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·特约综述·

克服ATP结合盒药物转运泵介导的肿瘤多药抗药性的研究进展

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摘　要:多药抗药性(MDR)是肿瘤化疗失败的主要原因。介导MDR的原因十分复杂,其中由ATP结合盒(ABC)转运泵,将抗癌药物泵出细胞外,使抗癌药物在肿瘤细胞中的积累减少,从而产生抗药性是介导MDR最常见的原因。克服MDR是肿瘤化疗领域急需解决的主要问题。本文综述ABC转运泵介导的肿瘤耐药及其逆转研究进展。

关键词:ABC药物转运泵;肿瘤化疗;多药抗药性

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Reversal of ATP Binding Cassette Transporters-mediated Multidrug Resistance in Cancer Cells: A Review

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Abstract: Multidrug resistance, MDR is main limit for successful cancer chemotherapy. The etiology of MDR is complicated. However, among of them, ATP Binding Cassett (ABC) transporters, such as ABCB1, ABCG2, ABCC1, being capable of transporting anti-cancer drug out of tumor cells, downregulating an intracellular accumulation of anticancer drug and resulting in MDR phenotype, are the most urgent cause. It is the most urgent to conquer MDR in the field of cancer chemotherapy. Here we summarized the ABC transporters-mediated MDR and its reversal.

Key words: ABC transporter; cancer chemotherapy; MDR

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因肿瘤而死亡的病人90%都与肿瘤细胞的抗药性有关，尤其是多药抗药性(multidrug resistance，MDR)。MDR是指肿瘤细胞对一种抗肿瘤药物产生抗药性的同时，对结构及作用机理不同的其他抗肿瘤药物产生了交叉抗药性。也就是说，MDR肿瘤病人不仅对已用的化疗方案无效，对其他化疗方案可能也无效，病人预后差。因此，MDR是化疗失败的主要原因，也是化疗领域急需解决的主要难题[1]。MDR的形成机制复杂，其中ABC药物转运泵(ATP Binding Cassette transporters)的过表达是介导MDR的主要原因[2]。结构上，ABC转运泵为跨膜糖蛋白；功能上，ABC转运泵如ABCB1(P-glycoprotein，P-gp)、ABCC1、ABCC2、ABCG2等将抗肿瘤药物从细胞内泵至胞外，使抗肿瘤药物于细胞内积累减少，从而产生抗药性。开发MDR逆转剂，与传统抗癌药物联合应用，恢复MDR细胞对传统抗癌药物的敏感性是克服MDR的主要策略[3]。事实上，ABC转运泵并非耐药的肿瘤细胞特有表达，在正常组织细胞如肝、肾、肠等细胞也表达ABCB1等。有人敲除小鼠的*mdr1*基因，发现小鼠的生命期无异常，这表明ABCB1并非正常生理功能所必需，同时表明抑制ABC转运泵逆转MDR策略可行[4-5]。已经或正在进行临床的有MDR逆转剂有CBT-1、Tariquidar、Zosuquidar及Br-Tetrandrine等。其中Br-Tetrandrine为中国康弘药业有限公司开发，已被CFDA批准进行临床试验。但至今，尚无MDR逆转剂开发成功并用于临床。尽管MDR逆转剂仍未用于临床，但已有四代MDR逆转剂被研究，第一代的MDR逆转剂只在体外具有逆转活性，体内无效，如维拉帕米(verapamil)；第二代MDR逆转剂不仅体外有效，而且体内也具有逆转MDR作用，但其改变了传统抗癌药物的血药动力学，因为这类MDR逆转剂常常也是P450 3A4(CYP3A4)的抑制剂。因此，可导致不可预测的毒副作用，不能用于临床，其代表物为S9788，PSC833等。我们期待开发第三代的MDR逆转剂，其特征为不仅体内外均有效逆转MDR，而且对传统的抗癌药物血药动力学无影响。其代表物为Tariquidar、Zosuquidar及Br-Tetrandrine等。所谓第四代MDR逆转剂，譬如Curcumin，是指在第三代的基础上，还能降低MDR基因的表达。第三、四代MDR逆转剂可望用于临床[2]。以下主要从我们的研究工作，包括肿瘤MDR的逆转剂及其逆转机制进行详细的阐述。

