Circulation Research

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Targeting Age-Related Pathways in Heart Failure

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Originally published 13 Feb 2020 | https://doi.org/10.1161/CIRCRESAHA.119.315889 | Circulation Research. 2020;126:533–551

Abstract

During aging, deterioration in cardiac structure and function leads to increased susceptibility to heart failure. The need for interventions to combat this age-related cardiac decline is becoming increasingly urgent as the elderly population continues to grow. Our understanding of cardiac aging, and aging in general, is limited. However, recent studies of age-related decline and its prevention through interventions like exercise have revealed novel pathological and cardioprotective pathways. In this review, we summarize recent findings concerning the molecular mechanisms of age-related heart failure and highlight exercise as a valuable experimental platform for the discovery of much-needed novel therapeutic targets in this chronic disease.

A major risk factor for heart failure (HF) and overall cardiovascular disease is age. Approximately 1% of individuals aged over 50 years are affected by HF, and this number doubles with each decade of life,[1] making HF the major cause of mortality in the elderly.[2] This is a matter of increasing concern in the United States, where the population aged 65 and over increased from 40 million in 2007 to 51 million in 2017 and is projected to reach 95 million in 2060.[2] Given this dramatic growth in the aged population, age-related HF represents one of the greatest challenges confronting global health care today.

Undoubtedly, an important part of the explanation for increased HF with increasing age lies in greater time for exposure to injurious stimuli, such as hypertension, metabolic stress, or ischemic injury. The heart's limited endogenous capacity for repair or regeneration implies that heart function

at any specific time reflects the cumulative burden of prior insults. Thus, it makes sense that older patients would have a greater impairment of cardiac reserves and elevated HF risk.

However, even in the absence of overt injury, structural and functional changes occur in the heart as it ages, which seem to contribute to the increased susceptibility to HF in older adults.[3,4] Normal aging is generally accompanied by a thickening and stiffening of the left ventricular walls, particularly the interventricular septum, an increase in left atrial dilation, and an overall increase in cardiac fibrosis.[5] Although resting cardiac function is not markedly impaired in the aged heart, both subclinical diastolic and systolic dysfunction are present.[6,7] However, the most notable functional change observed in the aged heart is the progressive decline in cardiac reserve, which not only contributes to the age-related decline in exercise capacity[8–10] but interestingly is also a major pathophysiological feature of HF with preserved ejection fraction, the most common form of HF in older adults.[11,12]

Although aging has long been considered an unmodifiable consequence of passage of time (chronological aging),[13] the observation that the rate of age-related deterioration (biological aging) differs substantially across species, individuals, and organs,[14] has led to a more nuanced understanding of biological aging as mutable and potentially amenable to manipulation. Thus, we and others have proposed that understanding the underlying biology of cardiac aging could potentially lead to the discovery of novel therapeutic targets for age-related cardiovascular diseases. Indeed, accumulating evidence suggests that it may be possible to target age-related pathways to counteract and even reverse some of the structural and functional changes that drive age-related HF.[15,16] Epidemiological data support the idea that age-related cardiac decline can also be modulated by lifestyle factors, such as diet and exercise, and experimental studies in animals suggest that behavioral, pharmacological, and genetic interventions can slow or accelerate age-related changes and the development of HF.[15–17] These studies suggest protective physiological pathways can counteract the effects of aging and prolong cardiac health.

One of the most striking behavioral modulators of cardiac aging is physical activity, which seems to prevent or mitigate cardiovascular disease in older adults and the elderly.[18–21] There is growing evidence that exercise is associated with lower HF risk and attenuation of age-associated intermediate phenotypes such as cellular senescence, telomere length, and cell survival signaling.[22–25] Although much of the human data suggesting that exercise can attenuate cardiac aging is cross-sectional and observational in nature, multiple prospective studies suggest exercise is capable of mitigating or even partially reversing at least some of the cardiac aging phenotypes associated with HF.[26–29] Thus, investigation into the physiological effects of exercise has the potential to complement therapeutic insights derived from investigation of the mechanisms of cardiac decline. Deciphering the mechanisms underlying the beneficial effects of exercise on cardiac aging could be helpful in the development of therapeutic interventions to curtail or even reverse age-related functional decline in the heart.

This review summarizes the pathophysiological changes in the aging heart, recent advances in our understanding of the underlying molecular mechanisms, and the potential therapeutic implications. The cardioprotective effects of exercise will also be discussed, with emphasis on the potential value

of exercise as an experimental paradigm for discovering cardioprotective pathways that can be exploited for prevention and treatment of aged-related HF.

Pathophysiological Processes Driving Cardiac Aging

Both systemic and cardiac-specific changes in cellular physiology likely contribute to age-related alterations in heart structure and function (Figure 1). Although, there is an increase in left ventricular wall thickness with age, this reflects an increase in size, and not number, of cardiomyocytes. In fact, aging is associated with a decrease in regenerative capacity, which may be compounded by an increase in cell death. This in turn may be related to an age-dependent decline in mitochondrial function and accumulation of senescent cells. At the same time, elevated inflammatory activity likely drives the increase in myocardial fibrosis with age. The following sections will discuss new insights into the cellular processes that contribute to cardiac deterioration with aging. While some of these are systemic processes that affect a range of organ systems, we will concentrate on the cardiac manifestations of these systemic processes.

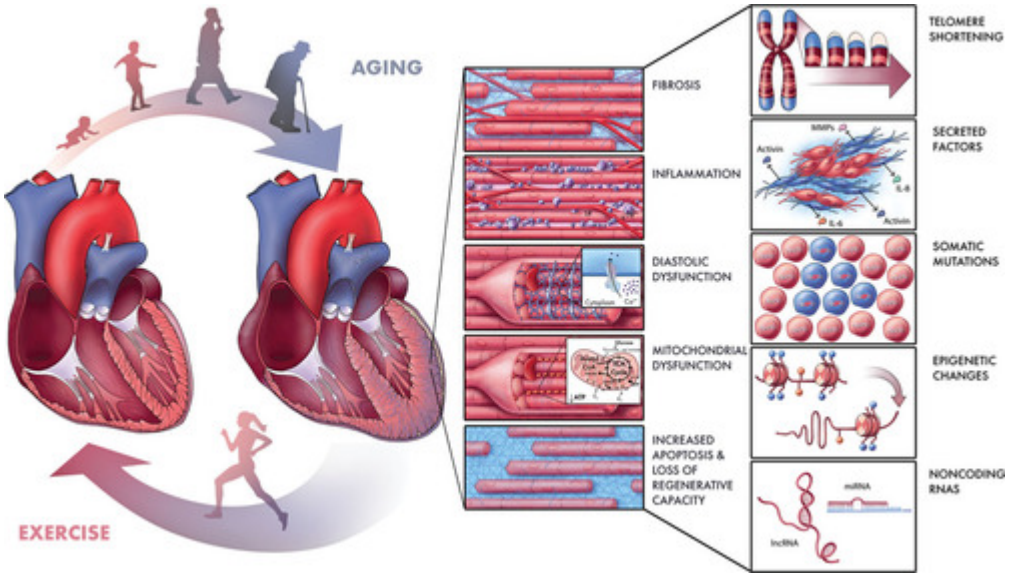

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Figure 1. Schematic of processes and pathways contributing to age-related cardiac disease. As we age, multiple processes likely contribute to cardiac dysfunction, including fibrosis, inflammation, mechanical stiffening and diastolic dysfunction, mitochondrial dysfunction, and a growing imbalance between loss and birth of cardiomyocytes (**center**). These processes are driven by molecular mechanisms (some of which are depicted at **right**) such as telomere shortening, senescence-associated secreted factors, accumulation of somatic mutations, epigenetic changes, and alterations in noncoding RNAs regulating gene expression. Some of these may represent targets for new therapeutic strategies to mitigate both age-related and other forms of heart failure. Since exercise mitigates many effects of aging (**left, bottom**), it may provide a useful tool by enabling us to prioritize candidate cardiac pathways exacerbated by aging and mitigated by exercise. Illustration by Nicole Wolf, MS, ©2019. Printed with permission.

