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SACRIFICED SURVEILLANCE PROCESS FAVOURS PLANT DEFENSE : A REVIEW

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Abstract

Plants are constantly exposed to pathogens, which lead to decrease in the productivity that would threaten food security. Sophisticated mechanisms have been evolved in plants to recognize and respond to such invading pathogens. Primary sensitization of plants to microbes is mediated largely by defense related genes and resistance (*R*) genes, whose protein counterparts' associate with avirulence (Avr) proteins secreted by the pathogens. Regulation of *R* genes has not been clearly understood. *R* genes and defense related genes are supposedly post-transcriptionally regulated by a eukaryotic surveillance mechanism known as nonsense-mediated mRNA decay (NMD). NMD is a quality control process that causes the shutting off of aberrant messenger RNAs (mRNAs) expression, thus enabling the cell to escape from any deleterious effect that might have resulted from the expression of faulty mRNAs. Excitingly, many defense related genes, which are involved in plant immunity, harbour NMD features that make their protein counterparts unavailable during normal growth conditions of a cell, suggesting the significance of NMD in plant immunity. NMD-defective mutants in *Arabidopsis*, shows concurrent phenotypes as those of pathogen resistant mutants. Also, the core NMD factors, UPF1 and UPF3 are known to be involved in plant defense. Still, details of NMD-mediated plant defense mechanism are less explored. Extensive studies would be needed to understand the role of NMD in plant immunity.

Key words: Nonsense-mediated mRNA decay, plant immunity, R genes, defense related genes, plant immune receptors.

Introduction

Nonsense-mediated mRNA decay (NMD) is a quality control mechanism in eukaryotes that plays a significant role in degrading aberrant mRNA transcripts. A number of genes are regulated by NMD. Although NMD occurs in plants, mechanisms'- underlying the process are not well understood. In plants, NMD is active during biotic and abiotic stresses. Defects in NMD arising from mutations in genes would ultimately lead to accumulation of truncated proteins and reports in mammalian system indicate that this condition can elevate the likelihood of cancer (Gardner 2008). NMD is also involved in the maintenance of telomere, genome stability and DNA repair. NMD is a universal surveillance mechanism among eukaryotes including mammals, yeast and plants. In plants, NMD-mediated regulation of cellular transcriptome modulates auxin response, thus affecting shoot regeneration process (Chiam *et al.*, 2019). Sacrificed NMD leads to pathogen susceptible condition in plants (Jeong *et al.*, 2011). Around 1% of the coding RNAs and 20% of the noncoding RNAs are regulated by NMD (Kurihara *et al.*, 2009; Rayson *et al.*, 2012). Evidences establish a link between loss of NMD process and plant immunity. Plant immune system might be less complex due to lack of circulatory system as compared to other eukaryotes, but even then, plants are able to recognize and respond whenever they are invaded by pathogens. Plant immune system also exhibit specific reactivity and memory, which are the major components in mammalian adaptive immune system (Spoel and Dong 2012). Co-evolving nature of plants and pathogens resulted in the development of multilayered defense system in plants, which primarily recognizes pathogens and responds accordingly by initiating various defense pathways (Li *et al.*, 2019). Essentially, plant cell wall restricts the entry of incoming pathogens and this encounter initiates the activation of several downstream processes. Plant immune system acts as a surveillance mechanism in order to detect pathogen invasion. Recent observations suggest that a zigzag mechanism exists as compared to the previously known gene for gene model. This networking

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of immune receptors enhances the effectiveness of plant defense response. Primarily, plants depend on an innate system, which is mainly composed of several receptors meant to recognize incoming microbes (Ausubel 2005). In this review, we have focussed mainly on the NMD process and plant immunity and we have tried to link the both, so as to cover an overview on NMD-mediated plant immunity.

