PHR1 Balances between Nutrition and Immunity in Plants

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Plants assemble beneficial root-associated microbiomes to support growth, especially in nutrient-poor conditions. To do so, however, plants have to suppress their immune system. Reporting in *Nature*, Castrillo et al. (2017) identified PHOSPHATE STARVATION RESPONSE1 (PHR1) as a central regulator in this balance between nutrient stress response and immune regulation.

The coevolution of plants and microbial organisms has led to well-established interactions that play key roles in the functioning of terrestrial communities and ecosystems. Some of these interactions are detrimental and lead to the development of defense mechanisms, whereas others turn out to be beneficial. The latter can be exploited by the plant and have evolved into the manifestation of stable root-associated microbiomes. How plants can become engaged in such interactions while staying protected against harmful relationships is an intriguing question. Well-balanced control of the plant immune system is thus very central, being even more challenging in changing nutrient conditions. In the latter case, plants will favor micro-organisms that might be beneficial in the given stress condition. For example, deprivation of phosphate, one of the most important plant macronutrients, leads to greater colonization by fungi that convert plant-inaccessible phosphate into bioavailable inorganic phosphate (Pi), thereby stimulating translocation of Pi in the root (Hiruma et al., 2016). Interestingly, phosphate deprivation leads simultaneously to the suppression of the plant immune system, opening the door for plant–microbe interactions. A recent study showed that a mutualistic interaction was made possible by repression of the immune response under phosphate starvation conditions (Hacquard et al., 2016). Such observations point toward a fine-tuned interaction between the phosphate starvation response (PSR) and the immune system.

Recent progress in PSR research led to the identification of key steps in its sensing and response: inositol polyphosphate molecules, assumed to show a positive correlation with Pi, bind to SPX proteins and trigger their association with other specific proteins, including the transcription factors PHOSPHATE STARVATION RESPONSE1 (PHR1) and PHR1-LIKE1 (PHL1) (Wild et al., 2016; Puga et al., 2014) (Figure 1). Free PHR1 transcription factors bind to the PHR1 binding site (P1BS) element that is present in the promoters of phosphate starvation-induced (PSI) genes. Although PHR1 possibly controls a wide variety of genes related to diverse processes (Bustos et al., 2010), PSI genes are mainly involved in mechanisms to increase Pi uptake (Figure 1).

Until now, it remained unclear how PSR can interact with the plant immune system. In a recent *Nature* paper, Castrillo et al. (2017) tackled this issue by exploiting a synthetic bacterial community (SynCom) representative for a wild-type root endophytic community and studying its effect on the PSR. By comparing wild-type plants with plants carrying a mutation in the *PHR1* gene, a master regulator of PSR, the authors could demonstrate an enhanced immune function in the mutants, arguing for PHR1 being involved in the PSR immune response crosstalk. In addition, different transcriptome and ChIP-seq experiments revealed a direct link between immune responses and the PSR: PHR1 itself directly targets genes involved in immune system responses such as jasmonic acid and/or salicylic acid (SA) pathway genes. Interestingly, the authors showed via mutant studies that PHR1 in general suppresses the SA-responsive genes, which were previously shown to be involved in the defense against improper root colonizers (Lebeis et al., 2015). In addition, responses triggered by the bacterial elicitor flg22 were increased in *phr1;phl1* mutants, again pointing to a negative regulation of the immune responses by PHR1 (Castrillo et al., 2017). Because PHR1 suppresses the immune response, Castrillo et al. (2017) hypothesized that *phr1;phl1* mutants should be less susceptible to pathogens. Indeed, although these mutants will not be able to cope with phosphate starvation, they showed an enhanced disease resistance to different pathogens.

