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Cloning, Subcellular Localization and Functional Analysis of TIR-NBS Family Members in *Arabidopsis Thaliana*

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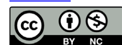
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Abstract

Recent studies have shown that truncated Toll/interleukin-1 receptor-NBS (TIR-NBS) protein plays a critical role in immune responses. In *Arabidopsis thaliana* ecotype type Col-0, the TIR-NBS family is encoded by 20 genes and one pseudogene. However, so far, our understanding of the subcellular localization and function of these TN genes is not very clear. In this article, we first conducted a brief analysis of the proteins and evolutionary tree expressed by these 20 TN genes. Furthermore, we focused on the TN genes on chromosome 1, which included 12 TN genes, TN1 to TN12, and observed different subcellular localization patterns of these proteins through fluorescence microscopy, including membrane, cytoplasmic, and/or nuclear localization, suggesting diverse roles for these proteins. Additionally, we identified four receptors, including TN2, TN9, TN11, and TN12, that can trigger visible cell death in *Nicotiana benthamiana*. Taken together, our study provides valuable clues for further investigating the activation mechanisms of TN family members.

Keywords

Arabidopsis, TIR-NBS, Cell Death, *Nicotiana benthamiana*

1. Introduction

Plants rely on two-levels of innate immune systems to defend against various pathogens in nature [1]. The first level of the immune system is activated by pattern recognition receptors (PRRs) located on the plasma membrane, which can recognize conserved pathogen associated molecular patterns (PAMPs), known as pattern triggered immunity (PTI). However, some host-adapted pathogens can enter

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plant cells by secreting effectors that contribute to pathogen virulence, thereby interfering with plant immunity [2]. Correspondingly, plants have evolved intracellular nucleotide-binding sites (NBS) and leucine-rich repeat (LRR) domain receptors (NLRs), also known as resistance (R) proteins, which activate the second level of the immune system called effector triggered immunity (ETI) by directly or indirectly recognizing these effectors. Compared to PTI, ETI typically responds stronger and faster, accompanied by hypersensitive responses (HR), which is programmed cell death at the site of infection [3].

Generally speaking, a typical plant NLR protein contains a specific N-terminal domain, a conserved NBS domain, and a highly variable C-terminal LRR domain. The N-terminal domain are typically coiled-coil (CC) domain, Toll/interleukin receptor (TIR) domain, or RESISTANCE TO POWDERY MILDEW 8 (RPW8)-like domain. Therefore, according to different N-terminal domains, NLRs can be roughly divided into three subfamilies: CC-NBS-LRR (CNL), TIR-NBS-LRR (TNL), and RPW8-NBS-LRR (RNL) [4]. Besides, plants also contain some truncated NLR receptors. For example, 21 truncated TIR-NBS (TN) proteins lacking the C-terminal LRR domain have been identified in the *Arabidopsis thaliana* ecological type Col-0 [4]. An increasing number of studies indicated that TN proteins also play a crucial role in plant immunity. Such as, the gain-of-function mutant of TN1, also known as CHILLING SENSITIVE 1 (CHS1), exhibits cold sensitivity at low temperatures, yet the cold sensitivity phenotype of chs1-2 mutant at low temperatures counts on the full-length TNL protein SUPPRESSOR OF chs1-2, 3 (SOC3) [5]. Further experiments revealed that SOC3 can interact with TN1 and TN2 respectively to monitor the homeostasis of *Arabidopsis* E3 ubiquitin ligase SENESCENCE-ASSOCIATED E3 UBIQUITIN LIGASE1 (SAUL1). Specifically, the excessive accumulation of SAUL1 is monitored by the SOC3-TN2 pair, meanwhile the disappearance of SAUL1 is guarded by the SOC3-CHS1 pair [6]. Ectopic expression of the TN2-TIR domain causes cell death in *N. benthamiana*. The autoimmune responses in *exo*70*B*1 mutants are caused by the activation of TN2, and co-expression of EXO70B1 and TN2 can inhibit the TN2-triggered cell death in *N. benthamiana*, suggesting that TN2 may monitor the presence or absence of EXO70B1 [7] [8]. Furthermore, TN2 associates with CALCIUM-DEPENDENT PROTEIN KINASE 5 (CPK5) and stabilizes its kinase activity [9]. The loss of function of TN8 and TN11 genes results in increased susceptibility to *Pseudomonas syringae* pv. *tomato* (*Pto*) strain DC3000 [10]. Additionally, TN13 is necessary to resistance against *Pto* DC3000 lacking the effectors AvrPto or AvrptoB [11].

