

· 专题论坛 ·

## 亲免疫素在植物体内的功能研究进展

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**摘要** 亲免疫素(immunophilin)是一种免疫抑制剂受体, 广泛存在于细菌、病毒、真菌、植物和动物等生物体中。植物体内亲免疫素由FK506结合蛋白(FKBPs)、亲环素(CYPs)和parvulin蛋白构成。大多数亲免疫素具有肽基脯氨酰顺反异构酶活性, 可以作为分子伴侣指导蛋白质的正确折叠。该文总结了亲免疫素在激素信号传递、光合作用、胁迫响应及基因表达等方面的最新研究进展, 并对今后该领域的研究进行了展望。

**关键词** 生长发育, 基因表达, 亲免疫素, 光合作用, 胁迫响应

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亲免疫素(immunophilin)在生物体内广泛存在, 可与免疫抑制剂他克莫司(tacrolimus, FK506)、雷帕霉素(rapamycin)及环孢素A (cyclosporin A)结合, 是含量比较丰富的一类细胞受体蛋白。根据与亲免疫素结合的免疫抑制剂不同, 可将其分为3类: 能与FK506和雷帕霉素特异结合的FK506结合蛋白(FK506 binding proteins, FKBPs)、能与环孢素A结合的亲环素(cyclophilins, CYPs)以及能与5-羟基-1,4-萘醌结合的parvulin蛋白(Hennig et al., 1998; He et al., 2004)。亲免疫素具有分子伴侣(molecular chaperone)的功能, 能够指导含有脯氨酸残基的蛋白质正确折叠、组装和转运。亲免疫素的这种功能主要依赖于其具有肽基脯氨酰顺反异构酶(peptidyl-prolyl *cis-trans* isomerases, PPlase, EC 5.1.2.8)活性, 该酶能够催化肽基脯氨酸的顺反异构化, 对蛋白质的正确折叠、运输及活性调节具有重要作用(Barik et al., 2006)。亲免疫素在哺乳动物体内还能作为免疫抑制剂药物的受体, 亲免疫素与免疫抑制剂药物形成的复合体能够抑制钙调磷酸酶(calcineurin, CaN)或者蛋白激酶TOR(target of rapamycin)活性, 抑制下游信号传递或细胞周期的正常进行, 从而达到免疫抑制的作用(Geisler and Bailly, 2007; 于彦丽等, 2014)。

从20世纪80年代初发现亲免疫素以来, 已有23个拟南芥(*Arabidopsis thaliana*)、29个水稻(*Oryza*

*sativa*)、4个酵母(*Saccharomyces cerevisiae*)、18个人类(*Homo sapiens*) FKBPs被鉴定出来(Ahn et al., 2010; Gollan and Bhawe, 2010)。同时, 越来越多的CYPs也已被成功鉴定, 如拟南芥有29个、水稻有27个、大豆(*Glycine max*)有62个、酵母有8个、人类有24个(Ahn et al., 2010; Trivedi et al., 2012; Mainali et al., 2014)。目前已发现的parvulin蛋白拟南芥有3个、苹果(*Malus domestica*)有1个、毛地黄(*Digitalis lanata*)有1个、百脉根(*Lotus japonicus*)有3个、棉花(*Gossypium hirsutum*)有1个、酵母有1个、人类有3个(Arevalo-Rodriguez et al., 2004; Wang et al., 2014; Paić and Fulgosi, 2016; Dunyak and Gestwicki, 2016)。植物中的亲免疫素数量众多, 可能是植物在进化过程中适应不同环境的结果。最新研究表明, 亲免疫素参与生长素与油菜素内酯的运输和信号传递过程, 对植物的生长发育和逆境胁迫响应等都具有重要作用(Geisler et al., 2003; Zhao et al., 2016; Chaiwanon et al., 2016)。本文主要对植物亲免疫素结构和功能的最新研究进展进行综述, 以期为进一步研究该类蛋白质的功能和作用机制提供参考。

