ABC转运蛋白及其相关的多药抗性研究现状

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摘要： ABC（ATP-binding cassette）转运蛋白是一类家族庞大、功能多样的跨膜转运蛋白，其广泛存在于原核和真核生物的各类细胞器中，负责多种物质的跨膜转运，从而调节生物体的一系列生命活动。近年来，越来越多ABC转运蛋白的种类及功能被报道，但是ABC蛋白家族的潜在成员以及功能仍然值得进一步探究和挖掘。该文对不同物种中ABC转运蛋白数量、结构域、功能、研究方法以及其参与调控病原菌多药抗性的研究现状进行综述，并对植物病原菌多药抗性的治理等进行展望。

关键词： ABC转运蛋白；蛋白结构；基因功能；多药抗性

Research status of ATP-binding cassette transporters and related multidrug resistance

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Abstract: ATP-binding cassette (ABC) transporters are a large family of transmembrane proteins with diverse functions, they are widely present in various organelles of prokaryotic and eukaryotic organisms and are responsible for the transmembrane transport of various substances, thereby regulating a series of life activities. In recent years, more and more types and functions of ABC transporters have been reported, however, the potential members and functions of the ABC protein family are still worthy of further exploration. The number, domains, functions, and research methods of ABC transporters in different species are reviewed, as well as their participation in regulating the multidrug resistance of plant pathogens are discussed. Besides, the management strategies for multidrug resistance of plant pathogens are also prospected.

Key words: ABC transporter; protein structure; gene function; multidrug resistance

在真核生物和原核生物中，ABC（ATP-binding cassette）转运蛋白是目前发现的最大转运蛋白家族之一，其通过分解腺苷三磷酸（adenosine triphosphate，ATP）释放的能量对包括氨基酸、多肽、蛋白质、糖类、脂质和药物等不同底物进行跨膜转运，参与生物体多种生命活动过程（Lane et al.，2016）。在哺乳动物、植物以及微生物中，ABC转运蛋白家族转运的底物最广泛，不仅参与外排作用（Jenness et al.，2019；Orelle et al.，2019；Lusvarghi et al.，2020），而且参与植物病原菌对杀菌剂多药抗性的形成过程

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（赵胡和李裕红，2012；Chen et al.，2016；Fletcher et al.，2016）。因此，全面了解不同物种中ABC转运蛋白的结构和功能，对探究植物病原菌多药抗性发生机制及田间多药抗性有效治理具有重要意义。

1 ABC转运蛋白的数量和结构域

不同物种间ABC转运蛋白的数量存在差异。枯草芽胞杆菌*Bacillus subtilis*、金黄色葡萄球菌*Staphylococcus aureus*和大肠杆菌*Escherichia coli*等原核生物含有多达30个假定的药物ABC转运蛋白（Paulsen et al.，2001；Hassan et al.，2007；Orelle et al.，2019），且这些ABC转运蛋白存在结构和功能上的高度重复；真核生物拟南芥*Arabidopsis thaliana*中有131个ABC转运蛋白，其分别由250~1 800个氨基酸构成（朱璐等，2012），而人类基因组中有48个ABC转运蛋白超家族成员（Dean et al.，2001）；真菌基因组都含有一定数量的ABC转运蛋白编码基因，且分别位于细胞膜、液泡、过氧化物酶体和线粒体等不同细胞结构中（Klein et al.，2011）；酿酒酵母*Saccharomyces cerevisiae*基因组具有30个编码ABC转运蛋白的基因（Grechko et al.，2020）；而在稻瘟病菌*Magnaporthe oryzae*中已经发现50个假定ABC转运蛋白基因，其被分为ABC-A、ABC-B、ABC-C、ABC-D、ABC-E、ABC-F、ABC-G、ABC-I和YDR061w-like九个不同的蛋白亚家族（Kim et al.，2013）；灰葡萄孢*Botrytis cinerea*中存在14个编码ABC转运蛋白的基因（Vermeulen et al.，2001）。