However, there have been no systematic studies published on the subcellular localization and function of TN receptors. In this article, we first conducted a brief analysis of the proteins and evolutionary tree expressed by these 20 TN genes. Furthermore, we focused on the TN genes on chromosome 1, which included 12 TN genes, TN1 to TN12, and observed different subcellular localization patterns of these proteins through fluorescence microscopy, including membrane, cytoplasmic, and/or nuclear localization, suggesting diverse roles for these proteins.

Additionally, we identified four receptors, including TN2, TN9, TN11, and TN12, that can trigger visible cell death in *N. benthamiana*. Taken together, our study provides valuable clues for further investigating the activation mechanisms of TN family members.

2. Materials and Methods

2.1. Plant Materials and Growth Conditions

Arabidopsis thaliana and *N. benthamiana* were cultivated in a plant greenhouse at 25˚C with 16 hours of light exposure, and regularly supplemented with Hoagland nutrient solution. This article employed about 4 weeks old *N. benthamiana* for transient expression analysis.

2.2. Plasmid Construction

We use cDNA from wild-type *Arabidopsis* leaves as initial template. Conditions for the PCR amplifications were: 35 cycles of a 15 second denaturation step at 95˚C, annealing at 53˚C - 60˚C for 15 seconds, and extension at 72˚C for 80 seconds. Then, we separately recovered the above fragments and cloned them into the modified pUC19 (containing attL1 and attL2 feature sequences). After extracting the plasmid, DNA sequencing was performed, and finally the correct plasmid was ligated to the expression vector pEreyGate101 fused with the YFP-HA tag using gateway technology. Subsequently, transfer the expression plasmid containing the TN gene into Agrobacterium tumefaciens strain GV3101 by electroporation.

2.3. Agrobacterium Tumefaciens-Mediated Transient Expression Assay

Agrobacteria carrying the constructs were cultivated overnight in LB medium containing Rifampicin and kanamycin. The Agrobacteria cells were centrifuged and resuspended in infiltration buffer to an OD_{600} of 0.8, and incubated at room temperature for 1 hour. The abaxial sides of *N. benthamiana* leaves were infiltrated with the suspension and cultured in a dark greenhouse for 24 hours, after which they were moved to a growth chamber with a 16 hours photoperiod.

2.4. Subcellular Localization Observation

The images were observed on the abaxial sides of leaves at 28/40 hours post target protein expression with a fluorescence microscope. YFP fluorescence was excited at 514 nm.

2.5. Sequence Alignment and Phylogenetic Analysis

The evolutionary history was inferred using the Neighbor-Joining method and the respective evolutionary analyses were conducted using MEGA-X. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Poisson correction method and are in the units of the number

of amino acid substitutions per site. This analysis involved 20 amino acid sequences. All ambiguous positions were removed for each sequence pair (pairwise deletion option).

2.6. Gene Accession Number

Sequence data for the genes described in this article can be found in TAIR under the following accession numbers: TN1 (CHS1) (AT1G17610), TN2 (AT1G17615), TN3 (AT1G66090), TN4 (AT1G72850), TN5 (AT1G72870), TN6 (AT1G72890), TN7 (AT1G72900), TN8 (AT1G72910), TN9 (AT1G72920), TN10 (AT1G72930), TN11 (AT1G72940), TN12 (AT1G72950), TN13 (AT3G04210), TN14 (AT4G04110), TN15 (AT4G09420), TN16 (AT4G16990), TN17 (AT4G23440), TN18 (AT5G40090), TN20 (AT5G48780), TN21 (AT5G56220).

3. Results

3.1. TN Proteins Basic Physicochemical Properties and Evolutionary Tree Analysis

Table 1. The protein data of the TIR-NBS receptors involved in this article.

