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Strapline: RNA helicases in mRNA decay

Title: Immunity gate-keepers

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Standfirst (here 40w, 270c):

Plants need to respond swiftly against attacks, but when pathogen pressure is weak, defence genes must be repressed as they impede development and growth. Three RNA helicases are now found to control decapping-dependant mRNA decay and negatively regulate plant immunity.

Main Text (Length: was 1614w, now 1153):

Plants are fast reacting organisms. They switch off their developmental programs to rapidly mount stress responses and prepare for adverse conditions. Immunity genes are controlled at transcriptional and post-transcriptional levels, in particular through the general 5'-3' and non-sense mediated mRNA decay pathways. In this issue, Chantarachot *et al.*, show that Arabidopsis RH6/8/12, homologs of the DHH1/DDX6 RNA helicases, are cofactors of the 5'-3' mRNA decay process and act as immunity controllers¹.

Cytoplasmic mRNAs are in a perpetual balance between active translation, degradation and storage. The regulation of this balance contributes to mRNA homeostasis and translation control under normal and

stress conditions. Translationally silent mRNAs are stored in two main types of membrane-less aggregates: processing bodies (PBs) that contain RNA decay and translation repression factors, and stress granules (SGs) only formed in response to stress, that contain translation components. Several types of mRNA degradation mechanisms exist, involving specific enzymes and a vast repertoire of cofactors. In Arabidopsis, at the end of their useful life, mRNAs are degraded in the cytosol following shortening of their polyA tail, either from 3' by the exosome complex or the exoribonuclease SOV (DIS3L2), or from 5' by XRN1/4 after removal of the cap structure by the decapping holoenzyme DCP1/DCP2/VCS. The 5'-3' mRNA decay also targets translating mRNAs in a conserved pathway called co-translational decay, which affects most of the transcriptome. In this process, mRNAs are decapped while still associated with polysomes and XRN1/4 digests the body of the transcript, chasing the last translating ribosome².

The Non-sense Mediated Decay (NMD) is a cellular mRNA quality control mechanism that protects the cell from truncated and putatively toxic protein production, but is also recognized as a genuine post-transcriptional regulation pathway. It detects, through translation, transcripts carrying premature termination codons arising from mutations, transcription errors or alternative splicing events. How plant NMD is orchestrated remains unclear.

Cofactors of these decay processes include decapping enhancers DCP1, VCS, DCP5 and PAT1; RNA helicase UPF1 which senses aberrant mRNAs; and SMG7 which activates UPF1 for NMD.

RNA degradation is crucial for many processes. Mutants of *DCP1*, *DCP2*, *VCS* or *DCP5* are post-embryonic lethal^{3,4} and *SMG7* and *UPF1* mutants are infertile because of gametogenesis defects, and exhibit a range of vegetative phenotypes⁵.

Upon recognition of invading pathogens, the plant defence response necessitates both a rapid induction of immunity genes and downregulation of repressors. Cytoplasmic RNA degradation pathways appear to be crucial in both phenomena. The general 5'-3' mRNA turnover and DCP2 and DCP1 in particular are necessary to induce immunity. DCP1 is necessary for the degradation of some immune negative

regulators, supporting that the 5'-3' turnover contributes to unbridle immunity upon pathogen infection⁶. In plants, PAT1 was found to carry the conserved function of decapping stimulator, and acts as an immunity regulator. The *pat1* mutants display dwarfism and derepressed immunity, but the exact molecular mechanisms remain unknown⁷. Nonetheless, these findings suggest that the 5'-3' turnover is involved in the negative regulation of immunity. The *upf1* and *smg7* mutants also display a pleiotropic autoimmune phenotype, supporting their role and that of NMD as negative regulators of immunity⁸.

