On the Separation of Normal and Abnormal Stem Cell-Derived Cardiomyocytes’ Calcium Transient Signals

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ABSTRACT
A data set of 438 calcium transient signals measured from induced pluripotent stem cell derived cardiomyocytes was collected to analyze and separate abnormal signals corresponding to aberrant cardiomyocytes from normal signals corresponding to normally developed cells. After the calcium transient peak detection, the authors computed peak variable values. Each signal peak was determined to be either normal or abnormal. The peak variables were used for machine learning algorithms to classify entire calcium transient signals into normal or abnormal types. The authors evaluated the classification power of 10 variables to separate normal signals from abnormal ones. This article obtained classification accuracies of up to 85-95%, around 5% better than the results in the preliminary research. The correctness of the classification of the signals was inferred either by a biotechnology expert or by an algorithm. The new results are promising for the continuity of this area of study in identifying aberrant calcium transients.

KEYWORDS
Calcium Transient Signal, Cardiomyocyte, Classification, Genetic Cardiac Diseases, Induced Pluripotent Stem Cell, Machine Learning, Peak Recognition, Signal Analysis

INTRODUCTION
Calcium cycling refers to the release and reuptake of intracellular calcium, and it is the central regulator of cardiac contraction and relaxation. Cardiac contractility is determined by the amplitude and kinetics of calcium cycling and therefore it has a great impact on the functionality of cardiomyocytes. It is initiated by action potential, and leads to the excitation-contraction coupling of the cardiomyocytes (Marks, 2013). Aberrant calcium cycling due to cardiac diseases or different drugs can lead to abnormal calcium transients, which can cause impaired contractility and fatal cardiac arrhythmias. It is therefore important to understand and analyze cellular calcium cycling.

Calcium imaging of cardiomyocytes is a method for monitoring calcium cycling activity in vitro. In recent years, the calcium cycling functionality of cardiomyocytes has been studied widely with induced pluripotent stem cell (iPSC) (Marks, 2013) -derived cardiomyocytes. Typically, the cells

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are generated from patients carrying different genetic cardiac disorders, and they offer a promising platform for studying the pathophysiology of various disorders and drug responses in human cells. These previous studies have offered new insights into different cardiac diseases by revealing substantial defects and abnormalities in the calcium cycling of these cardiomyocytes, reflecting the cardiac phenotype observed in patients (Takahashi et al., 2007; Penttinen et al., 2015a; Fatima et al., 2011; Jung et al., 2012; Kujala et al., 2012; Lan et al., 2013; Kiviaho et al., 2015; Ojala et al., 2016; Penttinen et al., 2015b). Recently studied diseases revealing calcium cycling abnormalities include catecholaminergic polymorphic ventricular tachycardia (CPVT), an exercise-induced malignant arrhythmogenic disorder (Penttinen et al., 2015a; Kujala et al., 2012), long QT syndrome 1 (LQT1), an electric disorder of the heart that predisposes patients to arrhythmias and sudden cardiac death (Kiviaho et al., 2015), and hypertrophic cardiac myopathy (HCM), a disorder that affects the structure of heart muscle tissue leading to arrhythmias and progressive heart failure (Ojala et al., 2016).

To accelerate the development, application, research, and innovations of stem cell-derived cardiomyocytes, we study the automatic separation of CPVT-, LQT1-, HCM-specific and control (WT) iPSC-derived cardiomyocytes into normal and abnormal groupings to distinguish aberrant cells from normally developed cells. This can be implemented by separating individual cells according to their calcium cycling. Thus far, this separation has been performed manually by biotechnologists or medical laboratory personnel. To gradually enable progress from theoretical research to medical practice, appropriate software based on signal analysis, pattern recognition, and machine learning algorithms is needed to automatize some of the routine-like but very demanding work of biotechnological experts.

BACKGROUND

The study was approved by the Ethics Committee of Pirkanmaa Hospital District (R08070). Patient-specific iPSC lines were established and characterized as described earlier (Penttinen et al., 2015a; Kiviaho et al., 2015; Ojala et al., 2016; Juhola et al., 2015). The studied iPSC lines were UTA.05605.CPVT, UTA.05208.CPVT, UTA.07001.CPVT, UTA.03701.CPVT, UTA.05503.CPVT, and UTA.05404.CPVT generated from CPVT patients carrying cardiac ryanodine receptor (RyR2) mutations; UTA.07801.HCMM, and UTA.06108.HCMM generated from HCM patients carrying α-tropomyosin (TPM1) and myosin-binding protein C (MYBPC3) mutations; UTA.00208.LQT1 and UTA.00118.LQT1 generated from LQT1 patients carrying potassium voltage-gated channel subfamily Q member 1 ( KCNQ1) mutations; and UTA.04602.WT generated from healthy control individuals (Table 1). IPSCs were differentiated into spontaneously beating cardiomyocytes and dissociated into coverslips for calcium imaging studies, which was conducted in spontaneously beating Fura-2 AM-loaded (Invitrogen, Molecular Probes) cardiomyocytes as described earlier (Penttinen et al., 2015a; Juhola et al., 2015). For calcium analysis, regions of interest were selected for spontaneously beating cells, and background noise was subtracted before further processing. Signals were acquired as the ratio of the emissions at 340/380 nm wavelengths.

The recognition of a peak in a calcium transient signal consists of finding its beginning, maximum, and end. Very small spikes with low amplitude and short duration are seen as noise and ignored. If the amplitude of a small spike is smaller than approximately 8% of the average amplitude estimate of large peaks of the signal analyzed, such a spike is defined to be noise, in other words, no actual peak. The recognition of peaks is based on first computing the approximated first derivative signal and second using appropriate thresholds for the derivative signal in order to recognize the beginning, maximum, and end of each peak. The suitable threshold values were found experimentally (Penttinen et al., 2015b; Juhola et al., 2015; Juhola et al., 2014).
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