Protein Name	Gene Number	Length	Molecular Weight	Isoelectric Point
TN1 (CHS1)	AT1G17610	420 aa	~47 KDa	6.15
TN2	AT1G17615	380 aa	~43 KDa	8.54
TN3	AT1G66090	429 aa	~48 KDa	7.55
TN4	AT1G72850	422 aa	~48 KDa	5.16
TN5	AT1G72870	512 aa	~59 KDa	6.44
TN6	AT1G72890	487 aa	~57 KDa	10.03
TN7	AT1G72900	363 aa	~41 KDa	8.19
TN8	AT1G72910	380 aa	~43 KDa	9.22
TN9	AT1G72920	275 aa	~32 KDa	9.88
TN10	AT1G72930	176 aa	~20 KDa	7.63
TN11	AT1G72940	371 aa	~42 KDa	9.39
TN12	AT1G72950	379 aa	~44 KDa	8.63
TN13	AT3G04210	531 aa	~60 KDa	9.73
TN14	AT4G04110	239 aa	~28 KDa	9.74
TN15	AT4G09420	457 aa	~51 KDa	6.04
TN16	AT4G16990	796 aa	~91 KDa	8.41
TN17	AT4G23440	964 aa	~109 KDa	9.81
TN18 (CHL1)	AT5G40090	459 aa	~52 KDa	5.26
TN20	AT5G48780	639 aa	~73 KDa	8.58
TN21	AT5G56220	973 aa	~108 KDa	8.68

Previous studies have proclaimed that in *Arabidopsis* Col-0, the TIR-NBS (TN) family is encoded by 20 genes and one pseudogene (TN19) [4]. We cloned 20 TN genes from *Arabidopsis* and designated as TN1-TN21. The physiological and biochemical properties of these proteins were characterized, and the general information for the 20 TN genes is shown in **Table 1**. The length of these TN proteins ranged from 176 to 973 amino acids, with predicted molecular weights of 20 kDa to 108 kDa. The theoretical isoelectric point of these TN proteins ranged from 5.16 to 10.03.

To explore the phylogenetic relationships of these TNs, phylogenetic analysis was carried out. The results indicated that TNs with similar sequences were clustered on the same branch, such as TN2 and TN6; TN9 and TN11. However, TNs with lower sequence identities were clustered on the different branches (**Figure 1**).

