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CIN-like TCP Transcription Factors: The Key Regulators of Plant Development and Immunity*

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Abstract The plant-specific TEOSINTE BRANCHED1, CYCLOIDEA, and PCF (TCP) transcription factors are classified into two classes, class Ⅰ and class Ⅱ TCPs according to the shared bHLH TCP domain. Accumulating evidences demonstrate that a subgroup of class Ⅱ CINCINNATA-like (CIN-like) TCP transcription factors plays a vital role in the establishment of plant architecture through modulating hormone biosynthesis and signaling. Recent advances have revealed their unexpected roles in mediating pathogenic effectors-triggered immunity (ETI), suggesting that the widely recognized developmental modulators are involved in fine-tuning plant immunity as well. Although the dissection of the regulatory pathway of CIN-like TCP proteins has begun to shed light on their mechanism of action, a unified and updated view based on the available information is urgently needed. This review aims to summarize the current knowledge about the functions of CIN-like TCPs in various regulatory cascades, and their roles as effector targets with an emphasis on the characterization of the available mutants, TCP interacting factors and the interconnected hormonal networks. Future perspectives for the research of these proteins are also discussed.

Key words CIN-like TCP transcription factors, plant development, immunity, interacting factors
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The TCP proteins are plant-specific transcription factors controlling diverse developmental and physiological processes. They are named for the first three identified members *TEOSINTE BRANCHED 1* (*TB1*) in maize (*Zea mays*), *CYCLOIDEA* (*CYC*) in snapdragon (*Antirrhinum majus*), and PCF-coding genes (*PCF1* and *PCF2*) in rice (*Oryza sativa*) [1]. Phylogenetic analysis reveals that TCPs share an approximately 60-residue homologous region, known as the TCP domain. This domain folds into basic helix-loop-helix (bHLH) structure, which is highly conserved and critical for DNA-binding and protein-protein interaction[1]. *Arabidopsis* TCP proteins comprising 24 members [2] are classified into two distinct groups, class Ⅰ and Ⅱ[3]. Recent studies indicate that class Ⅰ TCPs appear to promote cell division whereas class Ⅱ TCPs repress this process[2]. *Arabidopsis CINCINNATA-like* (*CIN-like*) *TCPs* form a subclade of the class Ⅱ TCPs, comprising five genes negatively regulated by miR319 (*TCP2*, *TCP3*, *TCP4*, *TCP10*, and *TCP24*) and three other genes not

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regulated by miRNAs (*TCP5*, *TCP13* and *TCP17*)[2]. *CIN* in *Antirrhinum* and miR319 regulated *CIN-like TCPs* in *Arabidopsis* and other plant species coordinate cell proliferation and growth during leaf development by making cells more sensitive to a growth-arrest signal at the leaf margins[2, 4]. *cin* mutants exhibit uncontrolled cell growth in the leaf margins and small, slightly curled, pale petals[5]. Likewise, down-regulation of *TCP* genes by the ectopic expression of miR319 induces a *cin*-like phenotype in *Arabidopsis*[6]. In contrast, plants with constitutive or mis-activation of TCP activity have a rapid onset of differentiation and a decrease of overall cell division[6], suggesting that CIN-like TCPs restrict the duration of the proliferative phase by promoting the onset of differentiation.

Eight *Arabidopsis CIN-like TCP* genes are expressed in an overlapping manner in various tissues and have similar functions. The *TCP3*, *TCP4*, and *TCP10* genes are expressed in cotyledons during embryogenesis[6]. However, their transcripts accumulation and respective promoter activity are neither evident in the shoot apical meristems (SAM) nor at cotyledon boundaries, which is consistent with the abundant accumulation of miR319 precursor in these areas[6]. Furthermore, seven of the eight *TCP* genes show similar expression patterns during the early stages of flower development[7].

CIN-like TCPs are the earliest known markers of lamina formation, based on their functions in the coordinated cell proliferation to generate a flat leaf surface[8]. Furthermore, CIN-like TCPs from diverse plant species have been demonstrated to regulate a large variety of biological processes, including cell differentiation[8–9], hormone biosynthesis and signaling[10–11], leaf maturation and progression of cell-division arrest front[12–13], leaf morphogenesis and senescence[6, 14], shoot lateral organ morphogenesis, petal and stamen development[15–16], and defense responses[17]. Moreover, CIN-like TCPs modulate simple and compound leaf formation in *Antirrhinum majus* and *Solanaceae* species[4, 18], and interact with clock proteins[19] and chromatin remodelers[11].

