A Precision Medicine Approach to Cancer: Epigenetic Inhibitors Induce Highly-Specific Apoptosis in High Risk Acute Lymphoblastic Leukemia

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Hypodiploid B-ALL is a high-risk form of acute leukemia with a dismal prognosis and an 8-year survival rate of only 37%. Because standard chemotherapy is largely ineffective, there is an urgent clinical need to develop a selective, precision medicine-driven treatment approach. Therefore, my research investigates the efficacy of epigenetic inhibitors for selectively targeting hypodiploid cells. Using in vitro methods, I discovered that panobinostat, a HDAC inhibitor, preferentially induced apoptosis in cancer cells at clinically optimal concentrations (IC50s<10 nM) , significantly more effective than nonspecific chemotherapy. Systematic analysis of cell-cycle and apoptotic machinery revealed that panobinostat displayed selective cytotoxicity at very low concentrations through the induction of c-Parp, c-Casp, and pro-apoptotic mediators. I also observed that Class IIa HDACs were selectively overexpressed in hypodiploid B-ALL, illustrating their potential as novel therapeutic targets. After establishing the therapeutic value of epigenetic inhibitors at a phenotypic level, I used machine learning analyses to map protein-gene relations between aberrantly expressed epigenetic modulators and genetic factors that induce leukemogenesis. Random forest and logistic regression analyses on hypodiploid patient data statistically validated the role of epigenetics in leukemia progression, confirming my in vitro findings. Overall, my research takes a precision medicine approach to identify the therapeutic potential of epigenetic inhibitors, which significantly surpasses current gold-standard chemotherapy efficacies for high-risk leukemia, and uses both in vitro studies and novel computational analyses to demonstrate the role of epigenetic modulators for the progression of this disease.

Awards Won: