PC biosynthesis are themselves unlikely to be drug targets, due to the high level of redundancy that characterizes different pathways of de novo biosynthesis, it is possible that proteins involved in lipid exchange and transport across the PVM and parasite membranes are potential targets. It will be important to confirm that human-infective species, such as *P. falciparum*, *P. vivax*, and *P. ovale*, are also dependent on PC uptake. Each of these species exhibits subtle differences in the time they take to develop in the liver (e.g., 2 versus 7 days for *P. berghei* and *P. falciparum*, respectively) and the final parasite burdens reached. Significant differences may also occur in the metabolic activity of murine and human liver cells, all of which could lead to species-specific differences in metabolic demands. Another intriguing possibility is that a decrease in hepatocyte PC biosynthesis, possibly as a result of choline deficiency, could trigger latency in some *Plasmodium* species. Latency is thought to be associated with the appearance of metabolically quiescent liver stages and is a distinctive feature of human infective *P. vivax* and *P. ovale*, resulting in nonsymptomatic infections that can reactivate long after the initial infection. Overall, these studies highlight the complex metabolic interactions that underpin all host-pathogen interactions and the need to study the metabolism of both partners together.

REFERENCES

Coppens, I. (2013). Nat. Rev. Microbiol. *11*, 823–835.

Fagone, P., and Jackowski, S. (2013). Biochim. Biophys. Acta *1831*, 523–532.

Grützke, J., Rindte, K., Goosmann, C., Silvie, O., Rauch, C., Heuer, D., Lehmann, M.J., Mueller, A.-K., Brinkmann, V., Matuschewski, K., and Ingmundson, A. (2014). Traffic *15*, 362–382.

Itoe, M.A., Sampaio, J.L., Cabal, G.G., Real, E., Zuzarte-Luis, V., March, S., Bhatia, S.N., Frischknecht, F., Thiele, C., Shevchenko, A., and Mota, M.M. (2014). Cell Host Microbe *16*, this issue, 778–786.

Labaied, M., Jayabalasingham, B., Bano, N., Cha, S.-J., Sandoval, J., Guan, G., and Coppens, I. (2011). Cell. Microbiol. *13*, 569–586.

Prudêncio, M., Rodriguez, A., and Mota, M.M. (2006). Nat. Rev. Microbiol. *4*, 849–856.

Thieleke-Matos, C., da Silva, M.L., Cabrita-Santos, L., Pires, C.F., Ramalho, J.S., Ikonomov, O., Seixas, E., Shisheva, A., Seabra, M.C., and Barral, D.C. (2014). Traffic *15*, 1066–1082.

Vaughan, A.M., O'Neill, M.T., Tarun, A.S., Camargo, N., Phuong, T.M., Aly, A.S.I., Cowman, A.F., and Kappe, S.H.I. (2009). Cell. Microbiol. *11*, 506–520.

Yu, M., Kumar, T.R.S., Nkrumah, L.J., Coppi, A., Retzlaff, S., Li, C.D., Kelly, B.J., Moura, P.A., Lakshmanan, V., Freundlich, J.S., et al. (2008). Cell Host Microbe *4*, 567–578.

Co-opting the Cell-Cycle Machinery for Plant Immunity

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Plant effector-triggered immunity is a robust cellular defense response activated by a family of intracellular receptors. In this issue of *Cell Host & Microbe*, Wang et al. (2014) show that receptor-activated defense pathways utilize several core cell-cycle regulatory components to induce resistance and programmed cell death against pathogens.

Individual plant and mammalian cells have the innate capacity to recognize interference by pathogens and activate disease resistance pathways. This provides a crucial early defense mechanism against infectious microbes and is broadly referred to as innate immunity. Without innate immunity, organisms rapidly succumb to disease. On the flip side, misregulation of cellular defenses can lead to autoimmunity with potentially catastrophic consequences for general health and growth of the host. To enforce tight control, structurally and functionally related nucleotide-binding/leucine-rich-repeat receptors (NLRs) have evolved independently in each kingdom as ligand-dependent molecular switches that sense pathogen-driven perturbations in different parts of the cell (Maekawa et al., 2011). NLR activation mobilizes host antimicrobial defenses and often induces programmed cell death (PCD). Additional components of innate immune signaling pathways have been characterized in both systems, but the processes by which activated NLRs connect molecularly to downstream pathways to elicit timely and effective resistance remain unclear (Maekawa et al., 2011; Griebel et al., 2014). Also, operational relationships between host defense and cell death programs have not been fully resolved. In plants, individual NLRs intercept the activities of specific pathogen effectors (virulence factors) that are delivered into host cells to disable basal resistance pathways. Thus, recognition by NLRs turns effector manipulation of basal defenses into effector-triggered immunity (ETI).

