IN BRIEF

Not Throwing Baby Out with the Bathwater

The degradation of proteins is critical in all kingdoms of life. In bacteria and eukaryotic organelles, specific energy-dependent proteases are responsible for destroying proteins that are no longer needed or desired. This process is particularly important during stress responses, as accumulation of damaged proteins can lead to toxic protein aggregation. The universal challenge that these systems face is the demand to robustly degrade particular targets rapidly without sacrificing the remaining pool of stable proteins. The chloroplast Clp protease family is particularly complex, with a hetero-oligomeric ClpP peptidase forming active proteases by partnering with three ATP-dependent ClpC/ClpD chaperones, additional plant-specific factors needed for protease assembly (ClpT1/2), and orthologs of known bacterial substrate adaptors (ClpS1/2). These proteases are critical for plant growth, but how substrates are delivered to these proteases in the chloroplast is poorly understood, and it is unclear what additional factors are needed to ensure protease specificity. In their Breakthrough Report, van Wijk and colleagues (Nishimura et al., 2015) identify a new regulator that may serve as this sought after connection between the Clp protease machinery and specific target substrates in the chloroplast.

The Clp family proteases in bacteria often use adaptors to regulate specificity, and the ClpS adaptor is known to deliver N-end rule substrates to the ClpA chaperone (a homolog of ClpC). Prior detailed analysis of the bacterial ClpS revealed a specific binding pocket for these N-end rule substrates (Wang et al., 2008). In a previous work, van Wijk and colleagues identified ClpF as an interacting partner with the chloroplast ClpS1 that does not depend on the substrate binding pocket (Nishimura et al., 2013). In the current work, they show that ClpF not only binds to ClpS1, but it also interacts with ClpC directly. Interestingly, there is a synergistic interaction between these components, where the ClpF-ClpS1-ClpC complex is more stable that any of the binary interactions alone.

Furthermore, ClpF also promotes ClpS1-ClpC complex formation in vivo, leading the authors to suggest a physiological role for ClpF in regulating ClpC-dependent protein degradation. Guided by bioinformatics, they use purified proteins to isolate specific domains within ClpF needed for each of these interactions, defining the minimal components needed. Using mass spectrometry-based proteomics, they show that cells deficient in clpF and clpS show similar trends in proteome changes and further find that ClpF binds a putative substrate of the Clp protease system, GluTR.

Together, these data support a model whereby Clp protease substrates such as GluTR are delivered via ClpF and ClpS1 to a ClpC protease complex (see figure). This concept of secondary adaptors working with primary adaptors to govern protease specificity is an exciting one, and it highlights the many cellular strategies that can regulate an irreversible process (protein degradation) through combinatorial use of modular adaptor proteins. Interestingly, similar types of regulatory architectures exist in other protease systems, most notably in the bacterium Caulobacter crescentus, where adaptor complexes hierarchically assemble to drive protein degradation during the cell cycle (Joshi et al., 2015).

This work by Nishimura et al. is a perfect example of the concept for Breakthrough Reports, as it reports that an unexpected factor potentially regulates a fundamental process in chloroplasts. The discovery and initial characterization of this regulator involved a fantastic combination of proteomics, cell biology, biochemistry, and bioinformatics. However, there are still several questions that must be addressed. Most pressing is that direct demonstration of the role of ClpF in regulating proteolysis in vivo is still very preliminary, with the best described potential Clp substrate, GluTR, showing only a minor change in levels upon loss of ClpF. In addition, deletion of ClpF does not produce a dramatic phenotype, however, neither does loss of ClpS1 (Nishimura et al., 2013). Given the critical role of protein degradation in chloroplasts, perhaps there is redundancy in the quality control system of this organelle that may suppress any detrimental effect arising from loss of any one pathway. It will be
exciting to see how these and other adaptor hierarchies have given rise to the complexity of protease control across all biology.

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REFERENCES


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