Aging Hampers Cardiac Stem Cell Regeneration Potential

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For many decades, the human heart has been considered a postmitotic organ composed of a predetermined number of cardiomyocytes, which is established at birth and is preserved throughout life. On this premise, the age of cardiomyocytes corresponds to the age of the organ and organism and chronological myocardial aging is viewed as the inevitable effect of time on the functional reserve of the heart. Cardiac failure in elderly patients is commonly interpreted as an idiopathic or secondary myopathy superimposed on the old heart independently from the aging process. The fascinating discovery that the human adult heart is a self-renewing organ regulated by a compartment of multipotent cardiac stem cells (CSCs) capable of regenerating cardiomyocytes and coronary vessels throughout life has imposed a reevaluation of the current view of cardiac homeostasis, aging, and pathology. A growing body of evidence has revealed that the changes in phenotypic and functional properties of human adult stem/progenitor cells may occur during chronological aging and have severe pathological consequences. Intense oxidative and metabolic stress and chronic inflammation, enhanced telomere attrition, progressive loss of telomeric DNA, and defects in DNA repair mechanisms may lead to severe DNA damages and genomic instability in adult stem/progenitor cells with advancing age that may in turn trigger their replicative senescence and/or programmed cell death. This age-associated decline in the regenerative capacity and number of functional adult stem/progenitor cells may increase the risk to develop certain diseases. Accordingly, we demonstrated that aging cardiomyopathy, i.e. dilated cardiomyopathy in old patients with heart failure that appeared to be age-related, is a stem cell disease (Chimenti et al 2003). A progressive loss of telomeric DNA in CSCs occurs with aging and, although the pool of functionally competent CSCs expands with time and generates a larger myocyte progeny, the newly formed cardiomyocytes inherit short telomeres and rapidly reach the senescent cell phenotype. The expression of p16INK4a, a marker of replicative senescence, becomes apparent, and apoptosis is markedly increased. Deficient CSCs generate old cardiomyocytes, with depressed contractile performance. Endomyocardial biopsies from 19 old patients with a dilated cardiomyopathy were compared with specimens from 7 individuals of similar age and normal ventricular function. Ten patients with idiopathic dilated cardiomyopathy were also analyzed to detect differences with aged diseased hearts. Senescent cells were identified by the expression of the cell cycle inhibitor p16INK4a and cell death by hairpin 1 and 2. Replication of primitive cells and myocytes was assessed by MCM5 labeling, myocyte mitotic index, and telomerase function. Aged diseased hearts had moderate hypertrophy and dilation, accumulation of p16INK4a positive primitive cells and myocytes, and no structural damage. Cell death markedly increased and occurred only in cells expressing p16INK4a that had significant telomeric shortening. Cell multiplication, mitotic index and telomerase increased but did not compensate for cell death or prevented telomeric shortening. Idiopathic dilated cardiomyopathy had severe hypertrophy and dilation, tissue injury, and minimal level of p16INK4a labeling. In conclusion, telomere erosion, cellular senescence, and death characterize aged diseased hearts and the development of cardiac failure in humans.

Future development will aim to the rescue or replacement of aged and dysfunctional endogenous adult stem/progenitor cells as potential therapeutic strategies for treating cardiac diseases characterized by premature aging and age-related heart failure.