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Abstract Title

Defining the ZSCAN10 Interactome and the Consequences of Its Loss in Human Stem Cell Models of Neurodevelopment

Authors

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Background

Children who inherit two faulty copies of ZSCAN10 develop a rare syndrome of developmental delay, facial asymmetry and ear malformations. ZSCAN10 is a transcription factor that helps maintain pluripotency in early embryonic cells, yet how its loss disrupts neurodevelopment is unknown: no unbiased survey of its protein partners or targets exists.

Objective

We hypothesize that ZSCAN10 times the exit from pluripotency toward neural and neural crest fates, and that its loss mis-times this transition.

Methods

Using CRISPR/Cas9, we generated isogenic human induced pluripotent stem cell (hiPSC) lines lacking ZSCAN10 (KO) and compared their proteomes with controls by mass spectrometry and STRING pathway enrichment. To identify ZSCAN10's partners, we inserted the biotin ligase TurboID into the endogenous

ZSCAN10 gene so that neighbouring proteins become biotin-tagged for mass spectrometry (EGFP-TurboID control). KO and control lines are being differentiated to neural progenitor and neural crest cells for proteome and transcriptome profiling.

Results

Proteomics identified 402 differentially abundant proteins in ZSCAN10 KO hiPSCs (4 replicates; FDR < 0.05): 250 increased and 152 decreased. Enrichment highlighted metabolic pathways such as the citrate cycle, cell-cycle regulators, and altered abundance proteins such as neurosecretory protein VGF (3.74-fold) and GPR143 (3.89-fold), a signature of cells poised to leave the pluripotent state. This is the first unbiased molecular phenotype of ZSCAN10 loss in human cells. ZSCAN10-TurboID clones express a fusion protein of the expected size by western blot; genomic validation and biotin-labelling optimization are underway, and neural differentiation is in progress.

Conclusion

ZSCAN10 loss reprograms the metabolic and cell-cycle machinery of human pluripotent cells and primes them to differentiate, supporting our hypothesis that ZSCAN10 gates the exit from pluripotency. Because this transition is a shared vulnerability across many neurodevelopmental and craniofacial disorders, the ZSCAN10 interactome and lineage-specific datasets underway should reveal mechanisms relevant beyond this rare syndrome.