1 研究团队在肿瘤多药抗药性方面的工作简介

我们研究团队自1993年以来，一直致力于克服MDR的研究。近年来，该领域取得如下进展。

1.1 筛选ABC转运泵介导MDR逆转剂的新方法建立

建立了以钙离子探针如Fura-2/AM等的高通量、快速筛选肿瘤多药抗药性(MDR)逆转剂(表1)的新方法。发现粉防已碱、FG020326、zosuquidar等具有强的体内外逆转MDR作用且对抗癌药物血药动力学无影响，为第三代MDR逆转剂，具有开发前景。

1.2 酪氨酸激酶抑制剂(TKI)与ABC转运泵交互作用的研究

发现许多TKI药物如erlotinib、afatinib、osimertinib、lapatinib、apatinib、sunitinib、vandetanib、cediranib、AG1478等具有强的逆转ABC转运泵介导的MDR的作用。同时，发现TKI增加传统抗癌药物的积累，这为TKI与传统抗癌药物联合应用提供理论基础；同时为解释联合应用的毒副作用提供依据。发现TKI如afatinib能增强传统抗癌药物对肿瘤干细胞的杀灭作用，这为肿瘤化疗提供新

表1 四代MDR抑制剂的不同特性

Table 1 The characteristics of 4 generations of ABC transporter modulators

Generation	Representative	In vitro	In vivo	PK	Downregulating ABC transporter
1st	verapamil，cyclosporin A	+	−	+	−
2nd	PSC833，S9788，MS-209	+	+	+	−
3rd	Tariquidar，Zosuquidar	+	+	−	−
4th	Curcumin	+	+	−	+

"+"：positive effective；"−"：ineffective；"PK"：pharmacokinetics. From Wu SC & Fu LW，Mol Cancer，2018，modified

思路。同时，有些TKI可能也是ABC转运泵的底物，也能将TKI外排，阐明TKI耐药新机制。

1.3　对MDR肿瘤细胞仍然有效的抗肿瘤化合物的发现

我们发现天然来源的化合物AMAD、Bullatacin、zsu442、Lgf-YL-9等不仅对敏感细胞有效，而且对多种ABC转运泵介导的MDR细胞也具有体内外的抗肿瘤作用。同时，阐明了蒽环类新化合物AMAD等诱导细胞凋亡不依赖反应性氧而依赖Caspase-8裂解Bid的线粒体凋亡通路新的作用机理，为新化合物AMAD的研发奠定基础。新近发现，MDR的肿瘤细胞对免疫治疗有效，这为MDR肿瘤治疗带来曙光。

1.4　shRNA/mdr1药物研发

CRISP/cas-9、siRNA技术敲除或沉默mdr1基因进行体内外逆转由ABCB1介导的MDR的研究，发现沉默mdr1基因能体内外增强MDR细胞对抗癌药物的敏感性，为克服MDR提供新思路。

1.5　肿瘤细胞瞬时获得耐药新机制

由于肿瘤细胞具有异质性，当耐药细胞与敏感细胞共培养时，耐药细胞的ABC转运泵可通过细胞的外泌体直接转至敏感细胞中，敏感细胞可瞬时获得耐药，从而逃避化疗药物的杀灭作用。这解释了肿瘤细胞瞬时获得耐药机制，也为MDR的预防提供新思路。

2　筛选ABC转运泵介导MDR逆转剂的新方法建立

MDR逆转剂的筛选大多是以特征耐药的细胞株及其相应的敏感细胞株为模型，以90%细胞存活的候选MDR逆转剂浓度联合不同浓度梯度的底物性抗癌药物进行比较研究，然后计算逆转倍数，进行体外逆转MDR活性评价。但这种方法筛选，工作量大，耗时长，不适合高通量筛选。为了快速高通量筛选，我们建立了以Fura-2/AM为探针荧光测定的快速、高通量筛选MDR的逆转剂新方法[6]。我们首次报道Fura-2/AM为ABCB1的底物，能为ABC转运泵外排，因此，胞内积累减少。而Fura-2/AM进入胞内后被非特异性酯酶水解为Fura-2和AM。Fura-2不是ABCB1底物，不能被外排，胞内Fura-2与Ca^{2+}结合产生强烈的荧光信号。利用这个原理，首次建立了Fura-2/AM为荧光探针的快速筛选MDR逆转剂的新方法。该法具有快速、高效、适合高通量筛选MDR逆转剂的特点，为新型MDR逆转剂的研发提供了新的方法[7]。其后，Rochester大学癌症中心Nelson等[8]发表非常相似的研究结果。这种方法已被广泛推广应用，也作为ABCB1功能的检测。

