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Epigenetic rewiring of breast cancer by targeting a metabolic switch

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The C-terminal binding protein (CtBP) is a family of dimeric nuclear proteins whose levels are increased in cancers of the colon, ovaries, prostate and breast. Elevated CtBP expression is associated with poor cancer survival. As a dimer, CtBP provides a scaffold that couples multiple different DNA-binding or DNA bound transcriptional regulators with a variety of chromatin modifying protein complexes to alter the epigenetic landscape throughout the nucleus. These properties provide the rationale for pharmacological targeting of CtBP to alter epigenetically changed and dysregulated genes in cancer cells. We employed computer assisted drug design to screen for optimal quantitative structure-activity relationships (QSARs) between small molecules and CtBP. Functional screening of these compounds identifies 4 lead compounds with low toxicity and high water solubility. Treatment at micro-molar concentrations of these small compounds induces significant de-repression of epigenetically silenced pro-epithelial genes and repression of drug resistance mechanisms in the mesenchymal triple negative breast cancer cell line, MDA-MB-231. This epigenetic re-wiring of gene expression is associated with eviction of CtBP from its respective gene promoters, disrupted recruitment of CtBP-chromatin modifying protein complexes, altered deposition of activating epigenetic histone marks, and upregulation of pro-epithelial gene expression. In functional assays, CtBP inhibition by these small molecule inhibitors disrupts CtBP dimerization, decreases cell migration, abolishes cellular invasion, improves DNA repair, and increases chemotherapeutic drug influx. These findings implicate a broad role for this class of compounds in strategies for therapeutic intervention that will increase the drug efficacy and decrease the acquired resistance to targeted therapeutic intervention through the targeting of CtBP.

Biography:

Dr. Jung S. Byun received her Ph.D. in chemistry and biochemistry from the University of Maryland, College Park. She pursued postdoctoral studies with Dr. Kevin Gardner at NCI, National Institutes of Health. During her postdoctoral residency, Dr. Byun carried out studies to define how histone acetyltransferase, p300, and the elongation factor, ELL, work in concert to control eukaryotic transcription by demonstrating the role of dynamic bookmarking by p300 RNA polymerase II complexes in transcriptional memory. She also discovered a new role for ELL (Eleven-nineteen Lysine-rich Leukemia protein), that it is required for early elongation and facilitating pol II pause site entry. Dr. Byun is currently a staff scientist with Dr. Kevin Gardner's laboratory. The lab's research interests focus on characterizing other potential transcription regulatory targets important in mammalian cancer cell biology that define a molecular link between metabolic imbalance and breast cancer and how this can modify risk and outcome to decrease health disparities in cancer.