HXR9 Inhibits the HOX-PBX Cluster, Inducing Glioma Apoptosis and Cell Cycle Arrest

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Introduction

- Primary brain tumors rank as the #1 cancer in terms of years of life lost
- Gliomas represent the majority (80%) of brain tumors and ATRX-deficient gliomas, i.e., astrocytoma, have the worst prognosis - average six years of survival.
- ATRX-loss gliomas cooccur with IDH-mut, Tp53-mut, and 1p/19q non-co-deletion.
- Current treatments include surgery, radiation and chemotherapy with significant side effects, including high morbidity and mortality.
- ATRX is a globally repressive chromatin remodeler through complexing with H3.3 and DAXX, depositing histone groups on chromatin.
- HOX genes are upregulated in developing fetuses to promote cell proliferation for development of the hindbrain and somites.
- HOX is overexpressed in ATRX deficient gliomas.
- Research into the mechanism of ATRX deficiencies in these tumors will have great implications for survival.
- HXR9 is small peptide sequence that inhibits heterodimerization of HOX:PBX, inhibiting cell proliferation.
- HXR9 is potent, clinically effective and blood-brain-barrier permeable peptide.
- Our aim is to establish HXR9 validity in promoting glioma stem cells apoptosis and elucidate the mechanism of action to better understand the role of HOX in gliomagenesis.

Methods

RNA-seq analysis shows increased expression of HOXA cluster genes in ATRX deficient gliomas

High expression of HOXA cluster genes is associated with poor prognosis in ATRX deficient gliomas

Dose dependent escalation of HXR9 drives patient derived gliomas towards apoptosis

Decrease in S-Phase of cell cycle upon treatment with HXR9 in patient derived gliomas

Conclusions

- Inhibition of HOXA cluster genes using HXR9 peptide, suggest its translational role in preclinical setting.
- Increase in apoptosis and reduced proliferation in HXR9 treated gliomas, open opportunity for in-vivo experiments.

Future Directions

- I plan to do qPCR to check if the HOX is suppressed.
- I can do western of a wide variety of proteins to confirm apoptosis.
- I can check the global transcriptional profile through RNA sequencing to detect different pathways the HXR9 peptide modulates.
- I can test HXR9 in TMZ-resistant, CD133+ stem cell lines.

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