In this review, we summarize the phenotypical features of *CIN-like TCP* mutants and transgenic plants expressing *SRDX*- (a chimeric suppressor domain) fused *TCPs*. In addition, the developmental roles of CIN-like TCP proteins and their interactions with other proteins and several hormones affecting both plant development and immunity are synoptically discussed. These recent advances in elucidating the physiological functions of CIN-like TCP factors significantly contribute to our understanding of how these proteins coordinate external environments with internal regulatory networks to modulate plant development and immunity.

1 Phenotypic features of CIN-like TCP mutants and TCP-SRDX transgenic plants

Mutants of single *TCP* gene often show weak phenotypic changes, or in most cases, do not have such alteration due to genetic redundancy[10, 14]. Thus the major known phenotypes of *Arabidopsis tcp* mutants are mainly attributed to double or multiple knockouts, or even the *SRDX*-fused *TCP* transgenic plants. Mutants that overexpressing the *jagged and wavy* (*jaw-D*) microRNA miR319, lead to down-regulation of five class Ⅱ *TCP*s: *TCP2*, *TCP3*, *TCP4*, *TCP10* and *TCP24*[6]. These *jaw-D* plants exhibit several aspects of changes in morphology, including crinkly leaves, altered petal development, and delayed leaf senescence[6, 14, 16]. Combining *jaw-D* mutant with other three *CIN-like tcp* mutants, in which *TCP5*, *TCP13* and *TCP17* are down regulated, deeply lobed and highly serrated leaves are produced[12]. Consistent with this, *tcp3 tcp4 tcp10* triple, *tcp3 tcp4 tcp5 tcp10* quadruple and *tcp3 tcp4 tcp5 tcp10 tcp13* quintuple mutants exhibit phenotypic alterations including epinastic cotyledons, serrated leaves with wavy margins (Table 1) in a TCP-dosage-dependent manner[20]. Furthermore, disruption of *CIN-like TCP*s results in distorted ovule arrangement in ovaries, while overexpression of *CIN-like TCP*s leads to aborted ovules[21]. Especially, the *tcp4* single mutant exhibits maternal effect embryo arrest[22], cotyledon epinasty, mild leaf serration and delayed flowering (Table 1), which can be enhanced by combining with other *CIN-like TCP* mutants[14].

Table 1 Phenotypes of CIN-like TCP mutants or TCP-SRDX transgenic plants

Mutants/*TCP-SRDX*	Phenotype	Function	Reference
tcp4	Embryo arrest	Early embryo development	[22]
tcp13	Susceptible to infection	Immunity regulation	[23]
tcp3/4/10	Serrated leaves	Leaf development	[20]
tcp3/4/5/10	Serrated leaves, distorted ovule	Leaf and ovary development	[20−21]
tcp3/4/5/10/13	Serrated leaves	Leaf development	[20]
TCP3-SRDX	Ectopic shoots on cotyledons	Shoot lateral organ morphology	[15]
TCP24-SRDX	Cell wall lignification	Anther development	[24]
jaw-D	Altered morphology	Leaf, petal and ovary development	[6, 21]
jaw-D tcp5/13/17	Lobed and serrated leaves	Leaf development	[12]

Alternatively, dominant-negative version with the plant specific chimeric repressor domain SRDX is used to characterize the functional redundancy of TCPs[25]. As a result, the *Arabidopsis* plants expressing *SRDX*-fused *CIN-like TCP*s exhibit a phenotype similar to the loss-of-function mutants, with wavy leaves, abnormal vasculature, and ectopic formation of meristems on cotyledons (Table 1), revealing the redundant roles of CIN-like TCPs in the regulation of cell differentiation in leaf and lateral organ morphogenesis[15]. For examples, *TCP3-SRDX* induces the ectopic expression of the boundary-specific *CUP-SHAPED COTYLEDON* (*CUC*) genes and suppresses the expression of miR164, a negative regulator of *CUC* genes, suggesting a role of TCP3 in regulation of shoot lateral organ morphogenesis *via* control of boundary specific genes[15]. Likewise, the levels of proanthocyanidins are slightly reduced in *TCP3-SRDX* plants [26]. *TCP24-SRDX* increases cell wall lignification and affects anther endothecium development (Table 1)[24], indicating a role of TCP24 as a negative regulator in secondary cell wall thickening.

