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Linking plant metabolism and immunity through methionine biosynthesis

Plants respond to pathogenic cues with a transcriptional reprogramming that leads to *de novo* production of defense-related proteins and a huge variety of secondary metabolites (e.g., phytoalexins, phenolics, etc.). Activation of these host defenses, which contribute to halt the intruder as part of the resistance, implies an increased demand for metabolic energy and carbon skeletons derived from primary metabolism (Bolton, 2009). Therefore, it could be anticipated that the energy expenditure associated with the upregulation of diverse pathways that contribute to disease resistance comes at the expense of a reconfiguration of primary metabolism, as occurs for the metabolism of amino acids. This holds true, for example, in the case of lysine catabolism, which is required for the synthesis of pipecolic acid, a regulator of systemic acquired resistance (SAR) (Návarová et al., 2013), or the accumulation of some amino acids and their metabolic by-products that function as triggers of resistance (Zeier, 2013). In this same regard, a link between methionine metabolism and plant defense has recently been unveiled by Zhai et al. (2021). Here, a novel deubiquitinase (named PICI1, which stands for pigmR-interacting and chitin-induced protein 1) from rice was shown to be key in the promotion of disease resistance to *Magnaporthe oryzae*, the causal agent of blast disease. The authors elegantly demonstrated that PICI1 functions in plant immunity by targeting and stabilizing by deubiquitination a methionine synthase (METS1) enzyme, which appears prone for protein degradation in disease states. The results, thus, bring to light a nexus between methionine metabolism and activation of immune responses in rice (Figure 1). Methionine (Met) is an essential amino acid important for diverse biological processes, including the translation of proteins, the biosynthesis of the plant hormone ethylene, or the methylation of DNA, to mention a few. Met biosynthesis depends on the availability of 5-methyl-tetrahydrofolate (CH_3-THF), produced by the folate pathway (Figure 1), and METS1 is the enzyme directly responsible for Met synthesis by transferring the methyl group from CH_3-THF to homocysteine in the one-carbon (C1) metabolic pathway. Subsequently, Met enters the Yang cycle to produce *S*-adenosylmethionine (SAM), the universal donor of methyl groups for methylation reactions in all biological processes, including the methylation of DNA or the biosynthesis of 1-aminocyclopropane-1-carboxylate (ACC) by ACC synthase, which is the immediate precursor of the plant hormone ethylene (ET). ET is required for disease resistance to fungal pathogens, such as *M. oryzae*, and, consequently, the ethylene pathway is a common target for pathogens, who deliver effectors to hijack the route and bypass plant immunity (Washington et al., 2016; Zhao et al., 2017). In the paper by Zhai et al. (2021) the authors demonstrate that METS1 targeting by PICI1 and its subsequent stabilization occurs during activation of both PTI (pattern-triggered immunity) and ETI (effector-triggered immunity) in response to the fungi. Consequently, resistance to *M. oryzae* is compromised in *PICI1* mutants *(PICI1*-KO) and, conversely, resistance is increased when PICI1 is overexpressed (*PICI1*-OE).

In response to *M. oryzae*, deubiquitinated METS1 leads to Met formation and, therefore, ethylene production, which ultimately results in plant resistance. In fact, external application of ACC or Met, or just simply overexpressing METS1 (*METS1*-OE), promotes plant resistance to *M. oryzae*. Conversely, external application of AVG (an inhibitor of ethylene biosynthesis) or alternatively suppressing gene expression (i.e., *METS1*-KO and *PICI1*-KO lines) promote enhanced susceptibility to *M. oryzae*, which was rescued by applying Met or ACC (Figure 1).

During the evolutionary arms race between rice and *M. oryza*, the fungi seems to have evolved effectors to bind and degrade PICI1, counteracting the PICI1-METS1-ET immune cascade. In a screen, Zhai et al. (2021) found seven fungal effectors (AvrPizt, AvrPii, AvrPia, AvrPWL2, AvrPi9, AvPikC and AvrPikD), which specifically bind to PICI1, although the seven effectors interacted with PICI1 *in vitro* pull-down assays, only three effectors (AvrPii, AvrPWL2, and AvrPi9) could execute their interactions with PICI1 in planta, as shown in Zhai et al. (2021). Interestingly, AvrPi9 was found to promote PICI1 degradation, which in turns results in increased METS1 ubiquitination and degradation. This reduction in METS1 leads to reduced Met and ET biosynthesis in what appears to be a fungal strategy to counteract plant resistance. In this tour de force, rice appears to have succeeded to counteract this fungal adaptation by expressing the intracellular NLR PigmR receptor, which binds PICI1 protein and yields a protective effect against the AvrPi9-mediated PICI1 degradation. In summary, the findings by Zhai et al. (2021) represent a case example on the inter-linkage and importance of primary metabolism (i.e., Met metabolism) for flexible immune adaptation of plants following pathogen attack.