A remarkable conclusion of the experiments using the SynCom communities is that the induction of PSI genes, and thus a functional PSR in low-phosphate conditions, depends on the presence of a microbial community. This supports the idea that plant roots are by definition accompanied by an ever-present association of micro-organisms that are able to respond to phosphate starvation conditions. This seems to be true for at least fungi, which have been hypothesized to have facilitated the colonization of land by plants 460 million years ago (Redecker et al., 2000). But why had plants not uncoupled the PSR and the immune response during evolution? Possibly, because phosphate is an essential element for plants, they redirect all available resources toward mechanisms to cope with phosphate starvation during phosphate stress. The risk for infections might be less detrimental than phosphate shortage, and hence plants may have prioritized the PSR and suppressed the immune system. PHR1, however, does not necessarily block the entire immune system. For

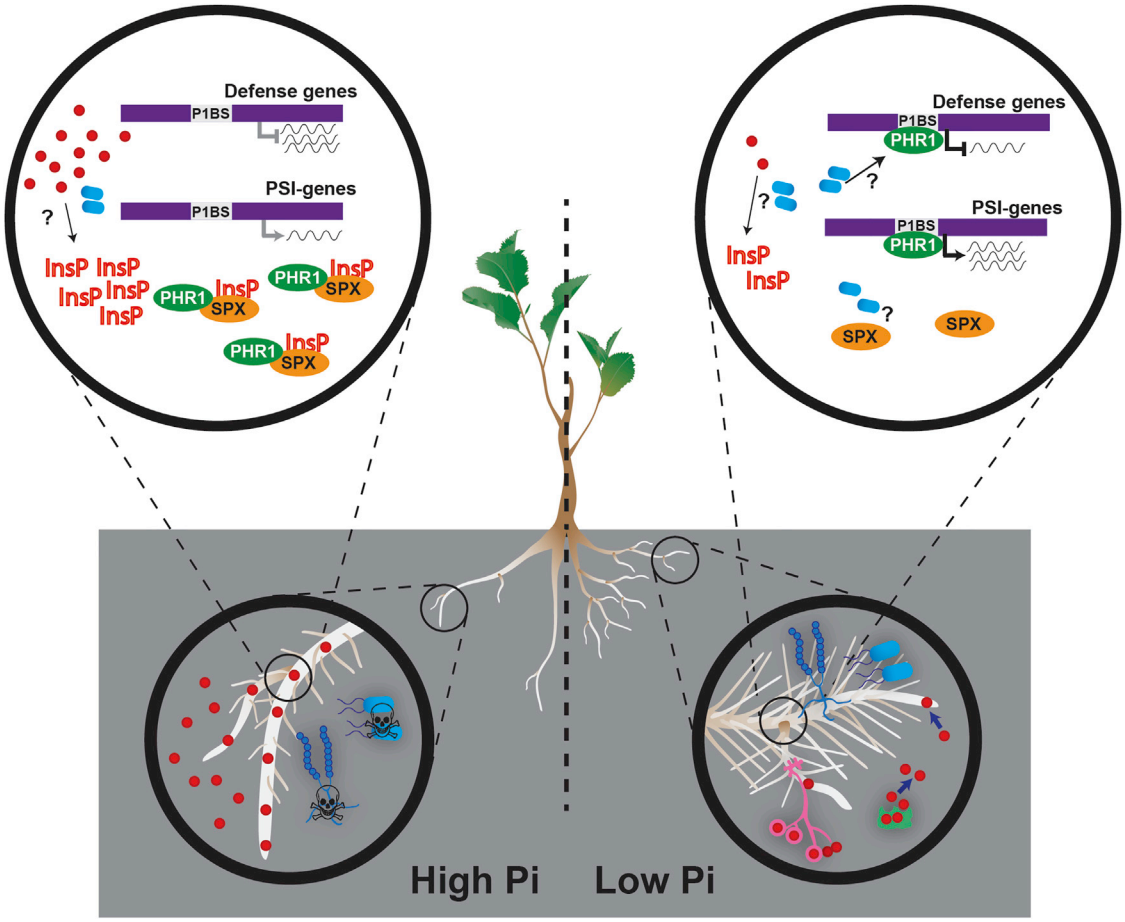

Figure 1. PHR1 as Central Regulator of Immune System Responses and Phosphate Starvation Response
On the left side, in high Pi conditions (represented by red balls), inositol polyphosphates (InsPs) trigger SPX proteins to bind PHR1. As a consequence, phosphate starvation-induced (PSI) genes are not or are poorly expressed. The plants acquire sufficient Pi by constitutive mechanisms and are able to activate defense mechanisms to prevent disease infection. On the right side, PHR1 is able to bind P1BS elements and thus activate PSI genes or repress certain defense genes (at least a portion of the defense genes are direct PHR1 targets and are suppressed by PHR1). In natural conditions, a microbial community appeared to be essential for this response, but it is unknown which steps are affected. As a result of the PSR, plants form a shorter root system with more lateral roots and root hairs, activate phosphate uptake transporters, excrete phosphatases to solubilize plant-inaccessible Pi, and attract mycorrhizae for extra mobilization of Pi. Due to the immune response suppression, however, the plants are more susceptible for improper root colonization and have less resistance toward pathogens.