虽然不同物种间ABC转运蛋白的数量存在差异，但其结构均具有一定的相似性，同源性约30%~40%（Higgins，1992），其核心拓扑结构包含高度疏水的跨膜结构域（transmembrane domain，TMD）和保守的核苷酸结合结构域（nucleotide-binding domain，NBD）。每个TMD通常由6个预测的跨膜区段（transmembrane segment，TMS）组成，TMD可形成底物转运通道，并参与底物的识别。NBD位于细胞质中，结合并水解ATP，为底物的转运提供能量。TMD和NBD可分别存在于不同的肽链上，也能以不同的组合及排列形式结合在一起（Orelle et al.，2019）。如在细菌中，ABC转运蛋白的外排泵通常由1个TMD结合1个NBD，它们可以形成同源二聚体或异源二聚体，进而对底物进行转运（Orelle et al.，2019）；在大部分真菌中，ABC转运蛋白由2个NBD和2个TMD组成（Stergiopoulos et al.，2002）。在ABC转运蛋白不同亚家族（Subfamilies）中，NBD和TMD以全分子或半分子形式存在，全分子即两者按照1∶1结合形成二聚体，半分子则为单体形式。另外，ABC蛋白结构域也包含少数具有保守二级结构的肽段，如Walker A（P结合环）、Walker B和Walker C（C结合环）（Monk & Keniya，2017）。

2 ABC转运蛋白的功能

ABC转运蛋白能够转运细胞内的多种物质，包括金属离子、糖类、核苷酸、氨基酸等无机和有机小分子及多肽和蛋白质等有机大分子。ABC转运蛋白在细胞中还参与代谢解毒、内外信号转导、脂质稳态平衡、病毒防御以及抗原逐级呈递等重要生理过程（Wilkens，2015；王晓珠等，2017）。目前，关于外排转运体转运底物的具体机制还存在争议。对于ABC转运蛋白来说，许多学者先后提出了不同的模型，但是认同度较高的只有2种。一种模型为疏水真空吸尘器模型，即生物转运体直接与细胞基质相连，把底物从基质中转移出来；另一种模型为翻转酶模型，即转运体可直接把底物从膜的内侧转移至外侧，该过程所需能量由ATP水解提供，该模型被用于ABC转运蛋白的大多数研究中（Gottesman & Pastan，1993；李志勇等，2016）。

按功能来说，ABC转运蛋白分为转入型蛋白（胞外转入胞内）和转出型蛋白（胞内转出胞外）两类。转出型ABC转运蛋白在原核生物和真核生物中均存在，而转入型ABC转运蛋白绝大多数存在于原核生物（ter Beek et al.，2014）。转入型运输蛋白可将底物从胞外转入胞内，包括糖、金属、肽、氨基酸和其他代谢物（Berntsson et al.，2010）。根据其总体结构和转运机制的差异将其分为Type I、Type II（Holland & Blight，1999；Rees et al.，2009）和能量耦合因子（energy-coupling factor，ECF）3种类型转运蛋白，但ECF型转运蛋白的转运机制尚未明确（Rempel et al.，2019）。Type I内向转运蛋白跨膜结构域最初在运输钼酸盐的ModB跨膜区上发现，Type II内向转运蛋白最早在BtuC和流感嗜血杆菌*Haemophilus influenzae*同源转运体HI1471（陈道波等，2021）上发现。在原核生物、古细菌和藻类中，转入型ABC转运蛋白被用于运输营养物质，有些原核致病菌可利用转入型ABC转运蛋白来躲避宿主细胞的先天性免疫应答机制（Rice et al.，2014），其在真核生物中极少存在，如在真核生物拟南芥中硫酸盐转运蛋白SULTR3（Choi & Ford，2021）的功能是运输营养物质和离子。