Messenger RNA Surveillance in Eukaryotes

In eukaryotes, nonsense-mediated mRNA decay (NMD) is one of the surveillance mechanisms that targets aberrant mRNA transcripts and contributes to their steady-state level in a cell. Primarily, NMD is a translation-coupled process. Targets of NMD usually harbour premature termination codons (PTCs). Essentially, PTCs result from mutations, errors during transcription and/or alternative splicing processes (Schweingruber *et al.*, 2013). The core NMD machinery comprises of three protein factors namely UPF1, UPF2 and UPF3, which are highly conserved across species. The degree of similarity displayed by NMD factors and their ubiquitous role in RNA decay process points out to the ancient origin of NMD process (Ohtani and Wachter 2019). UPFs play central role in the mRNA surveillance process. UPF1 is the most noteworthy factor, since it activates the NMD pathway. UPF1 is considered to be central factor of RNA decay processes, which provides novel mechanisms to alter the cellular transcriptome (Kim and Maquat 2019). In mammalian cells, UPFs are involved in recognizing their targets, subsequently leading to the decay of faulty mRNAs (Isken and Maquat 2008). During translation, UPF1 is recruited to the destined mRNAs, as and when ribosomes are stalled upon them due to premature termination (Kashima *et al.*, 2006). Subsequently, UPF1 gets phosphorylated, leading to the recruitment of downstream protein factors including SMG5, SMG6 and SMG7 which ultimately initiate degradation of mRNA (Unterholzner and Izaurralde 2004; Eberle *et al.*, 2009; Okada-Katsuhata *et al.*, 2012). In plants, homologs of SMG5 and SMG6 are absent (Riehs *et al.*, 2008). The Exon-Junction complex (EJC) positioned downstream of PTCs enhances NMD target detection by core NMD factors (Ballut *et al.*, 2005; Nyikó *et al.*, 2013). Y14, Barentsz and Magoh are the three core EJC factors. Substrates for NMD are diverse. NMD-eliciting features like, the presence of upstream open reading frames (uORFs), long 3' untranslated regions (UTRs) and introns in 3' UTRs sensitize several (around 20% of whole genome) transcripts which are destined to code functional proteins (Mendell *et al.*, 2004; Weischenfeldt *et al.*, 2008; Kurihara *et al.*, 2009; Drechsel *et al.*, 2013). NMD has several functions beyond its typical RNA surveillance function. It is involved in a broad range of cellular mechanisms. In mammals, NMD is well involved in biological processes including developmental cues and cellular stresses (Mendell *et al.*, 2004; Gardner 2008; Bruno *et al.*, 2012). There is always a fine tuning of NMD which primarily regulates NMD processes, thus ensuring a steady-state level of transcripts (Yepiskoposyan *et al.*, 2011; Bruno *et al.*, 2012). The significance of NMD in cellular process is reflected by the embryonic lethality in Drosophilla in the absence of NMD factors (Hwang and Maquat, 2011). Similarly, in plants, UPF1 and SMG7 null mutations cause death of seedling and retarded growth (Arciga-Reyes *et al.*, 2006; Riehs-Kearnan *et al.*, 2012; Yoine *et al.*, 2006). NMD mutilation in Arabidopsis is linked to systemic launch of immune responses, resulting in enhanced production of salicylic acid (SA), elevated level of defense genes and heightened resistance to invading bacteria (Jeong *et al.*, 2011; Rayson *et al.*, 2012; Riehs-Kearnan *et al.*, 2012). Interestingly, the effects of smg7 and upf1 mutations were reversed when the disease resistance pathways were dismantled (Riehs-Kearnan *et al.*, 2012). This signifies the importance of NMD in plant immunity, as a typical pathogen response pathway.

Although NMD is a universal surveillance mechanism among eukaryotes, the actual mechanism differs between the organism types. In case of mammals, a premature termination codon positioned at >55 nucleotide upstream of the final intron triggers NMD (Nagy and Maquat 1998; Ballut *et al.*, 2005). In yeast, initiation of NMD relies on specific downstream sequence elements (Zhang *et al.*, 1995; Ruiz-Echevarría *et al.*, 1998), explicit cis-elements located downstream of PTC (Ruiz-Echevarría *et al.*, 1998) and the distance between a stop codon and the poly (A) sequence (Amrani *et al.*, 2004). In plants, upstream of intron splicing, intronless genes activate NMD, in contrast to mammals (Voelker *et al.*, 1990; Dickey *et al.*, 1994; Isshiki *et al.*, 2001). Strictly, the NMD targets among different eukaryotes are not conserved (Cao and Parker 2003; Mendell *et al.*, 2004; Rehwinkel *et al.*, 2005). Primarily, the NMD mechanism in plants comprises of conserved early steps and non-conserved late steps (Fig. 1). Essentially, RNA polymerase II mediates early steps. 5' end capping, addition of poly (A) tail and splicing of pre-mRNA occur during early phase of NMD. Next, mRNAs are transported into the cytoplasm from nucleus through the nuclear pore complex. PYM factors associate with mRNAs, after which ribosome binds to them for initiation of translation. This marks the beginning of the late step

