Elucidating the Molecular Tumorigenesis of AT/RTs

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Background

- AT/RTs are aggressive pediatric tumors with treatment that has significant morbidity
- Most common brain tumor in infants less than 6 months of age
- Recent work demonstrated the existence of three subgroups with retrospective analysis showing differences in outcome
- Need to elucidate the tumorigenesis of the three subgroups
- Cell of origin for AT/RTs is debated

Objectives

- To develop a genetically engineered mouse model of rhabdoid tumors
- To determine if the mouse model faithfully recapitulates the human condition

Methods

- Using the P0 promoter, targeting neural crest cells, *SMARCB1* sequence had flox sequences
- RNA and DNA methylation sequencing done and compared to existing human data
- Immunohistochemistry done on tumor samples for *SMARCB1* loss

Results

- The *P0CreC;Smarcb1*$^{(flox/flox)}$ model faithfully recapitulates the three established subgroups based on initial RNA sequencing **(Figure 1).**
- Tumors arose from the meninges, palate, eyes.
- IHC demonstrating *Smarcb1* loss and GFAP positivity demonstrating aggressiveness of tumor **(Figure 2).**

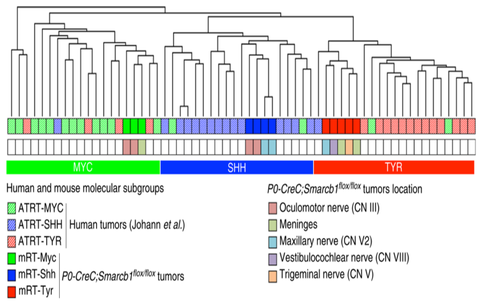

Figure 1: Inactivation of *Smarcb1* on E9.5 led to rhabdoid tumor development. Moreover, the *P0-CreC;Smarcb1*$^{flox/flox}$ model demonstrated the three molecular subtypes.

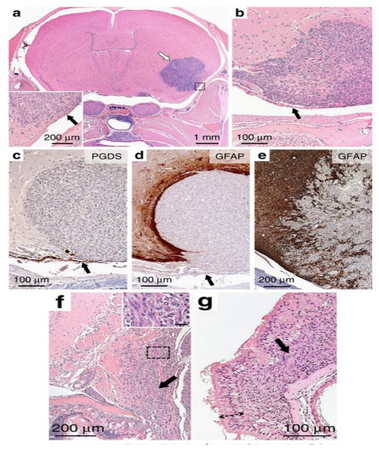

Figure 2: Mouse RT display same histological (and immunohistochemical) features as human tumors: primitive neuroectodermal pattern, mesenchymal pattern and nest of classic rhabdoid cells, neural crest cells-derives tissues like meninges and cranial nerves

Conclusions

- Neural crest cells could be the cell of origin of rhabdoid tumorigenesis.
- Early inactivation of *Smarcb1* leads to rhabdoid tumorigenesis.

Next Steps/Significance

- DNA methylation analysis is currently ongoing.
- Identify upregulated pathways (e.g., HOTAIR) to further elucidate the tumorigenesis of the subgroups.

Acknowledgements (and/or References)

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