

# Nutrient signaling and cardiovascular aging

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## Abstract

Aging is a major factor contributing to changes observed in the cardiovascular system in the elderly such as stiffening of the arterial tree and left ventricular diastolic function. These age-related changes in cardiovascular function lower the threshold at which cardiac diseases manifest. Evolutionarily conserved signals triggered by growth and hormones, eg, insulin and insulin-like growth factors, in response to the intake of specific macronutrients (proteins, carbohydrates, or fats), accelerate aging and mortality in animal models and humans. Dietary restriction, a ~25% reduction in calorie intake while maintaining micronutrients, by reducing the levels of aging-associated growth factors and hormones protects against cardiovascular diseases and against the decline in autonomic function. However, the role of nutrients and nutrient-associated signaling pathways in the decline in cardiac function and in the increase in cardiovascular diseases during aging is not completely understood. Here, we review the links between caloric intake, growth/hormonal factors, and intracellular signaling pathways in determining cardiac muscle (dys)function and regeneration during aging. ■ Heart Metab. 2014;63:4–7

**Keywords:** Aging; cardiac hypertrophy; cardiomyocytes; cardiomyopathy; cell signaling; growth factors; heart; laminin; mice models; nutrients.

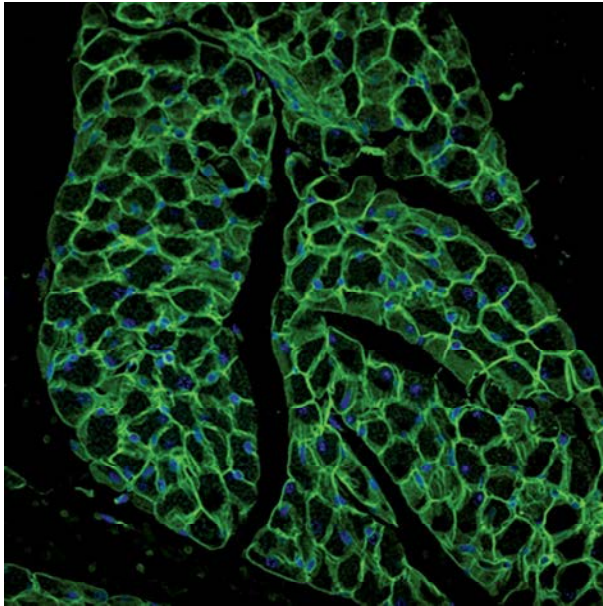
The performance of the heart decreases with age, and this decrement in performance is a major risk factor for cardiovascular disease and mortality in the human population. However, the molecular pathways underlying cardiac aging are just beginning to be understood. In fact, aging results in a progressive functional and structural decline in the heart and arterial system. Age-dependent cardiac and vascular changes include cardiomyopathy,<sup>1</sup> impaired endothelial function and proliferation, increased stiffness of the arteries,<sup>2–4</sup> left ventricular diastolic dysfunction, concentric hypertrophy, decreased systolic reverse,<sup>5,6</sup> and diminished heart rate variability.<sup>7</sup> Moreover, as a consequence of

the aging process, the interaction between the heart and arterial system adapts to preserve ventricle–arterial homeostasis. Hence, the age-associated structural and functional deterioration due to the intrinsic effects of aging on the myocardium together with the compensatory reactive cardiac modifications in response to the progressive increase of systolic load induced by elevated arterial stiffness, can have a detrimental effect on the aged heart. The view of the heart as a terminally differentiated postmitotic organ (*Figure 1*) that is unable to replace its damaged cells is shared by the scientific community and goes back to the 1960s. Recently, a dynamic concept of the heart in which cell

### Abbreviations

**FGF21:** fibroblast growth factor 21; **IGF-1:** insulin growth factor 1; **KO:** knockout; **PPARs:** peroxisome proliferators-activated receptors; **SIRT:** sirtuins

turnover is a crucial component of homeostasis, aging, and disease has been put forward, although this is a matter of much debate.<sup>8,9</sup>



**Fig. 1** Representative microscopic field of the mouse myocardium. The myocardium was stained with an anti-laminin antibody. Nuclei were counterstained in blue. Image taken by A. Planavila and F. Villarroya.

### Nutrient signaling and cardiac function

The prevalence of heart diseases, such as cardiac hypertrophy and/or the progressive development of congestive heart failure, increases with age. Compelling evidence implicates the protein deacetylases, sirtuins (SIRT), to act as metabolic sensors to regulate aging. SIRT proteins appear to link nutrition, caloric restriction, and heart disease.<sup>10,11</sup> The adult myocardium uses either fatty acids or glucose oxidation as its main energy source, providing 65% and 30% of the energy, respectively.<sup>12</sup> However, in contrast with other tissues, the heart is a ‘promiscuous’ substrate consumer. Thus, it adapts its metabolism depending on the type of substrates that are available in order to maintain the constant pump function. The fetal heart, which functions in a relatively hypoxic environment, derives energy from the catabolism of glucose and lactate. Immediately after birth, when the mammalian diet becomes high in fat, the heart switches to fatty

