Bromodomain Mutations Confer Resistance to SWI/SNF PROTAC-Mediated ATPase Degradation

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The SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin-remodelling complexes regulate transcription by repositioning nucleosomes; their paralogous ATPase subunits, BRG1 and BRM, are frequently altered in human disease. Mutations in SWI/SNF subunits occur in more than 20% of human cancers, underscoring the importance of these complexes in transcriptional regulation. AU-15330 is a proteolysis-targeting chimera (PROTAC) that targets BRG1, BRM, and the PBRM1 subunit of PBAF; however, the potential for acquired resistance remains unclear. This study investigated whether two bromodomain mutations identified in AU-15330–resistant BRG1 clones are sufficient to prevent BRG1 degradation. Wild-type and mutant BRG1 constructs tagged with 3×FLAG/HiBiT were generated, expressed in cells, and treated with AU-15330. HiBiT luminescence was normalized to cell count and reported relative to DMSO-treated controls. AU-15330 caused a substantial loss of wild-type BRG1 signal, reducing normalized HiBiT luminescence by 64% compared to DMSO. In contrast, the bromodomain-mutant BRG1 construct showed only a 4% decrease in signal, demonstrating that these two mutations render BRG1 largely resistant to PROTAC-mediated degradation. Western blot analysis confirmed robust degradation of endogenous BRG1. Although exogenous mutant BRG1 expression was below the limit of detection due to low expression, its strong HiBiT signal still indicated resistance relative to exogenous wild-type BRG1. Because these residues are conserved in the bromodomains of BRM and PBRM1, analogous mutations may similarly confer resistance and warrant further investigation. In addition, this system provides a tool to selectively preserve BRG1 while selectively degrading BRM and PBRM1 thereby enabling the study of paralogue-specific SWI/SNF functions.