The study by Wang et al. in this issue of *Cell Host & Microbe* (Wang et al., 2014) is

an important advance in our understanding of plant ETI signaling because it fills some of the gaps between NLR activation and the execution of disease resistance. The authors provide compelling genetic and molecular evidence that the induction of pathways leading both to immunity and PCD as part of ETI is accomplished through modulation of core regulators of the cell-cycle machinery. Therefore, components of mitotic cell-cycle progression that are highly conserved across eukaryotes have been coopted for plant immunity.

Piecing together the plant cell cycle-immunity connection by Wang and colleagues (Wang et al., 2014) started with a mutational screen for genetic suppressors of an *Arabidopsis* autoimmunity mutant, *cpr5* (*constitutive expressor of pathogenesis-related genes 5*), that displays constitutive PCD, enhanced basal immunity against virulent pathogens, and certain developmental abnormalities indicative of defective cell division and cell fate determination (Clarke et al., 2001; Kirik et al., 2001). One *cpr5* suppressor mutation was mapped to a member of the *KIP-related protein* (*KRP*) family of *cyclin-dependent kinase inhibitor* (*CKI*) genes, which are core regulators of a eukaryotic cell-cycle signaling pathway (Besson et al., 2008; Harashima et al., 2013). A major function of CKIs is to modulate the activities of cyclin-dependent kinase (CDK) complexes, which promote progression through the cell division cycle. During cell-cycle pathway activation, CDKs phosphorylate another core cell-cycle regulator, Retinoblastoma (RB). This promotes RB dissociation from a set of E2F transcription factors that become released for gene expression reprogramming (De Veylder et al., 2007; Polager and Ginsberg, 2008).

Combined *Arabidopsis* loss-of-function mutations in two other *KRP*-family genes, *SIAMESE* (*SIM*) and *SIAMESE-RELATED 1* (*SMR1*), strongly attenuate the *cpr5* autoimmunity and developmental phenotypes. Therefore, SIM and SMR1 are required for *cpr5*-induced immunity, PCD, and abnormal development. Strikingly, the *sim smr1* mutants in a *CPR5* wild-type background are also impaired in ETI and ETI-associated PCD against different NLR-recognized pathogenic strains. Similarly, an *Arabidopsis* E2F transcription factor triple signaling mutant (*e2fabc*) exhibits reduced ETI and PCD, although with different penetrance than in the *sim smr1* plants. Both types of *Arabidopsis* cell-cycle mutant have a less obvious effect on basal immunity against a virulent pathogen, suggesting that these core cell-cycle regulators might be preferentially engaged for ETI. A comparison of gene expression profiles between the different mutant lines and with published *Arabidopsis* expression data established that there is a significant overlap between the *cpr5*-induced *SIM/SMR1*-dependent and *E2F*-driven transcriptional defense programs. Together, the data suggest a model in which NLR-triggered resistance pathways converge on core cell-cycle signaling components to drive host immunity and cell death outputs. In the model, CPR5 has a negative or constraining function at a point downstream of the activated NLRs. A resistance-limiting role of CPR5 is further supported by the partial loss of ETI in *Arabidopsis* CPR5-green fluorescent protein-overexpressing lines.

