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**Mechanisms of resistance to inhibitors of bromodomain and extra-terminal domain (BET) proteins in MYC-driven medulloblastoma**

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Pediatric tumors of group 3 medulloblastoma (MBG3) are difficult to treat because the key oncogenic driver MYC is pharmacologically undruggable. Targeting its upstream epigenetic regulators might alleviate this problem. Inhibition of BET-proteins by small-molecule inhibitors JQ1 and OTX015 precluded activation of many oncogenic super-enhancers, including that of MYC, but only transiently suppressed tumor growth and did not improve survival. Current study aimed to determine molecular mechanisms underlying BETi-inefficacy in MBG3 and to suggest BETi-sensitizers. For that, MBG3-cell lines have been continuously exposed to BETi and underwent time-resolved growth monitoring, expression profiling, DECIPHER®- shRNA library-based viability screen, and partial validation of the major findings in vitro and in vivo. Transience, diminishing efficacy and post-withdrawal resurgence characterized growth-inhibitory action of BETi in MBG3. An early clonal outgrowth coincided with transcriptomic reprograming which activated neuronal while suppressing myogenic and photoreceptor features, disturbed mTOR signaling, and questioned BETi-relevance of MYC. Stable under long-term exposure, all rearrangements returned to a basal configuration upon BETi withdrawal. Viability screen corroborated significance of mTOR-signaling for BETi-resistant outgrowth. Nevertheless, mTORC1-inhibitor Everolimus failed to improve the therapeutic efficacy of these drugs. Although known feedback problems of this paralog could contribute to such outcome, a rather uncommon route of mTOR activation (lowering pAKT while increasing pERK1/2 levels) and constellation of genes enriching mTOR-signatures while controlling growth indicated a need for more specific targeting of mTOR within lipid sector, e.g., by reinforcing ELOVL5 upregulation or CD276 downregulation, or by eliminating WWTR1. Together, the spectrum, reversibility and relation of transcriptomic changes to differentiation and metabolism suggested that BETi may trigger neuronal MET (mesenchymal-to-epithelial transition). Generation of better differentiated tumor cells energetically adjusted to outgrow but not to migrate is a desirable aim of ‘differentiation therapy’ approach. Potentially anti-metastatic and chemo-resensitizing, such MET-status seems to be achievable in MBG3 by continuous exposure to BETi. Notably, MET-cells remain sensitive to alternative outgrowth-restricting interventions. Present study indicated that combination of BETi with the drugs blocking CD276 (e.g., antibodies Enoblituzumab/MGA271 or I131-8H9) or interfering with lipid metabolism (e.g., Atorvastatin®) deserves further investigation and clinical testing.