Cardiomyocyte Death and Regeneration

While neonatal mammals can regenerate myocardial tissue following damage, the adult mammalian heart does not regenerate after injury and has traditionally been understood to lack the capacity for cardiomyogenesis.[30] However, studies in mice and humans have revealed that adult cardiomyocytes renew at a rate of 0.5% to 2% per year, indicating that the adult heart has some, albeit limited, endogenous regenerative potential.[31–33] This renewal was found to decline with age implying a diminished ability to compensate for cardiomyocyte loss.[31–33] The consequences of this decline in regenerative potential could be serious as even very low levels of experimentally induced cardiomyocyte loss have been shown to result in cardiomyopathy and death.[34] Elevated rates of cardiomyocyte apoptosis may pose an additional challenge to cardiac homeostasis,[35] although the evidence for this is mixed, with recent human studies failing to detect a correlation.[36] Given the aging heart's declining regenerative potential, therapeutic interventions to promote endogenous regenerative capacity may be able to favorably tilt the homeostatic balance and improve performance in aging hearts.

Adult cardiomyocyte regeneration has been the subject of intense investigation and debate. Although there have been reports of cardiomyogenesis from bone marrow-derived and tissue-resident putative cardiac progenitors, many of the original reports have been discredited and some retracted.[37–39] In particular, cell fate-mapping studies have demonstrated that cells expressing the hematopoietic stem cell marker c-kit, once proposed as resident cardiac stem cells, give rise to remarkably few cardiomyocytes and do not appear to contribute to myocardial regeneration in a meaningful way.[40–43] Even these small numbers of labeled cardiomyocytes were further determined to be present independent of the ability of c-kit+ cell progeny to adopt a cardiomyocyte fate, reflecting the fusion of preexisting cardiomyocytes with labeled leukocytes, but not cardiomyogenesis.[44] The consensus that has emerged from these studies is that cardiomyogenesis in the adult heart results from division of preexisting cardiomyocytes and not from differentiation of stem cells.[31,37,45,46] Investigation into the cardiomyocyte populations mediating endogenous cardiomyocyte renewal and the factors regulating their proliferative activity over time will likely lead to new therapeutic targets relevant to aging. Indeed, several molecular mechanisms implicated in regulation of cardiomyocyte proliferation are now being investigated as potential therapeutic targets, some of which will be discussed in later sections. Interestingly, mechanical strain induced by hemodynamic forces has been shown to modulate the activity of yes-associated protein and transcriptional co-activator with PDZ-binding motif (TAZ), transcriptional co-activators implicated in proliferation, with implications for the development of atherosclerosis.[47] The potential impact of this mechanosignaling pathway in the age-related decline in cardiomyocyte proliferation is an intriguing topic for future investigation.

Mitochondrial Dysfunction

Mitochondria are not only the primary source of energy in the heart, in the form of ATP, but are also key regulators of cardiomyocyte survival. Mitochondrial dysfunction is a core feature of cardiac aging and is at the crossroads of multiple key pathways related to senescence.[48] Cardiac aging is accompanied by a general decline in mitochondrial function and the resulting increase in reactive oxygen species (ROS) production appears to be a major contributing factor in HF (Figure 1).

Recent studies of mitochondrial dysfunction in the aging heart are consistent with the oxidative stress hypothesis of aging, which posits that oxidative stress induced by excessive mitochondrial ROS generation damages mitochondrial DNA (mtDNA) and redox-sensitive mitochondrial proteins, leading to mitochondrial dysfunction and further increasing ROS production. This self-perpetuating cycle of oxidative damage is hypothesized to result in cellular and organ functional decline, limiting lifespan and healthspan. The direct role of mitochondrial oxidative damage in cardiac aging has been demonstrated using mitochondria-specific overexpression of human catalase, an antioxidant enzyme, in mice (mCAT). mCAT mice exhibited prolonged lifespan and displayed attenuated cardiac aging phenotypes including reduced cardiac hypertrophy, improved diastolic function, and improved myocardial performance. On the molecular level, these improvements were accompanied by reduced mitochondrial protein oxidative damage, mtDNA mutations, and deletion frequencies.[49,50]

Mitochondrial dysfunction is also sufficient to induce deterioration of cardiac function. In mice, knock-out of PGC-1α (proliferator-activated receptor γ coactivator 1α), a key regulator of mitochondrial biogenesis, resulted in suppression of mitochondrial gene expression within the heart and development of cardiac dysfunction at 7 to 8 months old.[51] Notably, the same PGC-1α knockout mouse line exhibited accelerated cardiac dysfunction when subjected to transverse aortic constriction (TAC).[52] This indicates a protective role of PGC-1α in cardiac function and highlights the increased vulnerability of the heart to insult once mitochondrial biogenesis is compromised.

Taken together, these findings suggest that mitochondrial dysfunction and the resulting ROS generation could contribute to age-associated cardiac dysfunction. Consequently, mitochondrial-targeted antioxidant therapies may have therapeutic value. However, the effects of mitochondrial ROS seem to be context-dependent, limiting the therapeutic potential of antioxidant therapy. In healthy young men, a 4-week intervention of physical exercise improved insulin sensitivity and induced endogenous ROS defenses as well as PGC-1α, but counterintuitively, these beneficial effects were blocked by antioxidant supplementation, demonstrating that under some conditions ROS production can be beneficial perhaps through induction of adaptive responses that mediate chronic benefit.[53] Indeed, small increases in mitochondrial ROS have been shown to increase cellular defenses[54] and in some cases extend lifespan.[55] Further evidence for the context-dependent effects of mitochondrial manipulations comes from experiments showing that upregulating mitochondrial biogenesis through cardiac-specific overexpression of PGC-1α has protective effects in young mice but accelerates cardiac aging in old mice.[56] Perhaps because of these complexities, multiple attempts to exploit antioxidant treatments for a range of cardiovascular diseases have thus far failed to demonstrate clinical benefits.

Recent research has suggested other possible approaches to targeting mitochondrial dysfunction and/or metabolic remodeling in heart failure. For example, complementary metabolomic and proteomic analyses in advanced human heart failure and animal models, respectively, suggest a reduction in fatty acid oxidation and an increased use of ketones and ketone bodies as fuel in heart failure.[57,58] While the pathophysiological consequences of this shift in substrate utilization remain incompletely understood,[59,60] prior work in murine models suggests ketone metabolism may be important in mitigating cardiac dysfunction.[61] In these studies, lineage-specific deletion of SCOT (succinyl-CoA:3-oxoacid CoA transferase), the enzyme mediating terminal oxidation of ketone bodies, in cardiomyocytes accelerated adverse remodeling and increased ROS production after

TAC.[61] Collectively, these studies raise the intriguing hypothesis that altering substrate availability through dietary interventions in patients could improve energy homeostasis in the failing heart.

