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Review

"Pro-youthful" factors in the "labyrinth" of cardiac rejuvenation

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ABSTRACT

The mechanisms of aging and senescence include various endogenous and exogenous factors. Among cardiovascular diseases, heart failure is a typical age-related disease. New strategies to restore cardiomyocyte cells have been reported: endogenous substances that can regenerate the heart's cardiomyocytes have been described: follistatin like 1 (FSTL1), growth-differentiation factor 11 (GDF11) and insulin-like growth factor 1 (IGF-I). Manipulation of the different anti and pro- pathways is essential to discover new approaches to regenerative therapies.

Contents

1. Introduction

Aging exacts an inevitable multisystem deterioration of function, which acts as a risk factor for a variety of age-related disorders. The heart is subjected to numerous alterations during aging, as a result of complex biochemical changes (Costantino et al., 2016). Cellular senescence is associated with the expression of cell cycle inhibitors such as p53, p21, p16. Indeed, the mechanisms of aging include various endogenous and exogenous factors (Fridlyanskaya et al., 2015). Calorie restriction (CR) and sirtuins (SIRTs) modulate aging in organisms ranging from yeast to mammals. Insulin/IGF-1 signalling also plays a critical role in aging (North and Sinclair, 2012). In this context, Forkhead transcription factors (FoxOs) are important regulators; they regulate the expression of genes involved in cell growth, and proliferation. FoxOs are modulated by SIRT1-mediated deacetylation and IGF-1 signalling (Gan et al., 2005). One feature of aging that appears to be common among tissues is the loss of regenerative capacity.

2. The myocardium is characterized by limited regenerative capacity

Among cardiovascular diseases, heart failure (HF) is a typical age-related disease and the number of patients with HF increases exponentially with aging. A major cause of heart disease such as HF is the massive loss and/or dysfunction of cardiomyocytes caused by cancer treatments (Rochette et al., 2015a), myocardial infarction and hypertension.

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Numerous studies have evoked a diversity of molecular mechanisms to explain the transition from cardiac hypertrophy to HF. Therapeutic strategies to enhance myocardial angiogenesis and cardio-myogenesis and to induce the differentiation of cardiac stem cells into cardiomyocytes have been investigated (Oka and Komuro, 2008). Restoration of normal contractile function is a crucial aspect of myocardial regeneration. A novel approach towards cardiac "rejuvenation" *via* endogenous "pro-youthful" factors has fostered progress in the regeneration of myocardial tissue, leading to improvements in cardiac performance (Fig. 1). The myocardium is characterized by limited regenerative capacity. The neonatal mammalian heart can substantially regenerate after injury through cardiomyocyte proliferation until postnatal day 7 (Porrello et al., 2011). One of the many factors shared by organisms able to regenerate the heart is the oxygenation state. It has been hypothesized that the transition to the oxygen-rich postnatal environment is the upstream signal that results in cell-cycle arrest of cardiomyocytes (Puente et al., 2014). The post-natal increase in mitochondrial activity is associated with increased levels of reactive oxygen species (ROS) and activation of the DNA damage response pathway. Finally, the effect of ROS on the cell cycle is complex and greatly influenced by the levels, the duration and the compartmentalization of various ROS.

How the adult heart is able or not to regenerate cardiomyocytes is widely debated. Tissue homeostasis in skeletal muscle is fundamentally different from that in cardiac muscle. Skeletal muscle is able to self-repair efficiently. During aging, however, there is a significant decline in skeletal muscle regenerative function and the central role of muscle stem cells has been demonstrated (Blau et al., 2015). In the heart, due to the limited regenerative range of the cells, stem cell therapies have emerged as attractive strategies to promote cardiac regeneration. These cell-transplantation therapies, however, still suffer from many limitations and barriers (Goichberg et al., 2014). It has been reported 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 (Bergmann et al., 2009). Recent analyses reveal that the cell renewal in the heart is primarily confined to the endothelial and mesenchymal cell populations and that there is a much more limited exchange of cardiomyocytes. Endothelial cells have the highest exchange rate, with the whole population being renewed every 6 years in adulthood (Bergmann et al., 2015).

