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Cardiomyocyte differentiation of human induced pluripotent stem cells: Modification of signaling pathways

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Introduction & Aim: Lately, cell replacement using human induced pluripotent stem cells (hiPSCs) is considered a promising therapeutic alternative for cardiovascular diseases. Human iPSCs are endowed with the potential to produce a huge number of functional cardiomyocytes from autologous cell sources without the concern of ethical problems or immunological rejection. However, existing protocols for cardiac differentiation of hiPSCs are inefficient limiting their applications. Therefore, the objective of our study was to examine the modulation of signaling pathways to efficiently enhance cardiac differentiation of NP0040 hiPSCs into cardiomyocytes.

Methods: Cardiac differentiation was assessed by temporally modulating the regulatory elements of the signaling pathways: Wnt, BMP-4, FGF-2 and ascorbic acid in a monolayer-based culture system under serum-free, feeder-free conditions with subsequent purification by lactate method.

Results: Here, we showed that sequential treatment with glycogen synthase kinase-3 (GSK-3) inhibitor, bone morphogenetic protein-4 (BMP-4), fibroblast growth factor-2 (FGF-2) and ascorbic acid followed by inhibitor of wnt production-2 (IWP-2) and ascorbic acid produced a high yield of pure (up to 92%) cardiac troponin-T (cTnT)-positive cardiomyocytes that contracted spontaneously as coordinated sheets in multiple (>15) independent experiments. These cardiomyocytes were maintained as spontaneously contracting cells in culture for more than 1 month. The cardiomyocytes exhibited normal cardiac sarcomere organization expressing sarcomeric α-actinin, cTnT, MLC2v and the gap junction protein, Connexin 43. Reverse-transcriptase PCR revealed the expression of Isl-1, NKx2.5, Tbx5, Tbx20, GATA4, Mef2c, Hand1, MYH6, MYL2, MYL7, TNNT2 and TNNI3. Field Potential recording indicated that cardiomyocytes were electrically coupled to one another. The characteristics of the recorded action potential showed mainly ventricular-like waveforms.

Conclusion: Our data indicated that induction of mesoderm and its subsequent specification into cardiac fate from hiPSCs requires well-orchestrated interaction between Wnt, BMP-4, FGF/MEK and MEK/ERK signaling pathways. Controlling these pathways allows efficient production of cardiomyocytes that may provide a possible source for cell-based therapy.

Biography

Taghrid Gaafar has completed her MD from Cairo University and Post-doctoral studies from Cairo University School of Medicine. She is a Professor of Immunology & Cell Biology at the Cairo University. She is the Director of RAMSES Stem Cell Research Unit, Children Hospital, Cairo University. She has published more than 20 papers in many reputed journals

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