DDX6/DHH1 are key actors of mRNA decay and major components of p-bodies in mammals and yeast. In the latter, DHH1 associates with slow-moving ribosomes triggering the decapping and 5'-decay of mRNAs with poor translation efficiency^{9,10}. Arabidopsis RH6/8/12 are putative homologs of the DDX6/DHH1 RNA helicases. They are in a complex with UPF1 and directly interact with DCP5, a translation inhibitor and decapping activator¹¹. RH6/8/12 helicases inhibit NMD through yet unknown mechanisms¹².

In this issue of *Nature Plants*, Chantarachot *et al.* show that Arabidopsis RH6/8/12 are novel cofactors of the plant general 5'-3' mRNA decay involved in the negative control of immunity¹. Loss-of-function plants suggest that these helicases are mostly redundant. The triple mutant exhibits dwarfism and phenocopies *dcp2* and *vcs* decapping mutants. The three helicases have identical nucleo-cytoplasmic distribution and are present in p-bodies and stress granules, and are required for the assembly of PBs and SGs.

To explore the roles of the RH6/8/12 triplet in mRNA homeostasis and translation control, the authors implemented a multi-transcriptomic approach based on sequencing of total and ribosome-associated polyA+ RNAs. Compared to wild type, the triple *rh6812* mutant bears an increase of stress and innate immunity transcripts both at total and ribosome-associated levels. Conversely, transcripts associated with primary growth were depleted in *rh6812*. To some extent, these helicases seem to be involved in ribosome associated mRNA homeostasis in normal conditions and as such were hypothesized to control the balance between growth and stress transcripts expression.

To confirm the involvement of RH proteins in mRNA metabolism, the authors applied a genome-wide mRNA decay analysis. Transcription was inhibited in wild type and triple mutant seedlings and mRNA half-life determined through RNA-seq over time. This approach revealed that the client mRNAs of the RH6/8/12 module are intrinsically short-lived, and strikingly overlap with those previously shown to decay through VCS-mediated decapping. Finally, Chantarachot *et al.* observed that mRNAs stabilized in the *rh6812* mutant also preferentially associate with ribosomes. Collectively, the data support a role for these helicases in the rapid decapping-dependant degradation of mRNAs, and a possible role in translation control. Once again, mRNAs destabilized by RH6/8/12 mostly encode for stress and immune genes. Indeed, the *rh6812* triple mutant shows all the hallmarks of a constitutive immune response.

This study broadens our understanding of the decapping-dependant degradation of mRNAs and further supports its crucial role in plant development and immunity control. It offers a novel view in which 5'-3' mRNA decay is essential to maintain defence mRNAs at basal levels under normal conditions. One major question in the field of post-transcriptional regulation is to know how regulated mRNAs are selected. This study now points at evolutionarily conserved helicases, which could be involved in the substrate choice of the decapping machinery. This hypothesis is backed up by the observations that only part of DCP2/VCS bodies contain the RH6/8/12 helicases, and that only a subset of VCS substrates are degraded depending on RH6/8/12.

Together with a previously observed interaction with the translation inhibitor DCP5¹¹, this new work places the RH6/8/12 module at a nexus between translation and 5'-mRNA decay, although further work is needed to understand its molecular mode of action. In yeast, DHH1 was proposed to be a translation repressor and to couple translation and mRNA decay, by directing the decapping machinery to transcripts with slow-moving ribosomes. Strikingly, a distinctive feature of slow-moving ribosomes is that they are found on short-lived mRNAs with sub-optimal codons⁹. It remains to be seen whether RH6/8/12 helicases play similar roles on their mRNA targets and whether a distinctive feature of these targets is enrichment in sub-optimal codons. In yeast, such coupling targets stress-activated mRNAs to fine tune their translation both in normal and stress response, contributing to protect the cell from an hyper-response¹³. This new study

by Chantarachot *et al.* opens the interesting concept that such protective role could be evolutionarily conserved in plants.