example, immune responses will still be activated by certain pathogens, even in low-phosphate conditions (Hacquard et al., 2016). Hence, it might be more likely that the coupling of the PSR and the immune system exists to allow, in low-phosphate conditions, colonization of the root by Pi-mobilizing micro-organisms. Accordingly, production of indole glucosinolates, also induced by PHR1, is known to stimulate the beneficial interaction with mycorrhizal fungi (Hiruma et al., 2016).

Overall, it seems that plants have difficulties coping with phosphate starvation and pathogens at the same time. If phosphate resources are depleted, PHR1 suppresses immune responses and prioritizes phosphate stress responses. Some pathogens apparently have evolved to exploit this vulnerability in low-phosphate conditions. For example, phytoplasmas (Lu et al., 2014) and presumably citrus pathogens from the genus *Candidatus* liberibacter (Zhao et al., 2013) both induce a PHR1-dependent PSR to suppress the defense mechanisms of the host plants and are as such able to infect them. In general, the finding of a direct coupling between PSR and the immune system may inspire new approaches toward tackling plant disease problems and nutrient stress.

In conclusion, Castrillo et al. (2017) demonstrated the direct integration of PSR and immune responses by PHR1 and provided useful insights that might be used to increase phosphate use efficiency and disease control. The question remains of how soil microbiota activate PHR1. Inositol polyphosphate decomposition, PHR1-SPX dissociation, or PHR1 itself might need extra factors that are induced by sugars or microbial metabolites or proteins. These parts of the PSR pathway are subjects for future research to further unravel the microbiota-dependent PSR.

REFERENCES

Bustos, R., Castrillo, G., Linhares, F., Puga, M.I., Rubio, V., Pérez-Pérez, J., Solano, R., Leyva, A., and Paz-Ares, J. (2010). PLoS Genet. *6*, e1001102.

Castrillo, G., Teixeira, P.J.P.L., Paredes, S.H., Law, T.F., de Lorenzo, L., Feltcher, M.E., Finkel, O.M., Breakfield, N.W., Mieczkowski, P., Jones, C.D., et al. (2017). Nature *543*, 513–518.

Hacquard, S., Kracher, B., Hiruma, K., Münch, P.C., Garrido-Oter, R., Thon, M.R., Weimann, A., Damm, U., Dallery, J.-F., Hainaut, M., et al. (2016). Nat. Commun. *7*, 11362.

Hiruma, K., Gerlach, N., Sacristán, S., Nakano, R.T., Hacquard, S., Kracher, B., Neumann, U., Ramírez, D., Bucher, M., O'Connell, R.J., and Schulze-Lefert, P. (2016). Cell *165*, 464–474.

