Niclosamide: CRL4AMBRA1 mediated degradation of Cyclin D1 following mitochondrial membrane depolarization

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Targeted protein degradation has emerged as a promising approach in drug discovery, utilizing small molecules like molecular glue degraders to harness the ubiquitin-proteasome pathway for selective degradation of disease-driving proteins. Based on results from proteomics screens we investigated the potential of Niclosamide, an FDA-approved anthelmintic drug with a 50-year history in treating tapeworm infections, as a molecular glue degrader targeting the proto-oncogene Cyclin D1. Proteomics screens in HCT116 colon carcinoma and KELLY neuroblastoma cells, found that Niclosamide induces rapid Cyclin D1 degradation through a mechanism involving the ubiquitin-proteasome pathway. A genetic CRISPR screen identified the E3 ligase CRL4AMBRA1 as a key player in this process. Structure-activity relationship studies highlighted critical features of Niclosamide necessary for Cyclin D1 degradation, demonstrating a correlation between mitochondrial membrane potential (MMP) disruption and Cyclin D1 downregulation. Notably, various mitochondrial uncouplers and other compounds with correlating drug sensitivity profiles suggesting that MMP disruption can trigger Cyclin D1 degradation, and that the cellular signal driving the degradation differs from previously described mechanism involving CRL4AMBRA1. Our findings underscore the complexities of proteostatic mechanisms and the multitude of mechanisms that contribute to degrader drug action.

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