Kovalchuk & Driessen(2010)对ABC转运蛋白进行系统进化分析,将真核生物体内的ABC转运蛋白分为8个亚家族(ABC-A~H)。此外,Orelle et al.(2019)对真菌中ABC转运蛋白基因进行系统发育关系研究并将其分为5个亚家族,分别命名为多种药物耐受性(pleiotropic drug resistance,PDR)、多药抗性相关蛋白(multidrug resistance associated protein,MDR)、多药抗性蛋白(multidrug resistance protein,MRP)/囊性纤维化跨膜转导调节器(cystic fibrosis transmembrane conductance regulator,CFTR)、肾上腺脑白质营养不良蛋白(adrenoleukodystrophy protein,ALDP)和酵母延长因子3(yeast elongation factor 3,YEF3)/核糖核酸酶抑制剂1(RNase L inhibitor 1,RLI)亚家族。在此基础上,本研究对近年来报道的不同物种中存在的ABC蛋白亚家族的结构形式、分布、功能及特点进行归纳,如表1所示。

3 ABC转运蛋白参与的多药抗性

病原菌对杀菌剂的抗性主要与转运蛋白外排、靶标基因变化和解毒酶代谢等作用导致的有效药剂浓度降低有关(Sanglard,2016)。大量医学研究表明病原菌通过ABC等外排转运蛋白的过表达对药物产生抗性(Sipos & Kuchler,2006;Li et al.,2015),如在对氟康唑耐药的白色念珠菌*Canidia albicans*中,有85%的菌株出现外排转运蛋白基因的过表达(史文娜,2010)。病原真菌不同,其含有的ABC转运蛋白数量和拓扑结构均不同(Sanglard,2016),如人类医学药物白色念珠菌和构巢曲霉菌*Aspergillus nidulans*中有多个相关ABC转运蛋白参与具体的外排和抗药性(Niimi et al.,1997;Andrade et al.,2000),如在抗吡咯的白色念珠菌株中PDR亚家族的CDR1和CDR2蛋白上调表达,念珠菌通过提高药物外排减少药剂在菌体内的积累,从而产生了抗药性(Sanglard et al.,2009);在构巢曲霉菌中至少有3个ABC转运蛋白相关基因与其多药抗性表型相关,其中ABC-B具有抵御大部分杀菌剂和天然有毒化合物的功能(Andrade et al.,2000),在多药抗性的产生过程中起重要作用;ABC-D与构巢曲霉菌对环己酰亚胺、环孢菌素衍生物、安定霉素和尼日利亚菌素的敏感性相关;ABC-G合成受到干扰后,构巢曲霉菌对唑类抑制剂(demethylation inhibitor,DMI)的敏感性降低(de Waard et al.,2006)。

与医学研究类似,植物病害研究领域也存在着多药抗性的情况,已有大量研究显示真菌ABC转运蛋白表达量变化也是引起植物病原菌对杀菌剂多药抗性的重要原因,这在灰葡萄孢、禾生球腔菌*Mycosphaerella graminicola*和青霉菌*Penicillium digitatum*中均有报道,本文将对这几种病原真菌中与杀菌剂多药抗性相关的ABC转运蛋白及其编码基因进行描述。

