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Insights of CBX2 transcription in human development &

Generation of a human ovarian granulosa cell model from induced pluripotent stem cells

Dirk Hart

Sex development is an intricate and crucial process in all vertebrates that ensures the continued propagation of genetic diversity within a species, and ultimately their survival. Perturbations in this process can manifest as variations/differences of sex development (VSD/DSD). Various transcriptional networks have been linked to development of the gonad into either male or female, which is actively driven by a set of genes that function in a juxtaposed manner and is maintained through the developmental stages to preserve the final sexual identity. One such identified gene is Chromobox homolog 2 (*CBX2*), an important ortholog of the Polycomb group (PcG) proteins that functions as both chromatin modifier and highly dynamic transactivator. *CBX2* was shown to be an essential factor for gonadal development in mammals, as genetic variants or loss-of-function of *CBX2* can cause sex reversal in mice and humans. Here we attempt to elucidate potential molecular components that play a role in the regulation of *CBX2* transcription and gene function, by identifying the putative *CBX2* promoter and potential endogenous promoter-bound transcription factors, which may have implications in human gonadal development and disease.

Primary gonadal somatic cells – the ovarian granulosa cells (GCs) in the case of women – represent the absolute model to investigate mechanism of disease in VSDs. Collection of these cells in humans is laborious and invasive, while classical animal models fail to recapitulate the human phenotype and function. Furthermore, in patients with the most severe forms of VSD gonadal cells are totally absent. It is therefore vital to develop an alternative cell-model. In view of this, we established an efficient method to reprogram donor-derived urinary progenitor cells (UPs) and differentiate iPSCs into granulosa-like cells (GLCs). The UPs presented a less invasive and high-quality cell source, improving the clinical applicability of the model along with utilising a non-integrative reprogramming method that eliminates alteration of the original genome. This novel GLC model closely resembles human GCs in morphology and marker gene expression of GC cell-fate and essential function. These results provide the prospect to generate patient-specific personalised GC models to investigate mechanism of disease in VSDs and could improve understanding of the intricacies in female gonadal development.

Jury:

Prof. Anna Lauber-Biason, University of Fribourg (thesis supervisor)

Prof. David Hoogewijs, University of Fribourg (internal expert)

Prof. Beat Thöny, University Children's Hospital Zürich (external expert)

Prof. Zhihong Yang, University of Fribourg (president of the jury)