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Regulation of Ca^{2+} signaling during differentiation of embryonic stem cells into cardiomyocytes and neuronal cells

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Proper intracellular Ca^{2+} signaling is essential for cell functions. However, the significance of intracellular calcium concentration ($[Ca^{2+}]_i$) regulated by Ca^{2+} release from endoplasmic reticulum (ER) during early developmental stage of myocytes and neuronal cells have not yet been fully understood. It is believed that endoplasmic reticulum (ER)-function is rudimentary in the fetal heart and embryonic stem cell (ESC) derived cardiomyocytes (ESCMs). Also it remains unclear whether intracellular Ca^{2+} mobilization from type 2 ryanodine receptor (RyR2) is required in the activity-dependent neurogenesis. Using murine ESCs as an *in vitro* model of cardiomyogenesis and neurogenesis, we demonstrate that functional RyR2 are essential to the rapid upstroke and frequency of Ca^{2+} transients, which regulate contractions with the differentiation of ESCMs; and neurogenesis induced by activation of $GABA_A$ receptors and L-type Ca^{2+} channels depends critically on the functional RyR2. These results reveal that ESCMs have the potential to form a functional ER that is necessary for eventual therapeutic viability. An intimate cooperation of L-type Ca^{2+} channels with RyR2 is crucial for the activity-dependent neurogenesis induced by paracrine and/or autocrine GABA signaling.

***Keywords*:** murine embryonic stem cells, calcium signaling, cardiomyogenesis, neurogenesis, endoplasmic reticulum, type 2 ryanodine receptor

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Huang-Tian Yang, MD, PhD, a Principal Investigator of Laboratory of Molecular Cardiology and Key Laboratory of Stem Cell Biology, Institute of Health Sciences in SIBS, CAS and SJTUSM. She received PhD in Medicine from Yamagata University School of Medicine, Japan in 1994, served as a faculty member in the Department of Pharmacology there to 1997, then moved to NIH/NIA, and took current position since 2000. The goal of Dr Yang's lab is to elucidate the regulatory mechanisms underlying the physiological and pathological alterations in cardiac development and contractile function, and to identify novel targets and therapeutic intervention for the prevention and treatment of ischemic injury and heart failure. The lab is currently conducting the researches in the following aspects: (1) differentiation of embryonic stem cells to cardiomyocytes and its regulation as well as therapeutic potential; (2) regulation of Ca^{2+} signaling in development and ischemic injury; (3) molecular and cellular basis of hypoxic adaptation, G protein-coupled receptors, and natural compounds-induced cardioprotection against ischemic injury.

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