ABC转运蛋白在灰葡萄孢的多药抗性中发挥着重要作用。Stergiopoulos et al.(2002)报道灰葡萄孢有14个ABC转运蛋白(BcatrA~BcatrN),其中BcatrB、BcatrD、BcatrK三个蛋白与多药抗性表型有关。灰葡萄孢的BcatrB蛋白有1 439个氨基酸,其底物大多数为芳香族化合物,受锌指结构转录因子*mrr1*的正调控(Mosbach et al.,2010)。BcatrB蛋白主要转运苯基吡咯类、二甲酰亚胺和甲酰亚胺类杀菌剂。Schoonbeek et al.(2001)通过测定*BcatrB*敲除和过表达突变体对白藜芦醇和苯基吡咯类杀菌剂咯菌腈的敏感性,证明了*BcatrB*基因在灰葡萄孢对2种药剂抗性中发挥着重要作用,同时发现在咯菌腈的诱导下,*BcatrB*基因的表达量明显增加。BcatrD蛋白包含1 502个氨基酸,对唑类、恶咪唑类和吡咯类杀菌剂具有转运外排的作用,其基因表达在异菌脲、多菌灵和放线菌酮的诱导下也增加(Hayashi et al.,2001)。BcatrK蛋白参与多氧菌素、有机磷类异稻瘟净等杀菌剂的转运,同时*BcatrK*敲除突变体对药剂敏感性增强(Nakajima et al.,2001)。Holmes et al.(2016)通过Northern blot分析发现咯菌腈、放线菌酮等杀菌剂可诱导*BcatrK*表达量上调。Firoz(2016)研究发现核盘菌*Sclerotinia sclertiorum*对咯菌腈及腐霉利、异菌脲等二甲酰亚胺类杀菌剂之间存在正交互抗性,这可能也与BcatrB蛋白可同时转运苯基吡咯类及二甲酰亚胺杀菌剂有关,当*BcatrB*基因过表达时,菌体可同时转运2类作用机制不同的杀菌剂,进而形成交互抗性。总之,在杀菌剂诱导下灰葡萄孢内*BcatrB*、*BcatrD*和*BcatrK*均可上调表达,通过对药剂外排转运的增强来降低其在菌体内的积累量,从而对不同作用机制杀菌剂产生抗性。

禾生球腔菌中有6个编码ABC转运蛋白的基因*MgAtr1~MgAtr6*(Zwiers & de Waard,2000;Stergiopoulos et al.,2002;Zwiers et al.,2007)。de Waard et al.(2006)研究结果表明*MgAtr1*基因的表达水平与禾生球腔菌菌株对环唑醇的敏感性有关,其他转运蛋白与菌株致病性及植株分泌的防御物质的转运有关(Stergiopoulos et al.,2003)。