### 1 亲免疫素的结构

高等植物体内FKBPs数量众多, 根据结构可将其分

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为2类: 一类是单结构域成员, 这类FKBPs仅含有1个FKB结构域(FKBD), 具有PPlase活性; 另一类是具有多个结构域的FKBPs, 一般包括3个FKBD、TPR结构域(tetratricopeptide repeat domains)和1个C末端的钙调蛋白结构域(calmodulin-binding domains, CaM-BDs) (Barik, 2006; Geisler and Bailly, 2007)。有些植物的FKBPs含有3个FKBD, 例如拟南芥FKBP62和FKBP65, 只有第1个FKBD具有PPlase活性, 与人类的FKBP51和FKBP52相似, 只有前2个FKBD具有活性(表1) (Vasudevan et al., 2015)。TPR结构域通常形成1个 $\alpha$ 螺旋区域, 提供与HSP90相互作用位点。CaM-BDs通常在FKBPs的C末端与CaM结合, 尽管哺乳动物体内CaM与FKBP结合具有指导HSP90与TPRs相互作用, 以及促进底物与FKBD结合的功能, 但植物体内FKBPs与钙调蛋白结合的功能还不明确(Schiene-Fischer, 2015)。高等植物中亲环素也分为2类: 一类是单结构域CYPs, 只含有保守结构域CYPD (CYP domain), 具有PPlase活性; 另一类是具有多个结构域的CYPs, 除了具有PPlase活性, 还含有WD40 (WD40 domain)、TPR (tetratricopeptide repeat)、U-box结构域(U-box domain)、锌指结构域(Zn-finger domain)、富含亮氨酸的结构域(Leu-rich)、RNA识别模体(RNA recognition motif, RRM)和螺旋束结构域(helical bundle domain) (He et al., 2004)。真核生物中的RRM能调节转录后基因的表达、蛋白-蛋白相互作用和形态建立, 人体中的RRM参与构成剪接体且能与mRNA结合(Maris et al., 2005; Wang et al., 2008; Schiene-Fischer, 2015)。植物体内CYPs参与调节基因的表达、热胁迫响应和叶绿体内复杂蛋白质的合成等(表1)。根据植物体内parvulin蛋白的底物特异性可将其分为依赖磷酸化(Pin1-type)和不依赖磷酸化(non-Pin1-type) 2类。目前发现parvulin蛋白参与植物的激素运输和胁迫响应(表1)。

## 2 亲免素与植物生长发育

### 2.1 FKBPs与植物生长发育

植物的生长发育与激素密不可分。亲免素与生长素、油菜素内酯、细胞分裂素等都具有复杂而密切的联系, 在植物的生长发育过程中具有重要作用。拟南芥

AtFKBP42 (TWISTED DWARF1, TWD1)参与多种激素的运输与分布。拟南芥ABC (ATP binding cassette)家族中的ABCB1、ABCB4和ABCB19等成员参与生长素运输。TWD1的N末端PPlase-like结构域与ABCB1和ABCB19的C末端相互作用, 揭示了TWD1可以调控生长素的运输和分布(图1) (Geisler et al., 2003; Wu et al., 2010; Wang et al., 2013)。目前报道TWD1定位在细胞膜、液泡和内质网, 其定位的多样性意味着功能的多样性(Kamphausen et al., 2002; Geisler et al., 2003; Wu et al., 2010)。近期研究表明, TWD1影响下胚轴表皮细胞内肌动蛋白束和肌动蛋白丝的动态平衡; ACTIN7是ABCB1-TWD1复合体的一部分, 能够调节ABCB、PIN和TWD1的表达和定位; 当TWD1突变后, 生长素运输和细胞骨架受到影响, 从而导致*twd1*突变体严重扭曲矮化的表型(Zhu and Geisler, 2015; Zhu et al., 2016)。

最新研究显示, 拟南芥TWD1也参与油菜素甾醇(brassinosteroid, BR)的信号传递。在根生长和下胚轴伸长过程中, *twd1-2*以及*twd1-5*对油菜素内酯(brassinolide, BL)的敏感程度降低; 在*twd1-5*中磷酸化和未磷酸化的BES1含量均降低。实验结果显示TWD1在植物体内能与BRI1和BAK1相互作用。以上表明TWD1与BRI1和BAK1相互作用影响了BR信号转导(图1) (Zhao et al., 2016; Chaiwanon et al., 2016)。

在哺乳动物中, FKBPs与转录因子相互作用较为常见, 在植物体内也发现FKBPs与转录因子相互作用调节细胞的分裂与分化。拟南芥突变体*pas1* (*pas-ticcione1*)的细胞分裂异常、分化紊乱, 对野生型植株施加外源性细胞分裂素后出现与*pas1*相似的表型。研究发现, PAS1 (即FKBP72)的C末端与FAN转录因子(FKBP-associated NAC)相互作用, 促进了FAN对细胞分裂的抑制(Harrar et al., 2003; Smoczynski et al., 2006)。另一方面, PAS1参与超长链脂肪酸(very-long-chain fatty acids, VLCFAs)的合成。PAS1的功能缺失后, VLCFAs在拟南芥体内的含量下降, 影响鞘脂类物质合成, 使细胞不能正常分裂分化(Roudier et al., 2010)。

