Delineating and targeting a novel metabolism-based post-translational mechanism regulating the abundance of the 'undruggable' oncoprotein c-MYC in medulloblastoma

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Brain tumors are the leading cause of cancer death in children, and medulloblastoma (MB) is the most common pediatric central nervous system malignancy. Amplification of the c-MYC oncogene is frequently observed in the most aggressive and lethal subgroup of this disease, group 3 (G3), but not in other subgroups. Patients that have G3 MB tumors with high c-MYC abundance are more likely to present as metastatic and are prone to develop fatal recurrent tumors. Unfortunately, the functional ubiquity and disordered structure of c-MYC makes it difficult to target for cancer treatment. Therefore, it is critical to identify novel, out-of-the-box strategies to suppress oncogenic c-MYC in highly aggressive G3 MB brain tumors. Recently, metabolism has emerged as a major regulator of overall cellular signaling processes through post-translational and epigenetic mechanisms. While c-MYC is known to regulate cellular metabolism, whether metabolism plays a role in reciprocally supporting enhanced c-MYC abundance in cancer is unknown. We hypothesize that an intrinsic feedback mechanism may exist where metabolic activity modulates c-MYC abundance that could be exploited as a therapeutic strategy to improve outcomes for G3 MB patients. Using various well-characterized G3 MB cells, orthotopic intracerebellar xenograft models, patient tumor bioinformatics analyses, and detailed biochemical characterization, we have identified a novel metabolism-dependent post-translational modification that regulates c-MYC stability in G3 MB. In-depth molecular analyses unveiled that c-MYC is susceptible to oxidation and proteasomal degradation under conditions of metabolic stress.

Targeting mitochondrial respiration via inhibition of complex-I led to the accumulation of reactive oxygen species (ROS) and depletion of c-MYC abundance, which impaired the growth of intracerebellar G3 MB xenograft tumors in mice, significantly prolonging animal survival. Altogether, these findings unveil a novel mechanism through which metabolism regulates the post-translational stability of c-MYC and provides insights for designing rationale therapeutic strategies for the treatment of MB patients.