Another approach to metabolic remodeling has focused on the NADH/$NAD^{(+)}$ ratio, as a critical determinant of electron transport, oxidative stress, and intracellular signaling.[62] In both experimental pathological hypertrophy and failing human hearts, NADH/$NAD^{(+)}$ ratios were increased.[62] Experimental models suggest $NAD^{(+)}$ may exert its functional effects in part through mitochondrial $NAD^{(+)}$-dependent deacetylases Sirtuin 3 (Sirt3) and Sirt4, which regulate cell survival and the mitochondrial permeability transition pore, important determinants of cardiomyocyte survival and function.[63,64] Importantly, normalizing NADH/$NAD^{(+)}$ ratios through either genetic or pharmacological interventions had important metabolic and functional benefits in murine models.[62] Since NADH/$NAD^{(+)}$ ratios can be modified through dietary nicotinamide riboside supplementation,[65] translation of preclinical findings to clinical trials to test this hypothesis in humans seems feasible.

Cellular Senescence and Inflammation

Cellular senescence is a state triggered by telomere attrition due to repeated replication,[66] or by other forms of cellular stress,[67] in which cells undergo permanent cell cycle arrest, functional decline, and take on a proinflammatory phenotype. Senescent cells progressively accumulate in tissues during life and confer deleterious paracrine effects on neighboring cells and systemic effects on other tissues/organs. These effects are mediated by secretion of proinflammatory cytokines, proteases, and insoluble extracellular matrix components, known as the senescence-associated secretory phenotype (SASP).[67] SASP signaling promotes inflammation as well as cell death and senescence in other cells, and growing evidence suggests that senescent cells contribute to cardiac remodeling and dysfunction during aging (Figure 1).[68,69]

Consistent with a role for cellular senescence in cardiac aging, there is evidence that senescent cells in the heart contribute to functional decline including decreased contractility and impaired mitochondrial function.[70,71] Furthermore, promoting senescence can accelerate the development of cardiac aging phenotypes. Cardiomyocyte death, hypertrophy, and HF were increased in mice with accelerated senescence resulting from a deficiency of telomerase, an enzyme that prevents senescence by combating the loss of telomeres during replication.[72] Similarly, in senescence-accelerated mice fed a high-fat, high-salt diet for 24 weeks, senescent endothelial cells were increased in the heart and this was associated with diastolic dysfunction and left ventricular hypertrophy,[73] suggesting a role for endothelial cell senescence in cardiac dysfunction in aged hearts.

Complementary findings suggest that reducing senescence can have cardioprotective effects. Elimination of cells expressing the senescence marker $p16^{Ink4a}$ inhibited aging phenotypes in the heart (eg, reduced cardiomyocytes size, preserved cardioprotective K_{ATP} channels, reduced cardiac fibrosis) and extended lifespan.[74] Similarly, clearance of $p16^{Ink4a}$-positive senescent cells in aged mice reduced cardiac hypertrophy and fibrosis and induced cardiomyocyte proliferation manifested as elevated EdU and Ki-67 positive cardiomyocytes.[75,76]

The beneficial effects of eliminating senescent cells suggest that these cells may be actively suppressing the function of otherwise healthy heart cells. In line with this, Anderson et al showed that during aging, human and murine cardiomyocytes exhibited a senescent-like phenotype, including secretion of nontypical SASP signals (Edn3 [endothelin 3]; Tgfβ2 [transforming growth factor β 2]; and GDF15 [growth differentiation factor-15]), and incubation of neonatal fibroblasts with conditioned culture medium from cardiomyocytes isolated from old mice resulted in fibroblast activation and senescence. This implies an interaction between senescent cardiomyocytes and fibroblasts during cardiac aging and dysfunction.[70]

These observations support a model in which, during aging, cellular stress induced by oxidative stress and inflammation leads to cardiomyocyte senescence. These senescent cardiomyocytes undergo functional decline, including decreased contractility, increased cell size, and mitochondrial dysfunction, negatively affecting cardiac performance. As aging progresses, senescent cardiomyocytes accumulate, interfere with intercellular communication, compromise cardiac function, and further induce chronic inflammation, resulting in cell death, and eventual cardiac dysfunction.[77]

Our current understanding of what drives senescence may not be sufficient to enable therapeutic strategies to prevent it. However, it may be possible to intervene further downstream. The dramatic beneficial effects seen with genetic elimination of senescent cells, described above, have prompted efforts to develop senolytics, small molecules capable of reducing or eradicating these cells.[78–81] While these approaches are novel and exciting, the clinical benefits will obviously need to be demonstrated in realistic clinical contexts where multiple cardiometabolic comorbidities coexist. A complementary strategy would be to target the downstream effectors mediating the adverse consequences of senescent cells. As noted, secreted proteins likely contribute to these adverse effects in many settings and in cases where the principal culprits can be identified, a variety of strategies could be used to mitigate the effects of these secreted proteins. Activin and the closely related family of growth/differentiation factors are senescence-associated secreted proteins that provide one example of this strategy. As detailed below, we recently described an increase in activin signaling in age-related heart failure that could be dramatically mitigated by either antibodies directed to the dominant activin receptors or a soluble-receptor acting as a ligand trap.[15]

Another consideration is that, although the findings described strongly indicate a mechanistic role of cellular senescence in the development of cardiac disease during aging, cellular senescence in specific cell lineages and conditions may actually be beneficial to the heart. In neonatal mice subjected to apical resection, a model for cardiac regeneration, senescent cells were identified in the peri-resected regions at several time points after apical resection but disappeared when the hearts were fully restored. Elimination of the senescent fibroblasts by fibroblast-targeted genetic deletion of Trp53 (tumor protein 53) inhibited regeneration after apical resection, indicating that senescent fibroblasts promote neonatal heart regeneration.[82] The regenerative activity of senescent fibroblasts is not limited to the neonatal heart. Meyer et al found that senescent fibroblasts accumulated in fibrotic regions of hearts subjected to TAC, and inactivation of cardiac senescent cells by double knockout of Trp53 and cyclin-dependent kinase inhibitor 2a genes further increased fibrosis and fibroblast proliferation leading to severe cardiac dysfunction. In contrast, activation of premature senescence by cardiac-specific overexpression of cellular communication network factor

1 reduced perivascular fibrosis after TAC and improved cardiac function.[75] These results indicate that, in contrast to the deleterious effects of senescence in the aging heart, fibroblast senescence in the apically resected neonatal heart and in TAC is actually beneficial. Thus, while there is strong evidence implicating cellular senescence in age-related cardiac deterioration, the effect of senescence on cardiac regeneration and disease may be complex and context-specific, perhaps varying depending on cell type, age, health, and other factors.

