The Aryl Hydrocarbon Receptor (AhR) as a Novel Therapeutic Target in Neuroblastoma
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Introduction

- Neuroblastoma is the most common extracranial tumor in children1.
- ~50% of high-risk patients die from relapses due to retinoic acid therapy resistance2,3.
- MYCN amplification correlates with poor response to retinoid therapies, but MycN is "undruggable."4
- The aryl hydrocarbon receptor (AhR) is a transcription factor that modulates Myc in other cancers5, but its role in neuroblastoma is poorly understood.

Hypothesis

AhR is a novel tumor promoter that regulates MycN and alters retinoic acid treatment efficacy in neuroblastoma.

Methods

- Genetically under-express AhR with shRNA or treat human neuroblastoma cells with the novel AhR antagonist, clofazimine (CLF)
- Assess:
  - Tumorigenicity by colony formation and in vivo tumor growth
  - AhR-MycN regulation by Western blot
  - Retinoic acid efficacy by microscopy

Conclusions

- AhR is a previously unrecognized and novel tumor promoter in neuroblastoma.
- AhR inhibition with CLF decreases neuroblastoma growth and MycN levels and augments retinoic acid therapy-induced differentiation.

Significance

- AhR is a novel therapeutic target in neuroblastoma.
- CLF, an FDA-approved novel AhR antagonist, is non-toxic, orally bioavailable & inexpensive6, representing a potential promising new neuroblastoma therapy.

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References