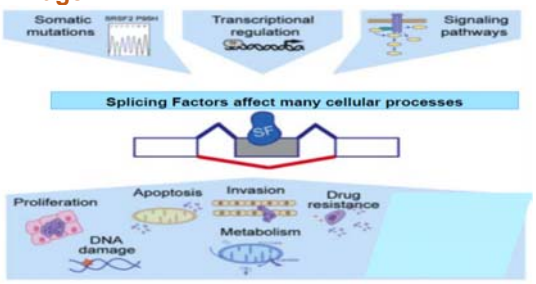
Splicing Factors as Novel Therapeutic Targets in Cancer

William T Beck, A Dirim Arslan, Tsui-Ting Ho, S Asztalos., Xiaolong He, Yves A Lussier, Debra A Tonetti
University of Illinois at Chicago, Chicago, IL USA

Abstract

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 upregulated 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 pre-treating 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.

Image



Recent publications

1. He X, … Beck WT. Alternative splicing of the multidrug resistance protein 1 (MRP1/ABCC1) gene in ovarian cancer creates functional splice variants and is associated with increased expression of the splicing factors PTB and SRp20. Clin Cancer Res, 10:4652-4660, 2004.
2. He X, … Beck WT. Knockdown of Polypyrimidine-Tract Binding Protein (PTB) Suppresses Ovarian Tumor Cell Growth and Invasiveness *In Vitro*. Oncogene 26:4961-4968, 2007.
3. He X, … Beck WT. Knockdown of splicing factor SRp20 causes apoptosis in ovarian cancer cells and its expression is associated with malignancy of epithelial ovarian cancer. Oncogene, 30:356-365, 2011
4. Arslan AD, … Beck WT. A high-throughput assay to identify small-molecule modulators of alternative pre-mRNA splicing. J Biomolec Screening, 18:180-190, 2013.
5. He X, … Beck WT. Involvement of polypyrimidine tract-binding protein (PTBP1) in maintaining breast cancer cell growth and malignant properties. Oncogenesis. 2014 Jan 13;3:e84.
6. Gardeux V, … Beck WT, and Lussier YA. Concordance of deregulated mechanisms unveiled in underpowered experiments: PTBP1 knockdown case study. BMC Med Genomics. 2014;7 Suppl 1:S1
7. Ho T-T, … Tonetti DA, Beck WT. The splicing factor SRp20 (SRSF3) is expressed in breast cancer and its inhibition is related to caspase-mediated apoptosis. Submitted.



Biography

William T. Beck, PhD, is 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.

Email: wtbeck@uic.edu