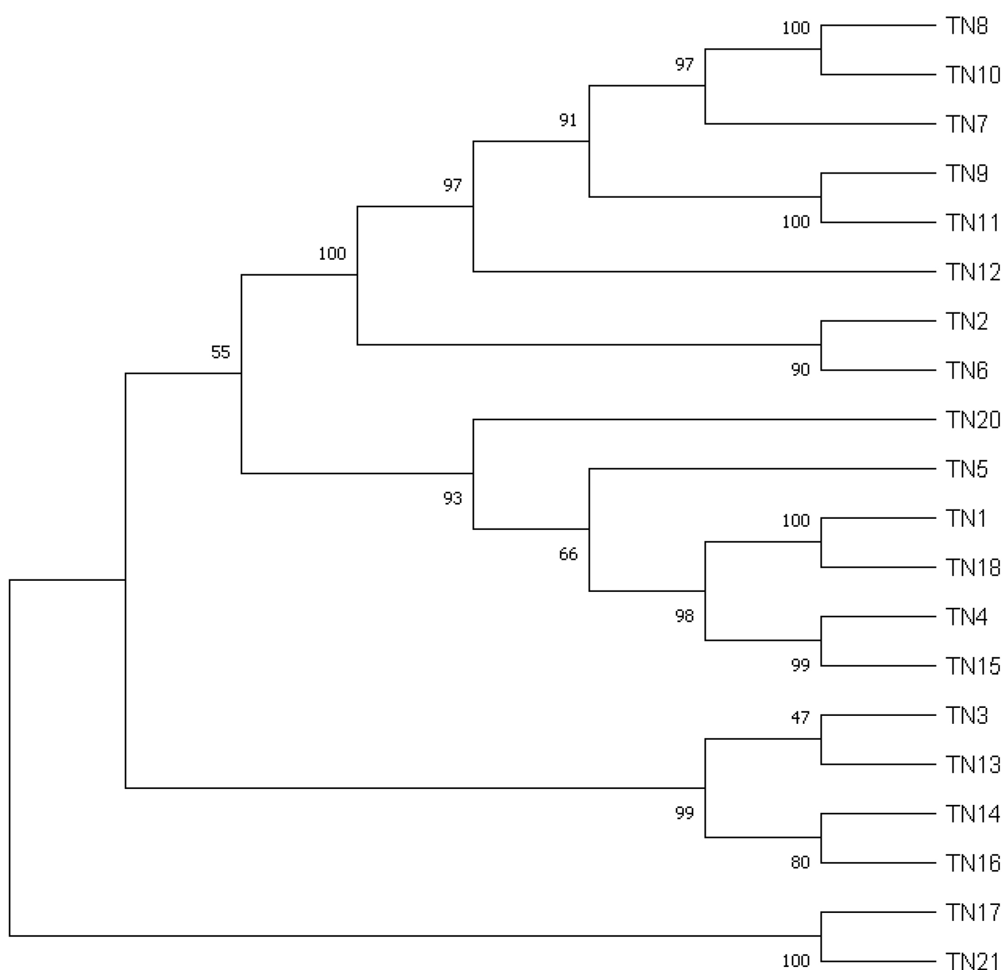

Figure 1. Phylogenetic analysis of the deduced amino acid sequences of the designed TN proteins.

3.2. Diversity of Subcellular Localization of TN Receptors

Following, we focus on the 12 TN genes located on chromosome 1, namely TN1 to TN12. The primer sequences used for molecular cloning were listed in **Table 2**.

Table 2. Primers used for cloning and transcript amplification in this study.

Primer Name	Sequence (5'-...- 3')
NotI-TN1-F	CTCCGCGGCCGCCACCATGTCTACTTCTTATTCTTTTTTGTTGGC
ASCI-TN1-R	GGTCGGCGCGCCCTCTTTGGGATGCTTCCACGATATC
NotI-TN2-F	CTCCGCGGCCGCCACCATGTATTCATCATCGTCTTCTTCTTC
ASCI-TN2-R	GGTCGGCGCGCCCAGAAGATTCAGTCCCGGATATAG
NotI-TN3-F	CTCCGCGGCCGCCACCATGGCTGCATCTACTTCTTCTTC
ASCI-TN3-R	GGTCGGCGCGCCCTACAAAATCAGCCAGAGACACTAG
NotI-TN4-F	CTCCGCGGCCGCCACCATGTCTTCATCCTCCAAATTTGAAG