in NMD. Here onwards, two distinct pathways exist. UPF1-SMG7 pathway is initiated prior to the availability of SMG7. Most importantly, the phosphorylated UPF1 triggers the process, resulting in relocalization of UPF1 from cytoplasm to the Processing bodies (P bodies) along with SMG7. Then, 5'-3' decay of mRNA occurs mediated by XRN4. There are no experimental reports on the NMD processes occurring in the P bodies. When SMG7 is limiting, it allows the initiation of UPF1-XRN4 mediated NMD process, eventually resulting in 5'-3' decay by XRN4 and 3'-5' decay primarily mediated by the poly(A) binding protein (PABP) and the eukaryotic releasing factor 1 (eRF1).

Plant immunity: nature's marvel

The recruitment of defensive layers is a primary strategy deployed by the plant immune system to evade pathogen attack. Plasma membrane-localized receptors constitute one of the primary defense systems which specifically detect conserved pathogen-associated molecular patterns (PAMPs) (Fig. 2). The association of the pathogen to the cellular membrane, triggers transcriptional reprogramming of numerous genes involved in plant immunity thus conferring PAMP-triggered immunity (PTI). PTI provides adequate resistance to counter act non adapted pathogens (Jones and Dangl 2006). Virulent (infectious) pathogens deliver a series of effectors into the invading cell, which are intended to interfere with host defense mechanisms. Eventually, plant system resists the effectors by means of basal resistance mechanism/s, primarily controlled by immune regulating factors, Phytoalexin deficient 4 (PAD4) and Enhanced disease susceptibility1 (EDS1), involved in providing resistance to slow infection (Rietz *et al.,* 2011), and along with the salicylic acid (SA) signalling pathway (Fu and Dong 2013). Subsequently, basal immunity reinforces cellular resistance to virulent pathogens by triggering several intracellular nucleotide-binding, leucine rich repeat (NLR) receptors. NLRs sense specific pathogen effectors resulting in activation of another arm of the plant defense, known as the effect or triggered immunity (ETI) (Dodds and Rathjen 2010). Since, plant-pathogen interaction is co-evolving; this resulted in evolutionary variations of NLRs, thus considered as one of the major and extremely variable plant gene families (Guo *et al.,* 2011). Because of ETI, machineries involved in basal resistance provide amplified response, resulting in programmed cell death at infection sites, known as the hypersensitive response (HR) (Maekawa *et al.,* 2011). Primarily, NLRs are categorized into two subclasses; the first category belongs to the class which carry an N-terminal Toll/interleukin-1 receptor (TIR) domain and the second category represents the class of genes which carry a coiled-coil (CC) domain, and collectively, both the classes are referred to as Toll-interleukin1-receptor domain NLRs (TNLs) and coiled-coil NLRs (CNLs), respectively, with genetically discrete signalling responses (Heidrich *et al.,* 2013). TNLs recruit heterodimeric EDS1 to activate the transcription process related to plant defense pathways (Bhandari *et al.,* 2019). Essentially, tightly regulated mechanisms constantly direct the expression of NLRs both at transcriptional and post-transcriptional levels (Staiger *et al.,* 2013), since misexpression of NLRs triggers autoimmunity resulting into fitness costs of the host (Alcázar and Parker 2011). Autoimmune phenotypes resulting from disruption of an NMD factor, SMG7, are due to misregulation of TNL transcript, pointing out to the role of NMD in regulating the steady state level of TNL receptors, thus essentially getting involved in the immune response (Gloggnitzer *et al.,* 2014).

Immune receptor networking in plants

Being physically unmovable, plants lack the ability to escape and thus are constantly exposed to a wide variety of stress, including pathogens. To overcome the adverse situations due to pathogens, plants have developed inbuilt immune response mechanisms which defend them and mitigate pathogen invasion. The resistance mechanism displayed by plants is intriguing. As soon as a plant comes in contact with a pathogen, a robust response is initiated against their biotic foes. The molecular basis of such fast response is yet to be clearly revealed. Initially, it was of the view that, one gene in plant and one gene in pathogens become responsible for the specific interaction and determine any outcome. This was commonly referred to as gene for gene interaction (Flor, 1942). However, recent studies point out to a highly complex networking instead of the classical binary system of gene for gene interaction. Plants harbour enormously diverse and active immune receptors that are involved in different crosstalk pathways. In parallel, pathogens also produce extremely diverse virulence proteins, known as effectors which mediate the safe stay of invading pathogens inside the host environment. A subset of these effectors activates the plant defense repertoire. Currently, it is of view that a complex interconnected web of immune pathways fortifies the initial plant pathogen interactions (Wu *et al.,* 2017). Three layers of complex network strengthen the plant defense against pathogens. The first component includes immune receptors which are involved in the recognition of pathogen molecules. The second component comprises receptors, chiefly involved in the transition of pathogen recognition to the generation of immune

