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SAP30, a Novel Oncogenic Transcription Factor in High-Risk Neuroblastoma: Clinical Significance and Role in Tumor-Progression, Survival, and Drug Resistance

Anup Pathania
University of Nebraska Medical Center

Philip Prathipati
National Institutes of Biomedical Innovation, Health and Nutrition

Nagendra K. Chaturvedi
University of Nebraska Medical Center

Subash Gupta
Banaras Hindu University

Don W. Coulter
University of Nebraska Medical Center

See next page for additional authors
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Authors

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

Anup S Pathania[1], Philip Prathipati[2], Nagendra K Chaturvedi[3], Subash C. Gupta[4], Siddappa N.Byrareddy,[1,5] Don W.Coulter[3], and Kishore B.Challagundla[1,6*]

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

Abstract:

Neuroblastoma is the most common devastating extracranial solid malignancy in children, accounting for 15% of childhood cancer-related mortality. Despite an intense treatment regimen, approximately 50% of children treated for high-risk neuroblastoma have more aggressive tumor relapse with less than 20% five-year overall survival. 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 and association with high-risk, progression, stage 4, and survival in neuroblastoma patients. We used three neuroblastoma patient datasets (n=1252 patients) and applied robust bioinformatic data mining tools such as Weighted Gene Co-expression Network Analysis (WGCNA), cisTarget, and Single-Cell Regulatory Network Inference and Clustering (SCENIC) to identify driver transcription factors (regulon) that associate with high-risk, progression, stage, and survival in neuroblastoma patients. 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. Higher SAP30 expression was found in high-risk neuroblastoma patients and progression-specific patient-derived xenograft tumors than their respective controls. The advanced pharmacogenomic analysis and CRISPR-Cas9 screens indicated that SAP30 essentiality correlated with Cisplatin resistance and further validated in Cisplatin resistant patient-derived xenograft tumor-derived cell lines. SAP30 silencing inhibited cell proliferation, slowed growth and induced cell death in vitro, and reduced tumor burden and size in vivo. Overall, our results indicate that SAP30 is a better prognostic and Cisplatin resistant marker associated with high-risk, stage 4 progression, and poor survival in neuroblastoma patients.