Lebeis, S.L., Paredes, S.H., Lundberg, D.S., Breakfield, N., Gehring, J., McDonald, M., Malfatti, S., Glavina del Rio, T., Jones, C.D., Tringe, S.G., and Dangl, J.L. (2015). Science *349*, 860–864.

Lu, Y.-T., Li, M.-Y., Cheng, K.-T., Tan, C.M., Su, L.-W., Lin, W.-Y., Shih, H.-T., Chiou, T.-J., and Yang, J.-Y. (2014). Plant Physiol. *164*, 1456–1469.

Puga, M.I., Mateos, I., Charukesi, R., Wang, Z., Franco-Zorrilla, J.M., de Lorenzo, L., Irigoyen, M.L., Masiero, S., Bustos, R., Rodríguez, J., et al. (2014). Proc. Natl. Acad. Sci. USA *111*, 14947–14952.

Redecker, D., Kodner, R., and Graham, L.E. (2000). Science *289*, 1920–1921.

Wild, R., Gerasimaite, R., Jung, J.-Y., Truffault, V., Pavlovic, I., Schmidt, A., Saiardi, A., Jessen, H.J., Poirier, Y., Hothorn, M., and Mayer, A. (2016). Science *352*, 986–990.

Zhao, H., Sun, R., Albrecht, U., Padmanabhan, C., Wang, A., Coffey, M.D., Girke, T., Wang, Z., Close, T.J., Roose, M., et al. (2013). Mol. Plant *6*, 301–310.

Hematopoiesis Lineage Tree Uprooted: Every HSPC Is a Rainbow

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Differentiation of hematopoietic stem cells into distinct cell types was thought to occur through a series of discrete, stable progenitor states. Work from Velten et al. (2017) now shows that hematopoietic cells differentiate via a mechanism of continuous lineage priming and thus represent a CLOUD-HSPC.

Traditional models of lineage progression from stem cells to their differentiated progeny are often thought of as hierarchical trees involving successive binary fate decisions as oligo-potent cells differentiate toward mature cell types with distinct functions (Figure 1A). Many of these hierarchies have been proposed based on phenotypic analysis of pre-defined subpopulations of cells within stem cell compartments (niches) or differentiated progeny. However, a recent study in *Nature Cell Biology* by Velten and coworkers (2017) has taken the approach of analyzing single cells within human bone marrow and has found that hematopoietic stem and progenitor cells (HSPCs) exhibit characteristics of multiple lineages and are thus likely to undergo direct lineage commitment to generate distinct blood cell types, as opposed to transitioning through a series of discrete and stable progenitors (Figure 1B).

Velten et al. (2017) performed single-cell immunophenotyping and transcriptional and functional analyses on two sets of lineage-negative (Lin^-; i.e., non-differentiated) cells: (1) $Lin^-CD34^+CD38^-$ cells, thought to contain HSCs, multi-potent progenitors (MPPs), and multi-lymphoid progenitors (MLPs), and (2) $Lin^-CD34^+CD38^+$, thought to contain lineage-restricted progenitors. The samples were taken from the bone marrow of two young adults (male and female). These analyses revealed that the $Lin^-CD34^+CD38^-$ compartment does not contain stable clusters of cell types; rather, the HSPCs are highly interconnected and represent a continuum of low-primed, undifferentiated (CLOUD)-HSPCs. Based on the authors' analysis, the HSCs in the center of the CLOUD are transcriptionally diverse and the least "primed" toward a specific lineage. These cells gradually acquire continuous lineage priming that nudges them toward either of two major hematopoietic branches, lymphoid/myeloid or megakaryocytic/erythroid. However, a clear separation into single lineages was only observed among cells in the $Lin^-CD34^+CD38^+$ compartment, when differentiation has progressed to the level of restricted progenitors.

These findings are consistent with the hypothesis that Conrad Waddington, the father of epigenetics, put forth in *The Strategy of the Genes* in 1957. He suggested that mechanisms are in place during embryonic development to allow a population of cells to inherit particular traits