As we reported, the adult mammalian heart has a very limited capacity to regenerate after injury. After myocardial injury, the healing process is divided into three phases: inflammatory, proliferative, and maturation phases. Early inflammatory activation is a necessary event for the transition to later reparative and proliferative programs. At the beginning of the proliferation phase, fibroblasts adopt a proliferative and secretory myofibroblast phenotype. Acquisition of a myofibroblast phenotype by infarct fibroblasts is associated with increased proliferative activity (Talman and Ruskoaho, 2016).

An important new concept in the field of heart "rejuvenation" is the genetic manipulation of cardiomyocyte senescence. Telomere length dynamics plays a crucial role in regulation of cellular processes and cell fate. Short telomeres are risk factors for age-associated diseases, including cardiovascular pathologies (Saliques et al., 2011). It is suggested that telomerase activation, a reverse transcriptase, could be a therapeutic strategy to prevent heart failure after myocardial infarction. Cardiac telomerase activity is detectable at the earliest stages of life and is down-regulated in adult myocardium. Re-expression of the catalytic subunit of telomerase, Tert, in a Tert-null mouse model reverses premature aging phenotypes in these mice, and, can delay physiological aging in WT mice (Bar et al., 2014). In the heart, a population of non-

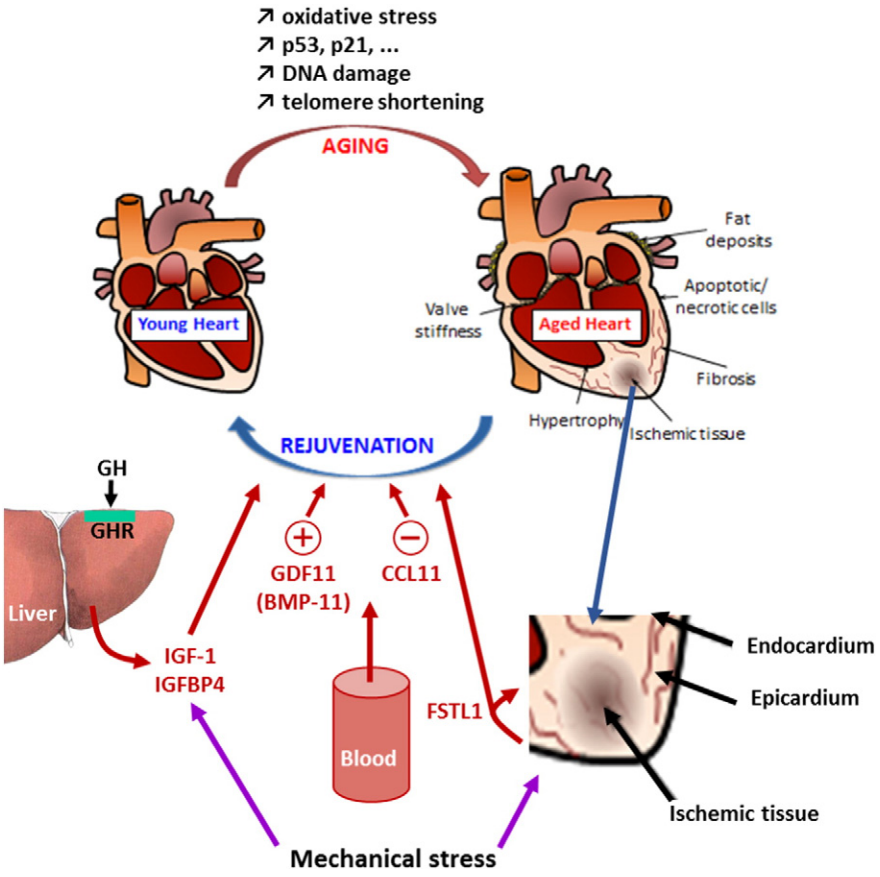

Fig. 1. "Pro-youthful" factors. Biochemical and morphological changes occur during cellular senescence. These include a number of factors such as DNA damage, oxidative stress and telomere shortening, and involve p53-p21. It has been suggested that soluble **"Pro-youthful" factors (GDF11, FSTL1, CCL11, IGF1, IGFBP4) and mechanical stress** present in young or aged blood may be able to improve cardiac rejuvenation.