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William T Beck

University of Illinois, USA

Splicing factors as novel therapeutic targets in cancer

Pre-mRNA splicing, mediated by splicing factors, is a normal biochemical phenomenon that accounts in large part for the proteomic diversity in our cells, as there are ~25,000 genes but ~100,000 proteins. Splice isoforms are specific for: Tissue, disease, population, individuals, and are related to drug response. Cancer-specific alternative splicing as well as aberrant expression of splicing factors is seen in tumors compared to normal tissues, but the mechanistic basis for this differential expression remains unclear. We found that increased splicing in ovarian and breast cancer cells is related to increased expression of some splicing factors, including the heterogeneous nuclear ribonucleoprotein, polypyrimidine tract binding protein 1 (PTBP1) and the serine-arginine rich protein, SRp20/SRSF3. Inhibition of expression of PTBP1 inhibits *in vitro* tumor cell growth, colony formation, invasiveness (metastatic behavior), aerobic glycolysis (Warburg effect) and tumor growth *in vivo*; alters expression of >1500 genes in many metabolic pathways and sensitizes cells to drugs. SRSF3 is up-regulated in breast tumor tissues compared to normal breast tissue and correlated with tumor grade. In addition, knockdown of SRp20 resulted in cell growth inhibition and apoptosis in a dose-dependent manner and was partially reversed by pretreating the cells with the pan-caspase inhibitor z-VAD-fmk, suggesting partial involvement of caspases in this apoptosis. Finally, we have identified by high-throughput screening an FDA approved small molecule inhibitor of PTBP1 that inhibits cancer cell growth. Future studies will be discussed.

Biography

William T Beck is a University Distinguished Professor and Former Head of the Department of Biopharmaceutical Sciences in the College of Pharmacy at the University of Illinois at Chicago. His research efforts have focused on understanding the molecular and genetic mechanisms of anticancer drug action and tumor cell resistance to anticancer drugs. His current research focuses on splicing factor genes and their involvement in cancer initiation, progression and resistance to therapy, as well as their potential as novel therapeutic targets in ovarian, breast and brain cancers.

wtbeck@uic.edu

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