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Journal
Cell Host and Microbe, 30(8)

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Publication Date
2022-08-10

DOI
10.1016/j.chom.2022.07.004

Peer reviewed

HHS Public Access

Author manuscript

Cell Host Microbe. Author manuscript; available in PMC 2023 August 10.

Published in final edited form as:

Cell Host Microbe. 2022 August 10; 30(8): 1061–1063. doi:10.1016/j.chom.2022.07.004.

LncRNA gets into the balancing act

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Abstract

The plant hormone salicylic acid plays an important role in balancing plant immunity and growth. In this issue of *Cell Host & Microbe*, Liu et al. (2022) discovered that a long non-coding RNA, *lncSABC1*, promotes growth in uninfected plants and unleashes defenses when pathogens attack by transcriptionally regulating salicylic acid biosynthesis.

Only a minor fraction of the eukaryotic genome encodes functional proteins. This baffling discovery, firmly established when the first complete drafts of eukaryotic genomes were published some twenty years ago, has provoked biologists to investigate whether the non-coding genome has functional roles in gene expression or if the majority of eukaryotic genomes really are just “junk DNA.” Unexpectedly, RNA sequencing (RNA-seq) revealed that much more of the non-coding genome is transcriptionally active than anticipated, producing diverse and abundant long non-coding RNA transcripts (lncRNAs). Some lncRNAs are then processed by endonucleases (such as Drosha and Dicer-like proteins) to produce small RNAs, including microRNAs (miRNAs) and short interfering RNAs (siRNAs), that guide transcriptional and post-transcriptional gene silencing (TGS and PTGS, respectively) via RNA-induced silencing complexes. With the exception of sRNA precursors, the molecular activity of most lncRNAs remains elusive, although several recent studies have revealed that lncRNAs cause or contribute to various human diseases and genetic disorders (Herman et al., 2022). In this issue of *Cell Host & Microbe,* Liu et al. (2022) took a reverse genetic approach, using the best-studied plant molecular genetics model, *Arabidopsis thaliana,* to identify lncRNAs with potential roles in plant immunity. They demonstrate that a lncRNA, dubbed *lncSABC1,* acts to balance tradeoffs between growth and pathogen defense by epigenetically modulating the expression of a key regulatory transcription factor, NAC3. NAC3 then promotes phytohormone synthesis to raise defenses against pathogens and repress growth.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

Plant immune systems comprise multilayer mechanisms. In the first line of defense, conserved pathogen molecular patterns (PAMPs) are detected by cell surface receptors, called PAMP recognition receptors (PRRs). This triggers a series of downstream defense reactions that defeats most invaders, which is called PAMP-triggered immunity (PTI) (Jones and Dangl, 2006). Although it is reported that application of double-stranded (ds)RNA triggers a co-receptor-dependent PTI response, a cognate PRR responsible for this response has not yet been identified in plants. Instead, viral dsRNA synthesized during viral replication or by plant RNA-dependent RNA polymerases is processed by Dicer-like enzymes to generate siRNAs, which are incorporated into ARGONAUTE proteins that direct cleavage or translational repression of viral RNA, a process called antiviral RNA silencing (Lopez-Gomollon and Baulcombe, 2022).

Pathogens that have adapted to specific host species deliver effectors to the surface or inside of the host cells that inhibit the perception of PAMPs or downstream signaling events. For example, bacteria and fungi can secrete inhibitory proteins that prevent the enzymatic processing of flagellin polypeptides and chitin oligomers needed for recognition by PRRs. Moreover, some microbes secrete effector proteins into the host cells to inhibit the kinase activity or accumulation of PRRs (Wang et al., 2022). To counteract antiviral RNA silencing, viruses evolve many different suppressors with diverse functions, such as binding to viral dsRNA to prevent Dicer processing or sequestering viral siRNA to prevent siRNA loading into ARGONAUTE (Guo et al., 2019). As a result, pathogens defeat PTI and cause diseases in plants.

To cope with the adapted pathogens, plants evolved effector-triggered immunity (ETI) as a second line of defense. In ETI, plant resistance proteins (R), including intracellular nucleotide-binding site leucine-rich repeat receptors (NBS-LRRs or NLRs) and some cell surface receptor-like proteins (RLPs), detect pathogen effectors through direct protein-protein interaction or indirect detection of effector activity (Jones and Dangl, 2006).