Exercise Counteracts Age-Related Pathophysiological Changes

Exercise is associated with improved cardiac function and may even partially reverse pathological cardiac remodeling in the elderly (Figure 1).[21] In one study, for instance, 3 to 6 months' aerobic exercise training improved peak oxygen consumption and exercise efficiency in elderly subjects (65–79 years).[83] While these benefits likely derive in part from peripheral conditioning, there is also evidence of cardiac remodeling through exercise training in the elderly. For example, 1 year of progressive and vigorous endurance exercise training in previously inactive individuals over age 65 induced physiological left ventricular remodeling, increasing left ventricular mass without affecting left ventricular mass-volume ratio.[26] These cardiovascular benefits have been attributed, in part, to antioxidant effects. Consistent with this, a 6-month exercise training regimen increased the activity of ROS scavenging enzymes in the skeletal muscle of HF patients relative to sedentary controls in a randomized controlled study.[84]

In line with its reported therapeutic effects in humans, experiments in animal models show that exercise has the potential to counteract many pathological processes thought to contribute to age-related HF, including senescence, inflammation, mitochondrial dysfunction, and declining cardiomyocyte regeneration (Figure 3). In mice, voluntary running for 21 days downregulated senescence gene markers in the heart including cell-cycle Chk2 (checkpoint kinase 2), p53, and p16, and upregulated cardiac telomerase activity by 2-fold.[22,23] These effects were abolished in TERT (telomerase reverse transcriptase) deficiency mice, suggesting an antisenescent effect of exercise on the heart. In line with this, exercise reduced age-related cardiac inflammation and fibrosis,[85] increased left ventricular mitochondrial number and volume[86] and induced expression of genes involved in mitochondrial biogenesis and antioxidant response.[87,88] Exercise also reduced cardiomyocyte apoptosis in aging animals[89] and in both young and old animals subjected to ischemia-reperfusion injury.[90] Furthermore, we demonstrated that exercise can promote cardiomyogenesis in young adult mice. We found that 2 weeks of swimming induced cell proliferation markers (eg, BrdU, phosphorylated histone H3, Aurora B kinase, etc) in young (12 weeks old) adult mouse hearts compared with sedentary controls.[91] Exercise also induced cell proliferation in adult cardiomyocytes, measured with multiphoton ionization mass spectrometry[92] based imaging using the stable isotope tracer 15N-thymidine,[93] and expanded the proliferative zone after myocardial ischemia reperfusion injury.[94]

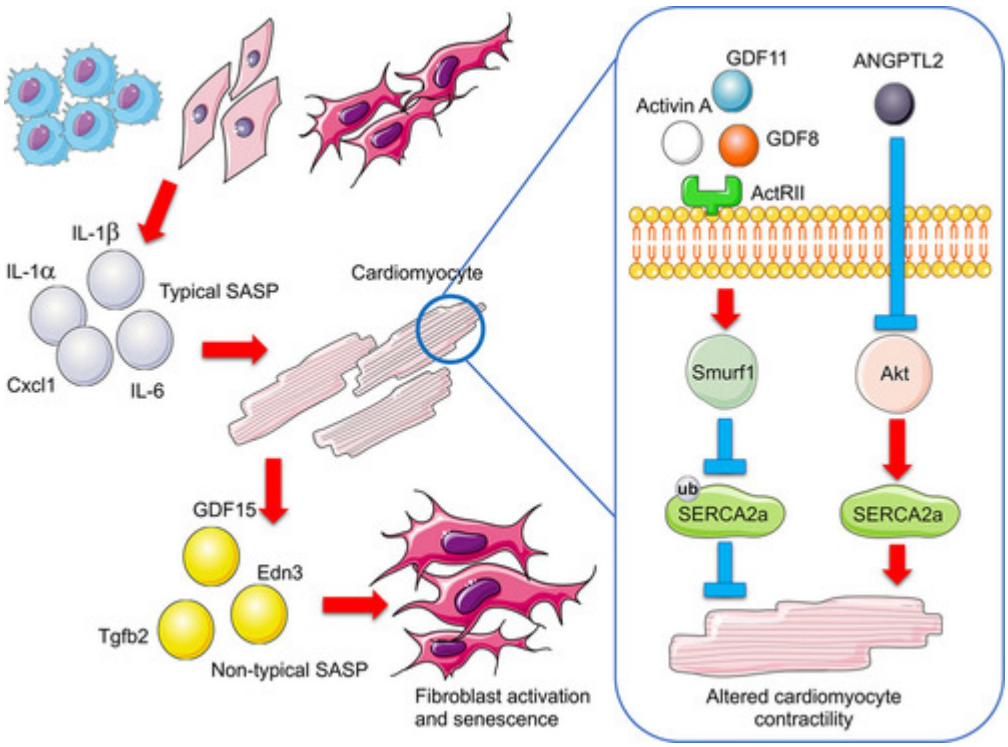

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Figure 2. Schematic of secreted factors contributing to age-related cardiac disease. Accumulating senescent cells adversely affect other cells (eg, cardiomyocytes and fibroblasts) through a senescence-associated secretory phenotype (SASP) which promotes inflammation, cell death and senescence. While systemic increases in senescent cells lead to increasing secretion of typical SASP proteins with age (eg, IL-1α, IL-1β, IL-6, Cxcl1), senescent cardiomyocytes secrete nontypical SASP (eg, GDF15, Tgfb2, and Edn3). Circulating activin and ANGPTL2 are also increased with age. Elevated activin, through binding to its receptor ActRIIb, triggers Smurf1-mediated ubiquitination and subsequent degradation of SERCA2a, while increased ANGPTL2 inactives Akt and thereby degrades SERCA2a. All of these processes contribute to cardiac aging and cardiac dysfunction.

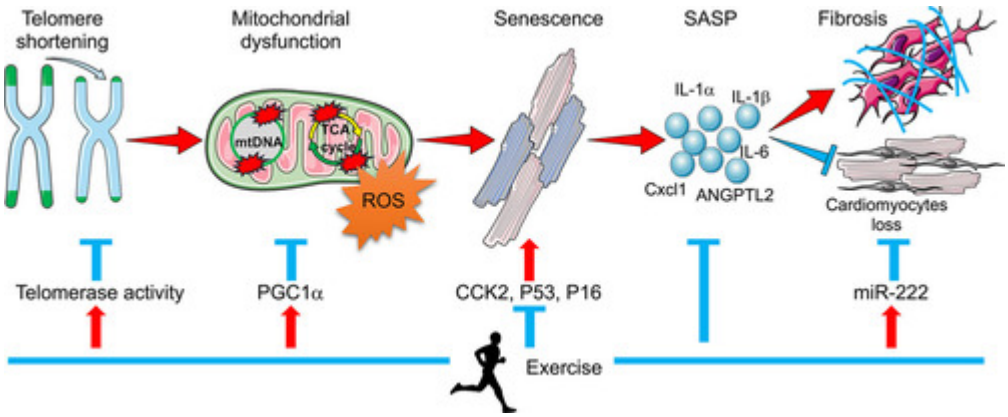

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Figure 3. Schematic of telomere shortening contributing to age-related cardiac disease. Telomeres shorten with cell division and aging is associated with reduced telomere length. Mitochondria are particularly vulnerable. Critically short telomeres lead to mitochondrial DNA damage, ultimately disrupting mitochondrial function and inducing senescence. Through secretion of senescence-associated secretory phenotype (SASP) factors, senescent cells induce fibrosis and promote cardiomyocyte loss, eventually leading to cardiac dysfunction. Exercise has been shown to protect the heart against cardiac aging and cardiac dysfunction by modulating each step in this sequence.

Interestingly, the cardiac response to exercise and pathological growth stimuli appear to involve distinct molecular pathways.[91] Thus, the study of exercise models is likely to yield different candidates for intervention than those identified through studies of disease models. Moreover, with remarkable consistency, pathways identified as functionally important in the cardiac response to exercise also protect the heart against pathological stress.[21,95] Examples include PI3-kinase,[96,97] Akt1,[98–100] eNOS,[101] PGC1α,[52,102] C/EBPβ,[91] CITED4,[103] and miR-222.[94] Thus, we suggest that exercise models provide platforms for discovery of new therapeutic target candidates likely to complement those gleaned from disease models. Below, we will discuss recent developments in our understanding of the molecular mechanisms underlying cardiac aging and the cardioprotective effects of exercise.

