Integrative mass spectrometry and RNA-seq sequencing identifies DLK1 as a candidate immunotherapeutic target in neuroblastoma

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Background
- Neuroblastoma is a solid extra cranial tumor arising from aberrant development of the sympathetic nervous system during embryogenesis.
- It is the most commonly diagnosed cancer within the first year of life with about 700 new cases diagnosed in the US each year.
- Despite current multimodal therapies, the survival rate for high-risk neuroblastoma remains lower than 50% and relapsed cases are generally incurable.

The cell surface landscape of primary and relapsed neuroblastoma (NB) is currently not well characterized. An unbiased survey of these proteins and their isoforms would greatly facilitate the identification of candidate immunotherapeutic targets for preclinical validation.

Study Approach

**Multi-omic data integration identifies DLK1**

- **A.** Cell surface mass spectrometry validates known targets in NB.
- **B.** Lack of correlation between RNA sequencing and protein mass spectrometry.
- **C.** Cell surface mass spectrometry identifies DLK1 as an immunotherapeutic target.
- **D.** DLK1 knockdown shows a role in differentiation.

**Conclusion**
- Parallel proteomic and transcriptomic studies in additional NB patient tumors are ongoing to determine the clinical potential of DLK1-based immunotherapy.

**Ongoing Work**
- We have defined the first MS-based surfaceome of NB.
- Identified DLK1 as an epigenetically regulated protein and candidate immunotherapeutic target using an integrative multi-omic approach.
- Ongoing efforts include assessing how the NB surfacome evolves under the selective pressure of chemotherapy using paired diagnostic and relapsed NB tumors and determining mechanism(s) of resistance to DLK1-directed ADC therapy.
- We will be applying our approach to other childhood cancers through a collaborative U54 in the Pediatric Immunotherapy Discovery and Development Network (P5-DDN).

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