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Study of the REST-USP37-p27 axis in cell proliferation and differentiation

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Medulloblastoma is a malignant pediatric brain tumor. These tumors are characterized by deregulated proliferation and poor neuronal differentiation. We previously demonstrated aberrant expression of the *RE1* Silencing Transcription Factor (REST) in human medulloblastoma samples. REST is a repressor of neuronal differentiation genes, and consistent with this REST expressing tumors fail to undergo neurogenesis. Here, we describe the identification of a novel function for REST in cell proliferation. REST expression in human tumors and in mouse granule cell progenitors (the cells of origin of a subset of medulloblastoma) was associated with lower levels of the cyclin-dependent kinase inhibitor p27. REST repressed the expression of a gene encoding a deubiquitylase USP37. Using genetic and biochemical approaches, we showed complex formation and USP37-dependent deubiquitination and stabilization of p27 *in vitro* and *in vivo*. USP37 and p27 expression ere also positively correlated in patient tumors and in the murine cerebellum. Constitutive *USP37* expression countered REST-mediated blockade of neuronal differentiation and prevented anchorage independent growth of medulloblastoma cells *in vitro*. In summary, our work has (a) attributed a novel function for REST in the control of cell proliferation (b) established a unique link between REST and p27 (c) identified the deubiquitylase USP37 as a novel REST target (d) and provided the first demonstration of a p27-associated deubiquitylase. These findings have implications for medulloblastoma development.

Biography

Dr. Gopalakrishnan completed her Ph.D from the University of Pittsburgh and her postdoctoral studies from Johns Hopkins University School of Medicine. She is currently an Assistant Professor of Pediatrics and Molecular and Cellular Oncology at the University of Texas MD Anderson Cancer Center. Her research is focused on developing mouse models for pediatric brain tumors, identifying novel molecules for targeted therapeutics and manipulating lineage specification in stem cells for neuro-regeneration. She has a number of publications in high impact peer-reviewed journals.