### 2.2 CYPs与植物生长发育

拟南芥CYPs能调节生长素的运输和信号转导, 从而

表1 部分植物亲免疫素在细胞内的定位及功能

Table 1 The localization and function of some immunophilins in plant cells

亲免疫素	定位	PPase 活性	功能	参考文献
AtFKBP12	细胞质	未知	与AtFIP37相互作用调节胚胎初期发育; 与转录因子PwHAP5相互作用调节花粉管极性生长	Vespa et al., 2004; Yu et al., 2011
AtFKBP13	叶绿体	无	与Rieske相互作用; 与AtVKOR相互作用; 参与调节氧化还原平衡	Gupta et al., 2002; Lu et al., 2014
AtFKBP16-1	叶绿体	无	与AtPsaL相互作用; 影响PSI-LHCI-LHCII复合体形成; 参与强光和干旱胁迫响应	Gollan et al., 2011; Park et al., 2013b
AtFKBP16-2	叶绿体	无	与NADPH脱氢酶复合体相互作用, 稳定NDH-PSI复合体	Peng et al., 2009
OsFKBP16-3	叶绿体	无	参与盐碱、干旱和强光胁迫	Park et al., 2013a
TaFKBP16-3	叶绿体	未知	与Thf1以及APO2相互作用, 参与调节光系统的组装	Gollan et al., 2011
AtFKBP42	内质网, 细胞膜	未知	影响生长素的运输和油菜素内酯的信号传递	Geisler et al., 2003; Geisler et al., 2004; Wu et al., 2010; Wang et al., 2013; Zhao et al., 2016; Chaiwanon et al., 2016
AtFKBP62	细胞质	有	与HSP90.1相互作用; 具有耐盐性	Meiri and Breiman, 2009; Karali et al., 2012
AtFKBP65	细胞质	有	参与热胁迫; 维持细胞内pH稳态; 参与抵抗病原体	Meiri and Breiman, 2009; Bisoli et al., 2012; Pogorelko et al., 2014
AtFKBP72	细胞核	有	与FAN相互作用; 参与细胞的分裂、分化和超长链脂肪酸的合成	Smyczynski et al., 2006; Rou-dier et al., 2010
AtCYP19-1	细胞质	有	参与抵抗丁香假单胞菌和黄单胞杆菌的感染	Pogorelko et al., 2014; Mok-riakova et al., 2014
AtCYP19-3	细胞质	有	与CaM相互作用, 可能参与Ca <sup>2+</sup> 的信号传递	Kaur et al., 2015
AtCYP19-4	内质网	有	与GNOM相互作用, 调节ARF GEF的功能, 参与囊泡运输; 抵抗寒冷胁迫	Grebe et al., 2000; Yoon et al., 2016
AtCYP20-2	叶绿体	有	参与NAD(P)H脱氢酶复合体的形成; 改变BZR1的构象, 控制花期	Sirpio et al., 2009; Zhang et al., 2013
TaCYP20-2	叶绿体, 细胞质	未知	参与赤霉素信号通路中DELLA蛋白的降解过程	Li et al., 2010
AtCYP20-3	叶绿体	有	与丝氨酸乙酰基转移酶相互作用, 参与半胱氨酸的合成和逆境响应; 与茉莉酮酸酯结合调节氧化还原平衡	Dominguez-Solis et al., 2008; Park et al., 2013b
AtCYP38	叶绿体	未知	参与组装和维持PSII及放氧复合体; 参与强光胁迫	Fu et al., 2007; Wang et al., 2015
AtCYP40	细胞核	有	与AGO1相互作用, 有助于HSP90调节RISC的组装; 参与转录后基因沉默	Earley et al., 2010; Vasudevan et al., 2015
AtCYP71	细胞核	有	参与染色质组装、组蛋白修饰和基因表达	Li and Luan, 2011
LeCYP1	细胞质, 细胞核	有	影响生长素运输和侧根形成	Jing et al., 2015
OsCYP2	细胞质, 细胞核	有	参与多种胁迫响应; 参与细胞生长、分化、核糖体的合成、RNA编辑、基因表达和信号转导过程	Jing et al., 2015
AtPin1	细胞质, 细胞核	有	调节开花时间; 影响生长素的运输和根的向地性	Wang et al., 2010; Xi et al., 2016
GhPPI	细胞核	有	参与盐胁迫	Wang et al., 2014