3　体内筛选MDR的逆转剂

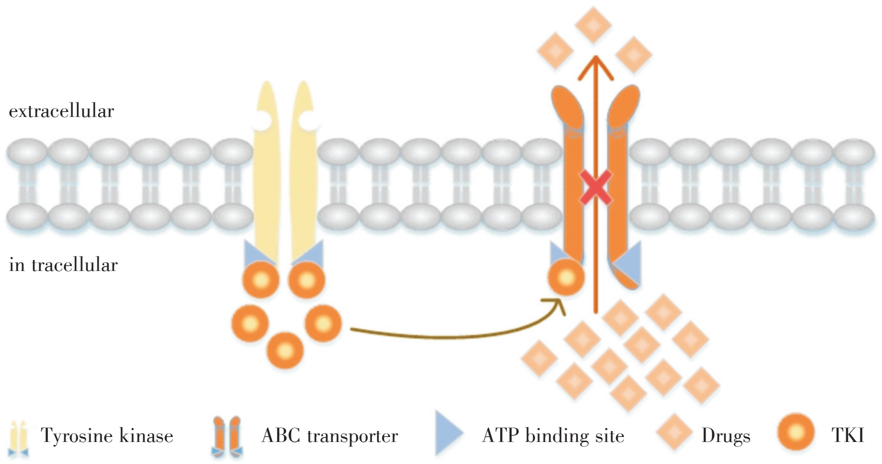
^{99m}锝-甲氧基异丁基异腈（^{99m}Tc-MIBI）是ABCB1底物，它的摄取与乳癌中ABCB1的表达呈负相关，可作为预测乳腺癌新辅助化疗敏感性的一种无创性手段，也可用于体内MDR逆转剂的筛选[9]。

4　酪氨酸激酶抑制剂与ABC转运泵的交互作用

由于酪氨酸激酶抑制剂（Tyrosine kinase inhibitors，TKI）能与TK的胞内区的ATP结合点结合，因此，推测TKI可能也可与ABC转运泵的ATP结合点结合，从而抑制ABC转运泵的功能，增加细胞内抗癌药物积累，从而逆转MDR（图1）[2]。

有研究发现不同靶点的TKI类药物如Imatinib[10]、Gefitinib[11]、Erlotinib[12-14]、Lapatinib[12,15-16]、Apatinib[17- 18]、Afatinib[19]、Osimertinib[20]、Sunitinib[21]、Nintedanib[22]等均能竞争性抑制ABC转运泵如ABCB1、ABCG2、ABCC1功能，具有强的逆转MDR的作用，但不同的TKI对不同的ABC转运泵成员如ABCB1/P-gp、ABCC1/MRP1、ABCG2/BRCP等介导MDR的逆转程度不同。有的TKI只逆转ABCB1介导的MDR，如Sunitinib只逆转ABCG2介导的MDR；有的TKI可逆转多种ABC转运泵成员介导的MDR。如Lapatinib、Erlotinib等能逆转ABCB1/P- gp、ABCC10/MRP7、ABCG2/BCRP介导的MDR；Erlotinib能逆转ABCB1及ABCG2介导的MDR（表2，含文献［3，7，10- 14，17- 19，21~60］）[2]。同时阐明了其逆转MDR的机理可能竞争性抑制ABCB1、ABCG2功能有关，与ABC转运泵的表达和其靶点信号分子及其下游信号分子如AKT、ERK的磷酸化水平抑制无关。

大多数TKI与传统抗癌药物联合应用可改变其药代动力学，增加药物峰浓度，延长其排泄时间，增加不可预测的副作用。如lapatinib可能为



Legend: Both TKI and ABC transporters compose of ATP binding site. TKI connect to ATP binding site of ABC transporters and inhibit its function of discharging anticancer drugs out of MDR cells. From Wu SC &Fu LW, Mol Cancer, 2018, modified.

