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Acute Leukemias

IDENTIFICATION OF WNK1 AS A DRUGGABLE TARGET IN TAL1-RELATED T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Protein kinase inhibitors rank among the most effective cancer therapies. However, in T-cell acute lymphoblastic leukemia (T-ALL), only few aberrantly activated targetable kinases have been identified, and no targeted therapies have been approved to date. By integrating proteomic and genomic data, we identified the atypical protein kinase WNK1 as a critical vulnerability in *TAL1* T-ALL subgroup, highlighting its therapeutic relevance in high-risk disease.
Methods: To profile kinase dependencies in T-ALL, we intersected the phosphoproteomic analysis of 11 T-ALL cell lines with genomic and functional data from the Cancer DepMap Project. WNK1, an atypical serine/threonine kinase, emerged as a top dependency in T-ALL cell lines, primary samples, and a patient-derived xenograft (PDX) model. Functional validation was achieved using the ATP-competitive WNK inhibitor WNK463 and CRISPR/Cas9 or shRNA-mediated *WNK1* knockout *in vitro* and *in vivo*.
Results: We demonstrated that in T-ALL, *WNK1* is the most highly expressed WNK family member and exhibits greater expression than in other tumors. Additionally, it is differentially expressed compared to lymphocytes and thymocytes, highlighting a potential clinical therapeutic index to explore. Moreover, in T-ALL patients, *WNK1* expression positively correlates ($p < 0.0001$) with *TAL1* oncogenic subgroup and consequently with *PTEN* mutations and del6q ($p < 0.05$), which are more prevalent in this context. Then, to validate WNK1 as a therapeutic target, we characterized the effect of WNK perturbation in T-ALL cell lines and primary samples upon WNK463 treatment or following *WNK1* knockout. Collectively, we demonstrated that WNK1 inhibition suppresses T-ALL viability, causing cell cycle defects, and ultimately leading to apoptosis, especially in TAL-related (TAL-R) T-ALL. Additionally, WNK1 repression promotes polyploidy, resulting in incomplete cell division or chromosome segregation defects. Consistently, transcriptional analysis in *WNK1* depleted cells revealed that the *WNK1* loss modulates G2M-checkpoint and cell cycle signatures, explaining the cellular phenotypes observed upon chemical inhibition. Given the WNK1 role for TAL-R survival, we established a *STIL::TAL1* PDX and evaluated its inhibition in two contexts: drug efficacy and leukemia establishment. First, we demonstrated that WNK463 effectively reduced leukemia burden by an on-target effect, improving survival without organ toxicity in treated TAL1 mice compared to non-TAL1 or vehicle. Secondly, *in vivo*, inducible suppression of *WNK1* delayed leukemia engraftment and spleen infiltration compared to WNK1-competent leukemia, further prolonging survival.
Conclusions: Our integrative proteogenomic analysis identifies WNK1 as a novel oncogenic driver in T-ALL. These findings underscore the role of atypical proteomes in carcinogenesis and support further development of selective WNK1 inhibitors as potential targeted therapy for high-risk T-ALL patients.