增强肿瘤细胞化疗敏感性,逆转肿瘤细胞耐药提供新的策略^[33]。ATO 通过诱导 DNA 脱甲基化激活了 microRNA-148a(miR-148a),通过靶向 p65 的 3'-UTR 抑制了 NF- κB 途径,抑制 CSC 表现型,降低肝细胞癌(HCC)的化学耐药性^[34]。QIU 等^[35]通过免疫染色,采用免疫沉淀法和原子荧光光谱法等发现,14-3-3 η /NF- κB 反馈回路在维持肝癌耐药性表型中起重要作用,ATO 可抑制 14-3-3 η /NF- κB 反馈回路,逆转 HCC 的化学耐药性。RSV 和 ATO 联合治疗可通过抑制 NF- κB 信号通

路而诱导 K562/RA 细胞凋亡^[21]。

3.3 下调 MDR1 基因

MDR1 基因负责编码 P-gp, 其过度表达是肿瘤细胞多药耐药的主要原因。有研究表明, ATO 能抑制白血病细胞 MDR1 基因的表达, 逆转白血病耐药性^[36]。WANG 等^[37]用雄黄转化液处理 K562/ADM 细胞 4 h 后, 细胞内砷的蓄积分别比 As₄S₄ 或 ATO 处理的细胞高 2 倍和 16 倍, MDR1 mRNA 和 P-gp 的表达水平下降。RSV 通过促进 ATO 的增殖作用可增强 K562/RA 细胞对 ATO 的敏感性, 降低耐药基因 MDR1 的表达水平, 最终提高 K562/RA 细胞对细胞凋亡的敏感性^[21]。

3.4 协同 DNA 损伤和干预 DNA 修复

大多数抗肿瘤药物可直接或间接破坏肿瘤细胞的 DNA, 干扰 DNA 修复。研究表明, DNA 的损伤与原发耐药密切相关^[38]。载有砷的双重药物(阿霉素和 ATO)纳米药物系统具有显著的药物协同作用和 pH 触发药物释放, 可有效治疗抗阿霉素的肝细胞癌细胞(HuH-7/ADM)。该纳米药物系统具有阿霉素对 DNA 损伤的协同作用及 ATO 对 DNA 修复的干扰, 对抗阿霉素癌细胞产生了极高的杀伤效率^[39]。载有顺铂和 ATO 的纳米复合物经基因表达谱发现, 处理后的原癌基因和 DNA 损伤修复相关基因 MYC, MET, MSH2 的表达减少, 肿瘤抑制基因 PTEN, VHL, FAS 表达的增加, 有效地克服了肿瘤的耐药性^[40]。将人上皮性卵巢癌(EOC)细胞在 37 °C 或 39 °C 下用顺铂和 20 μmol/L NaAsO₂ 处理 1 h, 调节 DNA 损伤反应使表达 p53 的 EOC 对顺铂敏感^[41]。

4 促进耐药性肿瘤细胞凋亡的信号通路

4.1 膜受体酪氨酸蛋白激酶信号传导途径(RAS/RAF/MAPK)信号通路

RAS/RAF/MAPK 是调控细胞增殖、分化、凋亡的重要信号通路。耐药胃癌细胞具有较高的 P-gp 和 RAS 表达水平, 无毒和中等毒性的 ATO 通过 RAS/磷酸化胞外信号调节激酶(p-ERK)1/2 信号途径降低胃癌细胞对 ADM 的耐药性^[16]。低剂量(< 2 μmol/L) ATO 可通过 RAS/RAF/MAPK 信号途径上调脂肪酸合成酶(FAS)和 NM23H1 基因, 下调 N-MYC 和 MTA1 基因, 抑制人卵巢癌细胞耐药细胞的生长和增殖能力^[8]。刘宝玲^[42]通过体外试验发现, ATO 可下调 RAS/p-ERK 信号传导通路中 RAS 和 p-ERK 的表达水平, 逆转胃癌细胞耐药性。亚砷酸可异常地高度激活 p38 MAPK 通路, NaAsO₂、加马布他汀和 p38 MAPK 抑制剂 SB203580 联合对抗胶质母细胞瘤, 防止肿瘤复发和耐药性的持续发展^[43]。