Previous work in *Arabidopsis* also revealed the importance of Met metabolism in mediating plant immunity. González and Vera (2019), through a chemical genetic approach, identified a number of sulfonamides, including sulfodiazine (SDZ), that, while acting as competitive inhibitors of the folate pathway, promoted resistance enhancement to the bacterial pathogen *Pseudomonas syringae* DC3000. SDZ, an analog of p-aminobenzoic acid (pABA), inhibits dihydropteroate synthase (DHPS), which is cardinal for tetrahydrofolate (THF) biosynthesis, which leads to Met biosynthesis by METS1 in the 1C metabolic pathway (Zhang et al., 2012) (Figure 1). Folic acid

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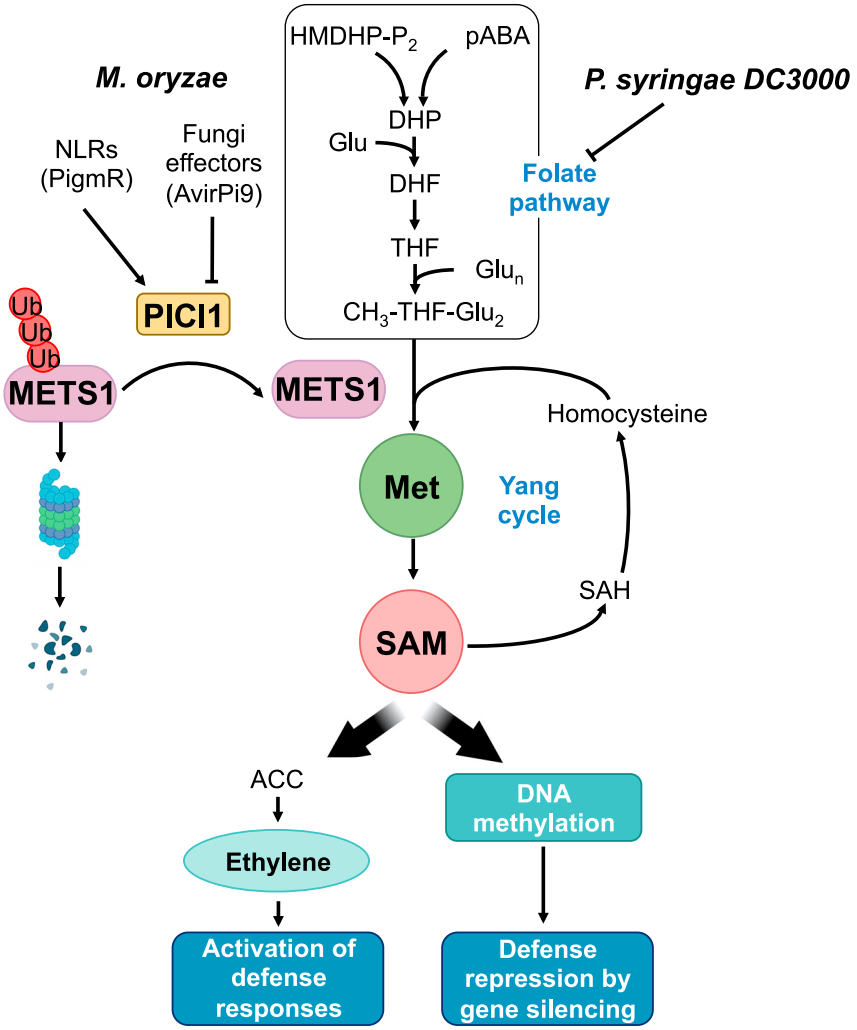

Figure 1. Methionine metabolism, a hub modulating plant immunity against *Magnaporthe oryzae* and *Pseudomonas syrinage* DC3000, two hemi-biotrophic pathogens with different life styles

Model depicting the role of methionine metabolism in plant defense. HMDHP, 6-hydroxymethyldihydropterin; *p*ABA, *p*-aminobenzoate; DHP, dihydropteroate; DHF, dihydrofolate; THF, tetrahydrofolateMet regulating plant immunity in response to different; Met, methionine; METS1, methionine synthase (EC 2.1.1.14); SAM, *S*-adenosylmethionine; SAH, *S*-adenosylhomocysteine; ACC, 1-aminocyclopropane-1-carboxylate; PICI1, pigmR-interacting and chitin-induced protein 1.