图1　TKI抑制ABC药物转运泵的功能

Fig.1　TKI inhibit ABC transporters

第二代的MDR逆转剂,增加paclitaxel的肝、肠毒性,因为正常肝、肠组织中ABCB1常高表达,其功能与分泌、排毒有关[61]。这为靶点药物的临床应用,特别是与传统抗癌药物如paclitaxel联合应用及药物剂量的选择提供理论依据和重要指导作用。能较合理地解释靶点药物如Lapatinib与紫杉醇的肝、肠(ABCG2和ABCB1高表达)毒副作用提供新的理论。

同时,许多TKI为ABC转运泵的底物,可能参与TKI耐药。研究发现许多TKI能刺激ABC转运泵ATP酶的活性,常表现为先升高(刺激作用),后抑制,并能竞争性抑制光标记IAAP与ABC转运泵的ATP结合位点结合。表明TKI为ABC转运泵的底物,能被ABC转运泵外排至胞外。这揭示了TKI新的耐药机理,为克服TKI的耐药性的研究提供新思路。

肿瘤干细胞是肿瘤复发、转移和耐药的主要原因。ABCG2是肿瘤干细胞的主要标志物,也是用于筛选侧群细胞的理论依据。TKI增强传统抗癌药物对肿瘤干细胞样细胞的杀灭作用。我们研究发现apatinib、axitinib等能增强paclitaxel对侧群(SP)细胞(肿瘤干细胞样细胞)的杀灭作用[18, 62]。这为靶向肿瘤干细胞的杀灭作用提供新思路。

5　老药新用,逆转MDR

已研究表明许多非抗癌药物,也具有体内外强的逆转MDR作用。经筛选我们发现粉防已碱具有强的体内外逆转MDR作用,且临床研究表明对耐药性白血病具有恢复其对传统方案的敏感性作用。由于粉防已碱不具有专利,在此基础上,王锋鹏教授进行了结构修饰,合成了新化合物溴化粉防已碱,转让给康弘药业有限公司开发。我们发现西地那非(万艾可,伟哥)也具有逆转ABCB1及ABCC10介导的MDR,其作用机制与抑制ABC药物转运泵功能,从而增加MDR细胞内抗癌药物积累有关[63]。黄连素对肠癌细胞HCT/VCR具有增效作用;Lu等[64]证明了姜黄素在体内外能逆转耐药,增加传统抗癌药物的敏感性,其机制可能与姜黄素下调ABCB1的蛋白表达有关。

6　新结构的第三代MDR逆转剂

我们以Fura-2/AM法与MTT法对2000多种特征化合物进行逆转MDR活性的筛选,希望能找到高效、低毒、对传统抗癌药物血药动力学无影响的MDR逆转剂(第三代MDR逆转剂)。首先从天然产物、海洋微生物产物中筛选出Sipholenol A、双苄基异喹啉生物碱等具有逆转ABCB1介导的MDR作用,其机理与抑制ABCB1功能有关,这为海洋产物开发为新型MDR逆转剂药物提供依据[65-66]。