Although the perception of pathogens by PRR-mediated PTI and ETI relies on distinct genes, their downstream signaling pathways converge. One of the shared downstream signaling molecules is the phytohormone salicylic acid (SA). SA biosynthesis is induced when pathogens are detected and then acts through nucleocytoplasmic SA receptors, NPR1 and NPR3/4, to induce the expression of defense-related genes. Beyond these local responses, SA signaling promotes systemic acquired resistance (SAR), the pre-emptive activation of some defenses in distant tissues to prevent infection by spreading or as-yet undetected pathogens. The combination of local and systemic responses ultimately results in the production of antimicrobial secondary metabolites, reactive oxygen species, defense enzymes, and structural modifications to plant cells that thwart most invading microbes.

Plant immune responses and growth are both energy- and nutrient-consuming processes. In circumstances when metabolic resources are limited, such as competitive ecosystems or in the face of abiotic stress, plants must balance the tradeoff between supporting new growth or defending existing tissues from pests and pathogens (Huot et al., 2014). Considering the critical role of NLRs, PRRs, and SA in plant immunity, it is not surprising that their accumulation in plants is subjected to tight regulation to coordinate investments in defense

versus growth. Plants dynamically modulate expression of these receptors and defenses in response to multiple factors, including pathogen infection (which broadly de-represses plant defenses) and developmental stage (sometimes focusing on growth over defense in young plants).

Plant genomes encode many NLRs to recognize diverse pathogens. To avoid autoimmunity due to the over-expression of NLRs spuriously triggering defenses, plants have evolved numerous miRNAs and phasiRNAs to repress *NLR* expression via RNA silencing pathways (Deng et al., 2018a). Interestingly, these NLR silencing genes are most likely generated during NLR duplication process via inverted duplication of partial NLR gene fragments, which means plants make swords and scabbards simultaneously (Deng et al., 2018a). Since host-adapted pathogens usually express suppressors of RNA silencing, these pathogens can also suppress miRNA-mediated *NLR* silencing and thus induce *NLR* expression upon infection (Deng et al., 2018a; Guo et al., 2019). Some of these miRNAs accumulate at higher levels in the young seedling stage than in the adult stage (Deng et al., 2018b), which is consistent with higher demand for growth in young seedlings than in older plants. Although this growth-defense model to explain the prevalence of miRNA-mediated regulation of *NLR* expression is popular, whether these miRNAs actually enhance plant growth in the absence of pathogen attack remains to be tested directly and is expected to be challenging because of the sheer number of genes that encode these miRNAs. *NLR* transcripts are also subjected to degradation via nonsense mediated decay (NMD) due to their long 3′ untranslated regions (3′ UTRs). Some NMD mutants display autoimmunity phenotypes and elevated *NLR* expression, demonstrating that NMD indeed confers growth benefits. More importantly, NMD can be turned off upon pathogen infection to unleash *NLR* expression (Wachter and Hartmann, 2014), making NMD a proper mechanism to balance immunity and growth (Figure 1).

Induction of SA biosynthesis is a critical step in both ETI and PTI. There are two SA biosynthesis pathways elucidated in plants, and the isochorismate synthase (ICS1)-dependent pathway plays a major role in Arabidopsis immune responses. Although previous studies established that *ICS1* gene expression is induced by pathogen infection, the underlying molecular mechanism regulating *ICS1* expression and the impact of infection-responsive *ICS1* expression were not known. In this issue, Liu et al. (2022) uncovered a role of a long non-coding RNA, *lncSABC1*, for pathogen-induced accumulation of SA and conferring growth benefit for plants. *LncSABC1* caught the authors' attention due to its high expression in uninfected plants and strong repression during ETI, as well as its natural antisense transcript relationship with a nearby transcription factor gene, *NAC3.* When induced, NAC3 promotes expression *of ICS1* to drive SA biosynthesis. *LncSABC1* recruits CURLY LEAF, the catalytic subunit of the polycomb repressive complex 2, to the *NAC3* gene body and represses its transcription by driving histone methylation, effectively repressing immunity by inhibiting SA synthesis in uninfected plants. Pathogen infection down-regulates *lncSABC1* expression, which required calcium influx and reactive oxygen burst. The authors further showed that mutation of *lncSABC* led to smaller size and shorter roots in young plants, indicating *lncSABC* has a role in promoting plant growth under normal conditions. Thus, in addition to miRNAs and NMD targeting upstream NLR

components, l*ncSABC* represents a new mechanism for plants to balance immunity and growth by controlling SA biosynthesis (Figure 1) (Liu et al., 2022).

