WES-LRF Research Summary
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Project Title: The cell-cycle regulator GON4L in B cell progenitor-derived acute lymphoblastic leukemia

We wish to thank the When Everyone Survives Leukemia Research Foundation for their generous support of our project, which examines the role of the cell-cycle regulator GON4L in B cell progenitor-derived acute lymphoblastic leukemia (B-ALL). B-ALL is a common cancer in children that also affects infants, adolescents and adults. Current B-ALL therapies rely on broadly-acting, toxic agents with long-term side effects, including the development of other cancers. Cure rates for B-ALL in infants, adolescents, and adults are low, and relapsing B-ALL is difficult to treat regardless of age. Thus, there is a clear need to develop new strategies for treating B-ALL.

GON4L is a large nuclear protein that likely functions as a gene regulator. Our previous work showed GON4L is essential for mitotic division by B cell progenitors, which are the point of origin for B-ALL. The fact that loss of GON4L potently halts B cell progenitor proliferation led us to think that GON4L may be critical for the growth of B-ALL. To probe for evidence, we used computer tools to query a large database of gene expression profiles from 41 different types of human cancer. Strikingly, this revealed that cancers expressing the highest levels of GON4L were overwhelmingly B-ALL. These results, combined with our data showing GON4L is needed for B cell progenitor proliferation, strongly suggested GON4L is critical for B-ALL growth.

Using special mouse strains we developed, we created B-ALL cell lines in which the gene encoding GON4L can be rendered nonfunctional, resulting in loss of GON4L protein expression. When GON4L was lost, our B-ALL cells stopped dividing and soon died. These exciting findings provide proof that GON4L is required for the growth and survival of B-ALL cells. We then injected our B-ALL cells into mice, which quickly developed B-ALL. Our next step will be to remove GON4L from B-ALL cells in mice to see if this can cure them of disease.

Using a screening method, we found that the proteins YY1 and NPAT interact with GON4L. Both YY1 and NPAT have important roles in regulating the expression of histones, which bind to DNA in cells and package it into chromatin. In addition, histones have key roles in gene regulation, while misexpression of histones can result in cell death. Given these findings, we asked how loss of GON4L in our B-ALL cell lines affected histone expression. Strikingly, we found that the absence of GON4L caused a massive increase in the levels of histones expressed within our B-ALL cells that strongly correlated with induction of their death. We also demonstrated that GON4L binds to histone gene promoters and gene bodies. Together, our findings indicate that GON4L and its associated factors act to tightly regulate histone gene expression, and that loss of this regulation is toxic to cells. Further, these results provide support for the idea that targeting GON4L or its cofactors could represent a new approach for halting the growth of B-ALL.