ASCI-TN4-R	GGTCGGCGCGCCCATCATCACTCAAGAGAATAAATGATGTG
NotI-TN5-F	CTCCGCGGCCGCCACCATGGCTTCTTCTTCCTCCTCATC
ASCI-TN5-R	GGTCGGCGCGCCCAAGTGACATGATATATGAAGGTGAATATTC
NotI-TN6-F	CTCCGCGGCCGCCACCATGAACACGATCTTTAAAAAATTATCCTG
ASCI-TN6-R	GGTCGGCGCGCCCAATGAATTTGTTGTGAACCGTC
NotI-TN7-F	CTCCGCGGCCGCCACCATGTCTTCTGCTACTGCGACTTATAAC
ASCI-TN7-R	GGTCGGCGCGCCCTATATACAAAGCCCACTCGAACG
NotI-TN8-F	CTCCGCGGCCGCCACCATGTCTTCTCATACTGCAACTAAG
ASCI-TN8-R	GGTCGGCGCGCCCAACTAAATCTGTCACTTTCCCATAAC
NotI-TN9-F	CTCCGCGGCCGCCACCATGTCTTCTCCTACTGCGACTAAG
ASCI-TN9-R	GGTCGGCGCGCCCCTCAGTTTTAAAAGAGTGATGTGATC
NotI-TN10-F	CTCCGCGGCCGCCACCATGTCTTCTCATACTGCAACTAAG
ASCI-TN10-R	GGTCGGCGCGCCCTATTGTTGCATAAATCGTCTTCTTG
NotI-TN11-F	CTCCGCGGCCGCCACCATGACTTCTCCTACTGCGACTAAG
ASCI-TN11-R	GGTCGGCGCGCCCACCAGATCTACCACTTAGACAACC
NotI-TN12-F	CTCCGCGGCCGCCACCATGTCAGATTCTTCAAACACCCTC
ASCI-TN12-R	GGTCGGCGCGCCCACCTGATCTACCACATATACAACC

