Mathematical Modelling of Electrotonic Interaction between Stem Cell-Derived Cardiomyocytes and Fibroblasts

Michelangelo Paci*, Laura Sartiani, Marisa Jaconi, Elisabetta Cerbai and Stefano Severi

Biomedical Engineering Laboratory, University of Bologna, Cesena, Italy

Introduction: Human embryonic stem cell-derived cardiomyocytes (hES-CM) represent a promising tool for cell therapy. Their functional properties must be assessed.

Methods: We characterized hES-CM at their early stage of development (15-40 days) with electrophysiological, RT-PCR and modelling tools. The hES-CM action potential (AP) was simulated on the basis of the Ten Tusscher model of human adult ventricular cell, modified to incorporate all the experimentally assessed modifications of ionic currents; in particular the hyperpolarization-activated funny current was introduced following a Hodgkin-Huxley formulation with a single activation gate. This led to an in silico cell showing a spontaneous beating activity. Electrotonic coupling with one or more fibroblasts, modelled both as having an ohmic (p̈assive) membrane resistance or considering time and voltage-dependent (äctive) currents, was simulated.

Results: the uncoupled hES-CM model well fitted our experimental data in terms of APD (experimental 228+/-11; simulation 231 ms), Vmax (4216+/-611; 4778 mV/s) and beating frequency (36+/-6; 35 bpm). MDP (-47+/-7; -79 mV), APA (63+/-5; 92 mV) and diastolic depolarization rate (DDR) (22+/-5; 13 mV/s) were out of range. Electrotonic coupling was assessed: fibroblast membrane potential was more and more similar to the hES-CM when increasing the coupling conductance. Coupling the hES-CM with 1 and 2 fibroblasts caused an increment of DDR (+4, +5 mV/s respectively) and beating frequency (+3, +6 bpm) and a reduction of the AP peak (-0.4, -1.3 mV). While the correct AP features reproduced by the uncoupled model were preserved, coupling the hES-CM with 1 and 2 äctivefibroblasts led to a better fit of DDR.

Conclusions: these results suggest that our novel mathematical model can serve as a predictive approach to interpret and refine in-vitro experiments on hES-CM and that few coupled fibroblasts can significantly affect DDR while their influence on the AP amplitude is relatively small.