从具有同一平面上两个苯环,一个以上叔氨

表 2 TKI 抑制 ABC 药物转运泵的功能

Table 2 TKI function as inhibitors of ABC transporters

TKI	Target	ABC transporter inhibitor	Applications	Approved by FDA	Reference
Afatinib	EGFR，HER2	ABCG2	NSCLC	2013	［19］
AG1478	EGFR	ABCB1，ABCG2	NA	Not approved	［23］
Alectinib	ALK	ABCB1，ABCG2	NSCLC	2015	［24］
Apatinib	VEGFR	ABCB1，ABCG2	Gastric carcinoma	2014	［17，18］
AST1306	EGFR	ABCG2	NA	Not approved	［25］
Axitinib	VEGFR，PDGFR	ABCG2	RCC	2012	［26］
Bosutinib	BCR-ABL，Src	ABCG2	CML	2012	［27］
Cabozantinib	VEGFR，Kit	ABCG2	Thyroid cancer	2011	［28］
Canertinib	EGFR	ABCB1，ABCG2	NA	Not approved	［29］
Cediranib	VEGFR	ABCB1，ABCC1	NA	Not approved	［30］
CEP-33779	JAK	ABCB1	NA	Not approved	［31］
Ceritinib	ALK	ABCB1，ABCG2	NSCLC	2014	［32］
Crizotinib	ALK	ABCB1	NSCLC	2011	［33］
Dasatinib	BCR-ABL，Src	ABCB1，ABCG2	CML	2006	［27］
Dacomitinib	EGFR	ABCG2	NSCLC	2018	［34］
EKI785	EGFR	ABCB1，ABCC1	NA	Not approved	［35］
Erlotinib	EGFR	ABCB1，ABCG2，ABCC10	NSCLC	2004	［12，14］
Gefitinib	EGFR	ABCB1，ABCG2	NSCLC	2003	［11，36］
GW2974	EGFR	ABCB1，ABCG2	NA	Not approved	［37］
GW583340	EGFR	ABCB1，ABCG2	NA	Not approved	［37］
Ibrutinib	BTK	ABCC1	Lymphoma	2013	［38］
Icotinib	EGFR	ABCG2	NSCLC	2011	［39］
Imatinib	BCR-ABL	ABCB1，ABCC1，ABCG2，ABCC10	CML，GIST	2001	［10，40，41］
Lapatinib	HER2，EGFR	ABCB1，ABCC1，ABCG2，ABCC10	Breast cancer	2007	［12］
Linsitinib	IGF	ABCG2，ABCC10	NA	Not approved	［42］
Masitinib	Kit	ABCG2，ABCC10	Mast cell tumor	Not approved	［43］
Motesanib	VEGFR	ABCB1，ABCG2	NA	Not approved	［44］
Neratinib	HER2，EGFR	ABCB1	Breast cancer	2017	［45］
Nilotinib	BCR-ABL	ABCB1，ABCG2，ABCC10	CML	2007	［27，41］
Nintedanib	VEGFR，PDGFR	ABCB1	NSCLC	2014	［22］
Osimertinib	EGFR	ABCB1，ABCG2	NSCLC	2015	［20］
PD173074	VEGFR	ABCB1，ABCC10	NA	Not approved	［46，47］
Ponatinib	BCR-ABL	ABCB1，ABCG2，ABCC10	CML	2012	［48，49］
Quizartinib	FLT3	ABCG2	AML	Not approved	［50，51］
Regorafenib	VEGFR	ABCB1	GIST	2012	［52］
Saracatinib	Src	ABCB1	NA	Not approved	［3］
Sorafenib	VEGFR，PDGFR	ABCB1，ABCC2，ABCC4，ABCG2	RCC，HCC	2005	［53］
Sunitinib	VEGFR，PDGFR	ABCB1，ABCG2	GIST，RCC	2006	［21，54］
Tandutinib	FLT3	ABCG2	NA	Not approved	［55］
Telatinib	VEGFR	ABCG2	NA	Not approved	［56］
Trametinib	MEK	ABCB1	Melanoma	2013	［57］
Vandetanib	VEGFR，EGFR	ABCB1，ABCC1，ABCG2	Thyroid cancer	2011	［58］
Vatalanib	VEGFR	ABCB1，ABCG2	Colorectal cancer	Not approved	［59］
WHI-P154	JAK	ABCG2	NA	Not approved	［60］

ABC-B1，C1，C2，C4，C10，G2：ATP binding cassette sub-family B member；ALK：ATP-competitive anaplastic lymphoma kinase；AML：acute myelogenous leukemia；BCR-Abl：Breakpoint cluster region-Abelson complex；BTK：Bruton's tyrosine kinase；CML：chronic myelogenous leukemia；EGFR：epidermal growth factor receptor；ERK：extracellular signal-regulated kinases；FLT3：FMS-like tyrosine kinase；GIST：Gastrointestinal stromal tumors；HCC：hepatocellular carcinoma；HER2：human epidermal growth factor receptor 2；IGF：insulin-like growth factor；JAK：janus kinase；Kit：Mast/stem cell growth factor receptor kit；MEK：mitogen-activated protein kinase；NA：not applicable；NSCLC：non-small cell lung cancer；PDGFR：platelet-derived growth factor receptors；RCC：renal cell carcinoma；Src：proto-oncogene tyrosine-protein kinase Src；VEGFR：vascular endothelial growth factor receptor.

