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MDB-32. TRANSLATION OF NON-CANONICAL OPEN READING FRAMES AS A CANCER CELL SURVIVAL MECHANISM IN CHILDHOOD MEDULLOBLASTOMA

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High-risk medulloblastoma is one of the most recalcitrant pediatric cancers, and children with MYC-amplified disease frequently succumb to relapsed disease. Extensive analyses of the coding genome in this disease have characterized additional somatic events in some subsets of patients, though most tumors lack targetable mutations and do not yield insights regarding their aggressive behavior. At the same time, medulloblastoma is known to exhibit extensive rewiring of translational control in MYC-driven tumors, consistent with recent genetic evidence that the impact of this transcription factor on control of mRNA translation may be the most critical aspect of its function during tumorigenesis. Therefore, to propose previously unknown mechanisms for this disease, we have investigated the functional impact of translation of non-canonical open reading frames (ORFs) across medulloblastoma model systems. We demonstrate that these ORFs are commonly translated in medulloblastoma model systems and patient tumors, correlating with disease subtype. Using genome-wide CRISPR/Cas9 screens, we found that ORFs are frequently essential for cell survival in medulloblastoma and describe widespread reliance on upstream open reading frames (uORFs) in particular. From these, we identify a uORF in the ASNSD1 gene that is selectively upregulated and required for maintenance of cell survival by coordinating the function of the prefoldin-like complex, a poorly understood complex implicated in post-translational control. Together, our findings provide a blueprint for oncogenic uORFs as critical disease mediators both in medulloblastoma and, by extension, human cancers more broadly.