Structure-Function Studies on Cereblon and the Implications for Novel Molecular Glue Discovery

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Targeted protein degradation is a relatively new field of drug discovery that is attracting massive global investment in both academic and industrial environments. The ability to trigger the destruction of disease-associated proteins with low molecular weight compounds has massive implications for drug discovery and could lead to numerous medicines. Although the first successes in degradation research were reported 20 years ago, it is over the last 10 years that several key advances took place, including the finding that several approved drugs achieve clinical effects through targeted protein degradation.

Cereblon is a component of the CRL4-CRBN E3 ubiquitin ligase and is the target of the myeloma drugs thalidomide, lenalidomide and pomalidomide. Following the discovery that cereblon directly binds thalidomide, structural studies were critical in understanding the molecular glue mechanism of action. These drugs bind to the surface of cereblon and repurpose the E3 ligase to recruit non-native substrates leading to ubiquitination and degradation. Repurposing of cereblon can be achieved through either heterobifunctional drugs or molecular glue degraders. Molecular glue drugs are lower molecular weight than heterobifunctional drugs and rely more extensively on stabilizing protein-protein interactions. Thalidomide analogs have been extremely well studied as archetypal molecular glues, with crystal structures determined for several cereblon complexes. In addition to cereblon-drug binary complexes, several substrate bound ternary complexes have been solved. A critical 'degron' feature required for substrate recruitment, enabling rational design for optimizing efficacy and selectivity. The degron is found in otherwise unrelated cereblon substrates that share no sequence, fold or functional similarity.

There are an estimated 600 E3 ubiquitin ligases in human cells, indicating considerable potential for the discovery of new molecular glues. In this talk structural studies on the cereblon E3 ligase will be described as a model system for understanding the principles of molecular glue drug discovery.

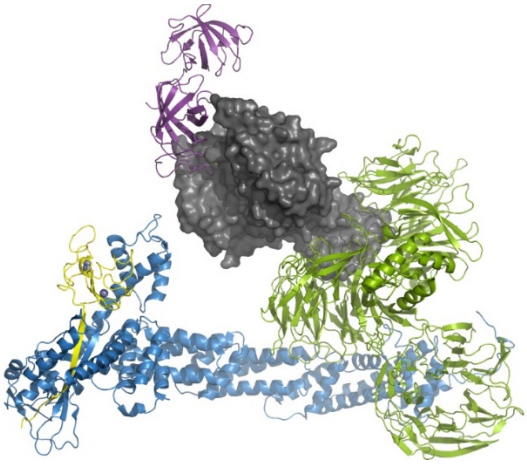

Figure 1