responses. This component includes several helper receptors, co-receptors and receptor-like regulatory scaffolds. The third component consists of complex receptors which display multifaceted actions by recruiting diverse overlapping downstream molecules resulting in the generation of ultimate immune response. Plant defense signalling exhibit cross-talk mechanisms, resulting in appropriate phenotypic modifications from biotic and abiotic stress conditions (Belkhadir and Jaillais 2015; Smakowska-Luzan *et al.*, 2018). Receptor like kinases (RLKs) and receptor-like proteins (RLPs)/intracellular receptors of the nucleotide-binding domain and leucine rich repeat-containing (NLR) family constitute different classes of plant immune receptors. Primarily, RLKs and RLPs make complexes at the cell membrane and initiate the recruitment of receptor-like cytoplasmic kinases (RLCKs) upon sensing an invading pathogen, resulting in activation of downstream immune pathways (Couto and Zipfel 2016; Ma *et al.*, 2016). RLKs participate in several physiological processes related to immunity and development (Ma *et al.*, 2016) as in case of somatic embryogenesis receptor kinase (SERK) family, such as SERK3, also known as brassinosteroid-associated kinase 1 (BAK1). Extracellular leucine-rich repeat (LRR) domains of RLKs mediate the formation of a complex web of signalling network by modulating interactions between several receptors. A number of RLKs act as junction nodes, involved in maintaining the integrity of the signalling network, like articulation point executive (APEX) and SERK3/BAK1, showing their importance in the event of multiple environmental challenges and responding accordingly (Smakowska-Luzan *et al.*, 2018). Suppressor of BIR1-1 (SOBIR1), an RLK is associated to RLPs through a network which includes SERK3/ BAK1 (Couto and Zipfel 2016). Revealing the role of cell surface receptors and subsequent activation of their