Molecular Mechanisms of Heart Failure During Aging

Our understanding of the fundamental mechanisms underlying cardiac aging, and aging in general, is limited. However, recent studies have begun to elucidate the molecular basis for cardiac decline as well as potentially protective molecular pathways. Molecular mechanisms underlying cardiac aging are multifactorial and interactive. Here, we will discuss important findings in recent years concerning the roles of telomere shortening and damage, circulating factors, epigenetic alterations, noncoding RNAs, and somatic mutations in cardiac aging, and insights into the protective effects of exercise (Figure 1).

Telomere Shortening and Damage

Telomeres are DNA repeats serving as protective caps at the end of chromosomes. Telomeric DNA is bound by the shelterin protein complex, which is essential for telomere structure maintenance. Telomeres are synthesized by telomerase, an enzyme composed of an RNA component (TERC) and a catalytic subunit (TERT).[104] Telomeres shorten with cell division and aging, or in response to stressors such as inflammation and oxidative stress. Critically short telomeres destabilize the shelterin complex, thereby disrupting the telomeric DNA structure, leading to DNA damage, cell cycle arrest, cellular senescence, and cell death.[105]

Telomere length is perhaps the best-known cellular marker of aging. Although rates of cardiomyocyte division are extremely low in adults,[33] resulting in minimal end-replication-associated telomere shortening, animal studies have consistently pointed to a key role for telomere shortening in cardiac aging and disease.[106] The wild mouse strain *Mus musculus castaneus* (CAST), which

bears short telomeres from birth, shows a premature cardiac aging phenotype.[107] Similarly, Wong et al[108] showed that breeding multiple generations of TERC-deficient mice induced critical telomere shortening, leading to cardiac dysfunction and myocardial remodeling, similar to the effects of aging. In cardiomyocytes from TERC-deficient mice, Aix et al[109] showed that critically short telomeres marked by γH2AX, a DNA double strand break biomarker, induced p21-dependent cardiomyocyte cell cycle arrest, consistent with senescence and an aging and diseased cardiac profile. In addition, accelerated telomere shortening has been linked to several hereditary cardiomyopathies in humans, including Duchenne muscular dystrophy,[110] with animal models supporting a causal relationship.[111] Together, these results suggest that accelerated telomere shortening phenocopies the effects of aging on the heart.

Conversely, slowing telomere shortening can protect the heart against pathological stress. Biomechanical stress induced by partial aortic constriction in mice caused reduction in TRF2 (telomeric repeat-binding factor 2), one of the shelterin proteins, leading to activation of the DNA damage response protein Chk2, a reduction in telomere length and cardiomyocyte apoptosis, and these changes were attenuated by cardiac-specific overexpression of TERT or overexpression of TRF2.[112] Cardiac-specific overexpression of telomerase also decreased cardiomyocyte apoptosis during myocardial ischemia reperfusion in vivo or serum-free insulin-free challenge in vitro.[113] Telomere shortening may affect the heart in part by triggering mitochondrial dysfunction. In the third generation $TERC^{-/-}$ telomerase-deficient premature aging mouse model, accelerated cardiac aging is associated with p53 mediated suppression of PGC-1α, leading to mitochondrial dysfunction. Furthermore, cardiac-specific overexpresssion of PGC-1α in $TERC^{-/-}$ mice partially rescued cardiac function, delayed the onset of age-related cardiac symptoms and extend healthspan.[56] It is worth noting, however, that the value of TERC deficient mice as a model for telomere-associated cardiac aging has been questioned as the degree of telomere shortening in late-generation TERC mice far exceeds the shortening experienced during normal aging.[114] Although there are some caveats to consider, overall results from animal models point to a critical role for telomere length in cardiac cells in mitochondrial function, cardiac aging and HF.

The role of telomere shortening in human cardiac aging and HF, however, is controversial. Terai et al reported that human myocardial telomere length is reduced at a rate of 20 base pairs per year.[115] Compared with cardiac tissues from age- and sex- matched normal or hypertrophic obstructive cardiomyopathy patients without pump failure, cardiac tissues from end-stage HF patients showed shorter telomeres and less TRF2, associated with increased cardiac apoptosis.[112] Similar results were observed in cardiac tissue from end-stage genetic hypertrophic cardiomyopathy and dilated cardiomyopathy patients as well as cardiomyocytes derived from patient-derived induced pluripotent stem cells.[110] These results were confirmed by a recent study showing that, compared with nonfailing controls, HF patients exhibited shorter telomeres specifically in cardiomyocytes but not in cardiac smooth muscle cells from the same hearts.[116] Further, this telomere shortening in HF patients was associated with extensive DNA damage in cardiomyocytes.[116] However, the authors did not observe any difference in cardiomyocyte telomere length between young and old nonfailing controls.[116] These results not only highlight the important role of telomere length in HF but also raise the possibility that telomere shortening does not reflect normal (physiological) cardiac aging. Indeed, most recently, Anderson et al demonstrated that in response to oxidative stress induced by mitochondrial dysfunction during cardiac aging, persistent telomere-associated foci, which contain

DNA damage response proteins and trigger cellular senescence and cell cycle arrest, increased in cardiomyocytes but not in other cell types. This suggests telomere damage in cardiomyocytes occurs independently of telomere length during cardiac aging.[70]

Secreted Factors

Given the progressive functional decline in multiple organ systems seen with aging, it has long been hypothesized that secreted or circulating factors might contribute to the systemic phenotypes seen with aging. The role of pro-inflammatory SASP factors, such as IL-1α, IL-1β, IL-6, Cxcl1, have been extensively studied in the context of chronic systemic inflammation leading to HF, but an increasing number of secreted proteins or RNAs other than traditional SASP factors are now also being found to contribute to the development of aging-related disease (Figure 2).[117] An interesting experimental approach to explore the role of circulating factors in aging phenotypes has been the use of the heterochronic parabiosis model, in which animals of different chronological ages are surgically sewn together to develop a shared circulatory system.[118] Indeed, a recent series of studies utilizing this approach in mice found that introducing youthful blood into the circulation of old animals improved age-related neurological, skeletal muscle, and cardiac phenotypes.[119–121] Aptamer-based proteomic analyses of plasma samples from these mice identified 13 differentially expressed proteins, of which circulating levels of growth differentiation factor-11 (GDF11), a secreted member of the TGFβ superfamily, was reported to be significantly lower in aged mice. Subsequent experiments suggested that increasing circulating levels of GDF11 was sufficient to improve neurogenesis, skeletal muscle regeneration, cardiac hypertrophy regression, and overall fitness in old mice, suggesting the exciting possibility that an age-related decline in a secretory factor like GDF11 might be causal in the systemic functional decline seen in aging.

