TARGETING RESISTANCE PATHWAYS IN BRAF-MUTANT PEDIATRIC GLIOMAS
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BACKGROUND: Mutational activation of BRAF is a common finding in pediatric gliomas. As many as 14% of pediatric high grade glioma and up to 66% of certain subtypes of low grade pediatric glioma contain the BRAFV600E mutation. Small molecule inhibitors that selectively target BRAFV600E, and that are FDA approved for treating melanoma, have shown significant efficacy in treating BRAFV600E glioma in pre-clinical studies. Nonetheless, and despite showing initial efficacy, acquired drug resistance significantly limits the use of BRAFV600E inhibitors in clinical settings. Here, we have identified molecular mechanisms of BRAFV600E inhibitor resistance in glioma, and our detailing of these adaptive mechanisms offer strategies to delay and/or overcome drug resistance. METHODS: To enable our studies, we generated multiple BRAFV600E inhibitor resistant glioma cell lines and tumor models. RESULTS: BRAFV600E inhibitor resistant AM38 and DBTRG-05MG human glioma cells, subjected to extended exposure to PLX4720, show reduced MAP kinase inhibition as well as reduced cell cycle arrest and apoptotic response, relative to corresponding naive cells that have not been previously exposed to inhibitor. In addition, BRAFV600E glioma xenografts, established by implantation with PLX4720-resistant glioma cells, do not respond to inhibitor treatment, resulting in lack of benefit to animal subject survival from treatment. By phospho-kinase array and gene expression analysis, we found that certain receptor tyrosine kinases, including EGF and Axl receptors, and pro-survival kinases involved in Wnt signaling, are hyperactivated in BRAFV600E inhibitor resistant gliomas. Armed with this information, we show that pharmacological and genetic inhibition of those pathways significantly reduces the viability of PLX4720 resistant cells. CONCLUSIONS: In summary, we have identified mechanisms of BRAFV600E inhibitor resistance from sustained BRAF inhibitor treatment of glioma cells, and these mechanisms involve activation of signaling mediators important to tumor cell proliferation and survival. Our results suggest novel therapeutic strategies for treating BRAFV600E-mutant pediatric glioma that should delay acquired resistance, and possibly take advantage of tumor adaptive mechanisms to BRAF inhibitor therapy. SECONDARY CATEGORY: Pediatrics.