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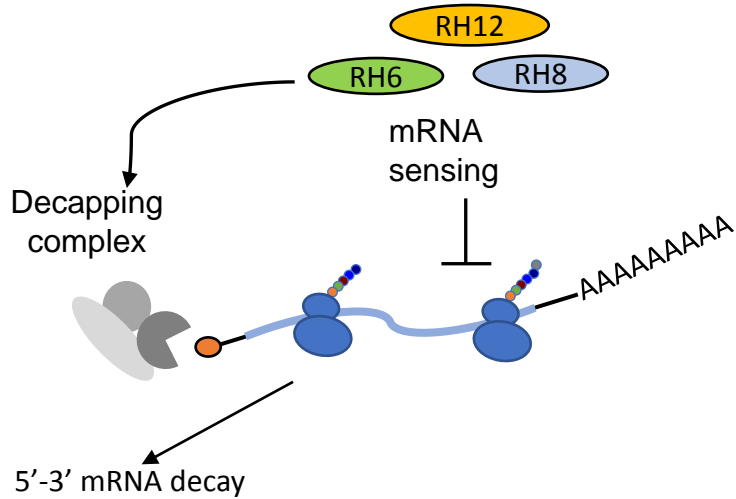
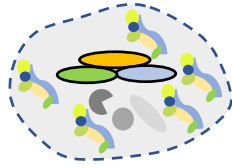
Competing interests: The authors declare no competing interests.

Figure Legend:

Figure 1. Model of action of the RH6/8/12 module in the negative control of plant immunity. Under pathogen-free conditions (left), the RH6/8/12 module recognizes, through yet unknown determinants, transcripts coding for immunity factors. It could act as an inhibitor of their translation and participate in the specific recruitment/activation of the DCP1/DCP2/VCS decapping complex to these mRNAs, permitting their 5'-turnover in the cytosol or possibly co-translationally. The *cis* determinant(s) driving immunity transcripts' recognition by RH6/8/12 are yet to be uncovered. Nonetheless, considering the known role of their yeast homolog DHH1, one possibility is that a common feature of immunity transcripts would be an intrinsically low translation efficiency. When facing a pathogen attack (right), the RH6/8/12 triplet would be downregulated putatively in part through sequestration in p-bodies and stress granules and the negative post-translational control they exerted on immunity mRNAs released. A similar effect would happen constitutively in the triple *rh6812* mutant. The RH6/8/12 would hence contribute to arbitrate the balance between growth/development and immunity.

No stress:
Free RH6/8/12

few
P-bodies



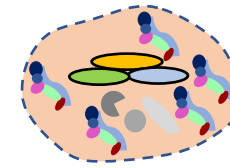
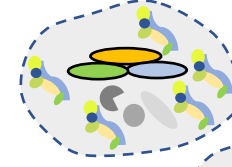
Slow
translation rate



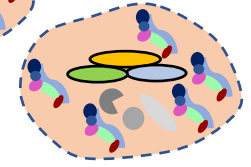
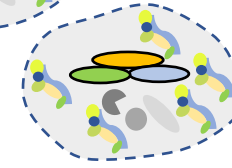
Growth/Development

Presence of pathogens:
Sequestered RH6/8/12

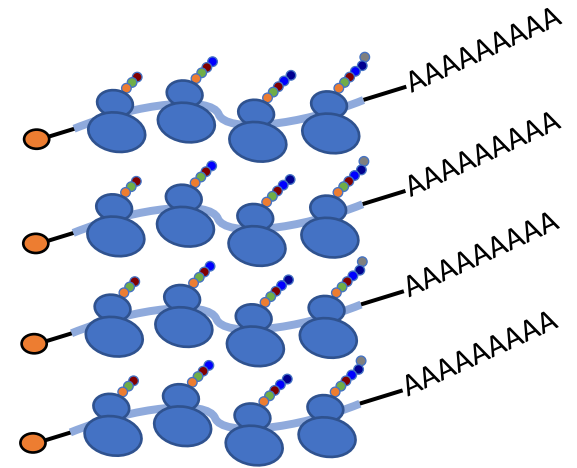
many
P-bodies



many
Stress Granules



Immunity/
Growth inhibition
transcripts



High
translation rate



Immunity