

Targeting the methionine salvage pathway as a metabolic point of leverage in novel therapeutic approaches for prostate cancer.

Polyamines are essential metabolites required for cellular proliferation and a multitude of cellular processes. The prostate is unique in that high levels of acetylated polyamine secretion into the lumen causes increased biosynthetic flux to replenish intracellular polyamine pools. This increased flux strains metabolic pathways such as one-carbon metabolism and the methionine cycle as well as depleting nucleotide and s-adenosylmethionine pools. More importantly, this stress is increased in prostate cancer (PCa) due to increased polyamine acetylation, DNA synthesis and cellular proliferation. We hypothesized that the methionine salvage pathway, responsible for recycling one carbon units to the methionine cycle, is critical to PCa due to high metabolic flux through polyamine biosynthesis. We propose this dependence can be enhanced by targeting two different aspects of the aforementioned metabolic pathways with the use of pharmacologics. In cell line studies, we pharmacologically increased polyamine flux in PCa cells with the use of a polyamine analogue N (1),N (11)-bis(ethyl)norspermine (BENSpm). BENSpm is found to upregulate spermidine/spermine N(1)-acetyltransferase (SSAT), an enzyme necessary for polyamine acetylation. We found that this synergized with an inhibitor of the methionine salvage pathway, methylthio-DADMe-Immucillin-A (MTDIA). By adding stress to an already strained system and blocking pathways that mitigate this stress with the use of pharmacologics, we were able to see a decrease in PCa cellular proliferation *in vitro*. Further studies hope to look at their effects *in vivo*.