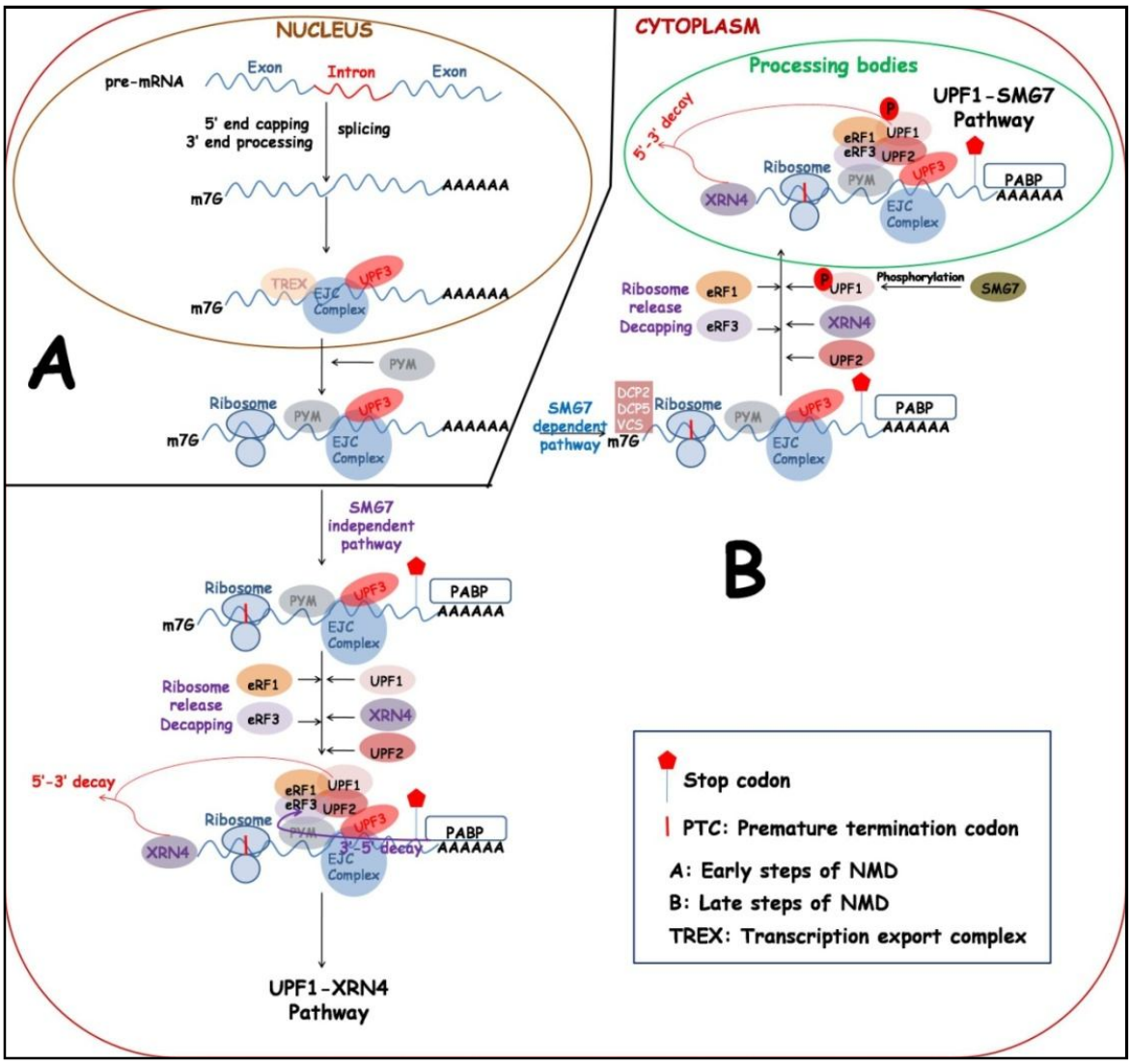

Fig. 1: NMD mechanisms in plants.

downstream counterparts would be vital in order to manipulate the key nodes of the highly complex network. Moreover, NLRs are involved in complex genetic interactions (Jones *et al.*, 2016; Wu *et al.*, 2017). At times, many NLRs also entail other NLR proteins to execute their role. Networking among NLRs is vital upon pathogen infection. More often, upon pathogen attack, the inhibition of sensor NLR by the auto-activity of helper NLR is released, thus displaying a negative regulation. The networking among NLRs operates against several pathogens (Wu *et al.*, 2017). Moreover, this complex networking is tightly regulated by different regulatory mechanisms. Interestingly, genes coding for paired NLRs are located in adjacent loci, in a head to head manner, since they bear a common promoter (Stein *et al.*, 2018). Since plant pathogen interaction is co evolving, combating diverse range of pathogens need unique architecture. These kind of networks involved in plant defense leads to robustness, a primary feature of immunity (Kitano and Oda 2006). A prominent aspect of plant defense network is the extrication of pathogen sensing from triggering of downstream processes leading to immune response, by virtue of which the evolving and expanding ability of receptors dedicated for pathogen perception is favoured. In turn, pathogens counteract plant defense by releasing effectors that aim to demolish multiple layers of host defense networks. Although, pathogen effectors target to restrain host defense armour, concurrently it may also activate NLR- mediated immunity (Win *et al.*, 2012), thus acting as an activator and a repressor to plant immune response.

NMD regulates plant immunity

There has been no direct evidence for the involvement of NMD in plant defense, though indirect evidences have pointed towards the importance of NMD factors. Accumulation of SUPPRESSOR OF NPR1 (SNC1) in UPF1 and UPF3 mutants (Yi and Richards 2007), shows that loss of NMD function favours the expression of genes involved in disease resistance. Conversely, it also indicates that many of the resistance genes bear NMD features as they are not accumulated under normal conditions in wild type. Alternative splice variants of SNC1, which have role in disease resistance bear PTC (premature termination codons), hence marking for NMD (Stokes *et al.*, 2002). Most importantly, the loss of UPF1 and UPF3 in Arabidopsis results in phenotypic abnormalities as compared to that of wild type (Arciga-Reyes *et al.*, 2006) which is concurrent with mutants displaying disease resistance, primarily by salicylic acid (SA) accumulation and pathogenesis-related (PR) expression (Heil and Baldwin, 2002). This resemblance in phenotype links the loss of NMD function to disease