基特征结构的合成化合物中筛选出FG0203具有强的逆转ABCB1介导MDR作用,以其为先导化合物合成系列同系物,新结构化合物FG020326(有自主知识产权)具有低毒、强的体内外逆转MDR作用,其逆转机理可能为直接结合至ABCB1,抑制其外排抗癌药物功能,同时,与抗癌药物合用,无药动学的交互作用,表明为第三代MDR逆转剂,且其体内外逆转MDR的活性较zusuquidar强(Lily公司开发)[67-69]。

7 对MDR肿瘤细胞仍然有效的新抗肿瘤化合物的发现

我们发现天然来源的化合物AMAD[70]、Bullatacin[71]、zsu442[72]、Lgf-YL-9[73]等不仅对敏感细胞有效,而且对多种ABC转运泵介导的MDR细胞也具有体内外的抗肿瘤作用。同时,阐明了蒽环类新化合物AMAD等诱导细胞凋亡不依赖反应性氧而依赖Caspase-8裂解Bid的线粒体凋亡通路新的作用机理,为新化合物AMAD的研发奠定基础,为克服MDR提供新思路。

蒽环类新化合物AMAD具有强的体内外抗MDR肿瘤活性和新的介导细胞凋亡的信号通路。其机理不依赖于反应性氧化(ROS),也不嵌入DNA小沟,而与Bid裂解激活有关,经线粒体途径诱导细胞凋亡有关。不同于阿霉素类化合物,为AMAD类化合物开发奠定基础[70, 74]。

对300多种来源于海洋生物产物的化合物单体(其中70多种新化合物)进行抗肿瘤作用研究,发现ZSU-442、1403P-2、1403P-3、T5、X1、H1等均具有较强的体外抗MDR肿瘤作用[72, 75-77]。由于1403P-3(蒽环类衍生物)资源丰富,以裸鼠移植瘤模型研究表明,1403P-3具有较强的体内抗肿瘤作用。机理研究表明,1403P-3、Lgf-YL-9也是通过ROS不依赖性线粒体凋亡途径介导细胞凋亡,改变了蒽环类化合物一般通过ROS引发细胞凋亡的观点。阐明了蒽环类化合物作用机制的多样性[77-78]。ZSU442是一种结构独特的化合物,体内外均具有较强的抗癌活性,机理研究表明,ZSU442能通过降低β-catenin/c-myc表达(Wnt通路),同时,也降低Bmi-1表达,抑制c-kit磷酸化,提示对肿瘤干细胞具有杀灭作用,为肿瘤治疗提供新思路。

8 沉默*mdr1*基因,克服ABCB1介导的MDR

ABCB1是介导MDR的主要原因之一。降低ABCB1的表达可能是克服MDR的重要策略。以shRNA技术,沉默*mdr1*基因,使ABCB1蛋白表达水平降低。我们发现以siRNA技术沉默*mdr1*基因,在裸鼠体内能增加MDR细胞对抗癌药物的敏感性。这为逆转MDR提供了新思路和新策略。

同时,研究发现MDR细胞中常伴有凋亡抑制蛋白(IAP)过表达,为进一步研究ABCB1和IAP两者是否具有相互调控作用。我们以基因转染或沉默技术和免疫共沉淀(IP)技术研究揭示ABCB1和IAP无相互调控作用,丰富了MDR细胞凋亡抗性的理论,为克服MDR的凋亡抗性提供新思路[4]。

9 细胞膜间ABC转运泵的转移,肿瘤细胞瞬时耐药的新机制

新近,研究发现表达ABCB1的耐药细胞与敏感的肿瘤细胞一起共培养时,ABCB1可通过微囊泡(microvesicles)从耐药细胞转移至药物敏感肿瘤细胞,从而使敏感肿瘤细胞瞬时获得MDR的耐药表型。这为解释肿瘤细胞瞬时获得性耐药提供依据[79]。

10 展望

由于MDR逆转剂开发的失败,有人提出ABC转运泵只是预测肿瘤预后的标志物,不是介导MDR的机制。事实上,介导MDR的原因十分复杂,有的逆转剂只逆转其中某一种如ABCB1或ABCG2介导的MDR,对另外因素介导的MDR不起作用,因此,MDR逆转剂的临床评价病例选择时显然应在检测其ABC转运泵的基础上进行,这可能是近年来MDR逆转剂临床评价失败的主要原因。ABC转运泵与肿瘤的局部免疫微环境是否有关,仍未见报道。MDR的肿瘤对PD-1/PD-L1抗体治疗疗效也未见评价。由于纳米给药系统药物进入细胞可能方式不同,这种方法用于逆转MDR尚需动物体内实验及临床试验评价。我们期待着新一代高效、低毒、广谱的MDR逆转剂用于临床,为MDR肿瘤病人带来曙光。

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