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The Impact of Growth Factors on Human Induced Pluripotent Stem Cells Differentiation into Cardiomyocytes

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Abstract:

Human induced pluripotent stem cells (hiPSCs) act as a promising therapeutic alternative for cardiovascular diseases. They yield a large number of functional cardiomyocytes (CMs) from autologous cell sources without ethical or immunological problems. However, significant limitations still remain in terms of line-to-line variability in CM yield and reproducibility. **Aim:** To efficiently enhance NP0040 hiPSCs differentiation into CMs. **Main methods:** Following a standard cardiac differentiation protocol using small molecules targeting the canonical Wnt signaling, growth factors (BMP4 and FGF2) and ascorbic acid were added further in order to increase the cardiac differentiation efficiency. All cultures were conducted in serum-free, feeder-free monolayer system followed by lactate purification**. Key findings:** Using NP0040 hiPSCs, the CM yield resulting from modulation of the Wnt signaling pathway alone was inefficient compared to previous studies while the addition of BMP4, FGF2 and ascorbic acid resulted in enhanced cardiac differentiation outcome. The later resulted in a high yield (up to 92%) of cardiac troponin-T (cTnT)+ CMs contracting spontaneously as organized sheets in 15 independent experiments**.** They were validated structurally and functionally using immunofluorescent staining for sarcomeric α-actinin, cTnT, MLC2v and Connexin 43. Reverse-transcriptase PCR revealed cardiac transcription factors and cardiac-specific genes expression. CMs were electrically connected to one another. Recorded action potential (AP) showed waves of relatively mature ventricular-like phenotype. **Significance:** We demonstrated that hiPSC lines respond differently to a standard cardiac differentiation protocol and that a well-orchestrated interplay between Wnt, BMP4, FGF/MEK and Ascorbic acid MEK/ERK1/2 signaling pathways is beneficial in enhancing the differentiation outcome.