acids for myocardial energy production. Cardiac hypertrophy and the development of heart failure are associated with suppression of fatty acid oxidation and metabolic reversion to increased glucose utilization. This shift in the source of energy from fatty acids to glucose is accompanied by a dramatic decrease in the expression of cardiac genes involved in fatty acid metabolism, which are regulated primarily by the peroxisome proliferator activated receptors (PPARs).<sup>13</sup> Therefore, the heart senses nutrient signals through PPARs, which, in fact, control the genes involved in fatty acid metabolism. Moreover, it has been shown that SIRT1 controls fatty acid metabolism through an interaction with the PPAR $\alpha$  pathway in the heart and prevents the development of cardiac hypertrophy, thereby linking sirtuins, nutrient signaling, and cardiac function.<sup>14</sup> Optimal therapeutic interventions that antagonize aging may reduce the occurrence and mortality of adult heart diseases. Therefore, molecular mechanisms mediating life span extension affect aging of the heart and its resistance to pathological insults. Caloric restriction (25% reduction in caloric intake) increases life span and prevents the development of age-associated changes in several animal models.<sup>15</sup> It has been shown that cardiac-specific overexpression of SIRT1 delayed aging and protected against oxidative stress in the heart.<sup>10,11</sup> Emerging evidence of the involvement of other sirtuins, namely the mitochondrial sirtuins, SIRT3 and SIRT6, reinforces the importance of this family of age-related controllers of heart function in response to nutrients. Modulation of the activity of sirtuins in the heart may represent a novel cardioprotection strategy against aging and certain types of cardiac stress, such as oxidative stress.

### Growth factor signaling and cardiac dysfunction during aging

Among the pathways whose inactivation is believed to mediate part of the protective effects of caloric restriction are the PI3K-AKT, Ras, TOR-S6K pathways, which are regulated by growth factors such as insulin, insulin growth factor 1 (IGF-1), and the fibroblast growth factor (FGF) family.<sup>11</sup> Here, as a proof-of-concept of the chief role of growth factor signaling in aging-dependent cardiac dysfunction, we will summarize the impact of IGF-1 and FGF21 overexpression in the heart. IGF-1 acts as an intermediate of several growth hormone (GH) responses and affects multiple signaling cascades, resulting in a potent proliferative signal that blocks apoptosis and

stimulates growth in many different cells and organs. The IGF-1 gene undergoes complex transcriptional and posttranscriptional regulation, generating isoforms that differ in their cardioprotective, cardiosensitizing, and regenerative effects.<sup>11</sup> In animal models, newly characterized molecular cross-talk with other signaling pathways involved in aging-associated damage and diseases such as SIRT1 have been identified.<sup>11,16</sup> The locally acting mIGF-1 isoform, which contains a Class 1 signal peptide and a C-terminal Ea extension peptide, is highly expressed in neonatal tissues and in the adult liver, but decreases during aging in the heart, where it is expressed only transiently in response to local damage.<sup>11</sup> Mouse genetics have shown that enhancement of the mIGF-1 signaling pathway is highly effective in counteracting tissue decline, possibly through its regenerative properties and its promotion of cell survival and renewal, as demonstrated in senescent skeletal muscle.<sup>11</sup> mIGF-1 overexpression is able to improve heart function after injury induced by ligation of the left coronary artery or cardiotoxins. This restoration of cardiac function in mIGF-1 transgenic mice after myocardial infarction or cardiotoxicity is facilitated by the modulation of inflammatory responses, the secretion of paracrine factors, and by a range of novel systemic effects, which, interestingly, all occur in a SIRT1-dependent manner.<sup>10,17,18</sup> The robust responses achieved by the mIGF-1 isoform suggest a potential mechanistic basis for therapeutic strategies to improve outcomes in age-related heart disease.

FGF21 is a putative mammalian starvation master regulator because it recapitulates the beneficial physiological changes seen in calorie-restricted animals, such as decreased glucose levels, increased insulin sensitivity, and improved lipid profiles. Ectopic overexpression of FGF21 in transgenic mice extends the life span to a similar extent as caloric restriction.<sup>19</sup> FGF21 functions as an endocrine hormone, secreted by the liver, and acts via autocrine mechanisms. Despite its role in nutrient metabolism and aging, there was, until recently, no knowledge about the function of FGF21 in the heart. FGF21 knockout (KO) mice display an increased relative heart weight and develop cardiac dysfunction in response to isoproterenol infusion, indicating eccentric hypertrophy development.<sup>20</sup> This phenotype is accompanied by the induction of cardiac hypertrophy markers and proinflammatory pathways as well as by blocking fatty acid oxidation. These deleterious effects could be reversed by FGF21 treatment

*in vitro* and *in vivo*.<sup>20</sup> It was also found that FGF21 is secreted by cardiomyocytes, protecting them against hypertrophic insults and is under the transcriptional control of SIRT1.<sup>20</sup> Thus, the heart appears to be a target of systemic and locally generated FGF21, which exerts a protective action.

## Conclusions

Nutrient signaling has a major impact on the way in which the heart ages. Multiple molecular actors (eg, SIRT1, PPAR $\alpha$ ) sense the type of nutrients and their availability, and subsequent responsive effectors (eg, FGF21, mIGF-1) have recently been identified as mediators affecting cardiac homeostasis and aging. These molecules constitute emerging potential targets, which are currently being targeted by several biotech and pharmaceutical companies through nutritional or pharmacological intervention. The ultimate aim of these approaches is to slow cardiac aging and improve human health. ■

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