The role of the tyrosine phosphatase PRL-3 in leukemia development and relapse

SPECIFIC AIMS

The aggressive and unpredictable behavior of T-cell acute lymphoblastic leukemia (T-ALL) presents a major clinical challenge in both the pediatric and adult setting. The challenges associated with T-ALL are two-fold: 1) the recently improved cure rate for primary T-ALL is largely attributed to highly toxic chemotherapy regimens that have both short- and long-term adverse effects in patients, and 2) chemotherapy is often ineffective against relapsed T-ALL, which has a dismal 5-year survival rate of <30% in children and <10% in adults. The development of new and better chemotherapies requires a detailed understanding of the genes and pathways that drive T-ALL malignancy. *Thus, a major imperative concerning T-ALL is the identification of druggable molecular targets.*

My *long-term goal* is to identify genes and pathways that drive T-ALL progression, leading to the development of novel targeted therapies. The *objective of this proposal* is to identify the role of the protein tyrosine phosphatase PRL-3 in T-ALL development and relapse. ***My central hypothesis is that PRL-3 activity plays a critical role in T-ALL invasion and spread, and that blocking PRL-3 activity will stop T-ALL progression.*** This hypothesis was formulated based on my own preliminary data using a zebrafish model of T-ALL, which demonstrated that PRL-3 expression significantly enhanced primary T-ALL onset, and increased T-ALL aggressiveness at relapse. Further, PRL-3 is genomically amplified in 16% of human T-ALL samples, and a majority of patient samples and cell lines express high levels of PRL-3. I have found that T-ALL cells are sensitive to inhibition of PRL-3 through induction of apoptosis, suggesting an important role for PRL-3 in T-ALL malignancy. Also in support of my hypothesis, others have found PRL-3 to be critical for the invasive and proliferative ability solid tumors, and PLR3 expression is associated with poor patient prognosis in other types of leukemia, including Acute and Chronic Myelogenous Leukemia and Multiple Myeloma. The rationale for the proposed research is that once it is known how PRL-3 promotes T-ALL progression, drugs targeting PRL-3 or its immediate downstream targets could be developed and used in pre-clinical trials for the treatment of T-ALL and other types of cancer.

I plan to test my central hypothesis and accomplish the objective of this application by pursuing the following two specific aims:

1. ***Determine how PRL-3 promotes T-ALL development and relapse.***
   a) Analyze the effects of PRL-3 gain-of-function on the formation and spread of T-ALL in an *in vivo* zebrafish model.
   b) Analyze the effects of PRL-3 loss-of-function on the formation and spread of T-ALL in an *in vivo* zebrafish model
   c) Determine the effects of PRL-3 knock-down on human T-ALL cells in a xenograft mouse model.

2. ***Identify the mechanism through which PRL-3 enhances T-ALL progression.***
   a) Determine the phosphorylation status of known PRL-3 targets in human T-ALL cells
   b) Identify novel PRL-3 substrates in human T-ALL cells using phospho-proteomic approaches
   c) Determine which PRL-3 target pathways promote T-ALL using epistasis experiments in zebrafish T-ALL and human T-ALL cell lines.

It is anticipated that these aims will yield the following expected outcomes. First, I expect to define the contribution of PRL-3 to T-ALL malignancy. Secondly, I expect to identify pathways that are deregulated in T-ALL due to PRL-3 over-expression, and to determine which of these pathways drive T-ALL progression. These results are expected to have an important positive impact, providing impetus for the development of specific small molecule inhibitors for PRL-3 and critical PRL-3 target pathways, for use in pre-clinical trials for T-ALL and other cancers with high PRL-3 expression.