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The oncogenic role of noncoding single nucleotide variants at adrenergic and mesenchymal neuroblastoma core regulatory circuitries active binding sites

Introduction

Neuroblastoma (NB) is a pediatric malignancy originating from neural crest cells (NCCs) during sympathetic nervous system development. NB is a heterogeneous tumor composed by two distinct cell identities: the most differentiated adrenergic (ADRN) identity, and the most aggressive mesenchymal (MES) one. Perturbations in the activity of transcription factors (TFs) involved in core regulatory circuitries (CRCs), transcriptional networks governing NB-specific gene expression programs, lead to the arising of ADRN an MES phenotypes. Our hypothesis is that somatic single nucleotide variants (SNVs) in CRCs active transcription factor binding sites (aTFBSs) underlie such perturbations, affecting the normal transcriptional activity of CRC TFs, impacting the normal differentiation of NCCs and driving NB onset.

Aim

Our aim is to investigate mutated CRCs aTFBSs, their target-genes and explore the role of selected putative noncoding drivers in NB tumorigenesis.

Methods

We identified aTFBSs analyzing 42 ChIP-seq and 12 ATAC-seq from 7 ADRN and 2 MES NB cell lines. Then, we applied Fisher test to test aTFBSs for the enrichment of SNVs from whole-genome sequencing (WGS) data of 397 NBs. We compared overall survival (OS) and event-free survival (EFS) rates between patients with and without SNVs enriching aTFBSs. Putative drivers affecting CRC TF binding were identified using the FABIAN-variant tool. Next, we identified aTFBSs target-genes through promoter capture Hi-C data of 2 ADRN and 2 MES NB cell lines and correlated their expression with clinical data from 498 NB cases.

Results

We found significantly mutated sets of aTFBSs interacting with 5 ADRN TFs (GATA3, HAND2, ISL1, MYCN, TBX2) and 1 MES TF (FOSL2) (FDR ≤ 0.1). Patients with SNVs enriching aTFBSs were characterized by lower survival rates compared to wild types, supporting the prognostic significance of these alterations. A total of 689 SNVs impairing CRCs TF binding (Fabian ≠ 0) were found to interact with genes of neuronal differentiation and MES cell proliferation, highlighting the role of SNVs in defining NB identities. Considering target-genes of aTFBSs with SNVs selected on a more stringent threshold (Fabian ≥ 0.1 or ≤ -0.1), we found several genes (*ROBO2, CACNB1, PIK3R1, MDGA1, HES6, LDLRAD4, DGUOK, IRX1, SPOCK2*) whose expression correlated with poorer NB outcomes (FDR ≤ 0.05).

Conclusions

These findings indicate that noncoding SNVs in NB CRC aTFBSs can jointly influence the expression of genes defining NB identities and lead to tumorigenesis.

Recent publications

1. Avitabile M, Bonfiglio F, **Aievola V**, Cantalupo S, Maiorino T, Lasorsa VA, Domenicotti C, Marengo B, Zbyněk H, Vojtěch A, Iolascon A, Capasso M. Single-cell transcriptomics of neuroblastoma identifies chemoresistance-associated genes and pathways. Comput Struct Biotechnol J. 2022 Aug 18;20:4437-4445. doi: 10.1016/j.csbj.2022.08.031. PMID: 36051886.
2. Bonfiglio F, Lasorsa VA, Cantalupo S, D'Alterio G, **Aievola V**, Boccia A, Ardito M, Furini S, Renieri A, Morini M, Stainczyk S, Westermann F, Paolella G, Eva A, Iolascon A, Capasso M. Inherited rare variants in homologous recombination and neurodevelopmental genes are associated with increased risk of neuroblastoma. EBioMedicine. 2023 Jan;87:104395. doi: 10.1016/j.ebiom.2022.104395. Epub 2022 Dec 6. PMID: 36493725.
3. Bonfiglio F, Lasorsa VA, **Aievola V**, Cantalupo S, Morini M, Ardito M, Conte M, Fragola M, Eva A, Corrias MV, Iolascon A, Capasso M. Exploring the role of HLA variants in neuroblastoma susceptibility through whole exome sequencing. HLA. 2024 May;103(5):e15515. doi: 10.1111/tan.15515. PMID: 38747019.

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