表1 ABC转运蛋白各亚家族分布及功能

Table 1 Distribution and functions of subfamilies of ABC transporters

亚家族 Subfamily	存在形式 Existence	分布 Distribution	功能 Function	特点 Characteristic	参考文献 Reference
ABC-A	全分子 Full length	人、植物、动物和原生生物等 Human, plants, animals and protists	对脂类的转运及代谢具有重要意义，如高密度脂蛋白的合成 Great significance to the transportation and metabolism of lipids, such as the synthesis of high-density lipoproteins	首个NBD结构域后存在磷酸化调节位点，在TMD结构域前2个跨膜域螺旋之间有突出的细胞外环 The presence of multiple phosphorylation regulatory sites following the first NBD domain and a large extracellular loop between the first two transmembrane helices in the TMD	Anjard et al., 2002; Peelman et al., 2003; Dean & Annilo, 2005; Wenzel et al., 2007; Verrier et al., 2008
	半分子 Half size	古细菌（蛙壶菌等） Ancient fungi like *Batrachochytrium dendrobatidis*			
ABC-B (MDR/ ALDP)	全分子或半分子 Full length or half size	人、动物和植物等 Human, animals and plants	参与多药耐药、抗原加工、线粒体肽和重金属耐药，生长素、次生代谢物和外源性物质的输出，癌细胞的耐药性 Involved in multidrug resistance, antigen processing, mitochondrial peptides and heavy metal resistance; the export of auxins, secondary metabolites, and xenobiotics; drug resistance in cancer cells	跨膜结构域–核苷酸结合结构域（TMD-NBD）为正向拓扑结构 Ttransmembrane domain-nucleotide-binding domain (TMD-NBD) has a forward topology	Kispal et al., 1997; Gottesman et al., 2002; Yazaki, 2006; Verrier et al., 2008; Lee et al., 2014; ter Beek et al., 2014
ABC-C (MRP)	全分子 Full length	植物和真菌 Plants and fungi	参与细胞解毒，将有毒物质（有机酸、重金属、毒素）排出细胞，提高植物和真菌重金属耐性 Involved in the detoxification of toxic compounds by transport complex organic materials	大部分在N端有1个额外的疏水区 Many, but not all contain an additional N-terminal hydrophobic region	Song et al., 2010; Park et al., 2012; 2014; Sousa et al., 2015
ABC-D	全分子 Full length	动物、植物、真菌和原生生物 Human, plants, animals and protists	从外界转入长链的脂肪酸 Mediated the import of long-chain fatty acids	TMD-NBD为正向 TMD-NBD has a forward topology	Hettema et al., 1996; Dawson & Locher, 2006; Locher, 2016
	半分子 Half size	植物 Plants			
ABC-E/F (YEF3/ RLI)	全分子 Full length	真核生物和古细菌 Eukaryotes and archaea	参与核糖体蛋白的合成、对转录调控和信使RNA的转运具有重要作用，或作为翻译延伸因子 An essential iron-sulfur protein required for ribosome biogenesis, transcriptional regulation and mRNA transport, or acting as translation elongation factors	ABC-E和ABC-F亚家族均由2个NBD构成，缺少跨膜结构域 Lack transmembrane domains and consist solely of two NBDs	Dong et al., 2004; 2005; Kispal et al., 2005; Kovalchuk & Driessen, 2010
ABC-G (PDR)	全分子或半分子 Full length or half size	真核生物，但动物细胞内尚未发现全分子结构 Eukaryotes other than animal	将药物分子排出细胞，甾醇吸收和厌氧生长的必需蛋白 An essential protein for exporting drug, sterol absorption and anaerobic growth	TMD-NBD形式为反向 The TMD-NBD has a reversed topology	Wilcox et al., 2002; Hlaváček et al., 2009; Choi et al., 2011
ABC-H	全分子 Full length	真菌 Fungi	参与控制mRNA的起始、延伸和降解 Involved in controlling mRNA initiation, elongation and degradation	暂未归类的ABC蛋白，没有TMD，但有ABC家族特征NBD结构域 Non-classified ABC proteins, lack TMDs but the existed NBDs demonstrate that they belong to the ABC proteins	Liu et al., 2001; Kovalchuk & Driessen, 2010

Nakaune et al.(1998)对青霉菌进行相关研究，结果显示PMR1和PMR5(与PMR1具有37%的同源性)与其多药抗性表型有关，并且具有一定的互补作用。PMR1与青霉菌菌体对DMI类杀菌剂的抗性相关，并且能够被特异性诱导表达。PMR5与青霉菌菌体对苯醌、噻菌灵、喜树碱和白藜芦醇的敏感性有关，且转录受地噻农和白藜芦醇特异性诱导(Nakaune et al.，2002)。

4 ABC转运蛋白的研究方法

对于ABC转运蛋白表达量主要采用实时荧光定量PCR(real-time quantitative PCR，RT-qPCR)技术检测或者采用基因特异性片段进行Northern blot分析(Vermeulen et al.，2001)。如Schoonbeek et al.(2003)采用RT-qPCR技术测定了ABC转运蛋白基因*BcatrA~BcatrK*在番茄灰霉病菌B05.10单倍体菌株的表达量。在真菌中主要通过基因敲除和过表达来确定ABC转运蛋白对药剂的外排功能，而这种外排引起的药剂在菌体内积累量的降低会导致病原菌对杀菌剂的敏感性下降。Schoonbeek et al.(2003)通过灰葡萄孢中*BcatrB*基因敲除试验验证其对不同药剂的敏感性变化，进而明确该基因在药剂外排功能方面的作用；Vermeulen et al.(2001)同样通过基因敲除发现*BcatrB*是苯吡咯类杀菌剂咯菌腈和拌种咯活性的决定因素。基因的定点突变技术与亚细胞定位相结合是揭示基因功能的有效手段。如Pan et al.(2021)通过同源与异源表达发现水稻、玉米和大豆对草甘膦产生了抗性，而CRISPR/cas9介导的*EcABCC8*同源基因*OsABCC8*的敲除增加了水稻对草甘膦的敏感性，并通过亚细胞定位分析和结构建模推测EcABCC8可能是一个质膜定位的转运蛋白，其将胞质中的草甘膦排到质外体。另外，可以采取分子对接方法对转运蛋白与药物的结合进行分析，从而提前预测转运蛋白与药剂的结合情况(潘显超，2013)。