2 Functions of CIN-like TCP transcription factors

2.1 CIN-like TCPs regulate plant development

The functions for most of the class Ⅱ TCPs have been reported so far. *Arabidopsis CIN-like TCP* genes act in a partially redundant manner to modulate several aspects of plant growth and development, such as leaf development, maturation and progression of the cell-division arrest front [12−13, 20]. Likewise, miR319-sensitive CIN-like TCP protein LANCEOLATE (LA) in tomato delays flowering and restricts the organogenic activity in the leaf margin, but promotes leaf maturation together with additional related LA-like proteins [27]. Similarly, overexpression of miR319 results in the expansion of leaf blade in rice[28]. Moreover, CIN-like TCPs promote leaf senescence by direct activation of the expression of *LIPOXYGENASE2* (*LOX2*) (Figure 1), which catalyzes the first dedicated step in jasmonic acid (JA) biosynthesis[14], and regulate the expression of *KNOTTED1-like HOMEOBOX* (*KNOX*) genes *BREVIPEDICELLUS* (*BP*) and *KNAT2*, by interacting with ASYMMETRIC LEAVES 2 (AS2) [29]. Additionally, CIN-like TCP factors have also been shown to modulate leaf shape by negatively regulating boundary specific *CUC* genes (Figure 1), and to control cell proliferation through activation of miR396, *CYCLIN-DEPENDENT KINASE INHIBITOR 1*/*KIP RELATED PROTEIN 1* (*ICK1*/*KRP1*) and JA biosynthesis[30], or by interfering with cytokinin (CK) signaling[11]. Recently, the activities of CIN-like TCPs have shown to be suppressed by interacting with transcriptional repressor SPOROCYTELESS (SPL) and TOPLESS (TPL) in ovule development regulation[21]. Especially, TCP4 is critical for early embryo development[22] and petal growth[16]. Activated TCP4 results in aberrant pollen grains that fail to produce viable seeds, and promotes organ initiation, maturation and senescence [9]. Moreover, TCP4 represses cell proliferation in developing leaves, and blocks cell division at G1-S transition in budding yeast[31].While the RABBIT EARS (RBE) regulated *TCP5* modulates the number and duration of cell division in the petal[32], and the heterodimerized TCP5 and TCP13 may also play a role in modulating the cessation of cell division

across the petal[33].

TCPs modulate many aspects of plant growth and development by regulating their target genes. The role of TCPs in leaf morphogenesis is partly mediated by NGATHA (NGA) factors, which are positively regulated by TCP2 and TCP3[34]. Several other targets of TCP3 have also been identified, including miR164, *AS1*, *INDOLE-3-ACETIC ACID 3/SHORT HYPOCOTYL 2* (*IAA3/SHY2*), and *SMALL AUXIN UP RNA* (*SAUR*) with functions in regulating shoot meristem formation[20]. Moreover, TCP3 is proposed to regulate the expression of *CUC1* and *CUC2* (Figure 1), genes function in delimiting boundaries between lateral organs[15]. TCP4 is a direct regulator of miR396, which encodes a miRNA that represses cell proliferation (Figure 1). Another newly characterized target of TCP4 is *ICK1/KRP1*, a gene known to be active in G2/M-phase of the cell cycle [30]. TCP24 negatively regulates secondary cell wall thickening in floral organs and roots, and modulates anther endothecium development[24]. It could also negatively regulate the expression of *CDT1a* and *CDT1b* (Figure 1), genes involved in G1/S-phase transition[35].

