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abstract

Post-translational modifications of histones play an important role in the regulation of gene expression. Enhancer of zeste homologue 2 (EZH2) is a subunit of polycomb repressive complex 2 (PRC2) that methylates histone H3 lysine 27 (H3K27) and leads to chromatin compaction and gene silencing. Dysregulation of enhancer of EZH2 is found in many types of cancers especially in highly progressive and aggressive ones. Specific catalytic inhibitors of EZH2 have high anti-tumour activity, particularly in lymphomas with EZH2 activating mutations. However, the clinical benefits of EZH2 catalytic inhibitors in tumours overexpressing EZH2 are still limited.

Here, we identified NPD13668, a novel modulator of EZH2-mediated gene silencing, from 329,049 small chemical compounds by cell-based high-throughput screening assay. NPD13668 reactivated the expression of silenced H3K27me3 target genes together with depletion of the H3K27me3 modification. In addition, NPD13668 repressed the cell growth of prostate cancer cell lines (PC3 and LNCaP) and ovarian cancer cell lines (SKOV3 and NIH-OVCAR3). NPD13668 partially inhibited the methyltransferase activity of EZH2 *in vitro*. Genome-wide expression analysis revealed that after NPD13668 treatment, about half of the upregulated genes overlapped with genes upregulated after treatment with GSK126, a EZH2 catalytic inhibitor, indicating that NPD13668 is a potential modulator of EZH2 methyltransferase activity. Our data demonstrated that targeting the pharmacological inhibition of EZH2 activity by NPD13668 might be a novel cancer treatment.