Background

Autophagy inhibition is a potential treatment for central nervous system (CNS) tumors. Autophagy, a heavily regulated process by which cellular waste is transferred to lysosomes for degradation and processing, is an integral part of tumor cell survival under stressful conditions including nutrient deprivation and chemotherapy. While the efficacy of autophagy inhibition has been demonstrated in CNS tumors with $BRAF^{V600e}$ mutations, it has yet to be explored in other CNS tumor types with MAPK pathway dysregulation including NF1-mutated tumors. Many tumors associated with the NF1 phenotype can be difficult to treat surgically thus development of further pharmacologic interventions is necessary.

Methods

A CRISPR/Cas9 mediated NF1 KO was derived from human immortalized Schwann cells and utilized as a tumor model. Autophagy inhibition was achieved pharmacologically by chloroquine (CQ) and genetically via shRNAi of ATG5 and ATG7. Trametinib was used for MEK inhibition. Cell growth and viability were determined by Incucyte, Cell Titer-Glo luminescent assay, and colony-formation assays. Protein expression was measured by western blot.

Results

We demonstrate increased autophagic activity in NF1 KO cell as compared to control lines both at baseline and in response to cellular stress. Furthermore, we describe that NF1 KO cells exhibit increased sensitivity to CQ alone, CQ in combination with trametinib, and shRNAi-mediated autophagy inhibition in combination with trametinib.

Conclusion

Here, we describe increased autophagic dependence of NF1 mutated tumors and demonstrate increased tumor sensitivity to autophagy inhibition both alone and in combination with MEK inhibition. These findings indicate that autophagy inhibition via CQ may be an effective adjunctive treatment for NF1 mutated tumors and suggests that diverse CNS tumor types with MAPK pathway dysregulation are susceptible to autophagy inhibition. Clinical investigation of combined MEK and autophagy inhibition has the potential to improve outcomes for NF1 patients with CNS tumors.