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EDITORIAL: REFLECTIONS ON PLANT CELL CLASSICS

Flor-iculture: Ellis and Dodds' Illumination of Gene-for-Gene Biology

Harold Flor, working alone in North Dakota on the interactions between flax plants (*Linum usitatissimum*) and their rust parasite, coined the term "gene-for-gene" resistance to describe race-specific interactions between plants and their fungal parasites. It was already well-known that many plant genes for resistance are dominant, suggesting they encode receptors. Crucially, Flor carried out genetics on the rust (*Melampsora lini*), and showed "avirulence" genes that specify recognizability are also dominant, because genes for virulence (evasion of recognition) are recessive. He may have wondered what biological processes were involved, and I suspect he would have been delighted to see the superb series of papers from the Canberra group over the last two decades that reveal the protein components and many aspects of their mechanisms.

The first breakthrough came from making transgenic flax plants that carried both a resistance gene (L6) and the maize *Activator* (*Ac*) transposon introduced via *Agrobacterium* (Lawrence et al., 1995). Mutants were revealed as susceptible to flax rust race that carries the recognized allele of *AvrL567*; this susceptibility betrays itself in an *L6* mutant as beautiful orange pustules after infection with the appropriate race. *L6* encodes a TIR-NLR protein, related to the tobacco *N* gene and the *Arabidopsis RPP5* gene. Flax is an ancient tetraploid, and the flax *M* gene encodes the homoeolog of the *L6* gene; intriguingly, though the *L* locus encodes a single gene, with extensive allelic diversity, the *M* locus is complex with multiple adjacent paralogs (Anderson et al., 1997).

Different alleles of the *L* locus recognize different races; what is the basis for recognition specificity? Despite the prevailing general view emerging from other systems that recognition was solely specified by the leucine-rich repeats (LRRs), careful analysis by the Canberra group showed that the TIR domain also contributed to specific recognition (Ellis et al., 1999; Luck et al., 2000). They also cloned the *N* and *P* genes for flax rust resistance; in the case of *P*, allelic variation in recognition specificity could mostly be explained by variation in the LRRs (Dodds et al., 2001).

To address Flor's model in full, one also needs to understand the fungal avirulence genes. At the dawn of the 21st century, this was still a substantial technical challenge for obligate parasites, and much harder than for bacterial effectors. In two key papers, Ellis and Dodds and their colleagues addressed this, making cDNA libraries from haustoria (Catanzariti et al., 2006) and identifying multiple recognition specificities, including the *AvrL567* gene recognized by L6 (Dodds et al., 2004). This began a productive collaboration with Bostjan Kobe's structural biology team, and after defining the structure of AvrL567, enabled the definition of surface-exposed amino acids that underpinned recognizability (Wang et al., 2007). In brief excursions outside the pages of *The Plant Cell*, the Ellis, Dodds, and Kobe teams showed evidence for direct interaction between both L6 and M effector/NLR pairs (Dodds et al. 2006), investigated the correlation between affinity and allelic specificity for the L6/AvrL567 system (Ravensdale et al., 2012), and defined the structure and many of the properties of the TIR domain of L6 (Bernoux et al., 2011).

So how do NLR proteins convert recognition of effectors into defense activation? The Dodds, Ellis, and Kobe teams proposed that in the pre-activation state, NLRs are inactive and bound to ADP, and upon engagement with ligand, a conformational change ensues which ejects an ADP and enables binding to ATP (Bernoux et al., 2016). This looks particularly prescient in the light of recent reports that the *Arabidopsis* ZAR1 NLR protein binds ADP, changes conformation upon engagement (via another protein) with a host protein after its modification by an effector, and then ejects ADP, and undergoes dATP-dependent oligomerization (Dangl and Jones, 2019).

This remarkable series of top-quality papers, many in *The Plant Cell*, provide a wonderful example of progress achieved by successive peeling back, layer after layer, of the gene-for-gene onion; first to isolate the cognate genes from host and pathogen, and then to dissect in atomic detail how their interactions lead to activation of defense. Of course, flax rust is not the most important agricultural disease, and it is also impressive how the Canberra team have used their expertise acquired in the flax/flax rust system to (with others) make a parallel series of advances in understanding the molecular basis of wheat interactions with its stem and stripe rust diseases. They have much to be proud of.

Jonathan D.G. Jones
The Sainsbury Laboratory
Norwich, United Kingdom
jonathan.jones@tsl.ac.uk
ORCID: 0000-0002-4953-261X

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