SOX11: A DEVELOPMENTAL AND DISEASE RELATED TRANSCRIPTION FACTOR WHICH CONTROLS MAJOR EPIGENETIC REGULATORS IN NEUROBLASTOMA

Louwagie Amber, Decaesteker B, Loontiens S, De Brouwer S, Nunes C, Denecker G, De Vloed F, Depestel L, Roels J, Verboom K, D'haene E, Van Loocke W, Afanasyeva E, Olexiouk V, Depuydt P, Sanders E, Dewyn G, Mus L, Lorenzi L, Van Dorpe J, Creytens D, Westermann F, Versteeg R, Durinck K, Menten B, Van Roy N, Henssen A, Schulte J, Pieters T, Van Vlierberghe P, Vanhauwaert S, Van Neste C, Ek S, van Nes J, Koster J, De Preter K and Speleman F

Department of Biomolecular Medicine, Ghent University, Ghent 9000, Belgium; Cancer Research Institute Ghent (CRIG), Ghent 9000, Belgium

The SRY-related (SOX) transcription factors are critical in normal development and implicated in congenital syndromic disorders and cancer. This is also illustrated by SOX11 which causes Coffin-Siris syndrome and is implicated in lymphoma, breast cancer and pediatric neuroblastoma (NB). We observed SOX11 amplification and overexpression in a subset of NBs. In vitro functional assays revealed strong dependency of NB cells on SOX11 expression. SOX11 controlled regulation of gene expression and chromatin status was analyzed by RNA- and ATAC-sequencing. We mapped SOX11 DNA binding sites using CUT&RUN, a novel method which outperforms classical chromatin-immunoprecipitation (ChIP) sequencing. Remarkably, we identified SOX11 controlled transcription of multiple components of major epigenetic modulating protein complexes implicated in chromatin remodeling and enhancer activation, chromatin modification and DNA methylation. Furthermore, ATAC-sequencing indicated SOX11 controlled chromatin opening, predominantly affecting distal enhancers marked by binding of members of the adrenergic core regulatory circuitry (https://doi.org/10.1101/2020.08.21.261131). Given the broad control of SOX11 of multiple epigenetic regulatory complexes, we propose that NB cells have co-opted the normal developmental role of SOX11 as a crucial regulator of chromatin accessibility and cell identity. As recent efforts increasingly uncovered novel approaches to pharmaceutical inactivate transcription factors, these findings are the first step toward the use of SOX11 as therapeutic target in high-risk NB.