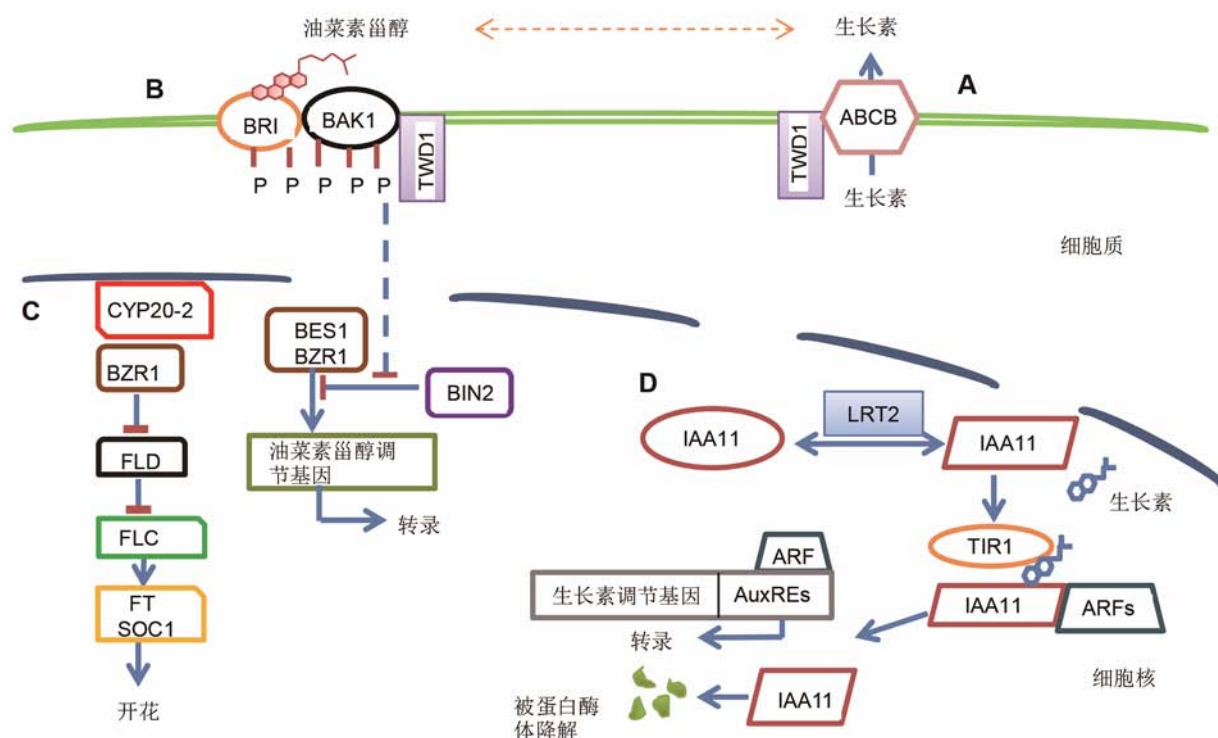


图1 亲免疫素与相关蛋白质相互作用调节下游信号的传递

(A) ABCB蛋白在TWD1的帮助下正确定位于细胞膜, 将细胞质内的生长素运出; 这个过程可能受BR (brassinosteroid)的影响 (Geisler and Bailly, 2007; Wu et al., 2010); (B) 在BR的作用下, TWD1与BRI1和BAK1相互作用促进其磷酸化, 抑制BIN2的活性, 影响BES1/BZR1的磷酸化, 从而调节BR响应基因的表达 (Zhao et al., 2016; Chaiwanon et al., 2016); (C) AtCYP20-2与BZR1相互作用改变BZR1的构象, 调节FLD的表达, 改变开花时间 (Zhang et al., 2013); (D) 在有生长素时, LRT2与OsIAA11相互作用, 使OsIAA11构象发生变化, 促进其与OsTIR1相互作用, 形成OsTIR1-OsIAA11复合体。在OsTIR1-IAA11复合体的帮助下泛素分子连接到OsIAA11上, 然后OsIAA11蛋白被26S蛋白酶体降解, ARFs形成有活性的形式, 从而激活生长素调节基因的表达 (Jing et al., 2015)。

Figure 1 Immunophilins regulate downstream signaling by interacting with related proteins

(A) TWD1 helps the correct secretion of ABCB transporters to the plasma membrane, thus regulating ABCB-mediated auxin transport; Brassinosteroid might affect this process (Geisler and Bailly, 2007; Wu et al., 2010); (B) TWD1 physically interacts with BRI1 and BAK1 in a BR-independent manner, which may facilitate the phosphorylation of BRI1 and BAK1, inhibit BIN2 activity, and affect BES1/BZR1 phosphorylation, eventually regulate the BR response gene expression (Zhao et al., 2016; Chaiwanon et al., 2016); (C) A conformational change of BZR1 mediated by AtCYP20-2 causes altered flowering time through the modulation of FLD expression (Zhang et al., 2013); (D) In the presence of auxin, OsIAA11 conformation was changed by interacting with LRT2, and then formed the OsTIR1-OsIAA11 complex. OsTIR1-OsIAA11 complex facilitated OsIAA11 binding to 26S proteasome and caused OsIAA11 degradation; Finally, ARFs became active and activated auxin-regulated genes (Jing et al., 2015).

影响植物的生长和组织器官的发育。早期的研究表明, 拟南芥PP2A (heterotrimeric protein phosphatase 2A) 的1个亚基A能够与AtCYP20-1相互作用调节PP2A的活性, 影响生长素转运蛋白的正确定位, 从而影响生长素的运输和植物生长 (Jackson and Söll, 1999)。最近的研究显示, CYP19-4s (AtCYP19-4和

OsCYP19-4)能与AtPP2A相互作用, OsCYP19-4过量表达植株与PIN1 RNAi植株表型相似, 说明OsCYP19-4可能影响生长素的极性运输和PIN的定位 (Yoon et al., 2016)。水稻lrt2 (lateral rootless 2, 即cyp2)突变体的表型与生长素突变体表型相似, 侧根发育不良、分蘖数和植株高度减少、花序发育受损, 表