Numerous follow-up studies, however, have questioned some of these results. More extensive validation of the GDF11 aptamer used in the proteomics analyses revealed that it recognizes not only GDF11, but also the closely homologous protein GDF8 (also known as myostatin), which is likely responsible for the decrease reported in the initial studies.[122] Of note, myostatin knockout mice have better preservation of cardiac function and less cardiac fibrosis as they age, arguing against an age-related reduction in myostatin being detrimental.[123] Interestingly, myostatin is a catabolic protein best known for inducing muscle atrophy and dysfunction, and subsequent work investigating the role of GDF11 overexpression in aged animals demonstrated that both GDF11 and myostatin have similar effects in the skeletal muscle and the heart.[15,124,125] This has raised a number of important questions, including whether this secretory pathway changes with age, and if so, what its functional effects are in aged cardiac and skeletal muscle. Most recently, our group conducted an extensive investigation of this pathway in humans and animal models of aging and HF.[15] We confirmed that circulating GDF8 levels indeed decline with age. However, we found that overall systemic activation of this secreted pathway is actually upregulated in aging and HF, and that its activation appears to be largely driven by an age-related increase in secreted activin, another TGFβ family member that binds the same receptors as GDF8 and GDF11. We further showed that activation of the ActRIIb receptor downstream of activin triggers Smurf1-mediated ubiquitination and subsequent degradation of the SERCA2a, a Ca^{2+} ATPase critical for normal cardiomyocyte contractility (Figure 2). Importantly, targeted inhibition of ActRIIb receptor signaling improved the

function and adverse remodeling of aged or failing hearts, confirming that these secreted factors likely play important roles in cardiac aging and HF.

ANGPTL2 (angiopoietin-like protein 2) is a glycoprotein that has recently been shown to be secreted by cardiomyocytes and adipocytes and to play a role in age-related HF in animal models. Cardiac ANGPTL2 is increased in mice subjected to TAC, angiotensin II-induced HF, and in HF patients. ANGPTL2 is also increased in hearts from aged mice compared with young mice,[126] and in senescent fibroblasts from patients with adult progeria Werner syndrome.[127] Overexpression of ANGPTL2 in the mouse heart induced inactivation of Akt and sarcoplasmic reticulum Ca^{2+}-ATPase signaling, leading to cardiac dysfunction, while knockdown of ANGPTL2 protected the heart against HF.[126] Interestingly, the same group further showed that, while circulating ANGPTL2 was increased both in dilated cardiomyopathy patients and in mice subjected to TAC-induced HF, experimentally increasing circulating ANGPTL2 did not induce cardiac dysfunction. Thus, cardiomyocyte-secreted ANGPTL2 may require other signaling mechanism to induce HF or could work through an autocrine/paracrine signaling mechanism not recapitulated with ectopic expression.[128] Interestingly, ANGPTL2 was decreased in exercised hearts,[126] indicating that exercise may protect against HF in part through lowering ANGPTL2 (Figure 3).

In nonpurified cardiomyocytes isolated from old mice compared with those from young mice, significant differences in gene expression of traditional SASP components (eg, IL-6 and Cxcl1) were observed. However, such differences in SASP were not observed in purified cardiomyocytes isolated from old and young mice, indicating that traditional SASP may be secreted from noncardiomyocytes.[70] Interestingly, in the purified cardiomyocytes isolated from old mice, three nontypical SASP signals were identified including Edn3, Tgfb2 and GDF15. Induction of Edn3, Tgfb2 and GDF15 induced neonatal fibroblast activation and senescence, while induction of Edn3 or Tgfb2 but not GDF15 increased neonatal cardiomyocyte size,[70] suggesting that senescent cardiomyocytes can induce senescence in neighboring cells through secretion of nontypical SASP. While these studies provide compelling evidence for a role of secreted factors in aging, further investigations are needed to better define this group of secreted factors and determine how to best target them therapeutically.

Given the antioxidant and anti-inflammatory effects of exercise, it is likely that exercise counteracts the age-related upregulation of some or all of these secretory signaling pathways. Consistent with this, twelve weeks of exercise training resulted in a reduction of myostatin levels in skeletal muscle of chronic HF patients.[129] In rats with chronic HF induced by coronary ligation, four weeks of treadmill training also reduced myostatin protein expression both in the skeletal muscle and the myocardium, and this was associated with improvement of cardiac function.[130] These data are consistent with our observation that cardiac structure and function are better preserved in aged myostatin knockout mice.[123] Other ligands in this family, including GDF11 and activin, were not investigated in these studies but would be of great interest given more recent findings cited above. Future investigation of the effects of exercise on age-related secretory signaling pathways may suggest new therapeutic approaches.

Epigenetic Alterations

Epigenetics refers to somatically-acquired and/or inherited modifications in gene function that occur, not as a consequence of changes in DNA sequence, but rather as a result of changes in DNA methylation, histone modifications, or chromatin remodeling.[131] Epigenetic changes are a hallmark of aging,[106] and likely contribute to cardiac aging and cardiovascular disease more generally.[132]

DNA methylation, which mainly occurs through attachment of methyl groups to the carbon-5 position in CpG dinucleotide sequences, generally represses gene activity by preventing transcription factors from binding to gene promoters, favoring instead the recruitment of chromatin modifying enzymes.[133] DNA methylation patterns are maintained by DNMT (DNA methyltransferase) 1, while *de novo* DNA methylation is typically mediated by DNMT3a and DNMT3b.[133] Global differences in DNA methylation patterns were observed in patients with two cardiomyopathy-prone premature aging syndromes, Hutchinson-Gilford Progeria and Werner syndrome.[134] DNA methylation increases with age and is negatively correlated with lifespan in mice and humans, and the gradual accumulation of this difference in DNA methylation with age constitutes an “epigenetic clock”, serving as a biomarker for chronological age, or even biological age.[135]

DNA methylation also appears to play a role in HF. In a community-based study involving 1568 residents over the age of 65, significant differences in methylation state at CpG sites were observed in peripheral blood from patients with left ventricular HF with preserved ejection fraction compared with controls.[136] Differential methylation patterns were also found in large genomic regions in cardiomyocytes from neonatal, adult heathy, and adult failing hearts.[137] Similarly, genome-wide DNA methylation profiling revealed significant differences in promoter CpG islands, intragenic CpG islands, and gene bodies in left ventricle tissue from HF patients compared with healthy controls. Among these, the DUX4 locus was associated with differential DNA methylation, which was responsive to DNA methylation inhibition. Gene knockdown of DUX4 in a mouse HL1 cardiac cell line led to a decrease in cell viability, suggesting a possible causal role for DUX4 methylation in cardiac dysfunction.[138] Further supporting a causal role for DNA hypermethylation in HF, hypermethylation was found in hearts from rats with norepinephrine-induced cardiac hypertrophy, associated with elevated ROS production in the heart. Inhibition of DNMT reduced norepinephrine-induced cardiac ROS level and reversed both norepinephrine-induced cardiac hypertrophy and HF.[139] Most recently, Dorn et al showed that enhancement of METTL3-mediated N^6-Methyladenosine methylation induced compensated cardiac hypertrophy, whereas its diminishment induced cardiac dysfunction,[140] pointing to the importance of methylation in cardiac disease.

Histone proteins are responsible for maintaining chromatin structure and mediating dynamic and long-term gene regulation. Reduction of histone expression, maturation or deposition during replication leads to histone depletion, a feature of cellular aging.[141] Telomere attrition-induced DNA damage triggers global histone depletion, chromatin disorganization and genomic instability, thereby inducing cellular senescence.[142] This, along with the fact that telomere attrition is a hallmark of aging that may contribute to HF in aging hearts, suggests a possible link between histone levels and HF during aging.

