Intrinsic BET inhibitor resistance in SPOP-mutated prostate cancer is mediated by BET protein stabilization and AKT-mTORC1 activation

Subject Code: H16

With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Wang Chenji (**王陈继**) from Fudan University, Prof. Huang Haojie (**黄浩杰**) from Mayo Clinic and Sun Yinhao (**孙颖浩**) from the Second Military Medical University have uncovered mutations in the SPOP gene, the most common genetic mutations seen in primary prostate cancer, making it resistant to a specific class of drugs. This finding was published in *Nature Medicine* (2017, doi: 10.1038/nm.4379).

BET proteins function as key factors in transcriptional activation of distinct sets of cancer-related genes through context-specific interaction with acetylated histones and/or transcription factors. Several small-molecule inhibitors specifically targeting the bromodomains of BET proteins have been developed and display promising anticancer activity. Although BET inhibitors are undergoing clinical trials as treatment for various cancer types, several mechanisms of drug resistance have been documented. At present, there are no genetic alterations that can be exploited as biomarkers to guide targeted use of these drugs.

Their groups found that that wild-type SPOP binds to and induces ubiquitination and proteasomal degradation of BET proteins (BRD2, BRD3 and BRD4) by recognizing a degron motif common among them. In contrast, prostate cancer-associated SPOP mutants show impaired binding to BET proteins, resulting in decreased proteasomal degradation and accumulation of these proteins in prostate cancer cell lines and patient specimens and causing resistance to BET inhibitors. Transcriptome and BRD4 cistrome analyses reveal enhanced expression of the GTPase RAC1 and cholesterol-biosynthesis-associated genes together with activation of AKT-mTORC1 signaling as a consequence of BRD4 stabilization. Their data show that resistance to BET inhibitors in SPOP-mutant prostate cancer can be overcome by combination with AKT inhibitors and further support the evaluation of SPOP mutations as biomarkers to guide BET-inhibitor-oriented therapy in patients with prostate cancer.

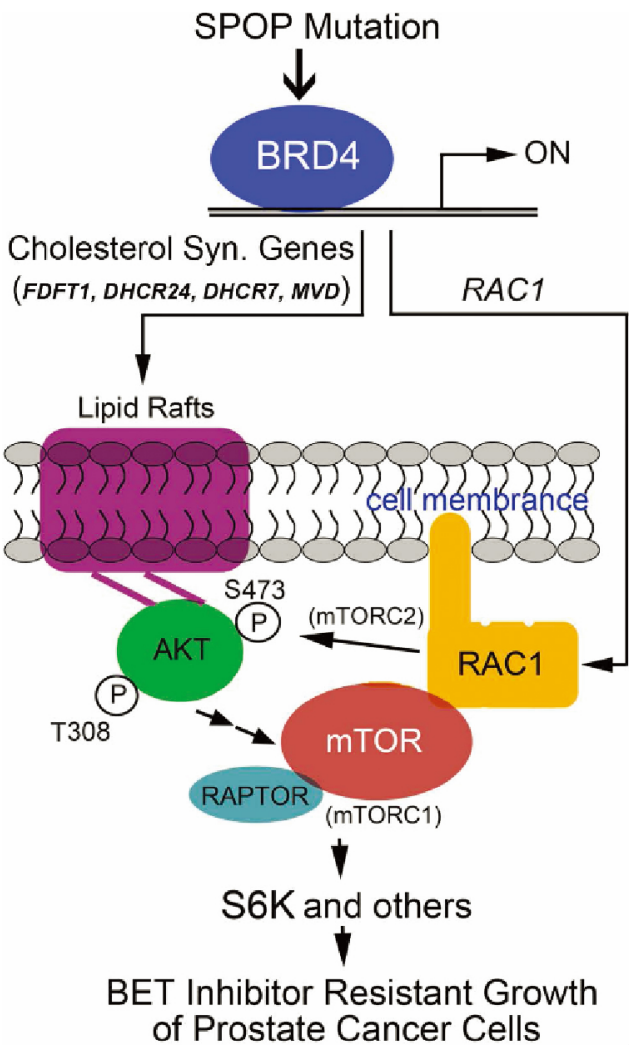

Figure A schematic diagram depicts a model that SPOP mutations in prostate cancer cause BET inhibitor resistance.