It is widely believed that subcellular localization of genes is crucial for understanding their cellular functions. To determine the subcellular localization of these TN receptors in planta, we created TNs tagged with yellow fluorescent protein (YFP) reporter at their C-terminus (e.g. TN2-YFP) under the control of the CaMV 35S promoter and transiently expressed them in *N. benthamiana* leaves using agroinfiltration. The results of fluorescence microscopy observation indicated that there are similarities and differences in the subcellular localization of TNs proteins (**Figure 2**). For example, TN1 and TN2 are mainly distributed in the cytoplasm in the form of cytoplasmic aggregates, with a small amount of fluorescence appearing on the plasma membrane, but it cannot be ruled out that the latter is formed by the bright particle background in the cytoplasm. Moreover, TN3, TN9 and TN10 demonstrated nuclear and cytoplasmic localization, while TN8 and TN11

were plasma membrane localized. Thus, TN proteins were localized to distinct, diverse cellular locations, suggesting diverse roles for these proteins.

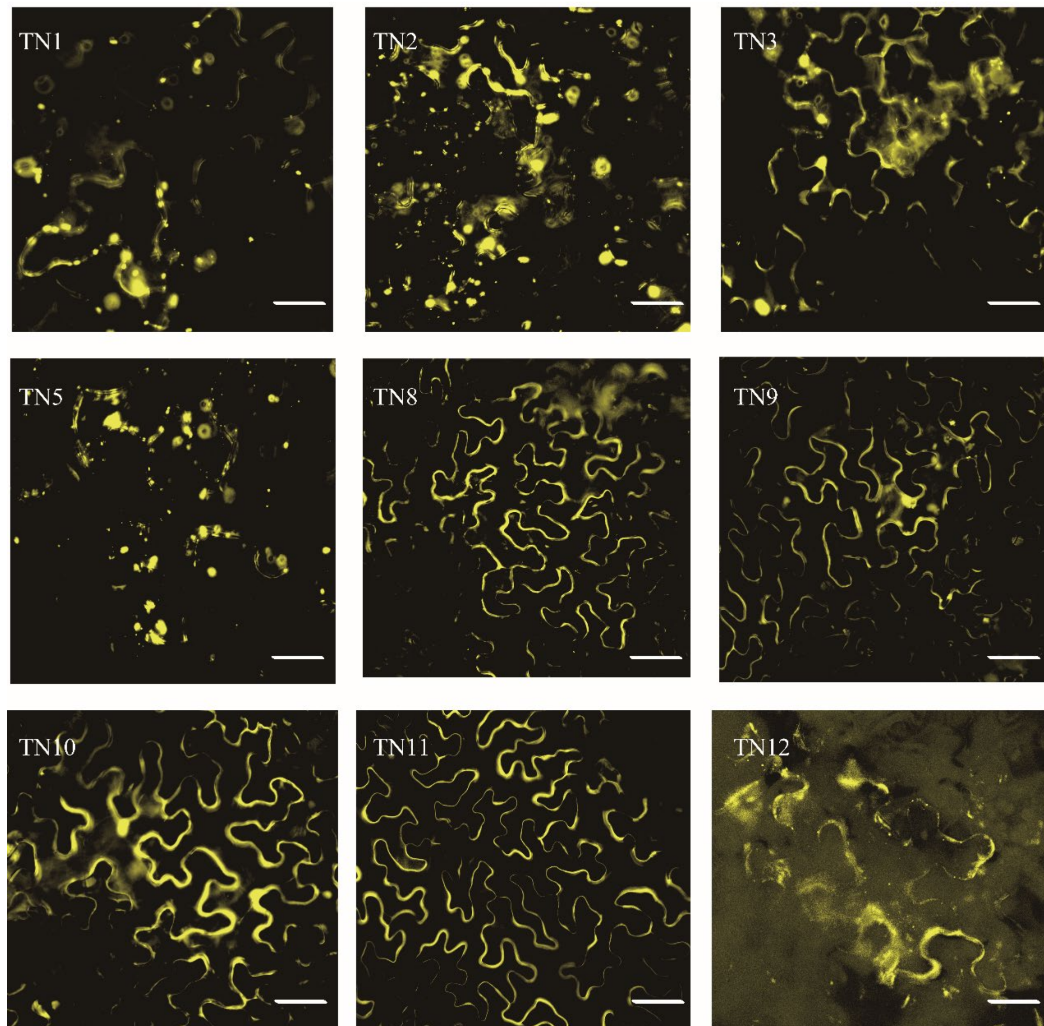

Figure 2. Transient overexpression of TN proteins in *N. benthamiana* leaves. TN8 and TN11 proteins show membrane localization. TN3, TN9 and TN10 show nuclear and cytoplasmic localization pattern in *N. benthamiana*. Transient overexpression of TN1 and TN2 show cytoplasmic aggregates and cytoplasmic localization. Bars = 20 μm.

3.3. Transient Overexpression of the TN Genes in *N. Benthamiana* Results in Cell Death Responses

We next sought to investigate the potential function of these genes using transient assays, knowing that transient overexpression of R genes may induce spontaneous HR [12]. The recombinant TN receptors (TN1-TN12) fused to a YFP-HA tag at the C-terminus was expressed under the control of 35S promoter, and 35:*YFP-HA* as a negative control. The results of immunoblotting showed comparable levels of fusion protein expressed (data not shown). Transient Agrobacterium tumefaciens-mediated overexpression of *Arabidopsis* TN proteins in *N. benthamiana* resulted in HR, a cell death phenotype, for four (TN2, TN9, TN11, and TN12) out

of 12 TN genes tested. The other 8 TN genes tested with transient overexpression in *N. benthamiana* did not display any visible phenotypes (**Figure 3**). Therefore, some members of the TN protein family can trigger cell death via ectopic expression, similar to previous reports that used N-terminal domains of the TNL genes RPS4 and RPP1A [13] [14].

