Supplementary Information

Supplementary Methods

qRT-PCR primer sequences

Mouse $p16^{INK4a}$

F: 5'- CGTGAACATGTTGTTGAGGC -3'

R: 5'- GCAGAAGAGCTGCTACGTGA -3'

Mouse Igf1

F: 5'- TGGATGCTCTTCAGTTCGTG -3'

R: 5'- CACTCATCCACAATGCCTGT -3'

Mouse H2A.X

F: 5'- GGTCAGAGAGACGCTTACCG -3'

R: 5'- GTAGTTGAGTCGCTGGGGAA -3'

Mouse p21

F: 5'- CCAGGATTGGACATGGTGCC -3'

R: 5'- GTGAGGAGGAGCATGAATGGAG -3'

Mouse Puma

F: 5'- CGGGCTAGACCCTCTACG -3'

R: 5'- AGCCCTCCAGAAGGCAAC -3'

Mouse Noxa

F: 5'- TTCAAGTCTGCTGGCACCCG -3'

R: 5'- AACGCGCCAGTGAACCCAAC -3'

Mouse p53

F: 5'- CTAGCATTCAGGCCCTCATC -3'

R: 5'- TCCGACTGTGACTCCTCCAT -3'

Mouse PCNA

F: 5'- TGGATAAAGAAGAGGAGGCG -3'

R: 5'- GGAGACAGTGGAGTGGCTTT -3'

Mouse PIDD

F: 5'- AAGGTTCCGTGGAGTCTGCT -3'

R: 5'- CAGAGTGGTCAGGGTTCCAT -3'

Mouse Trp53inp1

F: 5'- CTACCTCAGCACCCGCAG -3'

R: 5'- GCCCAATATCACAGACGAGA -3'

Mouse Mdm2

F: 5'- TCTGTGAAGGAGCACAGGAA -3'

R: 5'- CTGCTCTCACTCAGCGATGT -3'

Mouse b2-M

F: 5'- ATGTGAGGCGGGTGGAACG -3'

R: 5'- CTCGGTGACCCTGGTCTTTTG -3'

Legends to Supplementary Figures

Fig. S1. p53 and p53 target genes. (a-d) Expression of Bcl2 (a), Bax (b), Aogen (c) and AT1R (d) in cardiomyocytes of WT (n = 4-5) and p53-tg (n = 5-7). Loading conditions were established by Ponceau red, which was employed for normalization of protein expression. Please, note the unspecific band located above 26 kDa in the Bcl2 blot.

Fig. S2. p53 and p53-dependent genes. Time-dependent changes in the expression of p53 and p53-related genes in p53-tg-CPCs (green line) and WT-CPCs (red line) following exposure to Doxo; n = 3 in all cases.

Fig. S3. CPCs and the diabetic heart. (a-d) Areas of myocardial damage (*) in the LV wall; EGFP-positive (green) WT-CPCs are engrafted in some of these foci of injury.

Fig. S4. Early commitment of WT-CPCs. (a, b) GATA4 is expressed (left, white) in EGFP-positive cells (right, green) distributed within the damaged diabetic myocardium. Cardiomyocytes are labeled by troponin I (right, TnI: red).

Fig. S5. p53 and p53-dependent genes and their function. DNA damage activates pathways resulting in the inhibition of cell growth and apoptosis, or DNA repair and proliferation. Red arrows, WT; green arrows, p53-tg.

Research in context

Ongoing clinical trials with autologous cardiac stem cells (CSCs) are faced with a critical limitation which is related to the modest amount of retained cells within the damaged myocardium. We have developed a strategy that overcomes in part this problem enhancing the number of CSCs able to engraft within the pathologic organ. Additionally, these genetically modified CSCs can be generated in large number, raising the possibility that multiple temporally distinct deliveries of cells can be introduced to restore the structural and functional integrity of the decompensated heart.