Identification of a Novel TBX2-Dependent Mechanism Linking Pericyte Dynamics to Abnormal Vasculature in Lung Adenocarcinoma

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Tumor growth in lung adenocarcinoma (LUAD) – the most prevalent form of lung cancer, with a 5-year survival rate below 20% – is promoted by abnormal vasculature. Importantly, the mechanisms driving these vascular defects remain incompletely characterized. TBX2, a transcription factor selectively expressed by pericytes during capillary network assembly, is significantly downregulated in LUAD. Given the unknown role of TBX2 in angiogenesis, this study utilized a transgenic zebrafish model to elucidate its function in vivo, then proceeded to evaluate its relevance to LUAD. Loss of the zebrafish TBX2 homolog, tbx2b, was achieved via CRISPR-Cas9. Confocal imaging at 3 and 5 days post-fertilization (dpf) revealed dose-dependent pericyte loss; tbx2b -/- embryos demonstrated pericyte depletion ($p < 0.0001$) and failed proliferation between endpoints ($p < 0.0001$). This lack of mural cell support caused progressive vessel dilation ($p < 0.01$ at 5 dpf), mirroring the LUAD phenotype. To evaluate disease relevance, scRNA-seq data from LUAD patients was analyzed through a Bayesian workflow. TBX2 expression was positively associated (>98% probability) with pericyte proliferation and cell adhesion signatures, demonstrating mechanistic conservation with the tbx2b -/- zebrafish phenotype and significance of TBX2 loss in LUAD. Further analysis involving the TCGA-LUAD cohort identified miR-130b as a potential post-transcriptional repressor of TBX2 due to its upregulation in LUAD ($p < 0.0001$), 7-mer seed match, and negative correlation with TBX2 expression ($rho = -0.31$, $p < 0.0001$). Finally, to restore normal pericyte-endothelial cell dynamics in LUAD, a fusion protein was designed de novo in silico to reanchor pericytes to vessel walls, advancing towards normalizing LUAD vasculature.

Awards Won:

First Award of $6,000