Comparative assessment of different types of human stem cell derived cardiomyocytes for predictive electrophysiological safety screening

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Introduction

The need for new strategies in preclinical compound testing is intensively debated by the pharmaceutical industry. In this respect, cardiomyocytes generated from human stem cells (hSCs) are regarded as a promising source to develop meaningful in vitro test models of adverse cardiovascular effects, including electrophysiological safety screening. Our study is the first to compare the pharmacological profile between three types of commercially available hSCs by means of MEA recordings and to relate it to existing electrophysiological preclinical cardiac safety models.

Commercially available human embryonic or induced pluripotent stem-cell derived cardiomyocytes (hiPSCs, hESCs) from three providers were electrophysiologically validated against 28 compounds with different modes of action. Continuous field action potentials (fAPs) were recorded from the cells directly seeded on the recording electrodes of 6-well MEAs.

Conclusion

Compound effects comprised changes of the initial phase of the fAP (Na⁺ component), fAP duration as well as changes of the spontaneous beating frequency and variability of the beat-to-beat intervals plotted as coefficient of variation (CV). Numbers in brackets indicate number of data points. Error bars represent SD.

Comparison of Predicitivity

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<thead>
<tr>
<th>Provider</th>
<th>fAP duration</th>
<th>Effect on amplitude</th>
<th>Beat frequency</th>
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<td>I</td>
<td>11</td>
<td>Predictions</td>
<td>Correct hits</td>
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<tr>
<td>II</td>
<td>17</td>
<td>Predictions</td>
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<tr>
<td>III</td>
<td>13</td>
<td>Predictions</td>
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Field action potential (fAP) superpositions of recordings at different concentrations of procainamide. Data shown from a single experiment, cells from provider I. (A) Overview of the fAPs in low time resolution. Voltage deflections at the beginning of the fAPs are truncated for displaying reasons. Time resolved analysis is performed using self-written macros. Bottom: overview of the most relevant fAP parameters.

4. Characterization of hSC Cardiomyocytes

(A) Representative exemplary traces of field action potentials (fAP) in hSC derived cardiomyocytes from the different providers. Data were obtained under control condition. (D – G) Basic electrophysiological properties fAP: (D) average depleting component of the initial part of the fAPs; (E) fAP duration from initial phase of the fAP to the maximum of the repolarization deflection; (F) average heat frequency and (G) variability of the beat-to-beat variability expressed as coefficient of variation (CV). Error bars represent SD. Provider numbers in brackets indicate the number of data points.

5. Compound test

Cumulative concentration-response curves of electrophysiological properties of cardiomyocytes from provider I (open circles). (A) fAP amplitudes of the rapid component. (B) fAP duration. (C) Heat frequency. (D) beat-to-beat variability expressed as coefficient of variation (CV). Error bars represent SD. Numbers in brackets indicate number of data points. Error bars represent SEM. Star data points represent time-matched solvent controls. Data from procainamide application.