Therapeutic strategy of targeting epigenetic crosstalk for EZH2-aberrant solid tumors

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the team led by Geng MeiYu (耿美玉), Ding Jian and Tan MinJia at Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences revealed the mechanisms that essentially determine the therapeutic response to EZH2 inhibitors and proposed therapeutic solutions for EZH2-aberrant solid tumors, which was published in *Cell* (2018, 175(1): 186—199)

The abnormal epigenetic regulation is closely related to the prognosis of a variety of human tumors human cancer. EZH2, a histone methyl transferase subunit of a Polycomb repressor complex, is recurrently mutated in several forms of cancer and is highly expressed in numerous others. Nevertheless, both preclinical and clinical evidence suggest the very limited benefit of EZH2-targeted therapies in both hematological and solid tumors. There appears to be an apparent disparity between the recurrent EZH2 aberrations in human cancers and only small sets of cancers indeed benefited from the treatment. This remains a major barrier in translational medicine for EZH2 targeted therapies.

To understand the molecular basis behind, the scientists from SIMM discovered that EZH2 inhibition could lead to a global landscape change of histone marks. Among the globally altered histone marks, a specific interplay between methylation and acetylation on histone H3 lysine 27 (H3K27me-H3K27ac) was noted and shown to be critical for determining the drug response to the EZH2 inhibition via H3K27ac associated transcriptional output. The study further substantially extended earlier observations by showing that a methyltransferase, mixed-lineage leukemia 1 (MLL1), plays a key role in allowing the occurrence of H3K27ac. MLL1 forms a complex with p300 and facilitates p300-catalyzed H3K27ac upon PRC2 inhibition. The intrinsic MLL1 level varies between the different cancers, which explains the differential H3K27ac response between cancer cells despite the similarly suppressed H3K27me level.

These mechanistic insights led to a further discovery that concurrent inhibition of H3K27 methylation and acetylation results in transcriptional repression and, in certain cancer subsets, MAPK pathway dependency. With study in pre-clinical models encompassing a broad spectrum of EZH2-aberrant solid tumors, the study demonstrated strategies including a combination of EZH2 and BRD4 inhibitors or a triple-combination including MAPK inhibition display robust efficacy with very tolerable toxicity. These findings together suggest a personalized therapeutic strategy of patient stratification and precision medicine for EZH2-aberrant tumors.

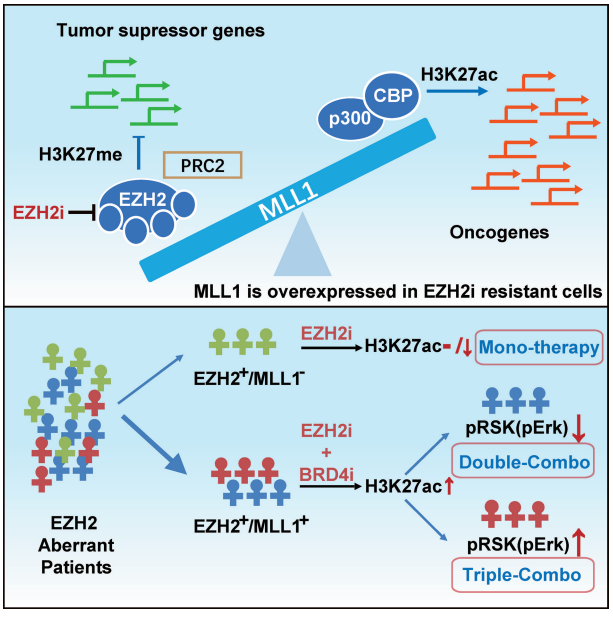

Figure Upper: MLL1 facilitated H3K27 acetylation drives oncogenic transcriptional reprogramming to EZH2 inhibition. Lower: therapeutic strategies for EZH2-aberrant tumors on the basis of MLL1 expression and feedback MAPK activation.