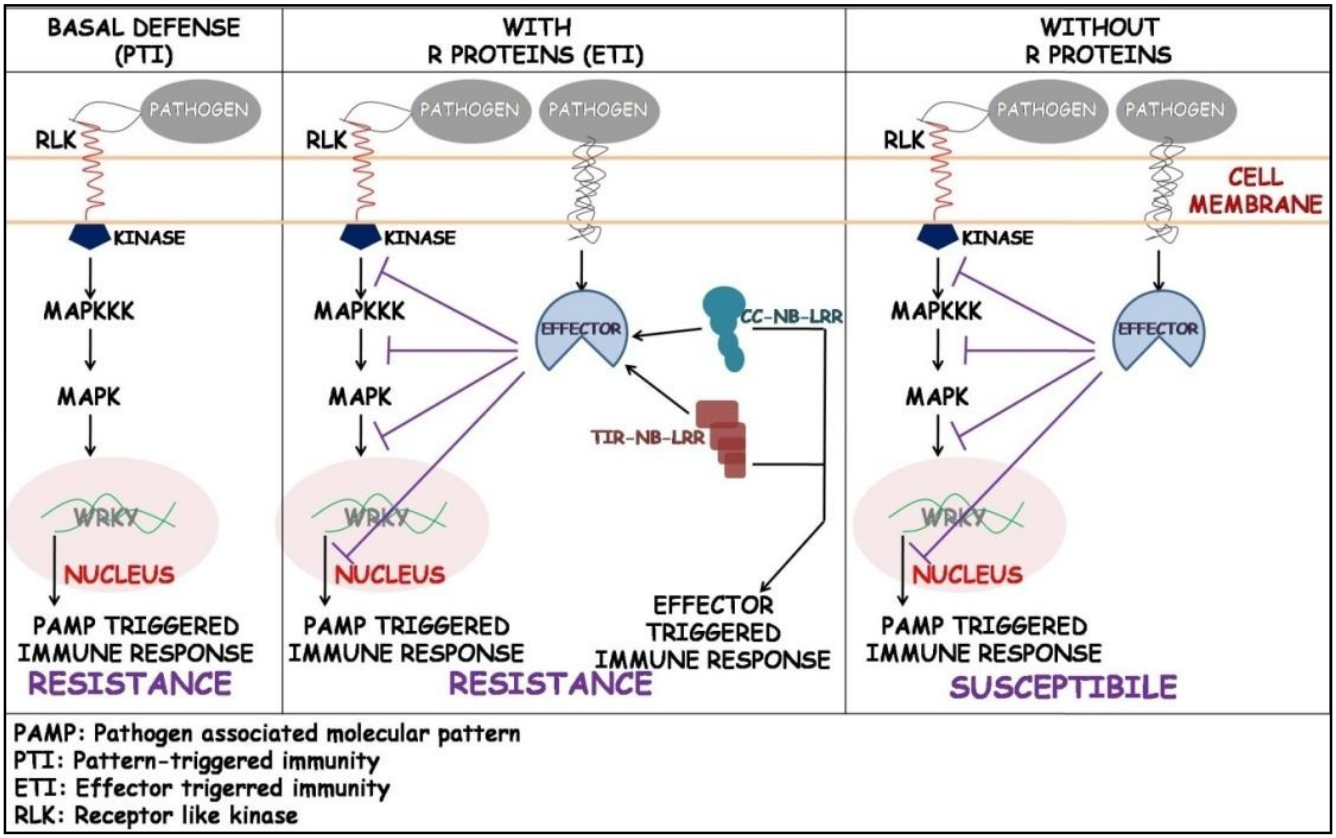

Fig. 2: Plant defense mechanism.

resistance in plants. NMD factors, UPF1 and UPF3 are involved in basal resistance as was evident from the fact that, the expression of NMD factors results in enhanced susceptibility of plants to pathogens, also loss of NMD results in elevated level of SA related components, resulting in heightened SA and *ISO-CHORISMATE SYNTHASE 1* (ICS1) (Jeong *et al.*, 2011). NMD as such elevates EDS1/PAD4-mediated SA-independent defense mechanism (Bartsch *et al.*, 2006). UPF1 and UPF3 modulate the NMD process resulting in homeostasis of aberrant mRNAs and endogenous mRNA of defense related genes. It is evident that NMD is one of the key processes involved in plant defense. It is established that NMD regulates the yield of several TNL transcripts, thus regulating immune response at posttranscriptional level (Gloggnitzer *et al.*, 2014). Moreover, NMD is the key mechanism which suppresses the expression of defense related genes under normal growth conditions, preventing inapt activation of TNLs, thus paving away the plants to be adversely affected, in terms of growth and productivity. Interestingly, many CNLs do not harbour NMD-eliciting features and are thus free from NMD regulatory mechanism.

