iPSCs-derived model to study Klinefelter syndrome

Created on: 05-01-2021 - Last modified on: 07-01-2021

Contact person

Christine Wyns

Organisation

Name of the organisation Université Catholique de Louvain (UCL)

Department Institut de recherche expérimentale et Clinique

Country Belgium

Geographical Area Brussels Region

Partners and collaborations

Geneva University Hospitals

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Basic Research, Translational - Applied Research
Type of method	In vitro - Ex vivo
Specify the type of cells/tissues/organs	Skin fibroblasts from KS patient

DESCRIPTION

Method keywords

Primordial germ cells

Germ cell differentiation

Post-meiotic cells

Klinefelter syndrome iPSCs

Scientific area keywords

Klinefelter syndrome

Male infertility

Induced pluripotent stem cells

Disease modelling

Method description

We developed an innovative model to study the effect of the supernumerary X chromosome on KS features. The model was generated using induced pluripotent stem cells (iPSCs) from patients with Klinefelter syndrome (KS) i.e. with a 47, XXY karyotype. In order to compare the potentials of both 47XXY-iPSCs and 46XY-iPSCs to differentiate into the germ cell lineage, we developed a directed differentiation protocol by testing different combinations of factors including bone morphogenetic protein 4 (BMP4), glial-derived neurotrophic factor (GDNF), retinoic acid (RA) and stem cell factor (SCF) for 42 days. Importantly, we found a reduced ability of 47XXY-iPSCs to differentiate into germ cells when compared to 46XY-iPSCs. In particular, upon germ cell differentiation of 47XXY-iPSCs, we found a reduced proportion of cells positive for BOLL, a protein required for germ cell development and spermatogenesis, as well as a reduced proportion of cells positive for MAGEA4, a spermatogonia marker. This reduced ability to generate germ cells was not associated with a decrease of proliferation of 47XXY-iPSC-derived cells but rather with an increase of cell death upon germ cell differentiation as revealed by an increase of LDH release and of capase-3 expression in 47XXY-iPSC-derived cells.

Lab equipment

- Cell irradiation for mitotic inactivation ;
- Culture facility.

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

Applicable to different cell lines for comparative studies.

Challenges

Define culture conditions to obtain sufficient amount of cells.

Modifications

- Not for the generation of iPSCs ;
- Ongoing studies to define optimized culture conditions.

Future & Other applications

Provides an excellent in vitro model to unravel the pathophysiology and to design potential treatments for KS patients.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

Botman O, Hibaoui Y, Giudice MG, Ambroise J, Creppe C, Feki A and Wyns C (2020) Modeling Klinefelter Syndrome Using Induced Pluripotent Stem Cells Reveals Impaired Germ Cell Differentiation. Front. Cell Dev. Biol. 8:567454. doi: 10.3389/fcell.2020.567454

Wyns C, Botman O. Induced pluripotent stem cell potential in medicine, specifically focused on reproductive medicine. Front Surg. 2014; 1: 5. Published online 2014 March 24

Links

Gynaecology research group

Coordinated by

Financed by