Cardioprotective role of exosomes in Doxorubicin-induced senescent human iPSC-derived cardiomyocytes

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Ageing involves several structural and functional changes at the heart level that may lead to the onset of heart failure (HF). Changes associated with cardiac aging include mitochondrial dysfunction, cellular senescence and increased risk of arrhythmias. Having shown that cardiac progenitor cells (CPCs) secrete nanoparticles named exosomes (EXO) enriched of cardioprotective factors, we are exploring EXO's capacity to ameliorate senescence-derived modification into CMs. However, human models of in vitro cardiac aging are currently missing. This study exploits CMs derived from human induced pluripotent stem cells (hiPSCs) as an in vitro model for cardiac senescence that will be used as platform to characterize mechanisms involved in cardiac ageing and to test CPC-derived EXO.

Cardiac progenitor cells (CPCs) isolated in vitro from human atrial explants have been reprogrammed into induced pluripotent stem cells (hiPSCs) and subsequently differentiated into cardiomyocytes (CMs). The CMs were then treated with low concentrations (0.2 μM) of Doxorubicin (DOX) in order to induce a senescence-like phenotype. Control CMs (CTR-CMs) and senescent-like CMs (SL-CMs) were characterized functionally and molecularly at different times from DOX treatment using electrophysiological, fluorimetric and biochemical assays.

Compared to CTR-CMs, SL-CMs showed an increased positivity for SA-β-galactosidase, depolarized mitochondrial membrane potential and ROS levels tended to increase. Electrophysiological analysis showed in SL-CMs a prolonged QT interval, justified by the reduction of I_{Kr}. Electrical dysfunction was also associated with alterations in Ca^{2+} handling. Indeed, both Ca^{2+} transient amplitude and sarcoplasmic reticulum Ca^{2+} content were decreased in SL-CMs compared to CTR-CMs. These DOX-induced effects were not associated with an increase in apoptosis.

In order to detect potential cardioprotective molecules, the effects of EXO, derived from the purification of conditioned culture media of CPCs of different patients, were tested. Compared to SL-CMs, EXO-treated SL-CMs showed a decrease in oxidative stress and an increase in mitochondrial membrane potential, indicating an improvement in mitochondrial function. Additionally, treatment with EXO mitigated the action of DOX on the QT interval.

The results obtained suggest that the developed model summarizes the phenotype of aged CMs, in terms of senescence markers and electrical properties. Moreover, the effects found after treatment with CPC-derived EXO suggest the presence of anti-ageing molecules within EXO that will be the subject of future studies.