4.2 磷脂酰肌醇激酶/蛋白激酶 B(PI₃K-AKT)信号通路

PI₃K/AKT 信号通路是一条酪氨酸激酶级联信号传导通路, 可促进细胞生长增殖, 参与肿瘤的发生、发展^[44], 影响细胞的增殖分化。WANG 等^[45]发现 As₄S₄ 通过抑制 AKT 和哺乳动物雷帕霉素靶蛋白(mTOR)激酶的活性而增加 As₄S₄ 诱导的细胞凋亡和自噬。As₄S₄ 和谷胱甘肽(GSH)合成酶抑制剂 L-丁硫氨酸-(S, R)-亚磺酰亚胺(BSO)联合治疗可协同抑制 PI₃K/AKT 信号逆转人乳腺癌中砷的耐药性^[46]。单独使用 ATO 或与 PI₃K/AKT 信号通路抑制剂 LY294002 联合处理急性粒细胞白血病(AML)细胞后, 黏附于基质的 AML 细胞对 ATO 的敏感性显著降低, AML 的抗药性部分消除^[47]。

4.3 内质网应激(ERS)反应

ERS 与肿瘤耐药密切相关。CHEN 等^[48]研究发现, ATO 对白血病 K562/ADM 耐药细胞有较高的凋亡诱导作用, 可明显提高内质网伴侣 78KDA 葡萄糖调节蛋白(GRP78/BIP)的表达水平。

4.4 Notch 信号通路

Notch 通路在调节干细胞增殖、分化、凋亡、黏附、耐药等方面起重要作用。研究表明, ATO 能抑制 Notch-1 的表达, 抑制 HEPG₂ 细胞的增殖和迁移^[49]。杨莉等^[50]研究发现, Notch-1 信号通路的异常, 参与了 HEPG₂/ADM 细胞耐药性的产生, 抑制 Notch-1 通路能有效抑制 HEPG₂/ADM 细胞的耐药性。

5 结语

砷化合物联用其他药物抗肿瘤 MDR 的作用机制涉及多因素、多基因、多水平、多结构的复杂过程。对于药物抗肿瘤 MDR 治疗的研究, 如 ATO 注射液通过体内外试验, 在细胞、分子和基因水平对肿瘤 MDR 疗效均较好; 在基因水平, 亚砷酸钠可调节 DNA 的损伤和修复; 在分子水平, 雄黄可诱导耐药肿瘤细胞发生自噬, 在基因水平抑制凋亡基因 Bcl-2 和 MDR1 的表达水平, 从而抑制 PI₃K/AKT 信号通路。

砷化合物联合其他药物在抗肿瘤 MDR 方面疗效更佳, 可降低毒副反应, 提高药物疗效。如 ATO 与 ADM 联合抑制耐药性肿瘤的侵袭和迁移, 下调 Stathmin; 与 RSV 联用可调节耐药性肿瘤基因的表达, 抑制 NF-κB 信号通路。As₄S₄ 与 BSO 联用抑制耐药性肿瘤的 PI₃K/AKT 信号通路, 提高治疗效果。除 ATO 和 As₄S₄ 外, 其他砷化合物临床应用范围也在扩大, 目前已有亚砷酸联合沙利度胺、维生素 C 治疗有明显耐药性的多发性骨髓瘤患者的临床疗效显著^[51]。有机砷、氯化砷、砷酸和五氧化

二砷等砷化合物抗肿瘤 MDR 的研究不断增多,但尚缺乏作用机制研究,包括药物靶标、端粒酶、HEDGEHOG 通路、骨形态发生蛋白质通路、WNT/ β -catenin 通路等。

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