5 展望

ABC转运蛋白家族庞大，在生物体中有着重要的生命活动功能，病原菌菌体内大多存在数种参与杀菌剂外排的ABC蛋白，其过表达可导致杀菌剂大量外排，通常是多药抗性产生的主要原因。病原微生物对杀菌剂的多药抗性无论在临床治疗还是农业生产中都是非常棘手的问题(孙影和顾觉奋，2018)。一般来讲，新作用机制杀菌剂的创制和不同作用机制杀菌剂的轮换或混合使用是田间病原菌抗性治理的主要途径(王文桥等，2019；李宝燕等，2021)。新药创制周期长，难度大，成本高，而有效的轮换或混合用药不失为多药抗性治理的一种好方法，但其关键要针对田间病原菌群体产生多药抗性的具体原因来选择轮换或者混合的杀菌剂。针对抗性群体多药抗性形成的不同原因用药策略有所不同，但其前提是做好多药抗性靶基因和外排相关基因的差异分析，在此基础上，针对病原菌同时对多种不同作用机制杀菌剂产生靶位点变化的多重耐药情况，可以选择未发生靶位点变化的杀菌剂类别进行轮换防治，而对于已发生转运蛋白过表达的群体，需要使用无交互抗性的杀菌剂进行轮换用药。在植物病原菌多药抗性治理研究领域，针对易产生ABC转运蛋白过表达的病原菌尚缺乏各类杀菌剂间交互抗性的系统研究，这限制了灰葡萄孢等多药抗性发生严重的作物病原菌的有效控制，但医学研究发现在转运蛋白过表达的癌细胞中大量植物化学物质仍有活性，甚至还有3%~8%的物质对多药抗性细胞具有更好的抑制效果(Efferth et al.，2021)。类似研究结果可为植物病原菌的多药抗性治理提供参考。

在医学研究中发现了一系列具有潜在临床应用价值的转运蛋白抑制活性物质(孙仲琳等，2019)，大部分外排转运蛋白在结构上具有一定的相似性，因此这为外排转运蛋白广谱抑制剂的研发提供了基础(黄娇和穆青，2019)，并可借鉴到植物病原菌外排抑制剂的开发。植物及微生物的天然产物及其类似物中具有多种外排抑制活性的化学物质，这些天然化学物质结构多样，不易产生抗性，为转运蛋白抑制剂的来源提供了保证(孙仲琳等，2019)。关于植物病原菌多药抗性的治理可以借鉴医学上的研究成果。如Leroux & Walker(2013)研究发现维拉帕米可以提高多药抗性灰葡萄孢对几种杀菌剂的敏感性，而本课题组近期也发现法尼醇(刘鹏飞等，2020a)、利血平(刘鹏飞等，2021a)和小檗碱(刘鹏飞等，2021b)等物质可与不同类别的杀菌剂协同应用，进而提高多药抗性灰葡萄孢菌株对杀菌剂的敏感性，而阿米替林也在辣椒疫霉*Phytophthora capsici*多药抗性菌株上表现出对杀菌剂的协同增效作用(刘鹏飞等，2020b)。初步推测这些物质对外排转运蛋白具有一定的抑制作用，但具体机制仍需要进一步研究。此外，应加强田间抗性菌株的抗性风险监测，结合用药情况判断田间是否出现多药抗性菌株，以便及时调整后期的用药方式与策略。

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