treatment, as well as Met treatment, counteracted the SDZ-mediated effect. Moreover, expression of *DHPS* is downregulated following *P. syringae* DC3000 infection. Interestingly, the observed SDZ-mediated resistance was not accompanied by salicylic acid (SA)-mediated defenses (i.e., PR1), indicating an SA-independent control. Furthermore, in the hypersusceptible *npr1* and *sid2* mutants (that lost SA-mediated resistance to *P. syringae* DC3000 by its defective SA perception and biosynthesis, respectively), SDZ treatment restored a normal disease susceptibility. In addition to this, a comparative proteomic analysis of two *scs9* allelic mutants, which display SA-independent disease responses (Ramírez et al., 2018) that evoke the SDZ-mediated response, identified enhanced accumulation of METS1 following *P. syringae* DC3000 infection when compared with Col-0 parental plants. This led to the observation that heterozygous *mets1/METS1* plants (*mets1* homozygosity is lethal in *Arabidopsis*) show enhanced disease resistance to the bacteria. Conversely, the overexpression of *METS1* (*35S::METS1*) leads to a notorious susceptibility enhancement that concurs with a marked reduction in defense gene activation. Notably, overexpression of *METS1* is accompanied by a genome-wide increase in DNA methylation leading to gene silencing, indicating that METS1 is an epigenetic regulator. This reveals that imposing a methylation pressure at the genomic level, as derived from the enhanced accumulation of Met and SAM, compromises plant immunity. Decreased DNA methylation leading to chromatin silencing release was subsequently corroborated in a partial loss-of-function mutant allele of *METS1* (*atms1-1*) identified by Yan et al. (2019), which was identified in a search for epigenetic regulators in *Arabidopsis*. All in all, these observations indicate that Met produced by METS1 via the 1C metabolic pathway represents an important node for an interplay between immunity, epigenetic, and metabolism. It remains to be evaluated whether *P. syringae* DC3000 infection in *Arabidopsis* affects METS1 deubiquitination and whether it has an effect on plant immunity. Also, evaluating the effect *M. oryzae* infection may have on epigenomic reprograming in rice and the participation of PICI1 in this process will help bring a consensus in the understanding of METS1 as a central metabolic node controlling plant immunity.

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REFERENCES

Bolton, M.D. (2009). Primary metabolism and plant defense—fuel for the fire. Mol. Plant-Microbe Interact. **22**:487–497.

González, B., and Vera, P. (2019). Folate metabolism interferes with plant immunity through 1C methionine synthase-directed genome-wide DNA methylation enhancement. Mol. Plant **12**:1227–1242.

Návarová, H., Bernsdorff, F., Döring, A.C., and Zeier, J. (2013). Pipecolic acid, an endogenous mediator of defense amplification and

priming, is a critical regulator of inducible plant immunity. Plant Cell **24**:5123–5141.

Ramírez, V., González, B., López, A., Castelló, M.J., Gil, M.J., Zheng, B., Chen, P., and Vera, P. (2018). A 29-O-methyltransferase responsible for transfer RNA anticodon modification is pivotal for resistance to *Pseudomonas syringae* DC3000 in *Arabidopsis*. Mol. Plant-Microbe Interact. **31**:1323–1336.

Washington, E.J., Mukhtar, M.S., Finkel, O.M., Wan, L., Banfield, M.J., Kieber, J.J., and Dangl, J.L. (2016). *Pseudomonas syringae* type III effector HopAF1 suppresses plant immunity by targeting methionine recycling to block ethylene induction. Proc. Natl. Acad. Sci. U S A **113**:E3577–E3586.

Yan, X., Ma, L., Pang, H., Wang, P., Liu, L., Cheng, Y., Cheng, J., Guo, Y., and Li, Q. (2019). METHIONINE SYNTHASE1 is involved in chromatin silencing by maintaining DNA and histone methylation. Plant Physiol. **181**:249–261.

Zeier, J. (2013). New insights into the regulation of plant immunity by amino acid metabolic pathways. Plant Cell Environ. **36**:2085–2103.

Zhai, K., Liang, D., Jiao, F., Yan, B., Liu, J., Lei, Z., Huang, L., Gong, X., Wang, X., Miao, J., et al. (2021). NLRs guard metabolism to coordinate pattern and effector triggered immunity. Nature https://doi.org/10.1038/s41586-021-04219-2.

Zhang, H., Deng, X., Miki, D., Cutler, S., La, H., Hou, Y.J., Oh, J.E., and Zhu, J.K. (2012). Sulfamethazine suppresses epigenetic silencing in Arabidopsis by impairing folate synthesis. Plant Cell **24**:1230–1241.

Zhao, S., Hong, W., Wu, J., Wang, Y., Ji, S., Zhu, S., Wei, C., Zhang, J., and Li, Y. (2017). A viral protein promotes host SAMS1 activity and ethylene production for the benefit of virus infection. Elife **6**:1–22.