Granule neuron differentiation status and ECM substrate modulate the Netrin-1 signaling response in the cerebellum

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Background
- Defects in granule neuron proliferation and migration can cause medulloblastoma in children and young adults.
- Netrin1 (Ntn1), a secreted guidance cue from the germinal zone, can elicit an attractive or repulsive migration response from granule cell neurons in the cerebellum.
- Ntn1 elicits cellular response by binding to neuronal transmembrane receptors Dcc and/or Unc5c.

Questions and Hypotheses

How do cerebellar granule neurons exposed to Ntn1 show different spatial and temporal responses to the same guidance cue?

Preliminary data

- Suggest different responses to Ntn1 based on differentiation status.
- Suggest a function of Ntn1 signaling into germinal zone exit.

In vivo analysis
- IHC and imaging after EdU staining to observe precursor migration phenotype in Atoh1::CreERT2; Ntn1 f/f mice.

Results

- Atoh1::CreERT2; Ntn1 f/f mouse line indicated less granule cell migration in the absence of Ntn1, p < 0.05.

In vitro analysis
- In vitro assay of Atoh1-GFP mouse line through FACS sorting.

Method

Results

- Western blots of progenitor and differentiated cells’ protein extracts confirm the observations in the EGL, with expression of Dcc and an increase of Unc5c protein level in differentiated cells.

Conclusion

- Effect of Ntn1 on migration in different populations on different substrates.
- Granule cells in different ECM substrate showed different Ntn1 responses, p < 0.05.
- Data indicate more neuronal attraction to Ntn1 on laminin and more repulsion from Ntn1 on vitronectin.
- Depending on receptor expression and the prolific ECM substrate, Ntn1 bifunctional signaling results in plastic guidance responses.
- Results support our hypotheses, showing that both differentiation status and ECM substrate modulate the granule neuron Ntn1 response.

Future research will involve investigating the mechanism through which ECM substrate affects neuronal migration, particularly focusing on integrin binding (α,β)3.

Acknowledgements

Support was provided by Rhodes College and St. Jude Children’s Research Hospital through the Rhodes-St. Jude Summer Plus Fellowship. L.S. also acknowledges support from Christophe Laumonnerie and David Solecki.