In addition to histone levels, post-translational histone modifications, particularly acetylation, are also implicated in the regulation of chromatin structure and cardiac function in aging. Histones are

acetylated by histone acetyltransferases and deacetylated by HDACs (histone deacetylases). The roles of HDACs in regulating cardiac homeostasis and longevity have been examined in various HDAC deletion or overexpression mouse models, which have led to the conclusion that loss of specific HDAC isoforms promotes cardiac hypertrophy, dysfunction and vulnerability to cardiac injury, in some cases mimicking the effects of aging.[143–145] Cardiac-specific knockout of Sirt1 (an $NAD^{(+)}$-dependent histone deacetylase) in young mice (4-6 months) recapitulates the exacerbated response to ischemia reperfusion normally observed in older mice (24-26 months), including cardiac dysfunction, cardiac metabolic phenotypes and mitochondrial dysfunction (increase in mitochondria fission, reduction in mitochondrial density, and increase in mitochondrial DNA damage) in response to ischemia reperfusion.[146] Mechanistically, cardiac specific Sirt1 knockout leads to mitochondrial biogenesis defects in which liver kinase B1 (LKB1) hyperacetylation compromises AMPK activation and acetyl-CoA carboxylase phosphorylation, resulting in cardiac dysfunction that can be reversed by Sirt1 overexpression.[146] Age-related chromatin modifications have also been linked to changes in DNA damage repair, potentially contributing to senescence and loss of functional cardiomyocytes. In aged mice, loss of histone 4 lysine 20 trimethylation disrupts DNA damage repair and causes TGF-β/miR-29-induced cardiac dysfunction, whereas disruption of TGF-β signaling restores histone 4 lysine 20 trimethylation and improves cardiac function. These findings are consistent with a role for histone modification in cardiac dysfunction during aging.[147]

Although loss of specific HDACs causes cardiac dysfunction in animal models, pharmacological HDAC inhibition appears to protect against age-related heart dysfunction. While cardiac diastolic function progressively declined in aged mice fed with normal chow, it was preserved out to 20 months of age in aged mice fed with ITF2357, an HDACs inhibitor currently in a phase 3 trial for treating patients with Duchenne muscular dystrophy, and this was associated with improved myofibril relaxiation.[16] The apparently conflicting outcomes of targeted elimination of specific HDACs versus pharmacological HDAC inhibition likely reflects the broad isoform specificity of pharmacological intervention. Interestingly, studies of exercise have revealed dynamic regulation of specific HDAC isoforms in the heart. High volume swimming exercise in rats induced physiological cardiac growth that was associated with down regulated HDAC3 and 4 but up regulated HDAC1.[148] Moreover, in aged mice (18-month-old) with myocardial infarction, eight weeks of swimming training improved cardiac function and mitochondrial biogenesis, which was associated with increased cardiac Sirt3.[149] Gain- and loss-of-function studies have yielded some insight into the specific mechanisms of action of different HDACs in the heart.[150] However, further investigation is needed to clarify their functional roles in exercise-mediated beneficial effects on the aging heart.

Bromodomain and extraterminal domain (BET) proteins are histone acetylation “readers” that recognize acetyl-lysine labels on histones and nonhistone proteins and serve to interpret and transmit the signals initiated by histone acetylation.[151] The BET family consist of BRD2, BRD3, BRD4, and testis-specific BRDT, with BRD4 being the most abundant isoform in the heart.[152] BET inhibition by the selective inhibitor JQ1 or siRNA reduced cardiac fibrosis and apoptosis and attenuated cardiac hypertrophy and pathological gene induction in phenylephrine-treated neonatal rat cardiomyocytes in vitro or in mice subjected to TAC or phenylephrine infusion in vivo. Further molecular analysis showed that BETs serve as co-activators for transcription factors implicated in HF, including NFAT (nuclear factor of activated T cells); NF-κB (nuclear factor-κB); and GATA4.[152] This effect of BET inhibition was confirmed by the same group in human induced pluripotent stem

cell-derived cardiomyocytes, where the BET inhibitor JQ1 blocked agonist-induced hypertrophy.[153] They further showed that BET inhibition confers this protective effect by blocking NF-κB and TGF-β-mediated innate inflammatory and profibrotic gene networks. Given the contributions of inflammatory and profibrotic genes to the pathogenesis of age-related HF, it is possible that pharmacological BET inhibition could also protect against cardiac aging phenotypes and age-related HF.

Noncoding RNAs

Noncoding RNAs (ncRNAs) are functional RNA molecules that are transcribed from DNA but not translated into proteins. In general, ncRNAs can be classified into two categories based on their length as small ncRNAs (< 200 nucleotides) and long ncRNAs (lncRNAs). ncRNAs have been increasingly recognized as important regulators and biomarkers of cardiac aging and disease.

MicroRNAs (miRNAs) are endogenous small ncRNAs, approximately 22 nucleotides long that work as post-transcriptional regulators by binding to complementary sequences of messenger RNAs (mRNAs) to inhibit mRNA translation or to promote mRNA degradation.[154] A number of miRNAs have been found to have pathophysiological roles in HF. In a screen for 380 miRNAs in cardiomyocytes, miRNA (miR)-22 was identified as an abundant and strong inhibitor of cardiac autophagy, whose expression level increased during aging in mice in vivo and in cardiomyocytes in vitro by a p53-dependent mechanism.[155] Pharmacological inhibition of miR-22 in mice prevented post-infarction cardiac remodeling and improved cardiac function by activating autophagy in old mice. Moreover, circulating miR-22 was increased in patients with systolic HF associated with early mortality.[155] miR-34a is predominantly expressed in cardiomyocytes, and is upregulated in aging mouse hearts and in biopsies from aging human hearts. Silencing of miR-34a reduced cardiomyocyte cell death in aged hearts and improved recovery of cardiac infarction. Phosphatase-1 nuclear targeting subunit (PNUTS) was identified as downstream target of miR-34a.[156] More recently, Lyu et al demonstrated that miR-29a and -29c mediated TGF-β/Smad-induced senescence by suppressing Suv4-20h. This reduces histone 4 lysine 20 trimethylation, which compromises DNA damage repair and genome maintenance, contributing to cardiac aging and cardiac dysfunction.[147] Moreover, miR-128 has been showed to increase progressively in cardiomyocytes during the postnatal switching from proliferation to terminal differentiation. Deletion of miR-128 promoted cell cycle re-entry in adult cardiomyocytes, reduced cardiac fibrosis and improved cardiac function after myocardial infarction.[157] Identification of noncoding RNA pathways where inhibition has cardiac benefits could have important practical implications given that modified oligonucleotide antisense approaches appear highly effective in both animal models and clinical trials.[158,159]

In contrast to these pathological miRNA-dependent pathways, other miRNAs promote cardiac health. The miRNAs miR-18 and miR-19 were down regulated in HF-prone but up regulated in HF-resistant aged hearts, where they regulated aging cardiomyopathy through targeting profibrotic pathways involving TGF-β and thrombospondin-1 signaling.[160] Eulalio et al found that induction of miR-199 and miR-590 promoted cell cycle re-entry of adult cardiomyocytes ex vivo, and that overexpression of these miRNAs in adult mice undergoing myocardial ischemia reperfusion can induce cardiac regeneration and improve cardiac function.[161]

We and others have also identified miRNAs that act as important mediators of exercise-induced cardiac growth and cardiomyogenesis, further expanding the repertoire of potential therapeutic targets of cardiac aging and cardiac disease. Cardiac miR-222 is upregulated in mice after swimming or voluntary wheel running exercise training, and this was associated with physiological cardiac growth and birth of new cardiomyocytes.[93,94] This effect was abolished by inhibition of miR-222, indicating miR-222 is necessary for exercise-induced physiological cardiac growth (Figure 3). Molecular studies further indicated that miR-222 acts through downregulation of HIPK1, p27, and HMBOX1.[93,94] Interestingly, the exercise-induced downregulation of the pathophysiological secreted signaling protein ANGPTL2 was also blocked by miR-222 inhibition.[126] An area of growing interest concerns the role of exercise-induced exosomes in cardiac health. Exosomal miR-342-5p was increased in plasma from volunteers who had been on a rowing team for over 1 year and in rats with 4 weeks of swimming training. Increase miR-342-5p protected cardiomyocytes against hypoxia reoxygenation-induced cell apoptosis via Jnk2/Caspase 9 and Ppm1f/Akt signaling.[162] All of these data point to miRNAs as important mediators of the beneficial effects of exercise on the heart. However, whether or not miRNAs play a role in the beneficial effects of exercise in the aging heart needs further investigation. Moreover, given that a single miRNA may have over 100 predicted targets, additional studies delineating miRNA biology, and identifying the relevant downstream targets in cardiac aging, are needed.

