Cell Research (2008) 18:s131.

www.nature.com/cr

Functional sarcoplasmic reticulum for calcium-handling of human embryonic stem cell-derived cardiomyocytes: Insights for driven maturation

Jing Liu[1,2], Ji-Dong Fu[1,2], Chung-wah Siu[1,2], Ronald A Li[1, 2, 3]

[1]Stem Cell Program and [2]Department of Cell Biology and Human Anatomy, University of California Davis, Davis, CA; [3]Institute of Pediatric Regenerative Medicine, Shriners Hospital for Children of North America, Sacramento, CA

Cardiomyocytes (CMs) are non-regenerative. Self-renewable pluripotent human embryonic stem cells (hESCs) can differentiate into CMs for cell-based therapies. In adult CMs, Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (SR) via the ryanodine receptor (RyR) is key to excitation-contraction coupling. Therefore, proper Ca^{2+} handling properties of hESC-derived CMs are required for their successful functional integration with the recipient heart. Previously, it has been reported that hESC-CMs do *NOT* express functional SRs. Here we performed a comprehensive analysis of CMs differentiated from the H1 (H1-CMs) and HES2 (HES2-CMs) hESC lines, human fetal (F) and adult (A) left ventricular (LV) CMs. Upon electrical stimulation, all of H1-, HES2- and FLV-CMs generated similar Ca2+ transients. Caffeine induced Ca^{2+} release in 65% of FLV-CMs and ~38% of H1- and HES2-CMs. Ryanodine significantly reduced the electrically-evoked Ca^{2+} transient amplitudes of caffeine-responsive but not –insensitive HES2- and H1-CMs and slowed their upstroke; thapsigargin that inhibits the SERCA pump reduced the amplitude of only caffeine-responsive HES2- and H1-CMs and slowed the decay. SERCA2a expression was highest in ALV-CMs but comparable among H1-, HES2- and FLV-CMs. NCX was substantially expressed in both HES2- and H1-CMs relative to FLV- and ALV-CMs. RyR was expressed in HES2-, H1- and FLV-CMs but the organized pattern for ALV-CMs was not observed. The regulatory proteins junctin, triadin and calsequestrin were expressed in ALV-CMs but not HES2- and H1-CMs. We conclude that functional SRs are indeed expressed in hESC-CMs, albeit immature. A better understanding is crucial for improving the safety and functional efficacy of hESC-CMs.

***Keywords*:** human embryonic stem cells, cardiomyocytes, maturation, Ca^{2+} handling, sarcoplasmic recticulum
Cell Research (2008) **18**:s131. doi: 10.1038/cr.2008.221; published online 4 August 2008

Correspondence: Ronald Li
E-mail: ronaldli@ucdavis.edu