Cornelia de Lange Syndrome

Cornelia de Lange Syndrome (CdLS) is a rare developmental disorder affecting almost any organ including the Central Nervous System (CNS), inducing a variable neurodevelopmental delay. CdLS is characterized by intellectual disabilities and behavior of the autism-spectrum disorder, multi-organ defects, and they present distinctive facial features.

Previous studies and molecular mechanism

Our previous studies on zebrafish (Danio rerio) nipblb-MO-injected embryos showed that Wnt pathway expression is severely altered. The canonical Wnt pathway is downregulated in animal and human models of CdLS. We can appreciate the reduction of CyclinD1 (CCN1D and ccnd1) respectively in NIPBL-mutated patients and in nipblb-loss-of-function embryos compared to healthy controls.

Chemical induction by lithium chloride of the canonical Wnt pathway showed significantly reduced levels of apoptosis compared to control embryos and can rescue nipblb deficiency phenotype.

Our working Hypothesis:

Cohesin defect → ↓WNT → ↓β-catenin → CCND1 → Cell death

CdLS is caused by mutations in NIPBL, SMC1A, SMC3, RAD21, and HDAC8 genes encoding for proteins of the cohesin complex, involved in gene expression regulation and chromatin organization.

Mammalian Neural Stem Cells (NSCs) model to study the role of Nipbl and Hdac8, the two most commonly mutated genes in CdLS patients, during neurodevelopment.

Upon cohesins chemical inactivation or siRNAs depletion, CdLS-NSCs showed a significant reduction in proliferation rate and differentiation capabilities toward the neuronal lineage. Interestingly, when CdLS-NSCs were exposed to lithium chloride (LiCl) such defects were rescued, restoring physiological levels of proliferation and differentiation.

LCL – CdLS

We explored possible ameliorative effects of chemical activation of Wnt pathway in in vitro CdLS models (lymphoblastoid cells - immortalized lines) with LiCl and other activators (not shown) in lymphoblastoid cell lines from healthy donors and CdLS patients.

Conclusions

Our data confirm that the canonical Wnt pathway is impaired in CdLS models, possibly explaining the neurodevelopmental alterations of CdLS patients. In addition, our rescue experiments could pave the way for future therapeutic strategies.

↑WNT → ↑β-catenin → ↑CCND1 → Cell survival

Paving the way for future therapeutic strategies in Cornelia de Lange Syndrome modulating defective Wnt pathway

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