Name(s)
Ruhi Sayana

Project Number
S0523

Project Title
A Precision Medicine Approach: Epigenetic Inhibitors Induce Highly-Specific Apoptosis in High Risk Acute Leukemia

Abstract

Objectives/Goals
Acute lymphoblastic leukemia is the most prevalent form of cancer that affects children. Despite advancements in treatment, high-risk forms including hypodiploid B-ALL display dismally low prognoses. Epigenetic modulators are genetically altered in hypodiploid B-ALL and could play an important therapeutic role. The goals of my project were to investigate the therapeutic potential of targeting histone deacetylases and the role of epigenetics for the oncogenesis of hypodiploid B-ALL.

Methods/Materials
To evaluate therapeutic potential, a panel of seven histone deacetylase (HDAC) inhibitors with varying specificities across the four HDAC classes was developed and tested on three hypodiploid B-ALL cell lines and healthy cell lines via cell proliferation and caspase activation assays, and IC50 values were computed. Western blots for c-Parp, Bim, and p27 were conducted on hypodiploid samples to determine levels of apoptosis, Bcl-2 dependency, and induction of cell cycle arrest. Western blots screening for Class I and Class IIa HDACs were conducted. Logistic regression models that ranked 25 mutated histone and histone modifier genes according to their relevance for the activation status of the tumor suppressor were developed for seven tumor suppressors.

Results
Specific HDACi blocked cell proliferation with IC50s < 10 nM across all hypodiploid B-ALL cell lines and induced c-Caspase and c-Parp, demonstrating their strong apoptotic effects. Overall, pan-HDACi were found to have low IC50s and induce cancer-specific apoptosis, unlike Class I and Class IIb specific HDAC inhibitors. In addition, Class IIa HDACs were found to be consistently overexpressed in hypodiploid cells via western blot. Seven logistic regression models with accuracies over 75% tested on gene expression data from 96 hypodiploid B-ALL patients revealed that mutated epigenetic genes heavily influenced aberrant tumor suppressor expression.

Conclusions/Discussion
For the first time, HDACi were identified as a cancer-cell specific therapy for hypodiploid B-ALL; their low IC50 values and cytotoxic effects indicate ease of clinical translation. Class IIa HDACs could be a potential therapeutic target to exploit for the treatment of this disease. The computational analysis reveals the novel role of altered epigenetic genes on the oncogenesis of hypodiploid B-ALL. This work also highlights the vitality of epigenetics for the development of precision medicine

Summary Statement
My project aims to evaluate the therapeutic potential of epigenetic inhibitors in high-risk acute leukemia and characterize their relevance for the progression of this disease and in precision medicine.

Help Received
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