明LRT2参与生长素的信号通路并且在调节侧根发育方面具有重要作用(Kang et al., 2013; Zheng et al., 2013)。另有研究表明,在生长素存在时,LRT2使OsIAA11构象发生变化,促进其与TIR1 (transport inhibitor response 1)相互作用形成OsTIR1-IAA11复合体,在OsTIR1-IAA11复合体的帮助下,泛素分子连接到OsIAA11上,然后OsIAA11蛋白被26S蛋白酶体降解,ARFs (auxin response element)形成有活性的形式,从而激活生长素调节基因的表达(图1) (Jing et al., 2015)。最近的研究表明,番茄(*Lycopersicon esculentum*)的DGT (LeCYP1)可以通过筛管运输,将野生型嫁接到*dgt*突变体,可使突变体的表型得到一定程度的恢复;LeCYP1具有提高植株对生长素的响应能力和调节根冠比的作用(Spiegelman et al., 2015)。另外,DGT能够影响根部和茎部生长素的运输,控制侧根的形成;在酵母和烟草(*Nicotiana benthamiana*)系统中,DGT通过影响生长素转运蛋白PIN在细胞膜上的定位调节生长素的输出(Ivanchenko et al., 2015)。CYPs主要通过调节生长素转运蛋白的定位和生长素调节基因的表达,影响生长素的运输和生长素信号通路,进而调控植物的生长发育。

在拟南芥开花信号途径中,*FLC* (*FLOWERING LOCUS C*)通过抑制成花信号*FT* (*FLOWERING LOCUS T*)和转录因子基因*SOC1* (*SUPPRESSOR OF OVEREXPRESSION OF CONSTANS1*)的表达抑制开花。研究发现,拟南芥AtCYP20-2与BZR1相互作用改变BZR1的构象,调节*FLD* (*FLOWERING LOCUS D*)的表达;过量表达CYP20-2使*FLD*表达量增加,而*FLD*能抑制*FLC*染色质的甲基化和乙酰化,从而导致开花提前(图1);而过量表达小麦CYP20-2后开花延迟,其原因可能是TaCYP20-2参与赤霉素信号通路中DELLA蛋白的降解过程(Li et al., 2010; Zhang et al., 2013)。

拟南芥ROC1 (AtCYP18-3)与光敏色素、隐花色素共同参与幼苗的去黄化过程。突变体*roc1*和*roc1-D*能够改变转录因子BES1的磷酸化模式,但ROC1不能与BES1相互作用;CYP18-3的作用机制可能与TWD1相似,通过与BRI1和BAK1相互作用影响BES1的磷酸化(Trupkin et al., 2012)。有趣的是,在茎伸长过程中,赤霉素与ROC1具有拮抗作用,AtCYP18-3也许不仅参与BR的信号通路,还可能间接

参与赤霉素的信号传递过程(Ma et al., 2013)。

## 2.3 Parvulins与植物生长发育

目前,关于parvulin蛋白的研究相对较少。研究表明,parvulin蛋白能调节植物的生长发育和抗逆性。拟南芥依赖磷酸化的AtPin1有1个PPlase结构域,能够改变PIN1的构象,使其极性定位发生改变,进而影响生长素的运输和根的向地性;另外,Pin1At与AGL24 (AGAMOUS-LIKE 24)和SOC1相互作用改变其构象,调节开花时间(Wang et al., 2010; Xi et al., 2016)。棉花GhPPI在盐胁迫下表达量升高,该蛋白是目前已报道的唯一与盐胁迫相关的parvulin蛋白(Wang et al., 2014)。

## 2.4 叶绿体内亲免素的功能

拟南芥叶绿体定位的亲免素多达17种,包括11种FKBPs、5种CYPs和1种parvulin蛋白。定位在叶绿体的亲免素中,只有AtFKBP13和AtCYP20-2具有PPlase活性,但是AtFKBP13和AtCYP20-2的双突变体无论是在正常条件下、寒冷胁迫下还是强光胁迫下与野生型相比都没有太大差异(Ingelsson et al., 2009)。由于其它定位在叶绿体的亲免素都没有PPlase活性,因此定位在叶绿体内的亲免素的功能可能与PPlase活性无关(Ingelsson et al., 2009)。叶绿体是光合作用的场所,定位在叶绿体的亲免素在植物光合作用中具有重要作用。

小麦TaFKBP16-1和TaFKBP16-3在光系统I (PSI)的组装过程中扮演着重要角色。TaFKBP16-1与PSI的1个亚基PsaL (PSI subunit L)相互作用,TaFKBP16-3与Thf1 (Thylakoid Formation 1)和APO2 (Os02g50010)存在相互作用,因此TaFKBP16-1和TaFKBP16-3可能调控PSI的组装(Gollan et al., 2011)。最近研究显示,AtFKBP16-1能够稳定PSI的亚基PsaL在细胞内的含量,并且AtFKBP16-1影响LH-CII转移到PSI-LHCI上形成PSI-LHCI-LHCII复合体的过程,说明FKBPs与PSI的组装和功能有着密切关系(Seok et al., 2014)。

拟南芥AtFKBP20-2和AtCYP38在PSII的组装和维持中发挥重要作用。拟南芥*Atfkbp20-2*突变体生长缓慢,光系统II (PSII)复合体含量下降,PSII的单体和二聚体比野生型含量多,说明FKBP20-2对PSII的组装和稳定有一定的影响(Lima et al., 2006)。拟南芥类

