

Telomere maintenance mechanisms regulate pluripotency and cancer stemness in high-risk neuroblastoma

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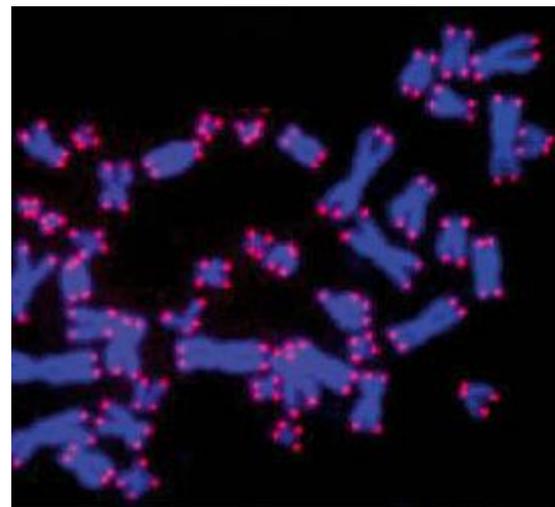
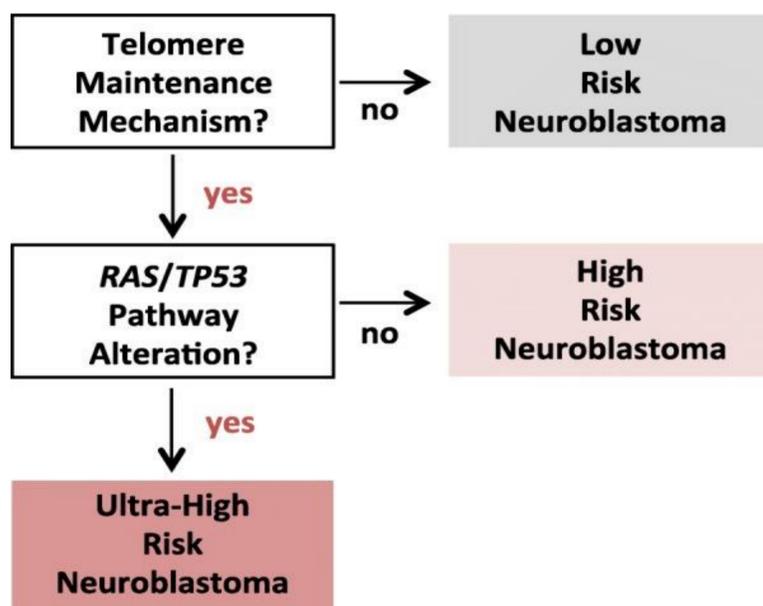


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Introduction: High-risk neuroblastoma (HR-NB) has one of the lowest survival rates of childhood cancers. Most children with HR-NB already have metastatic disease at diagnosis and despite therapies, more than half either do not respond or subsequently relapse. Once HR-NB relapses, there are no curative therapies available and long-term survival is only 10%. HR-NB is a highly heterogeneous tumor and identification of relapse prone disease is a major challenge in the clinical management of HR-NB. The project outlined below seek to understand molecular mechanisms that drive neuroblastoma and to identify potential new therapeutic targets.

Project outline: Telomeres are specialized DNA-protein complexes found at the ends of chromosomes, which play a critical role in protecting chromosomes from degradation. Activation of a telomere maintenance mechanisms (TMM) is a hallmark of cancer that prevents shortening of telomeres, thereby facilitating continued sustained proliferation of cancer cells. Telomere activation in neuroblastoma is driven by mutually exclusive, genetic aberrations (MYCN amplification, TERT re-arrangements, and ATRX mutations), each capable of promoting TMM through telomerase or alternative lengthening of telomeres (ALT). TMM activation correlates with poor survival in neuroblastoma. Cancer stem cells (CSCs) play a crucial role in neuroblastoma metastasis, chemoresistance and relapse. Recent studies have shown a potential role of telomere activation in contributing to stemness and immortality. However, the molecular features that regulates stemness and self-renewal properties in neuroblastoma is not characterised. In this study, we will investigate how telomere maintenance affects cancer stemness in neuroblastoma and delineate the mechanisms by which telomere activity and CSC properties are linked.



Telomere FISH analysis

Hypothesis: Neuroblastoma cells maintain pluripotency and cancer stem cell characteristics through activation of TMMs.

Aims:

- Generate bulk and CSC variants of telomerase/ALT dependent neuroblastoma primary cells
- Determine telomerase activity and telomere length in neuroblastoma bulk vs CSCs
- Evaluate the correlation between telomere maintenance and pluripotency in neuroblastoma
- Determine the effect of telomere inhibition on stemness phenotype and CSC mediated oncogenic signalling.

Techniques involved: Confocal microscopy, Flow cytometry, Western blotting, RT-PCR.

References: Ackermann et al, Science (2018). PMID; 30523111.