Stress-induced premature senescence in hiPSC-derived cardiomyocytes recapitulates aging-induced cardiac remodelling

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Aging of the heart involves adverse remodeling in Cardiomyocytes (CMs), resulting in heart failure. This study exploits CMs differentiated from Human Induced Pluripotent Stem Cells (hiPSC) as a tool to reproduce and characterize mechanisms involved in cardiac aging. A stress–induced premature senescence was induced by short exposure to Doxorubicin (Dox) at the Sub-Lethal Concentration (Sen-CMs). We explored Sen-CMs in comparison to untreated CMs, correlating them with the results obtained in CMs isolated from young (7 weeks, y-mCMs) and old (18 months, o-mCMs) C57BL/6 mice. Dox treatment induced expression of cyclin-dependent kinase inhibitors and increased positivity to senescence-associated β-galactosidase, typical markers of senescence. Moreover, Sen-CMs showed increased oxidative stress and a depolarized mitochondrial membrane potential, which resulted in decreased ATP production. Functionally, Sen-CMs showed altered electrical activity in terms of prolonged QTc interval and Action Potential Duration (APD). This was ascribable to increased I NaL and reduced I Kr . In parallel, o-mCMs in comparison to y-mCMs, showed APD prolongation and INaL enhancement, thus reproducing Dox-induced abnormalities. Moreover, in both Sen-CMs and o-mCMs, pCAMKII level was increased in comparison to untreated CMs and y-mCMs respectively. Overall, Sen-CMs largely recapitulate the phenotype of aged primary CMs and thus they can be considered a novel *in vitro* platform to study aging mechanisms.

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