The Time Course of Murine Cardiomyocyte Maturation

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Cardiovascular disease (CVD) is the leading cause of death in the world, and the mature human heart has little capacity to regenerate. Recently, induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) have emerged as a promising therapeutic treatment for CVD, however they remain in a fetal state when derived in vitro. Studying cardiomyocyte maturation patterns may reveal why iPSC-CMs persist in a fetal-like state, since little is known about their development and organization patterns between birth and adulthood. I investigated subcellular development patterns of cardiomyocytes, particularly mitochondria, sarcomeres, and T-tubules because of their prominent functional roles in cardiomyocytes. Hearts were isolated from CD-1 IGS-strain mice at postnatal days (PD) 6, 10, 13, and 18, in addition to 5 months. The hearts were digested in a collagenase II solution and then filtered to isolate cardiomyocytes. They were stained with cytochrome oxidase subunit IV, troponin I, and wheat germ agglutinin antibodies. The stained cardiomyocytes were imaged and analyzed using self-developed Haralick texture correlation software. Mitochondria and sarcomeres were visible but disorganized at PD-6 but fully developed by PD-18. In comparison, T-tubules were nearly absent at PD-6 but accelerated development until adulthood. Further analysis showed that the distance between T-tubules closely matched with sarcomere length, indicating that T-tubules form at the Z-disks. I conclude that there are temporally distinct phases for murine cardiomyocyte maturation at a subcellular level. My results may help identify which parts of iPSC-CMs are underdeveloped. Further elucidating the mechanisms of cardiomyocyte development holds great potential to treating CVD.

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