Having built a genetic framework in *Arabidopsis*, the authors explore the molecular processes underpinning recruitment of *Arabidopsis* CPR5 and the canonical CKI-CDK-RB-E2F cell-cycle regulators in NLR-conditioned ETI. CPR5 resides at the nuclear membrane where it interacts with SIM. Interestingly, CPR5-SIM association is markedly reduced upon NLR induction of ETI, suggesting that CPR5 negative regulation of SIM is disrupted downstream of NLR-effector recognition, potentially releasing SIM from the nuclear rim to connect with CDK-cyclin complexes. The precise functional relationship between the *Arabidopsis* SIM/SMR1 CKIs and CDKs in ETI is not clear because CKIs can have both CDK-inhibitory and stabilizing effects (Besson et al., 2008). Mammalian CKI counterparts bind to and modulate CDK phosphorylation of RB leading to E2F release to activate steps in cell-cycle progression. There is also evidence that CKIs can have a number of CDK-independent roles in transcriptional reprogramming and promotion of cell death, depending on the cellular or stress context (De Veylder et al., 2007; Besson et al., 2008). Notably, Wang et al. (2014) show that *Arabidopsis* RBR1, which is a conserved ortholog of the mammalian CDK target, RB, is more highly phosphorylated in a SIM/SMR1-dependent manner in both the *cpr5* constitutive resistance mutant and after pathogen elicitation of ETI. The same level of RBR1 phosphorylation was not detected in a nonrecognizing *NLR* mutant or after inoculating plants with a virulent pathogen to induce basal resistance. Therefore, the phosphorylation status of RBR1 and hence its power to activate E2F-mediated transcriptional defense outputs might be a key driver of ETI. The authors propose that this resistance circuit takes canonical cell-cycle components out of their normal cell-cycle progression mode toward noncanonical activities mediating ETI responses and PCD. It will be interesting in future studies to measure the RBR1 phosphorylation dynamics in ETI and basal resistance and test whether RBR1 phosphorylation is causal for mobilizing E2F transcription relay and defense. Also, since NLRs can be activated at different cell locations, events connecting NLRs to the nuclear cell-cycle and transcriptional machineries need to be resolved. Here, a role for the nuclear trafficking machinery and nucleocytoplasmic coordination in ETI is well supported (Maekawa et al., 2011).

Data presented in this paper are significant in two further respects. First, they highlight the importance of E2F transcription factors in plant immunity. E2Fs represent a versatile family of canonical and noncanonical transcriptional regulators that can interact with other transcription factors and chromatin modifiers to mediate cell-cycle progression, cell death, and immunity outputs (De Veylder et al., 2007; Polager and Ginsberg, 2008; Chandran et al., 2014). Therefore, like the CKIs, E2Fs are important integrators of cellular homeostasis and stress. Second, they suggest a mechanism by which host PCD during ETI can be initiated inside nuclei, perhaps representing an important checkpoint between basal defense activation and cell survival or a commitment to cell death. ETI-related PCD pathways can proceed in different parts of the cell (Maekawa et al., 2011), so the events described here likely represent one of several avenues to cell death. In mammals and plants, a variety of cell death morphologies have been discovered with different immunity outcomes (Maekawa et al., 2011). Since PCD can often be uncoupled from disease resistance in ETI, this leaves open the

important question of what actually stops the pathogen from growing.

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REFERENCES

Besson, A., Dowdy, S.F., and Roberts, J.M. (2008). Dev. Cell *14*, 159–169.

Chandran, D., Rickert, J., Huang, Y.X., Steinwand, M.A., Marr, S.K., and Wildermuth, M.C. (2014). Cell Host Microbe *15*, 506–513.

Clarke, J.D., Aarts, N., Feys, B.J., Dong, X.N., and Parker, J.E. (2001). Plant J. *26*, 409–420.

De Veylder, L., Beeckman, T., and Inzé, D. (2007). Nat. Rev. Mol. Cell Biol. *8*, 655–665.

Griebel, T., Maekawa, T., and Parker, J.E. (2014). Trends Immunol. *35*, 562–570.

Harashima, H., Dissmeyer, N., and Schnittger, A. (2013). Trends Cell Biol. *23*, 345–356.

Kirik, V., Bouyer, D., Schöbinger, U., Bechtold, N., Herzog, M., Bonneville, J.M., and Hülskamp, M. (2001). Curr. Biol. *11*, 1891–1895.

Maekawa, T., Kufer, T.A., and Schulze-Lefert, P. (2011). Nat. Immunol. *12*, 817–826.

Polager, S., and Ginsberg, D. (2008). Trends Cell Biol. *18*, 528–535.

Wang, S., Gu, Y., Zebell, S.G., Anderson, L.K., Wang, W., Mohan, R., and Dong, X. (2014). Cell Host Microbe *16*, this issue, 787–794.