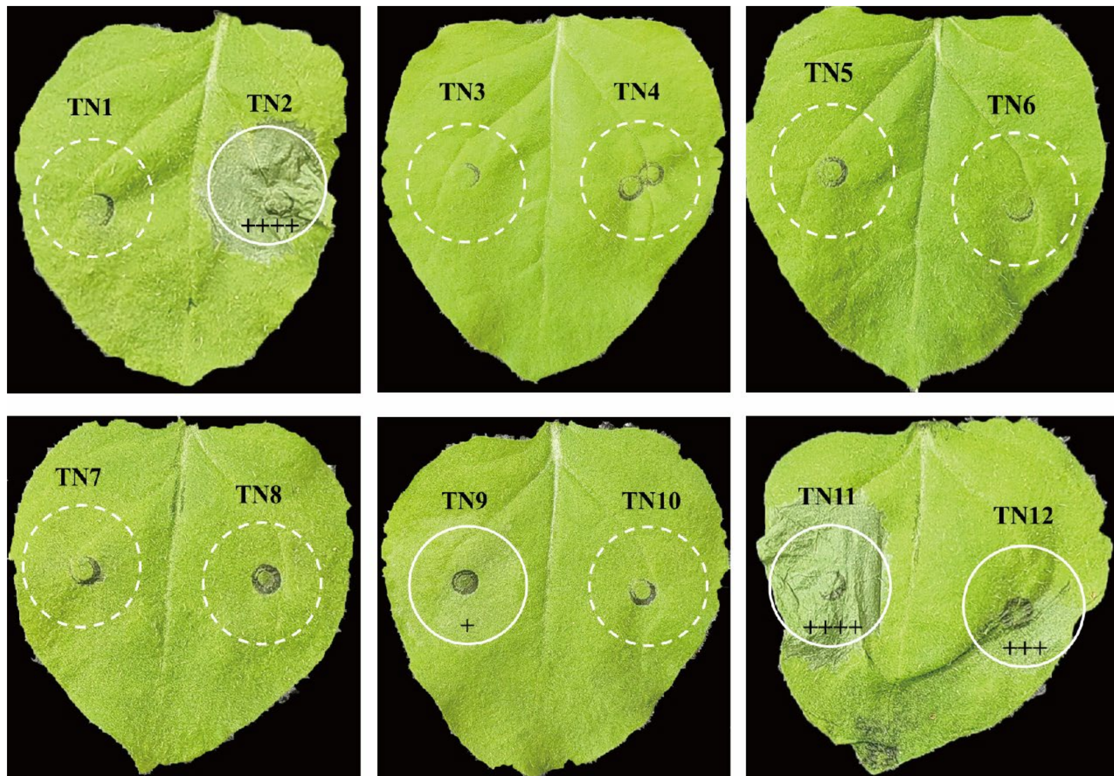

Figure 3. Transient overexpression of *Arabidopsis* TN genes in *N. benthamiana* results in partial cell death response. The constitutive promoter drives the transient expression of the TN proteins in *N. benthamiana* (OD600 = 0.8). The white solid circle represents obvious cell death. The white dashed circle indicates no visible cell death. The symbol (+) refers to the severity of cell death. The photo was taken 72 hours after infecting *N. benthamiana*.

4. Conclusion

In this article, we focused on analyzing the subcellular localization and function of 12 TN receptors (TN1-TN12) derived from *Arabidopsis*, confirming that TN receptors have diverse cellular localization, including cytoplasm, cell membrane, nucleus, etc. Additionally, we observed that transient expression of four TN proteins, including TN2, TN9, TN11, and TN12, can trigger significant cell death in *Nicotiana benthamiana* leaves. Subsequent focus would be on screening the interacting proteins of these receptors, especially full-length TNL or CNL receptors, to observe whether these TNs need to interact with full-length NLRs receptors to mediate defense responses.

5. Discussion

We have demonstrated that the localization of 12 designed TNs from *Arabidopsis*

is not entirely identical (**Figure 2**), but we cannot rule out the possibility that TNs may have other subcellular localization. According to reports, some NBS-LRR proteins, such as MLA10, N, and RPS4, can relocate to the nucleus after activation [13] [15] [16]. Therefore, studying whether TNs receptors can be repositioned would help analyze the activation mechanism of these proteins. Coincidentally, animal NBS-LRR has also been observed in different subcellular locations, requiring similar partners to maintain pre-activation ability and can be repositioned during activation to participate in various signaling complexes. Mammalian CIITA NBS-LRR receptors function in the nucleus [17]. NOD2 exists on the plasma membrane and recruits downstream partners to the membrane; the mutation of its LRR causes NOD2 to appear cytoplasmic and non-functional [18]. NOD1 and NOD2 recruit autophagic components locally at the plasma membrane site of bacterial infection, while common NOD2 variants associated with Crohn's disease fail to do so [19]. These studies indicate that mammalian NBS-LRRs are located at different positions in the cell before activation and can dynamically relocate, and their cellular localization affects downstream functions. The sum of data on intracellular immune receptors of NBS-LRR in plants and animals is consistent with the conceptual role of NBS-LRR protein as a cell homeostasis monitor, which studies a wide range of cellular defense mechanisms through various subcellular addresses.

Out of 12 TN genes tested for transient overexpression in *N. benthamiana*, four of the TN genes induced macroscopic cell death responses (**Figure 3**). Induction of a localized cell death has been demonstrated previously in *N. benthamiana* when an R gene is transiently overexpressed in the absence of a corresponding Avr protein [12]. Cell death induced in response to the transient overexpression of TNL genes was shown in the cases of RPP1A and RPS4 [13] [14]. Therefore, the TIR domain is shared between TN and TNL proteins and may have a common role in triggering cell death.

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Conflicts of Interest

The authors declare that they have no known competitive economic interests or personal relationships that may affect the work reported in this article.

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