BACKGROUND: Diffuse midline gliomas (DMG) are uniformly fatal pediatric brain cancers, refractory to current standards of care. Based on genomic and transcriptomic profiling data, we previously proposed that platelet-derived growth factor receptor alpha (PDGFRA) is crucial to the tumorigenic potential and maintenance of stem-like DMG cells and that targeting PDGFRA is an important therapeutic avenue in DMG. In comprehensive pre-clinical studies, we identified avapritinib, an FDA-approved PDGFRA inhibitor, to be highly effective in patient-derived xenograft (PDX) DMG models. We further reported the first clinical experience using avapritinib in recurrent DMG and demonstrated preliminary safety, tolerability, and efficacy of the drug in this population. While a subset of patients experienced a strong clinical response from avapritinib, tumor progression...
was eventually observed in all patients. METHODS: Here, we investigated the molecular mechanisms that DMG cells upregulate following avapritinib treatment, with the aim to exploit them therapeutically. To uncover these mechanisms, we performed transcriptomic, metabolic and functional assays along with a combinatorial drug screening. RESULTS: Transcriptional analysis of patient-derived DMG cell lines revealed an upregulation of genes associated with fatty acid metabolism and oxidative phosphorylation (OXPHOS) following treatment with avapritinib. Functional assays confirmed elevated OXPHOS in avapritinib-treated cells with significant (i) increase in mitochondrial energy transduction, (ii) increase in palmitate- (a product of fatty acid metabolism) driven oxygen consumption rate and (iii) greater incorporation of palmitate-derived carbons into the tricarboxylic acid cycle. To determine which therapies could target this dependency on OXPHOS and fatty acid metabolism, we performed a metabolic drug screening in patient-derived DMG cell lines and identified two metabolic drugs to have synergistic cytotoxic effects with avapritinib. CONCLUSION: We revealed distinct metabolic reprogramming in avapritinib-treated DMG cells and showed that targeting these metabolic vulnerabilities might further increase the clinical benefit of PDGFRα inhibitor avapritinib.