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616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Demethylation Strategies for the Treatment of Acute Myeloid Leukemia: Targeting Protacs That Degrade DNA Methyltransferase

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Background
DNA methylation is crucial in the pathogenesis of acute myeloid leukemia (AML), characterized by abnormal proliferation of myeloid cells and disrupted DNA methylation patterns. These aberrant patterns contribute to the dysregulation of key genes involved in AML development and progression. Therefore, targeting DNA methyltransferases (DNMTs) to restore proper DNA methylation patterns has emerged as a promising therapeutic strategy. However, traditional demethylation therapies (e.g. azacytidine, decitabine) face challenges in effectively and selectively targeting DNMTs.
Methods
In this study, we investigated the potential of a novel approach utilizing proteolysis targeting chimeras (PROTACs) for selective degradation of DNMTs in AML cells. A series of PROTAC molecules was designed and synthesized, with GSK3685032 serving as the ligand for DNMTs. The E3 ligase CRBN was employed to mediate the proteasomal degradation process.
Results
The designed PROTACs efficiently degraded DNMTs in AML cell lines, as demonstrated by immunoblotting and immunofluorescence assays. Genome-wide DNA methylation analysis revealed a significant reduction in global DNA methylation levels following PROTAC-mediated DNMT degradation.In AML PDX models, the PROTACs effectively decreased DNMT protein levels, resulting in substantial reduction of global DNA methylation and significant inhibition of tumor growth. Furthermore, combination studies revealed synergistic effects when the PROTAC-mediated DNMT degradation was combined with standard clinical therapeutic agents.The combination approach showed enhanced therapeutic efficacy compared to either treatment alone, suggesting a potential strategy for improved AML treatment outcomes.
Conclusions
The study highlights the potential of PROTAC-mediated DNMT degradation as a promising targeted demethylation strategy for AML. This approach holds promise for improving treatment outcomes, particularly in AML patients with DNMT mutations. Further research is warranted to fully evaluate the efficacy of this approach in clinical settings.
Keywords: Acute myeloid leukemia, DNA methylation, PROTACs

Disclosures No relevant conflicts of interest to declare.

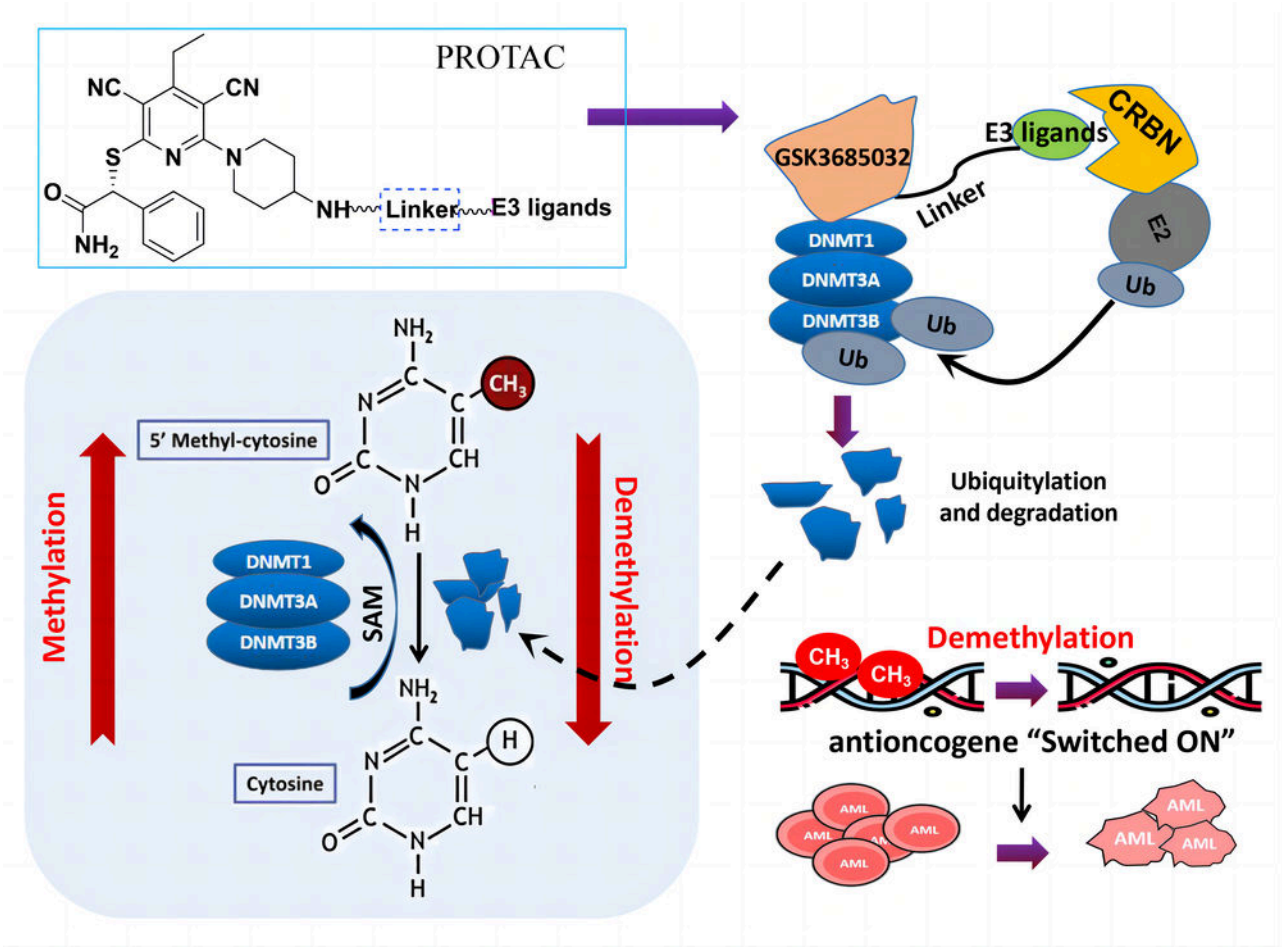

Figure 1

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