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POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

The PP2A-B56α Heterocomplex Regulates Response to Venetoclax Plus Azacitidine Treatment in AML

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Venetoclax (VEN), a selective inhibitor of BCL2, combined with azacitidine (Aza) has emerged as the new standard of care for patients with acute myeloid leukemia (AML) ineligible for intensive chemotherapy. However, the long-term medical benefit is modest, and relapse appears to be unavoidable. We have recently reported that PP2A activators enhance the efficacy of VEN and VEN+Aza in primary samples and pre-clinical models of AML, and that the PP2A-B56α complex drives the synergistic pro-apoptotic activity observed. Our aim here is to further decipher the role of PP2A-B56α in VEN+Aza treatment response in AML. We used CRISPR-Cas9 to generate HL-60 sublines lacking the B56α or B55α PP2A regulatory subunits. Interestingly, while there were no significant differences in their baseline rate of proliferation, HL-60 B56α knockdown (KD) clones were significantly more resistant to VEN and VEN+Aza than wild type (WT) cells. In contrast, HL-60 B55α KD clones were sensitive to VEN+Aza, pointing out a specific role for specific PP2A heterotrimers, in this case the PP2A-B56α complex in the combined treatment response. Protein expression analysis of known substrates of PP2A-B56α demonstrated that pSer62-MYC and total MYC decreased after VEN+Aza treatment in WT cells but not in KD cells. It is known that the PP2A-B56α complex directly dephosphorylates MYC-Ser62, inducing MYC ubiquitin-mediated proteasomal degradation. Moreover, p21/CDKN1A, that is transcriptionally activated by p53 and inhibited by MYC, was up-regulated at both the mRNA and protein level after VEN+Aza treatment in WT cells but not in KD cells. HL-60 is a p53 null cell line; therefore, p21 up-regulation upon the combined treatment might be MYC-dependent. Of note, treatment of HL-60 B56α KD cells with the MYC inhibitor MYCi975 rescued the VEN+Aza synergy seen in these cells, confirming the relevance of MYC degradation to VEN+Aza response. Interestingly, VEN+MYCi975 had synergistic anti-leukemic effects in these same cell lines. Furthermore, *CDKN1A* expression was also rescued upon the triple therapy consisting of VEN+Aza+MYCi975. Combined, our results suggest that the PP2A-B56α complex is involved in the regulation of VEN+Aza response through changes in MYC expression. Interestingly, a novel small molecular glue (PMG) developed by our group, which specifically stabilizes the PP2A-B56α complex, enhanced VEN plus Aza response *in vitro*; however, this triple therapy did not work in HL-60 B56α KD cells and we observed a clearly decrease in MYC protein expression upon the triple therapy only in HL-60 B56α WT cells, supporting the rationale to translate these novel PMGs into the clinic. Altogether, our data suggest that PP2A-B56α might have an important role in VEN plus Aza treatment response through the regulation of MYC degradation.

Disclosures No relevant conflicts of interest to declare.

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