



**Karolinska
Institutet**

Institutionen för Cell- och Molekylärbiologi

Studies on Myocardial Regeneration

AKADEMISK AVHANDLING

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ABSTRACT

Heart disease is one of the leading causes of adult and child morbidity and mortality. The underlying pathology leads typically to a loss of functional cardiomyocytes that causes heart failure. Because of the insufficient regenerative capacity of the human heart, cardiomyocytes have been thought to be incapable of renewing after the postnatal period.

In **Paper I**, we investigated the capacity of the human heart to generate cardiomyocytes. We have taken advantage of the integration of the carbon isotope ^{14}C (carbon-14), generated by nuclear bomb tests during the Cold War, into DNA to establish the age of cardiomyocytes in humans. Using cardiac Troponin T and I and pericentriolar protein 1 (PCM-1) as a specific marker to isolate cardiomyocyte nuclei by flow cytometry (**Paper I and II**). We report that cardiomyocytes renew, with a gradual decrease from 1% turning over annually at the age of 25 to 0.45% at the age of 75. Fewer than 50% of cardiomyocytes are exchanged during a normal life span. The capacity to generate cardiomyocytes in the adult human heart suggests that it may be rational to work toward the development of therapeutic strategies aimed at stimulating this process in cardiac pathologies.

After cardiac infarction the formation of inappropriate scar tissue and cardiac remodeling further contribute to cardiac dysfunction. We provide evidence in **Paper III**, that inhibition of PDGF signalling reduces scar formation and an augmentation of cardiomyogenesis modulated by increased neoangiogenesis.

These findings points to the possibility to therapeutically exploit physiological cardiomyocyte renewal by better understanding processes that modulate cardiac regeneration after heart infarction.

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