RX-3117 promotes epigenetic effects in cancer cells through enhanced degradation of DNMT1

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AIM OF THE STUDY

How does RX-3117 mediate down regulation of DNMT1?

Mechanism of DNA methylation
- Cysteine in DNMT attacks cytidine and a covalent DNA-enzyme complex is formed
- S-adenosyl-L-methionine (SAM) donates its methyl group to cytidine
- Protein elimination and release of cysteine

RESULTS

RX-3117 down-regulates total DNA methylation and traps DNA-DNMT1

The proteasome inhibitor bortezomib prevents RX-3117 mediated downregulation of DNMT1

A549 and SUIT-028 cells were treated with 1 µM RX-3117 and nuclear trapping was analyzed using ImageStream FACS analysis.

Nuclear trapping of DNMT1 upon RX-3117 treatment

Quantum Modeling (QM) of DNMT1:
- VDD charge analysis of RX-3117

Molecular modeling (MD) of RX-3117 interaction with DNMT1

METHODS

CONCLUSIONS

- RX-3117 downregulates DNMT1 protein
- RX-3117 causes epigenetic changes in the cell by trapping DNMT1 to DNA
- DNMT1 is then translocated to the cytosol to the proteasome for degradation
- MD and QM leave the possibility open for a nucleophilic attack at C6 and of trapping by affecting the methyl transfer or leaving Cys81

References