Balancing growth and immunity is not only important for plant success evolutionarily but also for crops to achieve optimal yields. Although the above mentioned and other studies had placed some key pieces of the puzzle, more studies are necessary to put together a whole picture. In particular, how these immunity regulatory modules are plugged into the pathogen responses and developmental programs remains largely unclear; for example, how pathogens without known silencing suppressors inactivate NLR silencing miRNAs, how these miRNAs are regulated by developmental programs, how early immune responses repress *lncSABC,* and whether *lncSABC* and other immunity regulators, such as NLR protein and SA degradation/modification enzymes, are also subjected to developmental regulation. Deep understanding of the molecular mechanisms balancing plant growth and immunity, like the study by Liu et al. in this issue of *Cell Host & Microbe,* will be essential for a greener, more sustainable, and more reliable agricultural future.

ACKNOWLEDGMENTS

The authors are thankful to the funding from National Natural Science Foundation of China (91940301) and from the National Institutes of Health, United States (NIH DP5-OD023072). The authors also would like to apologize for not discussing many excellent related works due to limited space.

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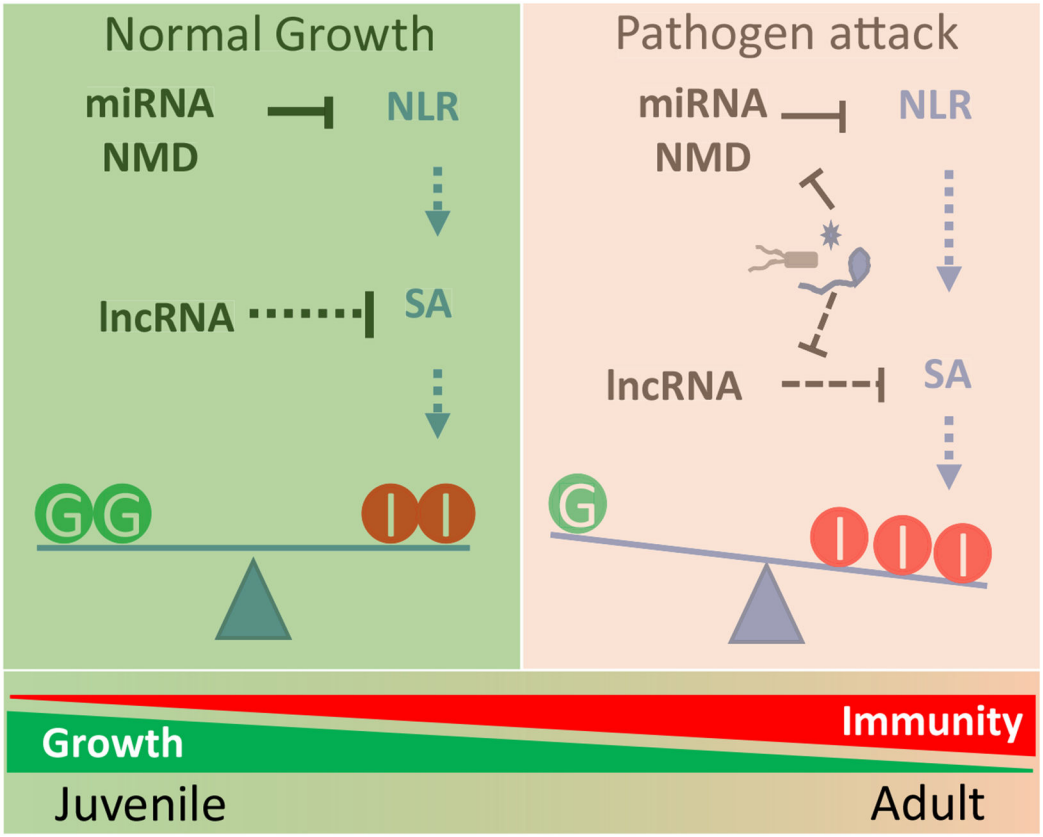

Figure 1. Balancing growth and immunity under different situations

Top left: under normal growth conditions, immunity is repressed by miRNAs and NMD directly targeting *NLR* transcripts or lncRNA indirectly targeting SA biosynthesis; top right: pathogen attack inhibits miRNA-, NMD-, and lncRNA-mediated repression of immune responses, effectively inducing pathogen defenses; bottom: growth is promoted in juvenile stage by keeping immunity at lower level, which is gradually increased as plants mature.