ETMR-25. UNRAVELING THE ROLE OF SHH SIGNALING PATHWAY IN RETINOBLASTOMA
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BACKGROUND: Retinoblastoma (RB) is a pediatric cancer affecting the retina, often requiring surgical removal of one or both eyes due to the limited effectiveness of current treatments. There is an urgent need for advanced therapeutic strategies capable of effectively eliminating tumors, thereby obviating the need for surgical removal of eyes in affected children. Achieving this goal requires a deeper understanding of the cellular and molecular mechanisms governing RB initiation and progression.

METHODS: Using a transgenic mouse model, we identified the crucial role of the Shh signaling pathway in Rb1 mutation-induced tumorigenesis, highlighting its potential as a novel therapeutic target for RB treatment.

RESULTS: We have observed frequent overexpression of Shh signaling proteins (SHH, GLI1, and GLI2) in human RB, correlating with aggressive clinico-pathological features. GLI2 overexpression is necessary for Rb1 deletion-induced RB tumor initiation in mouse retinal progenitor cells (RPCs). These mouse intraocular tumors accurately replicate human RB at both cellular and molecular levels. Additionally, Shh pathway activation extends to normal retinal cells adjacent to human RB tumors, suggesting the involvement of Shh signaling in RB-microenvironment interactions. Importantly, our studies have identified a novel small molecular inhibitor targeting the Shh pathway, effectively inhibiting RB growth in vitro and in vivo by targeting both tumor cells and the tumor microenvironment (TME).

CONCLUSIONS: The proposed research aims to provide unprecedented insights into the role of SHH signaling pathway in RB initiation and progression and the supporting...
communication network between RB tumors and TME. These outcomes have the potential to treat RB effectively while improving the well-being of young individuals with RB and those at risk of RB.