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Sox2-mediated 5hmc dysregulation in gbm stem cells

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Primary brain tumors are among the most devastating forms of cancer and glioblastoma (GBM) represents the most aggressive and lethal form of the disease. We now know that GBM contain small subsets of cells that display tumor-propagating stem-like phenotypes (i.e. glioma stem cells or GSCs) that act as critical determinants of GBM resistance to current treatments and tumor recurrence for which there is no proven therapy. Altered patterns of DNA methylation are widely reported in human GBM.. Understanding and ultimately targeting the epigenetic mechanisms that induce and maintain these tumor-propagating cell subsets is critical to improving GBM therapy and patient outcomes. DNA methylation is a reversible process and is partially mediated by the ten-eleven translocation (TET) family of enzymes which function as deoxygenases to catalyze the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). Levels of 5hmC negatively correlates with glioma grade and loss of 5hmC correlates with poor prognosis of GBM patients, strongly suggesting that these enzymes activate tumor suppressing mechanisms. We show that TET2 loss associates with GBM stem cells and correlates with poor survival of GBM patients and identify a SOX2:miR-10b-5p:TET2 axis that represses TET2 expression and induces GBM cell stemness and tumor-propagating potential. In vivo delivery of a miR-10b-5p inhibitor normalizes TET2 expression and function to induce regression of orthotopic GSC-derived xenografts and prolongs animal survival. These findings highlight the importance of TET2 and 5hmC loss in Sox2-driven oncogenesis and their potential for therapeutic targeting.

Biography

I was born in Paraguay, South America and moved to the United States after completing high school to pursue a career in science in the United States of America. Early on in my career I took an interest in personalized medicine and molecular therapies. The long-term goal of my research is to understand the molecular mechanisms involved in regulating stemness and differentiation in neoplastic cells. We want to better understand Glioblastoma (GBM) by studying the molecular mechanism by which these cells acquire a stem-like phenotype and use this knowledge to develop new ways to treat and diagnose the disease

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