We have recently demonstrated that human Cardiac Stem Cells isolated from explanted failing hearts (E-CSC) are characterized, in vitro, with respect to those isolated from healthy donors (D-CSC), by a senescent phenotype: a reduced telomere length and telomerase activity, telomere erosion, the occurrence of telomere dysfunction foci and the accumulation of senescent markers, as p16INK4A.

In this study, we newly demonstrate that, compared to healthy D-CSC, senescent E-CSC show an impaired regenerative ability when injected in the peri-infarct region of an infarcted mouse heart. E-CSC treated animals display a reduced Ejection Fraction, depressed positive and negative dP/dt, a larger scar size, a lower density of capillaries, small arterioles and cycling myocytes, an enrichment in senescent, apoptotic and autophagic myocytes and a reduced number of cardiac primitive/progenitor cells recruited in the site of injury. In addition, we demonstrated that the E-CSC secretome was not able to protect rat adult cardiomyocytes exposed in vitro to SI/RO injury, while the D-CSC’s one did. This negative effect was abolished blocking the IL1ß secreted by E-CSC.

We then looked for possible mechanisms responsible for E-CSC dysfunction, focusing on molecular pathways associated with cell senescence and ageing. We identified that E-CSC are characterized by: 1. a higher activity of TORC1/pS6K complex and an arrest of the autophagic flux; 2. a reduction of AKT and CREB activation and a decreased transcription of the cardioprotective miR-132.

On the basis of these findings, we screened drugs capable to interfere with the above described pathways; we identified that a 3-days treatment with a combination of Resveratrol (0.5μM) and Rapamycin (10nM) is able to reduce the fraction of E-CSC affected by cell senescence in vitro and to diminish the secretion of proinflammatory cytokines, thus restoring the protective effects of CSC on cardiomyocytes exposed in vitro to SI/RO injury. These improvements are associated with a reduction in TORC1 activity and an increase in AKT, CREB, SIRT-1 and miR-132 levels, in addition to the restoration of the autophagic flux.

Last, we tested if the pre-conditioning of E-CSC with the combination of the two drugs, prior to the injection in the peri-infarct region in a mouse MI-model, is able to restore their reparative ability. This was the case: mice treated with preconditioned E-CSC showed cardiac functional and dimensional parameters similar to those of D-CSC treated mice; also histological analysis gave positive results.

In conclusion, the treatment of senescent CSC with a combination of Rapamycin and Resveratrol represents a promising strategy to improve autologous cardiac stem cell therapy.