Modeling cardiac disease mechanisms using induced pluripotent stem cell-derived cardiomyocytes in propionic acidemia

Álvarez M², Marcos-Herraiz S¹, Pérez Bl2, Desviat LR1,2, Richard E1,2, ¹Centro de Biología Molecular Severo Ochoa, Universidad Autónoma, Madrid, Spain; ²CEDEM, Universidad Autónoma, Madrid, Spain

Metabolic cardiomyopathies develop secondary to a broad range of pathological conditions including inherited metabolic diseases. One such example is propionic acidemia (PA), a rare metabolic disease associated with mutations in genes encoding α and β subunits of the enzyme propionyl-CoA carboxylase (PCC). A significant number of PA patients develop cardiac complications (hypertrophy, dilated cardiomyopathy, long QT) and available evidence suggests that this cardiac dysfunction is driven mainly by the accumulation of toxic metabolites. The goal of this work was to investigate the molecular mechanisms underlying the cardiac phenotype using cardiomyocytes (CMs) differentiated from PCCA and PCCB patients-derived induced pluripotent stem cells (iPSCs).

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1899+4_1899+7delAGTA</td>
<td>Increase of Lys, Gly, methylcarantine, propionylglycine, propionylcarboxylic acid. Decrease of carmitine. 8% PCC activity.</td>
<td>Dietary restriction and carmitine supplementation</td>
<td>Developmental delay, hypotonia, infections and chronic pancreatitis</td>
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<tr>
<td>c.1210_1211delinsTAGAGCGACAGGA</td>
<td>Increase of 3-hydroxypropionyl methylcarinate, propionylglycine and tiglylglycine. PCC activity undetectable in lymphocytes.</td>
<td>Dietary restriction and carmitine supplementation, metformin, digoxin and O10 coenzyme</td>
<td>Developmental delay, hypotonia, small size and dilated cardiomyopathy</td>
</tr>
</tbody>
</table>

**ICMs Generation**

**ICMs Characterization**

**Conclusions**

1- PA patients’ cardiomyocytes exhibit alterations in several cellular processes such as mitochondrial function, autophagy, ribosomal biogenesis and connexions between endoplasmic reticulum and mitochondria. 
2- The different miRNA expression pattern between the two PA iPSC-CMs could be due to phenotype differences.
3- MitoQ treatment could be an adjuvant treatment to improve the quality of life of PA patients.
4- The differentiation of PCCA and PCCB iPSCs to iCMs has provided new PA cellular models that offer an unprecedented opportunity to gain deeper insight into PA-related cardiomyopathy and evaluate new therapeutic approaches.