AB010. Metabolic disturbance for prostate cancer therapy

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Abstract: Cancer metabolism is emerging with great interest as a therapeutic target for cancer management. Prostate cancer is especially unique in this aspect since benign prostate tissue exhibits truncated Krebs cycle to secret citrate due to high level of prostatic zinc concentration but prostate cancer cells fully oxidize citrate for energy production through Krebs cycle. In addition, most cancer cells maintain functional mitochondria with reprogrammed metabolism, and prostate cancers only present Warburg effect at the late stage of the diseases different from other solid tumors. These metabolic features warrant an advantage of targeting mitochondrial Krebs cycle for prostate cancer management. Despite prostate cancers exhibit massive genetic heterogenicity, metabolic abnormalities appear to be ubiquitous and constant as measured by *in situ* ion imaging of metabolites and lipids. Thus, it is possible to target Krebs cycle for a unified response. So far, multiple efforts have focused on single specific metabolic enzymes responsible for the altered Krebs cycle in human cancers, including metformin for ETC complex I, IDH1/2 inhibitors, PDH inhibitor CPI-613, MPC1/2 inhibitor UK5099, MCT1 inhibitor AZD3965, CPT1 inhibitors etomoxir/perhexiline/ST1326, FASN inhibitor orlistat/TVB-2640, MCD inhibitor CBM-301106, ACAA2 inhibitor trimetazidine. Ideally, a therapeutic drug for curing cancer should have a cancer preference with a minimum side effect on benign tissues. We previously demonstrated that a natural compound Alternol exerts a cancer-specific killing effect with very limited side effect. Through a comprehensive approach, we identified 4 Krebs cycle enzymes as Alternol-interacting proteins. Alternol disturbs their functions and reduces ATP production only in malignant cells or tissues while sparing benign cells. Therefore, it possesses great hope for a successful clinical implication.

Keywords: Prostate cancer; metabolic disturbance; Krebs cycle; Warburg effect

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