**Targeting DHODH modulates mitochondrial plasticity to suppress bladder cancer cell survival**

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Bladder cancer (BCa) is the 6th most commonly diagnosed malignancy in the US. Most bladder tumors (~ 70%) are non-muscle-invasive bladder cancers (NMIBC) at diagnosis and require prompt intervention to prevent progression. Transurethral resection of the bladder tumor (TURBT) followed by intravesical administration of Bacillus-Calmette-Guerin (BCG) has remained the gold standard treatment for decades. Unfortunately, in many patients, tumors recur within months to years after TURBT, become BCG non-responsive, and may progress to MIBC with metastatic potential. Therefore, alternative interventions to prevent disease progression are needed. Dihydroorotate dehydrogenase (DHODH) is an essential enzyme in the de novo pyrimidine biosynthesis pathway, vital for synthesizing DNA and RNA. Cancer cells often have increased metabolic demands, making them highly dependent on this pathway. Recent studies and The Cancer Genome Atlas (TCGA) data have demonstrated that BCa exhibits elevated DHODH expression. Here, we investigated the role of DHODH in BCa and explore anticancer mechanism associated with its inhibition using FDA approved drug, leflunomide. Our data demonstrated that DHODH overexpression in multiple BCa cell lines. We found that treatment with leflunomide significantly reduced the proliferation of BCa cells and spheroids in vitro. Furthermore, we found that DHODH inhibition enhances the anti-tumor effects of cisplatin by inducing cell cycle arrest and apoptosis in BCa cells. Drug induced cell death was associated with depolarization of mitochondrial membrane potential, mitochondrial ROS production, enhance caspase-3 and poly (ADP-ribose) polymerase (PARP) cleavage. Leflunomide synergizes with chemotherapeutics by modulating mitochondrial fission and fusion via DRP1 in BCa. These findings suggest that leflunomide could be an effective anticancer treatment option alone or in combination with other therapies for BCa prevention and treatment. *[Partly supported by P30CA225520 (NCI) and 134128‐IRG‐19‐142‐01 (ACS)]*.