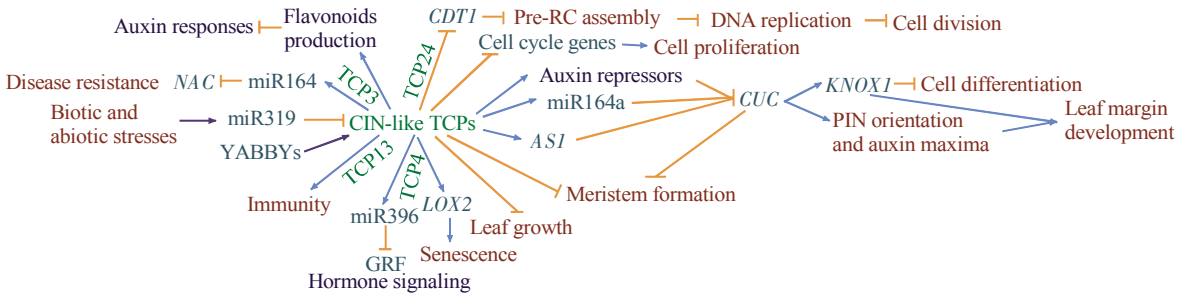

Fig. 1 Molecular networks of CIN-like TCP protein action

Arrows and bars at the end of each line indicate positive and negative regulations, respectively.

2.2 CIN-like TCPs regulate plant defense responses

The plants must fine-tune immune responses both positively and negatively to prevent deleterious developmental phenotypes, poor growth and reduced fertility, thereby maintaining normal growth and health [36]. Although the diversity of pathogens is immense, various attackers from different kingdoms utilize independently evolved virulence factors (effectors) that interacting with a limited set of highly connected cellular hubs in host biological networks, to hijack cellular machinery in a manner conductive to diverse pathogenic life cycle strategies[37-38]. It has been shown that single *tcp13* mutant exhibits enhanced disease susceptibility to pathogen infection (Table 1, Figure 1), and that *TCP13* expression significantly responds to pathogen infection, suggesting of TCP13 as a positive regulator of plant immunity [23, 39]. Additionally, the SAP11, a secreted small virulence effector from *Aster Yellows phytoplasma* strain *Witches' Broom* (*AY-WB*), binds and destabilizes CIN-like TCPs[17], leading to dramatic changes in leaf morphogenesis, reduction of JA biosynthesis and increased susceptibility to *phytoplasma* insect vectors[40-41].

2.3 Intertwined functions of CIN-like TCPs with other TCP members

Interplay between class Ⅰ and class Ⅱ TCPs in rice has been described for their distinct but overlapping consensus binding site: G(T/C)GGNCCC[3]. Both classes of TCPs may perform their functions coordinately or competitively by interacting with similar sets of target genes[3, 42]. An example of class Ⅰ TCP and class Ⅱ CIN-like TCP coordinately regulate transcription is that the class Ⅰ TCP15 indirectly regulates *CUC* genes through binding the promoters of *IAA3/SHY2* and *SAUR*, which are also binding targets of CIN-like TCPs for regulating *CUC* gene expression[43] (Figure 2). Interestingly, an antagonistic regulation of class I TCPs and class Ⅱ CIN-like TCPs in the control of leaf development by affecting JA biosynthesis is shown (Figure 2). Class Ⅰ TCP20 negatively regulates the expression of JA biosynthesis gene *LOX2*, which is positively regulated by CIN-like TCP4 [44] (Figure 2).

Moreover, down-regulation of miR319 regulated *CIN-like* TCP genes leads to the prolonged mitotic activity and consequently increased cell proliferation[12], while single or double mutant of class Ⅰ *TCP9* and *TCP20* results in decreased cell production accompanied with an increased cell size[44]. Opposing functions of class Ⅰ TCPs and class Ⅱ CIN-like TCPs have also been shown recently for anthocyanin biosynthesis, which is positively regulated by CIN-like TCP3[26], but negatively regulated by class Ⅰ TCP15 during exposure of plants to high light intensity[45] (Figure 2), and thus further support the hypothesis that the two classes of TCPs have intertwined functions in plant growth and development.

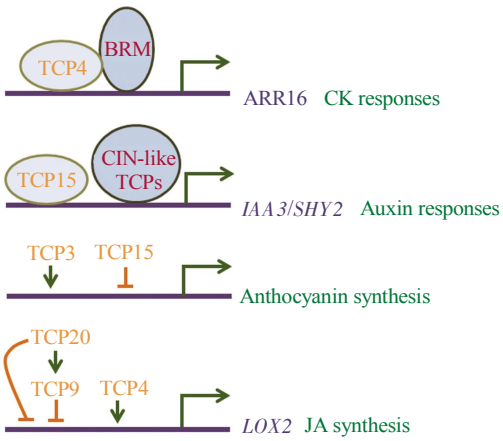

Fig. 2 Scheme of the CIN-like TCP regulated genes involved in phytohormone synthesis or responses

TCP4 forms a complex with BRM and both of them can bind to the promoter of *ARR16*, a negative regulator in CK responses. CIN-like TCPs and TCP15 have a coordinated function as indicated by directly binding and transcriptional regulation of *IAA3/SHY2*. An opposite function of TCP3 and TCP15 is revealed in the regulation of anthocyanin biosynthesis. TCP20 directly regulates the expression of *TCP9* and consequently inhibits the transcription of JA synthesis gene *LOX2*, which is also regulated by TCP4 in an opposing manner. Arrows and bars at the end of each line indicate positive and negative regulations, respectively.

