MYC-amplified medulloblastoma is a lethal pediatric tumor lacking effective treatment options. Targeting of mitochondrial activity through inhibition of a novel, noncanonical Notch/PINK1 signaling pathway was recently shown to attenuate the viability of human glioblastoma as performed by our laboratory (Lee KS et al., Genes and Development, 2013). As such, we set out to investigate the role of such the same pathway trafficking mechanisms in medulloblastoma (group III) tumorigenesis and its impact on mTORC2/Akt signaling. Our results suggest both Notch1 and Notch2 involvement in noncanonical mitochondrial Notch/PINK1 signaling in human MYC-amplified medulloblastoma. In vitro inhibition of this axis targets cell viability in a tumor-selective manner. In vivo replication of such trends in currently pending in established murine models. Such preclinical findings highlight the promise of an increased focus on mitochondrial-specific therapies in the development of novel agents for MYC-amplified medulloblastoma.