囊体膜的氧化还原酶AtVKOR-DsbA定位于类囊体腔,其参与氧化还原反应、催化二硫键的形成、维持细胞内ROS的平衡以及PSII的组装。酵母双杂交实验显示,AtFKBP20-2与AtVKOR存在相互作用,暗示AtFKBP20-2可能参与PSII的组装(Lu et al., 2014)。Atcyp38突变体植株发育不良,对光敏感,不能正确组装PSII超级复合体;并且AtCYP38也参与放氧复合体的正确组装(Fu et al., 2007; Sirpio et al., 2008; Vasudevande et al., 2012)。研究表明,菠菜(*Spinacia oleracea*) TLP40是拟南芥AtCYP38的同源蛋白,能够调节PSII系统中磷酸蛋白酶的活性。不过, TLP40具有PPlase活性,而AtCYP38不具有PPlase活性,具体原因需要进一步研究(Rokka et al., 2000)。

NADPH脱氢酶NDH复合体能够调节PSI的循环和叶绿体内的电子传递,NDH与PSI形成NDH-PSI复合体,AtFKBP16-2能与NADPH脱氢酶复合体相互作用,从而稳定NDH-PSI复合体(Peng et al., 2009)。AtCYP20-2是定位于类囊体腔且具有PPlase活性的亲环素,其基因表达受光调控。最初报道AtCYP20-2与PSII的组装有关,但是cyp20-2在有光和无光条件下均能生长,且其PSII均无异常。后续研究表明,AtCYP20-2与NAD(P)H复合体的形成有关,其在NDH疏水结构域的形成中起作用,并且在NAD(P)H脱氢酶复合体的形成过程中作为重要的分子伴侣发挥作用(Sirpio et al., 2009)。

## 2.5 亲霉素调节基因表达

基因沉默、表观遗传学调控和转录水平的调控对植物的生长发育产生重要影响。拟南芥cyp40突变体叶片数量减少和形态改变与microRNA活性减弱有关。成熟的microRNA能够与RNA诱导沉默复合体(RNA-induced silencing complex, RISC)结合,形成具有切割活性的RNA沉默复合物,该复合物与靶基因互补配对使靶基因沉默或抑制靶基因的翻译。AGO1(ARGONAUTE1)是RISC的重要组成部分(Voinnet, 2009; Earley et al., 2010)。AtCYP40与AGO1相互作用促进或维持AGO1的活性,从而有助于HSP90调节RISC的组装,影响基因沉默或基因的翻译(Earley et al., 2010; Vasudevan et al., 2015)。

拟南芥突变体cyp71茎尖分生组织活性下降,侧生器官发育异常,花的形态发生改变,根的生长受抑

制(Li et al., 2007)。AtCYP71定位于细胞核,其N末端有4个重复结构域WD40, CYPD结构域在C末端,AtCYP71的重复结构域WD40与组蛋白H3相互作用,影响H3K27的甲基化水平,从而导致cyp71出现异常表型(Li et al., 2007)。进一步研究证明,AtCYP71能与FAS1和LHP1相互作用,参与染色质组装和组蛋白修饰(Li and Luan, 2011)。其它细胞核定位的亲霉素,如AtFKBP43和AtFKBP53,具有多个结构域,FK-BPD在C末端,N末端结构域具有高度可变性,可能与核酸或者蛋白质相互作用(He et al., 2004)。AtFKBP53被证明在植物体内作为组蛋白的分子伴侣,与组蛋白H3通过N末端的酸性结构域相互作用。有趣的是, PPlase活性对AtFKBP53的分子伴侣功能不重要,AtFKBP53能够抑制核糖体RNA基因的表达,具有使染色质重塑和调节转录的功能(Li and Luan, 2010)。

## 3 亲霉素对非生物及生物胁迫的响应

### 3.1 亲霉素对非生物胁迫的响应

FKBPs对热胁迫、盐胁迫、干旱及强光胁迫都有响应。拟南芥中2个高度同源的基因FKBP62 (AtROF1)与FKBP65 (AtROF2)参与植物耐热性调控。但是在热胁迫下,2个基因的表达量和调节方式不同,AtROF1促进热激蛋白的表达而AtROF2抑制热激蛋白的表达(Aviezer-Hagai et al., 2007; Meiri and Breiman, 2009)。AtROF2二级结构主要是 $\beta$ 折叠、无规则卷曲及转角等,仅含少量的 $\alpha$ 螺旋;不同温度下AtROF2的二级结构呈2种形式,当温度达到65°C时,AtROF2结构发生轻微变化以适应高温,直到温度达到97°C该结构仍然稳定。AtROF2在高温下结构稳定的特性,可能在研究植物耐热性方面具有重要作用(Lighezan et al., 2013)。在盐胁迫下,过量表达AtROF1的拟南芥种子萌发率提高,AtROF1的FKBD可以与作为第二信使传递信号的磷脂酰肌醇-3-磷酸和磷脂酰肌醇-3,5-二磷酸相互作用。因此,AtROF1可能通过与其相互作用影响细胞内的信号传递,激活植物对逆境的响应。另外,ROF2还能调节细胞内的酸碱度,植物体过量表达ROF2能提高对有毒阳离子的耐受性(Karali et al., 2012; Bissoli et al., 2012)。