Conclusion and perspectives

The efficiency of plant defense system relies on its competence to detect incoming pathogens. Primarily, efforts are made to enhance immune receptors focusing on its ability to sense broad spectrum of pathogens (Cesari 2018). Manipulation of the immune system for economically important plants needs a clear and precise understanding of the receptor networking mechanisms. Enhancing the expression of receptors and co-receptors would help in intensifying immune response. Often failure results when an individual receptor gene is transferred across distantly related plants. Whereas, delivering paired receptors (receptors and co-receptors) may result in heightened plant defense. Also, generating receptor variants capable of evading pathogen suppression could be critical. Decoding the underlying molecular basis of the complex immune receptor network would help in modulating immune system in crop plants, resulting in enhanced productivity. Studies'-underlying the mechanisms involved in regulation of defense related genes are also highly relevant. How might a pathogen entry facilitate the destruction of the host proteins at the early infection phase, which causes the accumulation of defense related gene transcripts of the host? This question is elementary to understand the arms race linking host and pathogen (Fig. 3). Investigating the fate of NMD core factors post pathogen infection would be significant in terms of understanding the molecular mechanism/s involved upon plant-pathogen interaction, particularly in revealing the correlation between NMD and plant immunity. Understanding the role of NMD in plant immunity for sure will widen up the pre-existing functions of NMD. Thus, understanding the contribution of NMD in plant immunity is also essential for the further understanding and manipulations in the field of plant breeding for better productivity.

Author contribution statement

KBS and GKP conceived the idea. GKP drafted the manuscript and was responsible for literature collection and KBS helped revising the draft. Authors have read and approved the final manuscript before submission.

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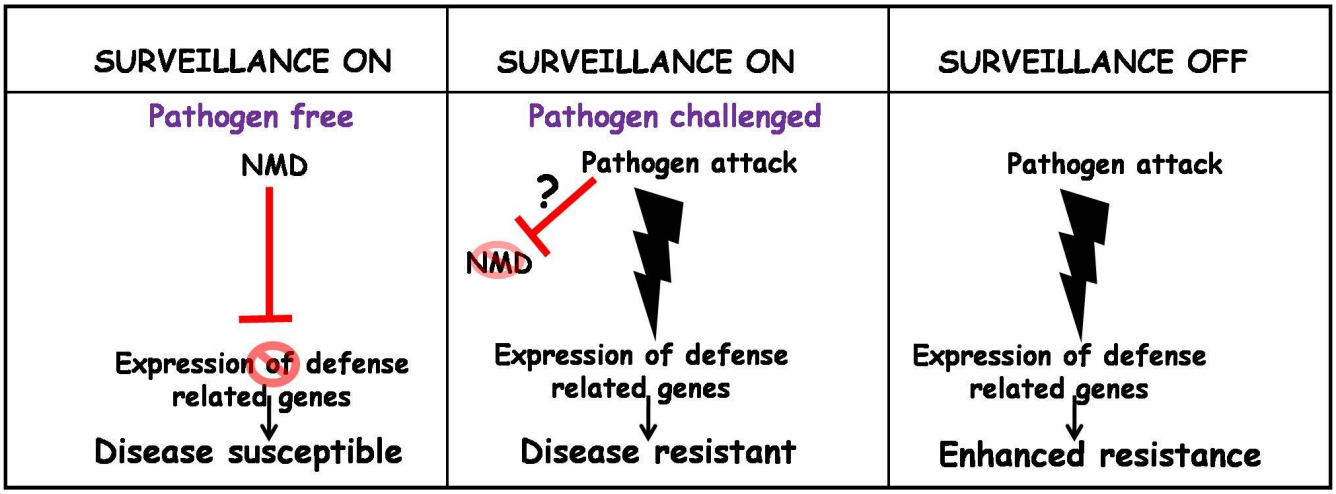

Fig. 3: Fate of R gene expression upon pathogen infection.

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Conflict of interest

The authors declare that they have no conflict of interest.

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