
Embryonic cell senescence at the origin of the cohesinopathy Cornelia de Lange syndrome

Michel Puceat*^{1,2}

¹INSERM U1251 – Institut National de la Santé et de la Recherche Médicale - INSERM – France

²INSERM U1263 C2VN Marseille – Institut National de la Santé et de la Recherche Médicale - INSERM – France

Résumé

Cornelia de Lange Syndrome (CdLS) largely caused by mutation of the cohesin DNA loader NIPBL is a rare multi-organ developmental disorder left without any therapeutic strategy. To faithfully mimic the disease and to identify a therapy, we generated a novel C57Bl/6J *Nipbl*-haplo-insufficient mouse model of the disease.

Under this genetic background the mice recapitulate many of the defects observed in CdLS patients. These mice featured a severe growth delay. Both the proliferative and hypertrophic zones of bones were reduced. *Nipbl*^{+/-} embryonic and neonatal hearts developed ventricular hypertrophy, aortic and valve defects associated with a persistent truncus arteriosus and a ventricular septal defect. Neck, face and oesophageal muscles derived from the embryonic second heart field were less developed in *Nipbl*^{+/-} than in wt embryos.

Adult hearts featured aortic senescence, stenosis, as well as left ventricular hypertrophy.

Using proteomics and RNA-sequencing, we identified a dysregulated TGF β pathway in the outflow tract of embryonic hearts. We found senescent cells in *Nipbl*^{+/-} embryonic hearts, limb primordium cartilage and in post-natal tissues including muscle and brain cortex. Treatment of pregnant *Nipbl*^{+/-} mice with a TGF β R inhibitor (galunisertib) prevented cell senescence and rescued both the cardiac phenotype and the size of mice at birth. The drug used in oncology also blocked senescence of IPS cell-derived smooth muscle cells from CdLS patients.

Altogether we report that an exacerbated TGF β pathway associated with embryonic programmed cell senescence is responsible for many defects in a CdLS mouse model.

We hypothesized that the glucocorticoid receptor associated with Nipbl within the topology associated domain play a role in cell senescence

This druggable cell senescence pathway opens the path toward a preventive and/or therapeutic strategy for post-natal CdLS patients.

Mots-Clés: nipbl, cohesin, cell senescence

*Intervenant