在盐碱、干旱和强光等逆境胁迫下,水稻Os-

*FKBP16-3*的表达量增加,将*OsFKBP16-3*转化拟南芥,转基因植株对盐碱、干旱和强光的耐受性提高(Park et al., 2013a)。在极端环境下,植物体内会产生活性氧簇(ROS)。*FKBP16-3*定位在叶绿体内,其含有一段保守的氧化还原位点CxxxC,能被ROS氧化形成二硫键;*FKBP16-3*可能通过修饰CxxxC调节氧化还原过程,以减少逆境对植物的伤害(Park et al., 2013a)。另外,ROS在环境胁迫或者生物胁迫下可以作为信号分子通过诱导特殊的激酶激活MAPK通路。因此,亲霉素也可能通过调控ROS的产生激活MAPK通路参与植物对胁迫的响应(Pogorelko et al., 2014)。

CYPs在植物抵抗盐碱、干旱、寒冷和强光胁迫方面具有重要作用,并且能够增加水稻分蘖,从而提高产量。过量表达*OsCYP2*可以提高水稻种子的耐盐性,并且*OsCYP2*可能通过调节抗氧化酶活性控制细胞内ROS的含量,从而提高植株的耐盐性(Ruan et al., 2011)。*OsCYP18-2*与*OsSKIP* (ski-interacting protein)相互作用,使*OsCYP18-2*的定位从细胞质转移到细胞核,*OsCYP18-2*-*OsSKIP*复合体可能参与mRNA的转录和mRNA前体剪接或稳定性等;并且过量表达*OsCYP18-2*能提高水稻的耐旱性,原因可能是*OsCYP18-2*-*OsSKIP*复合体在细胞核中调节与抗逆相关的基因表达(Lee et al., 2015)。内质网定位的*OsCYP19-4*具有PPlase活性,在水稻中过量表达*OsCYP19-4*能够增强其耐寒性,并且显著提高水稻的分蘖和穗的数量,从而使产量提高(Yoon et al., 2016)。*Atcyp38*突变体光合作用受到一定程度的抑制。研究显示,CYP38参与强光胁迫响应,突变体*cyp38*在强光下PsbO2表达量增加,导致D1蛋白降解,ROS产量增多;野生型在强光下细胞质内Ca<sup>2+</sup>和CaM3含量增多以促进CYP38的表达,CYP38能够抑制PsbO2的活性,减少D1蛋白的降解,从而降低ROS以及强光对植物体的伤害(Wang et al., 2015)。

叶绿体内半胱氨酸合成过程中的重要酶(丝氨酸乙酰基转移酶(SAT1))能与*AtCYP20-3*相互作用,指导SAT1的正确折叠,保证半胱氨酸合成通路,以适应各种逆境(Dominguez-Solis et al., 2008)。植物激素中茉莉酮酸酯家族对植物的生长发育和胁迫响应具有重要作用。在胁迫响应过程中,*AtCYP20-3*能与植物激素茉莉酮酸酯结合调节细胞内氧化还原平衡(Park et al., 2013b)。研究表明,*AtCYP19-3*具有PP-

lase活性,并且对Cu<sup>2+</sup>敏感,而Cu<sup>2+</sup>能与巯基反应,这意味着PPlase可能参与调节氧化还原反应(Kaur et al., 2015)。无论体内还是体外,*AtCYP19-3*的N末端都能与CaM相互作用,并且这种相互作用依赖Ca<sup>2+</sup>,但是CaM不影响*AtCYP19-3*的PPlase活性,这可能意味着*AtCYP19-3*参与Ca<sup>2+</sup>的信号传递过程(Kaur et al., 2015)。作为第二信使的Ca<sup>2+</sup>对植物响应生物和非生物胁迫具有重要作用,而*AtCYP19-3*能与CaM相互作用影响Ca<sup>2+</sup>,说明*AtCYP19-3*可能从上游调节植物对各种胁迫的响应。

### 3.2 亲霉素对生物胁迫的响应

生物胁迫对作物生产具有严重危害。研究发现,病原体入侵时,*AtCYP19*、*AtCYP57*和*AtFKBP65*的表达量显著提高。*AtCYP19*、*AtCYP57*和*AtFKBP65*基因的缺失突变体更易感染丁香假单胞菌和黄单胞杆菌,突变导致对其病原体表面保守分子特征(pathogen associated molecular patterns, PAMPs)的识别有缺陷;过量表达*AtCYP19*、*AtCYP57*和*AtFKBP65*的拟南芥对丁香假单胞菌的抵抗力增强;并且*AtCYP19*、*AtCYP57*和*AtFKBP65*能够激活病原体相关分子模式触发免疫(PAMPs triggered immunity, PTI),使胼胝质沉淀和过氧化氢积累以抵抗病原体(Pogorelko et al., 2014; Mokriakova et al., 2014)。

