# Aging induced cardiac remodelling: a human and animal *in vitro* cellular study

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**Abstract**:
Aging of the heart involves adverse remodeling in cardiomyocytes (CMs), resulting in heart failure, which increases with age. This study exploits CMs differentiated from human induced pluripotent stem cells (iCMs) as a tool to reproduce and characterize mechanisms involved in aging. A senescent-like phenotype (Sen-iCMs) was induced by short exposure (3 hours) to doxorubicin (Dox) at the sub-lethal concentration of 0.2 µM. We explored phenotypic and functional properties of Sen-iCMs in comparison to untreated iCMs, correlating them with the results obtained in mouse CMs (mCM) isolated from young (7 weeks) and old (18 months) C57BL/6 mice.

Dox treatment induced expression of cyclin-dependent kinase inhibitors p21 and p16, and increased positivity to senescence-associated beta-galactosidase (SA-β-gal), typical markers of cellular senescence. Moreover, Sen-iCMs showed an increase in oxidative stress markers and a depolarized mitochondrial membrane potential, which resulted in decreased ATP production. Functionally, compared to iCM, Sen-iCMs showed altered electrical activity in terms of prolonged action potential duration (APD) and increased incidence of delayed after-depolarizations (DADs). APD prolongation was ascribable to increased late sodium current ($I_{NaL}$) and reduced rapid delayed rectifier potassium current ($I_{Kr}$). Old mCMs in comparison to young mCMs, showed APD prolongation and $I_{NaL}$ enhancement, thus reproducing Dox-induced electrical abnormalities in iCMs. Moreover, in both Sen-iCMs and old mCMs, pCAMKII level was increased in comparison to iCMs and young mCMs respectively.

Overall, we showed that Sen-iCMs largely recapitulate the phenotype of aged primary CMs and thus they might represent a platform to study *in vitro* human cardiac cellular senescence.