Role of cereblon and its endogenous substrates on therapeutic efficacy in acute myeloid leukemia

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Abstract**:** Cereblon (CRBN) is an E3 ligase substrate adapter that is modulated by thalidomide and its derivatives to achieve therapeutic efficacy in several hematopoietic malignancies, including acute myeloid leukemia (AML). These findings have driven a vast growth in targeted protein degradation modalities using CRBN in the clinic and clinical trials. However, despite the existing and increasing therapeutic engagement of CRBN in the clinic, the influence of endogenous substrates on therapeutic outcomes is unknown. Recently, we reported the exact substrate selection mechanisms of CRBN through a chemical mark termed the C-terminal cyclic imide. This mark arises as a form of protein damage during protein aging and on enzymatic induction resulting in substrate removal by CRBN. Many of these substrates play a role in normal hematopoiesis and other cellular differentiation pathways. Hematopoietic malignancies like AML result from dysregulated self-renewal pathways and an altered differentiation program. CRBN and its substrates may therefore play an overlooked role in hematopoiesis and the therapeutic response. Here, we will investigate the role of endogenous substrates of CRBN on therapeutic efficacy with the following Specific Aims: Aim 1. Molecular characterization of endogenous CRBN substrates in acute myeloid leukemia. Aim 2. Investigate the role of CRBN on leukemogenesis and identify new CRBN dependent sensitizers. Collectively, these aims will establish a novel biological pathway associating CRBN with substrates that play a fundamental role in differentiation pathways during normal and leukemogenic hematopoiesis underlying the development and treatment of AML.