Child Health Research Institute
University of Nebraska Medical Center
Children's Hospital & Medical Center

SAP30, a novel oncogenic transcription factor in high-risk neuroblastoma: Clinical significance and role in tumor-progression, survival, and drug resistance

Anup Pathania[1,2,7], Philip Prathipati[3], Nagendra Chaturvedi[4,7], Subash Gupta[5], Siddappa Byrareddy[6,7], Don Coulter[4,7], Kishore Challagundla[1,2,7]

[1]Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE 68198, USA
[2]The Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE 68198, USA
[3]Laboratory of Bioinformatics, National Institutes of Biomedical Innovation, Health and Nutrition, 7-6-8 Saito-Asagi, Ibaraki City, Osaka 567-0085, Japan
[4]Department of Pediatrics, Division of Hematology/Oncology, University of Nebraska Medical Center, Omaha, NE 68198, USA
[5]Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India
[6]Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE 68198, USA
[7]The Child Health Research Institute, University of Nebraska Medical Center, Omaha, NE 68198, USA

Neuroblastoma is the most common devastating extracranial solid malignancy in children. Neuroblastoma (neuro=nerve; blastoma=cancer) develops from immature nerve cells, most commonly in adrenal glands situated above the kidney. The overall 5-year survival rate in children with high-risk neuroblastoma (stage 4) is <40% suggesting that treating high-risk group patients is challenging in the clinic. Despite aggressive multimodal therapy, more than 50% of children with high-risk neuroblastoma relapse and eventually die from the disease. Amplification of the oncogene MYCN is associated with a high risk of relapse. However, only 25% of high-risk neuroblastomas are MYCN-amplified, indicating that the rest are driven by factors other than MYCN. Therefore, it is essential to identify novel driver transcription factors but not passenger genes that improve prediction efficacy of therapy response. This study aims to identify a novel driver transcription factor other than MYCN that can be used as a better prognostic factor and associated with neuroblastoma patients' therapy response, stage, risk, progression, and survival. We used three neuroblastoma patient datasets (n=1252) and applied robust bioinformatic data mining tools to identify driver transcription factors (regulon) that associate with high-risk, progression, stage, and survival in neuroblastoma patients. We also employed neuroblastoma-specific patient-derived xenografts, chemo-resistant cells, and in vivo models in the present study. We applied co-expression and motif analysis using three data mining tools including Weighted Gene Co-expression Network Analysis (WGCNA), cisTarget and Single-Cell rEgulatory Network Inference and Clustering (SCENIC) to identify a distinct transcription regulator signature from three neuroblastoma patient microarray datasets. Based on the regulon specificity score, we derived a 10-transcription factor signature and prioritized Sin3A Associated Protein 30 (SAP30), given its highest regulon specificity score, especially in high-risk and aggressive stage cohorts. Regulon specificity score analysis indicates that SAP30 is associated with mortality, disease, progression, higher risk, and stage 4 in neuroblastoma patients. Higher SAP30 expression was found in high-risk neuroblastoma patients and progression-specific patient-derived xenograft tumors. The advanced pharmacogenomic analysis, CRISPR-Cas9 screens, cisplatin resistant patient-derived xenograft tumor-derived cell

lines and cisplatin resistant neuroblastoma cell lines indicated that SAP30 essentiality correlated with cisplatin resistance. SAP30 silencing inhibited cell proliferation in vitro, and reduced tumor burden in vivo. Overall, our results indicate that SAP30 is a prognostic and cisplatin resistant marker associated with high-risk, stage 4 and poor survival in neuroblastoma patients. We identified SAP30 as a novel prognostic and chemotherapy-resistant marker that could be considered a potential drug target to treat high-risk neuroblastoma patients.