Facilitated maturation of Ca2+ handling properties of human embryonic stem cell-derived cardiomyocytes by calsequestrin expression.

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Authors: Jing Liu, Deborah K Lieu, Chung Wah Siu, Ji-Dong Fu, Hung-Fat Tse, Ronald A Li

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Public Summary:
Cardiomyocytes (CMs) are nonregenerative. Self-renewable pluripotent human embryonic stem cells (hESCs) can differentiate into CMs for cell-based therapies. We recently reported that Ca(2+) handling, crucial to excitation-contraction coupling of hESC-derived CMs (hESC-CMs), is functional but immature. Such immature properties as smaller cytosolic Ca(2+) transient amplitudes, slower kinetics, and reduced Ca(2+) content of sarcoplasmic reticulum (SR) can be attributed to the differential developmental expression profiles of specific Ca(2+) handling and regulatory proteins in hESC-CMs and their adult counterparts. In particular, calsequestrin (CSQ), the most abundant, high-capacity but low-affinity, Ca(2+)-binding protein in the SR that is anchored to the ryanodine receptor, is robustly expressed in adult CMs but completely absent in hESC-CMs. Here we hypothesized that gene transfer of CSQ in hESC-CMs suffices to induce functional improvement of SR. Transduction of hESC-CMs by the recombinant adenovirus Ad-CMV-CSQ-IRES-GFP (Ad-CSQ) significantly increased the transient amplitude, upstroke velocity, and transient decay compared with the control Ad-CMV-GFP (Ad-GFP) and Ad-CMV-CSQDelta-IRES-GFP (Ad-CSQDelta, which mediated the expression of a nonfunctional, truncated version of CSQ) groups. Ad-CSQ increased the SR Ca(2+) content but did not alter L-type Ca(2+) current. Pharmacologically, untransduced wild-type, Ad-GFP-, Ad-CSQDelta-, and Ad-CSQ-transduced hESC-CMs behaved similarly. Whereas ryanodine significantly reduced the Ca(2+) transient amplitude and slowed the upstroke, thapsigargin slowed the decay. Neither triadin nor junctin was affected. We conclude that CSQ expression in hESC-CMs facilitates Ca(2+) handling maturation. Our results shed insights into the suitability of hESC-CMs for therapies and as certain heart disease models for drug screening.

Scientific Abstract:
Cardiomyocytes (CMs) are nonregenerative. Self-renewable pluripotent human embryonic stem cells (hESCs) can differentiate into CMs for cell-based therapies. We recently reported that Ca(2+) handling, crucial to excitation-contraction coupling of hESC-derived CMs (hESC-CMs), is functional but immature. Such immature properties as smaller cytosolic Ca(2+) transient amplitudes, slower kinetics, and reduced Ca(2+) content of sarcoplasmic reticulum (SR) can be attributed to the differential developmental expression profiles of specific Ca(2+) handling and regulatory proteins in hESC-CMs and their adult counterparts. In particular, calsequestrin (CSQ), the most abundant, high-capacity but low-affinity, Ca(2+)-binding protein in the SR that is anchored to the ryanodine receptor, is robustly expressed in adult CMs but completely absent in hESC-CMs. Here we hypothesized that gene transfer of CSQ in hESC-CMs suffices to induce functional improvement of SR. Transduction of hESC-CMs by the recombinant adenovirus Ad-CMV-CSQ-IRES-GFP (Ad-CSQ) significantly increased the transient amplitude, upstroke velocity, and transient decay compared with the control Ad-CMV-GFP (Ad-GFP) and Ad-CMV-CSQDelta-IRES-GFP (Ad-CSQDelta, which mediated the expression of a nonfunctional, truncated version of CSQ) groups. Ad-CSQ increased the SR Ca(2+) content but did not alter L-type Ca(2+) current. Pharmacologically, untransduced wild-type, Ad-GFP-, Ad-CSQDelta-, and Ad-CSQ-transduced hESC-CMs behaved similarly. Whereas ryanodine significantly reduced the Ca(2+) transient amplitude and slowed the upstroke, thapsigargin slowed the decay. Neither triadin nor junctin was affected. We conclude that CSQ expression in hESC-CMs facilitates Ca(2+) handling maturation. Our results shed insights into the suitability of hESC-CMs for therapies and as certain heart disease models for drug screening.