iPSCs-derived model to study Klinefelter syndrome

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Organisation
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Country: Belgium
Geographical Area: Brussels Region

Partners and collaborations
Geneva University Hospitals

SCOPE OF THE METHOD

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