Pathogen Protein Modularity Enables Elaborate Mimicry of a Host Phosphatase

Pathogens have developed an extensive array of proteins during the co-evolutionary arms race with their hosts. This is particularly true for *Phytophthora*, a genus that causes significant damage to agriculture and forestry. One well-known species, *Phytophthora infestans*, caused the devastating late blight pandemic during the Irish potato famine. Each *Phytophthora* species encodes hundreds of effector proteins that play essential roles in manipulating host cellular processes and promoting disease development.

A previous report demonstrated that the *Phytophthora* suppressor of RNA silencing 2 (PSR2) exhibits a conserved modular fold that contributes to its virulence. The (L)WY motifs within PSR2 form distinct structures, which affect the surface residues of effector proteins and likely impact their ability to interact with plant molecules. This raised questions among researchers about whether these repeated modules serve specific functions within effector proteins, aiding their evasion of plant immune defenses and facilitating their evolution.

In the study published in *Cell*, researchers from the Institute of Biophysics (IBP) of the Chinese Academy of Sciences and The Sainsbury Laboratory made an exciting discovery. They found numerous effectors from *Phytophthora* that possess a conserved PP2A interacting module, mimicking the regulatory subunits of PP2A to hijack the PP2A core enzyme.

To investigate the role of (L)WY units in virulence and effector evolution, the researchers used the PSR2 effector from the soybean pathogen *P. sojae* as a model.

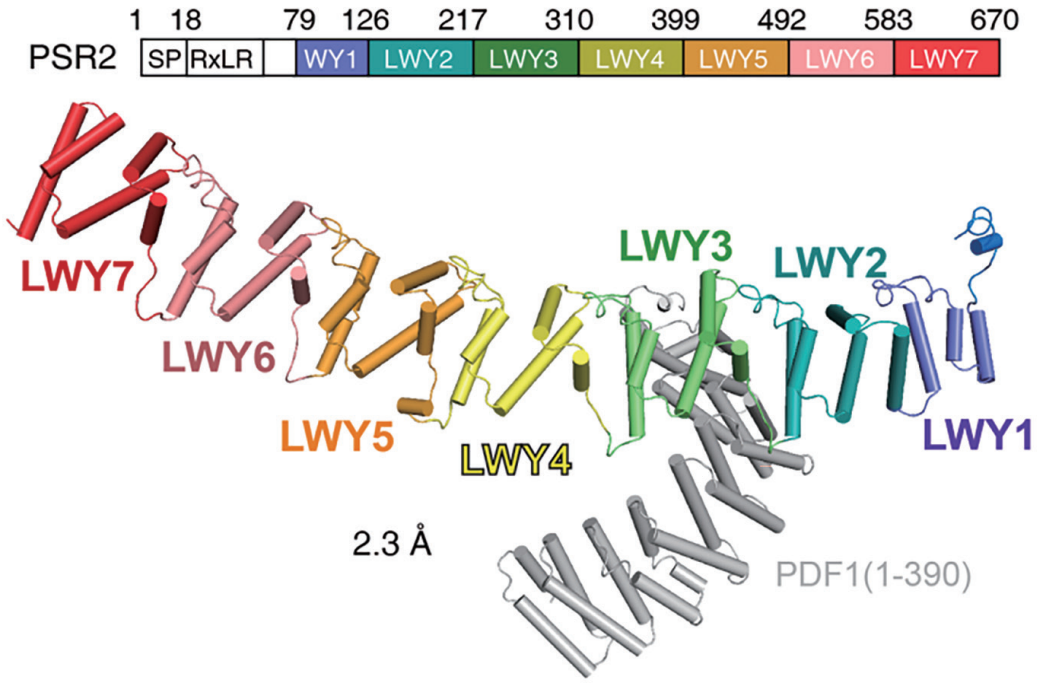

Figure 1. The crystal structure of PDF1-PSR2 binary complex. (Image by IBP)

They found that PSR2 interacts with the PP2A enzyme in the host plant, a major phosphatase, and modifies its phosphorylation function to promote disease.

Through crystal structure analysis and biochemical experiments, the researchers revealed a specific LWY2-LWY3 combination within PSR2, referred to as the PP2A interacting module, which competes for the recruitment of the PP2A core enzyme (Figure 1). Furthermore, through sequence alignment and structural comparison, they observed a high degree of structural and sequence conservation in the amino acid region corresponding to the PP2A interacting module among the identified WY1-(LWY)n effector proteins. They selected 15 highly conserved effector proteins for further screening and confirmed that twelve of them also hijack the PP2A core enzyme in host cells. To validate these findings, they focused on one of the proteins, PITG_15142, and obtained its crystal structure. Structural analysis and *in vitro* biochemical experiments confirmed the conservation of the PP2A interacting module. These results are illustrated in Figure 2.

Together, this study shows that (L)WY tandem repeats serve as functional modules in the *Phytophthora* effector, and a specific (L)WY-LWY combination enables the hijacking of the host PP2A core enzyme. In addition, multiple effectors adopt this module to hijack the host PP2A core enzyme. This publication provides the first evidence of how functional diversity and novel virulence activities can arise within a pathogen's effector repertoire. It sheds light on how protein modularity promotes diversity within this repertoire.

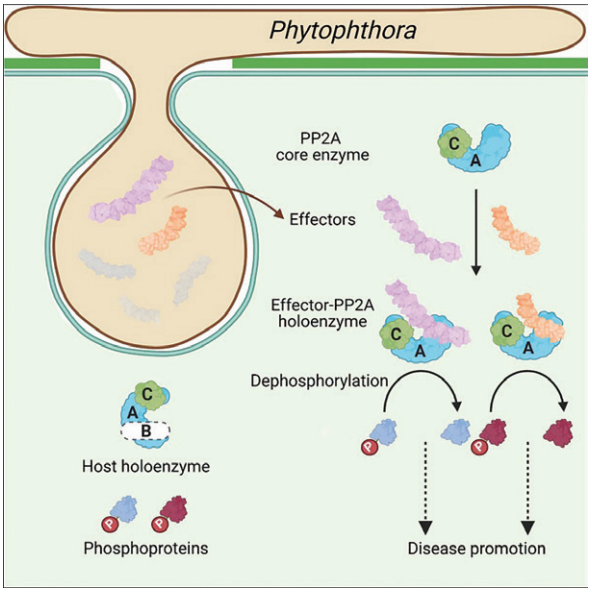

Figure 2. Schematic diagram of the mechanism of *Phytophthora* infecting the plant host. (Image by IBP)

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Reference

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