然而,最近研究发现,*AtCYP18-3* (ROC1)在植物免疫系统中具有负调控作用,ROC1能与效应子触发免疫(effector triggered immunity, ETI)的受体RIN4相互作用,减少RIN4的磷酸化,使抗性基因*RPM1*不能够识别效应因子,从而不能激活ETI途径;而大豆CYP1能激活疫霉属效应因子Avr3b的酶活性。这说明亲霉素参与生物胁迫的方式较多,其作用机制有待进一步研究(Li et al., 2014; Kong et al., 2015)。

## 4 展望

近年来的研究表明,FKBPs与多种激素关系密切。拟南芥中调节生长素运输的TWD1与人类FKBP38结构相似,人类FKBP38的PPlase活性能够促进囊性纤维化跨膜传导调节蛋白(CFTR)的翻译后折叠,并且其TPR结构域与Hsp90相互作用能够抑制PPlase活性,对CFTR的合成进行负反馈调节(Banasavadi-Sid-



degowda et al., 2011)。TWD1调节ABCBs的方式是否与人类的FKBP38相似,即作为分子伴侣指导ABCBs转运蛋白的折叠和运输还有待证明。动物的FKBP51和FKBP52作为甾醇类激素受体的分子伴侣,能够与HSP90形成复合体,帮助受体的正确定位以及激素与受体的结合(Sivils et al., 2011)。同样,拟南芥TWD1参与油菜素甾醇的信号传递途径,但不同的是,TWD1通过与磷酸激酶BRI1和BAK1相互作用调节对BR的响应(Zhao et al., 2016; Chaiwanon et al., 2016)。这在一定程度上说明,拟南芥TWD1与动物FKBP52在功能上有相似性但在执行功能的方式上有所不同。另外,TWD1与BRI1和BAK1的哪个结构域相互作用,是否与PPlase活性有关,也需要进一步验证。

CYPs参与生长素、油菜素内酯、赤霉素和茉莉酸等激素的信号转导途径,其中生长素、赤霉素和茉莉酸均以蛋白酶体降解抑制子的方式激活信号通路(Jing et al., 2015)。有趣的是,TaCYP20-2与赤霉素的信号抑制子Rht/DELLA蛋白的降解有关;OsLRT2/CYP2参与生长素抑制蛋白Aux/IAA的降解;表明亲环素在调节激素信号通路过程中具有重要作用(Li et al., 2015; Jing et al., 2015)。

在哺乳动物中,亲免疫素的主要功能是与小的配体结合(如免疫抑制剂),或者作为分子伴侣调节蛋白质的结构、活性和稳定性。在高等植物中,亲免疫素通过与相关蛋白质相互作用调控生长发育;并且FBKPs对免疫抑制剂不敏感,PPlase活性也不保守;而亲环素对免疫抑制剂敏感,PPlase活性也较为保守。例如,AtROC1、LeCYP1和OsCYP2都具有PPlase活性(表1)。高等植物中亲免疫素对免疫抑制剂的不同敏感性,可能是由于在进化中丢失了PPlase活性所致。迄今为止,关于parvulin蛋白的研究相对较少。有研究将parvulin蛋白归类于不同于亲免疫素的PPlase,主要是由于它不能被FK506、雷帕霉素和环孢素A等免疫抑制剂抑制(Rahfeld et al., 1994; He et al., 2004; Dunyak and Gestwicki, 2016)。最新研究发现,拟南芥parvulin蛋白Pin1At能够改变PIN1的构象,影响PIN1的极性定位,进而影响生长素的运输和根的向地性;LeDGT/CYP1具有PPlase活性,也影响PIN在细胞膜上的定位和生长素的运输;但PIN蛋白的正确定位与PPlase活性的关系还需要进一步验证(Ivan-

chenko et al., 2015; Xi et al., 2016)。

植物体内的亲免疫素能够对环境胁迫做出响应。例如,它通过与热休克蛋白、磷脂酰肌醇、钙调蛋白的相互作用,激活某些信号通路、参与氨基酸(如半胱氨酸)合成等响应环境胁迫。叶绿体内的亲免疫素与光合膜的组装和氧化还原过程等有关,但是亲免疫素在叶绿体内的功能对胁迫响应有何影响需进一步探明。亲免疫素在抵抗外界胁迫及在叶绿体中的功能已在农作物中进行了相关研究,并且在水稻耐盐增产和小麦抗旱等方面取得了一定的进展。因此,亲免疫素在农作物改良和分子育种等方面有着广阔的应用前景。

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## Advances in the Functions of Immunophilins in Plants

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**Abstract** Immunophilins are receptors for immunosuppressive drugs that exist widely in bacteria, viruses, fungi, plants and animals. In plants, immunophilins have three subfamilies: FK506-binding proteins, cyclosporine A-binding proteins (cyclophilins) and parvulins. Many members of immunophilins are peptidyl-prolyl *cis-trans* isomerases that may act as molecular chaperones for protein folding. In this review, we summarize the research progress in the functions of plant immunophilins in hormone signaling, photosynthesis, stress response and gene expression etc., to provide valuable information for further study of immunophilin functions.

**Key words** growth and development, gene expression, immunophilins, photosynthesis, stress response

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