3 CIN-like TCP interacting factors

3.1 Interacting proteins

Homo- or heterodimerization of TCP proteins and interaction with numerous other proteins improve TCP action in recognizing target genes with various affinities, which can account for the activity of these proteins in divergent pathways[3, 46], and the CIN-like TCPs are not exceptional (Table 2). CIN-like TCPs physically interact with AS2, and by working together they negatively regulate a group of *KNOX* genes[47]. *SPL*, the earliest gene controlling germline development, recruits TPL co-repressors *via* its EAR motif at the C-terminal end, binds and inhibits CIN-like TCPs through its N terminal part[21, 48]. As plants age, accumulated SPL acts as a timing cue that destabilizes TCP-CUC interaction, consequently releasing CUC activities and gradual increasing of newly formed organ complexity[49]. TIE1 (TCP INTERACTOR CONTAINING EAR MOTIF PROTEIN 1), a novel transcriptional repressor, regulates leaf size and morphology by recruiting TPL co-repressors and physically interacting with CIN-like TCPs[50] and other TCPs including TCP18[51]. Recent advances also reveal that TEAR1 (TIE1-ASSOCIATED RING-TYPE E3 LIGASE 1) mediated TIE1 degradation positively regulates CIN-like TCP activity in leaf development[52]. TCP3 as the founding member of CIN-like TCPs, is shown to interact with one of the circadian clock components TOC1 (TIMING OF CAB EXPRESSION 1)[19]. Moreover, TCP3 interacts with R2R3-MYBs TT2, PAP1, PAP2, MYB12, MYB111, MYB113 and MYB114, proteins involved in flavonoid biosynthesis[26]. TCP13 interacts with AHPs (HISTIDINE PHOSPHOTRANSFER PROTEINS), indicating its role in CK signaling[53]. TCP24 forms a complex with ABAP1 (ARMADILLO BTB PROTEIN 1) in regulation of a negative feedback loop modulating mitotic DNA replication during leaf development[35].

Table 2 CIN-like TCP interacting proteins

TCP	Interacting proteins	Function	Reference
TCP2/3/10	AS2	Leaf development	[47]
TCP2/3/5/10/17	SPL	Ovule development	[21, 48]
TCP2/3/4/5/10/13/17/24	TIE1	Leaf size and morphology	[50]
TCP3	TOC1	Circadian clock	[19]
TCP3	R2R3-MYBs	Flavonoid biosynthesis	[26]
TCP13	AHPs	CK signaling	[53]
TCP24	ABAP1	Mitotic DNA replication	[35]

3.2 Interacting hormones

CIN-like TCP transcription factors play an important role in the regulation of plant growth *via* hormonal signaling (Table 3). It has been shown that the plant hormone CK negatively regulates leaf maturation by promoting mitotic cell division, marginal leaf serration and blastozone activity[54], and that the CK responses can be attenuated by CIN-like TCPs in promoting leaf maturation[11]. TCP3 modulates the auxin responses through transcriptional activation of the auxin signaling repressor *IAA3*/*SHY2* [20]. Activated TCP3 induces anthocyanin biosynthesis, which may further negatively regulate the auxin responses, thereby causing auxin-related pleiotropic developmental defects [26]. TCP4 interacts with the SWI/SNF chromatin remodeling ATPase BRAHMA (BRM), and both of them can bind to the promoter of *ARR16* (Figure 2), an inhibitor of CK responses [11]. Likewise, TCP4 determines leaf size, plant maturity, and regulates the expression of the JA biosynthesis gene *LOX2* [14]. It has also been documented that TCP4-mediated control of leaf growth is influenced simultaneously by multiple phytohormones, including auxin, gibberellin (GA) and abscisic acid (ABA) [55]. *TCP5* is regulated by strigolactone (SL) and CK, and its expression is negatively correlated with mesocotyl length in rice [56]. In tomato, the activity of CIN-like TCP paralogue LA is partly mediated by positive regulation of the GA response through regulation of GA level[18].

