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EDITORIAL: REFLECTIONS ON *THE PLANT CELL* CLASSICS

Early Leads to Mechanisms of Plant Cultivar-Specific Disease Resistance[OPEN]

Science progresses in waves, and in 1991, the year my two chosen articles were published in *The Plant Cell*, a fresh wave of research had started to transform our understanding of plant host-pathogen interactions for the next three decades. The **Whalen et al. (1991)** and **Dong et al. (1991)** articles came from the groups of Brian Staskawicz at University of California, Berkeley, and Fred Ausubel at Massachusetts General Hospital in Harvard, respectively. These scientists were coordinating efforts to build a robust genetic system in Arabidopsis (*Arabidopsis thaliana*) for determining mechanisms underlying plant cultivar-specific disease resistance. This was an absolutely critical nut to crack to make molecular sense of the gene-for-gene model developed by Harold Flor in the 1940s and 1950s. Flor used the flax (*Linum usitatissimum*) and the flax rust fungus (*Melampsora lini*) interaction to establish that simply inherited, dominant or semi-dominant, plant host *Resistance* (*R*) and pathogen *Avirulence* (*Avr*) genes cause rust resistance. The model thus predicted specific recognition between matching *R* gene and *Avr* gene products to trigger a resistant response, whereas a mismatch would lead to disease susceptibility.

An important step forward had already been made by 1991 in that several bacterial *Avr* genes were cloned from libraries of genomic fragments and shown by conjugation into virulent bacteria to be recognized in a cultivar-specific manner in crop plants such as soybean (*Glycine max*) and tomato (*Solanum lycopersicum*). Getting at the corresponding crop *R* genes (or loci) was, however, a much trickier proposition. The staggering sizes of some crop genomes were beginning to be realized, and the requisite genomic and molecular tools were not yet in place for many crop species to clone *R* genes. Also, while studies of biochemical and physiological plant responses to virulent and avirulent pathogens or microbe-derived elicitors had provided interesting leads to induced plant defense pathways, there lacked a genetic underpinning to identify key host and microbial factors, and signal transduction pathways, responsible for resistant or susceptible outcomes. Critically, community-wide development of genetic and genomic technologies in Arabidopsis provided a platform in the late 1980s (and beyond) for fine-mapping and walking to plant genes conferring important phenotypes. These tools, together with new Arabidopsis gene-tagging and mutagenesis strategies, prompted researchers to explore Arabidopsis as a model host-pathogen system for cloning *R* genes. Claims in some quarters that Arabidopsis did not have pathogens had been dispatched by demonstrating that different Arabidopsis ecotypes (accessions) were naturally infected by microbes such as *Xanthomonas* bacteria and downy mildew (now known as *Hyaloperonospora arabidopsidis* [*Hpa*]). Later articles revealed the extent of natural genetic variation in Arabidopsis-*Hpa* interactions mediated largely by simply inherited *R* genes (Holub, 2001).

The work of Whalen et al. (1991), Dong et al. (1991) and others opened the door to the isolation of plant *R* genes, their molecular characterization, and ultimately to modern engineering of crop disease resistance traits (Arora et al., 2019). The significance of the Whalen et al. (1991) and Dong et al. (1991) data struck me as a new postdoctoral researcher at The Sainsbury Laboratory in Norwich, UK. Looking over the experiments again emphasizes their value for the research field at that time. Both groups surveyed panels of *Pseudomonas syringae* isolates, known to cause disease on crucifer and/or tomato varieties, for infection phenotypes on a range of ~30 Arabidopsis genetic accessions. As part of the analysis, the authors assessed different ways of infecting Arabidopsis leaf tissues with bacteria and tested whether the growth of drug-resistant bacterial strain derivatives inside leaves correlated with disease-like symptoms, which was generally the case. They discovered that some *P. syringae* strains, which did not produce disease symptoms and grew to low titers when inoculated at low doses, elicited an early leaf necrotic response at high doses, consistent with a host hypersensitive response (HR). This necrotic reaction is now often used as an indicator of R-Avr recognition in transient expression assays. The upshot of the experiments was identification of one or two *P. syringae* strains that differed reproducibly in their ability to infect certain Arabidopsis accessions, suggesting that these strains are recognized by particular Arabidopsis genotypes in a gene-for-gene manner. By cloning genomic segments from the recognized bacterial strain and conjugating plasmids into a virulent recipient *P. syringae*, the authors isolated a fragment of bacterial DNA containing a presumptive *Avr* gene, which they named *AvrRpt2*. Interestingly, the *AvrRpt2*-containing fragment elicited a cultivar-specific HR on turnip (*Brassica rapa*) and soybean leaves, suggesting the presence of *AvrRpt2*-recognizing *R* genes in these crop species. The *AvrRpt2*-recognizing Arabidopsis *RPS2* and *RPM1* genes were in the first wave of plant *R* genes to be isolated and found to encode intracellular NLR receptor proteins. Detailed molecular analyses of these NLRs was central to formulating a paradigm for host NLR indirect recognition of bacterial pathogen effectors (Dodds and Rathjen, 2010).

Some other pointers that were prescient to later plant immunity research can be found in the two *Plant Cell* articles. First, Dong et al. (1991) monitored the expression of host genes encoding phenylalanine ammonia lyase (PAL) and β-1,3-glucanase (BG) enzymes that had been implicated as induced mediators of plant antimicrobial defenses. This analysis revealed that the amplitude of early *PAL* expression, but not that of *BGs*, correlated with *Avr* (effector)-specific resistance. The *BGs* were used to unravel

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salicylic acid-based resistance mechanisms against virulent pathogens (Cao et al., 1997). Subsequent Arabidopsis gene expression studies revealed that robust effector-triggered immunity mediated by NLRs against bacteria depends on early, high-amplitude defense gene expression (Tao et al., 2003; Mine et al., 2018; Bhandari et al., 2019). Second, both the Dong et al. (1991) and Whalen et al. (1991) authors noticed a disconnect between bacterial growth in leaves and HR-eliciting strength between the *AvrRpt2*-harboring recipient strain and the original avirulent donor bacteria. This, as the authors pointed out, suggested actions of further *Avr* genes present in the donor strain, which is borne out by activities and epistasis of multiple *P. syringae*-delivered effectors (Xin et al., 2018). Moreover, it suggested that the relationship between bacterial growth in leaves and host HR-like cell death is not a simple one, as reinforced by later research.

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*References highlighted for the 30th anniversary of *The Plant Cell*.