Table 3 CIN-like TCP interacting hormones

TCP	Associated genes/proteins	Hormones	Reference
TCP3/4/5	BRM	CK responses	[11]
TCP3	*IAA3/SHY2*	Auxin signaling	[20, 26]
TCP4	*LOX2*	JA biosynthesis	[50]
TCP4	–	Auxin, GA, ABA responses	[55]
TCP5	–	SL and CK	[56]
LA	–	GA	[18]

4 Concluding remarks and future prospects

In this review, we summarize the CIN-like TCP-governed regulatory modules that could be important to explain plant development and immunity. Therefore, it will justify further work that could provide novel insights in elucidating basic questions on the establishment of plant morphology, as well as identify new targets for improving crop performance. A good example for potential use of TCPs as an important tool for the genetic improvement of crops is that the miR319-targeted *TCP4* or *TCP24* in Chinese cabbage regulates the round shape of leafy heads through differential cell division arrest in leaf regions [57–58]. However, functional redundancies and posttranscriptional down regulation by miR319 of *CIN-like TCP*s complicate and hamper further characterization of these TCP proteins. To circumvent these obstacles, multiple *tcp* mutants coupled with dominant-negative form of *SRDX*-fused constructs have been used. Alternatively, identification of target genes and further elucidation of their functions will shed more light on the signaling pathways that CIN-like TCP proteins participate in. There exists an orchestrated transcriptional interplay between miR319 and *CIN-like TCP* genes under diverse biotic and abiotic stresses. Despite the well-known post-transcriptional regulation of *CIN-like TCP*s by miR319, the transcription factors that control miR319 expression in response to variable physiological conditions still need to be identified. How miR319 and other unknown transcription factor participate in a combinatorial and complex regulation of *CIN-like TCP*s also needs to be addressed. It has been reported that *yabby* mutants fail to activate expression of *CIN-like TCP*s and the resultant leaf lamina programs [8]. More studies are required to further unravel the nature of the interaction between YABBY and CIN-like TCP proteins. Notably, CIN-like TCPs and hormonal pathways are inextricably connected. Further investigations of the molecular basis of these connections and how they operate to regulate plant development must be oriented. Although CIN-like

TCP proteins are found to interact with and be destabilized by pathogen effector SAP11, whether these TCP factors directly or indirectly regulate the levels of immunity still remains an open question. Further studies need to focus on gaining a deeper understanding of how diverse pathogen effectors target TCP factors to provoke virulence. This discussion does not cease here. Rather, it paves the way for new avenues of research and highlights critical questions related to the multi-functional roles that CIN-like TCPs play in the nexus.

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CIN-like TCP 转录因子：植物发育及免疫的关键调节因子 *

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摘要　TEOSINTE BRANCHED1、CYCLOIDEA 和 PCF(TCP)是植物特有的一类转录因子，具有由碱性螺旋 - 环 - 螺旋(bHLH)基序组成的 TCP 结构域．根据 TCP 结构域的不同特征将 TCP 分为 2 个家族：class Ⅰ TCP 和 classⅡ TCP．越来越多的证据表明，class Ⅱ TCP 的亚家族成员 CINCINNATA-like(CIN-like)TCPs 通过激素合成及信号转导在植株形态建成等方面起关键作用．最近研究表明，CIN-like TCP 除了调控植物生长发育外，还介导植物抵御病原菌入侵的免疫反应，称为效应因子引发的免疫反应(effectors-triggered immunity，ETI)．目前，虽然 CIN-like TCP 的调控机理已有较多报道，但其发育及免疫方面的调控较为复杂，有必要基于目前的研究对该亚家族成员的功能做进一步梳理．因此，本文对 CIN-like TCP 在发育及免疫调控中的作用机理进行了综述，着重论述了 CIN-like TCP 相关突变体特征及其与蛋白质及植物激素之间的互作关系，也讨论了目前研究中仍然存在的问题，为今后该亚家族基因的进一步功能解析提供新的思路．

关键词　CIN-like TCP 转录因子，植物发育，免疫，互作因子
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