Unlike miRNAs, lncRNAs are poorly conserved across species, and most known lncRNAs are tissue- and developmental stage-specific. lncRNAs regulate cardiac development, cardiac aging, and disease through multiple mechanisms including epigenetic regulation, transcriptional regulation, nuclear compartmentalization, and post-transcriptional gene regulation, and by acting as competing RNA sponges. Zhang and colleagues found that lncRNA H19 is down regulated in D-galactose-induced senescence in neonatal rat cardiomyocytes associated with loss of cardioprotection of ischemic postconditioning. Furthermore, H19 gene silencing exacerbated post-hypoxic cell injury in senescent cardiomyocytes by releasing miR-29b-3p, thereby down-regulating cIAP1.[163] lncRNA metastasis-associated lung adenocarcinoma transcript 1 is decreased in aged hearts and in senescent hearts induced by D-galactose. Infusion of umbilical cord mesenchymal stem cell–derived exosomes from young mice into D-galactose-induced senescent hearts improved cardiac function and increased telomere length by downregulating TNFα and p65, while these effects were reduced by silencing metastasis-associated lung adenocarcinoma transcript 1 in umbilical cord mesenchymal stem cell–derived exosomes. This suggests that the age-related decline in exosomal metastasis-associated lung adenocarcinoma transcript 1 may contribute to cardiac dysfunction in aged hearts, and that combating this decline could have beneficial effects.[164]

By microarray screening, lncRNA ENSMUST00000134285 was found to be upregulated in aged mouse hearts (18 months) compared with young mice (8 weeks). Interestingly, lncRNA ENSMUST00000134285 knockdown increased while overexpression decreased post-hypoxic cell apoptosis in neonatal mice cardiomyocytes through miR-760/MAPK11 signaling.[165] This suggests a protective role for the aging-dependent increase in lncRNA ENSMUST00000134285, which is somewhat counterintuitive given the evidence of increased cardiomyocyte loss in aging.

Circular RNAs are a newly identified subtype of lncRNAs, which are generated from back-splicing of premRNA. Specific circular RNAs have recently been shown to have a role in cardiac regenerative

repair. circNifx was upregulated in adult heart under the regulation of a super enhancer. Knockout of circNfix promoted cardiomyocyte proliferation and angiogenesis and improved post-infarction cardiac functional recovery through suppression of Ybx1 ubiquitin-dependent degradation and enhancement of miR-214 activity.[166] In separate studies, cardiac circFndc3b was found to decrease after ischemia-reperfusion injury in animals and in ischemic cardiomyopathy patients. Induction of circFndc3b through FUS/VEGF-A axis promoted cardiac repair after ischemia reperfusion injury.[167] Interestingly, circFndc3b was also downregulated in hearts from 22-month-old as compared with 1-month-old mice,[168] raising the possibility that downregulation of circFndc3b contributes to cardiac aging and that overexpression of circFndc3b may provide cardiac protective effects in aging hearts. However, research determining the role of lncRNA in cardiac aging is still in its infancy. Further investigation is needed to unveil fully the role of lncRNAs in cardiac aging.

Somatic DNA Mutations

Somatic DNA mutations accumulate over time in many tissues, representing not only a hallmark of the aging process but also a potential cause of cardiac aging and diseases.[169,170] Due to the high rate of mutation and limited repair capacity of mitochondrial DNA, mtDNA mutation is a common feature in cellular aging and cardiac disease.[170] Mitochondrial DNA mutations compromise the integrity of the mitochondrial genome, thereby impairing mitochondrial biogenesis and increasing mitochondrial ROS production, and are perhaps the best-studied somatic DNA mutations in cardiac aging and disease.[104] The direct roles of mtDNA mutations in cardiac aging and disease have been supported by evidence from several mouse models. In “mutator” mice with homozygous mutation of mitochondrial polymerase gamma ($Polg^{m/m}$), and in mice with disruption of the mitochondrial DNA helicase Twinkle (Twnk), mitochondrial function was compromised, leading to oxidative damage as well as accelerated cardiac aging and cardiac dysfunction.[171–173] As early as 8 weeks old, the accumulation rate of mtDNA mutations is 3 to 5 times higher in mutator mice compared with wild-type controls in multiple tissues including the heart. By 6 months, mutator mice develop premature aging phenotypes. Within the first year after birth, mutator mice exhibit cardiac hypertrophy and dilated cardiomyopathy as well as cardiac fibrosis, with an average lifespan of 12 months.[171,173] Although ROS markers were normal in $Polg^{m/m}$ mice, the accelerated cardiac aging and HF phenotypes in these animals were partially rescued by crossing with mCAT antioxidant overexpressing mice, suggesting a role for oxidative damage.[174–176] Similarly, in mice overexpressing dominant-negative Twnk helicase in the myocardium, mtDNA deletions accumulated at an accelerated rate in cardiomyocytes, and this was paralleled by mitochondrial deficiency and the development of arrhythmias, a common correlate of aging.[172] In contrast, mice with targeted mutation of the $p66^{Shc}$ gene involved in mitochondrial ROS production display prolonged lifespan, reduced ROS production and resistance to ROS-mediated apoptosis.[177] Moreover, disruption of $p66^{Shc}$ protected against angiotensin-II induced cardiac hypertrophy and cardiomyocyte apoptosis as well as reducing oxidative damage in multiple cardiovascular lineages in diabetic mice.[178–180] All of these observations highlight the importance of mtDNA mutations in cardiac aging and diseases. Notably, in mutator mice, 6 months of treadmill exercise training reduced mtDNA mutation, attenuated mitochondrial dysfunction and extended lifespan,[181] indicating a protective role of exercise in mtDNA repair during aging.

In another example of the detrimental effects of somatic mutations, using whole-genome sequencing of blood-derived DNA in humans, Jaiswal and colleagues demonstrated that clonal expansion of hematopoietic cells with somatic mutations in leukemogenic genes increased with age and correlated with increased mortality. They termed this phenomenon clonal hematopoiesis of indeterminate potential (CHIP).[182] They further showed that CHIP in peripheral blood cells was associated with a nearly doubled risk of coronary heart disease or early-onset myocardial infarction.[183] This was supported by mouse models with CRISPR-mediated inactivation of ten-eleven translocation enzymes 2 (Tet2) or DNA Methyltransferase 3a (Dnmt3a), the two commonly mutated genes in CHIP. Inactivation of Tet2 or Dnmt3a in hematopoietic stem/progenitor cells also worsened cardiac function in mice infused with angiotensin-II, and this was mediated by elevated inflammation.[184] Similar effects of Tet2 inactivation in hematopoietic cells were observed in two other heart failure mice models. Sano et al showed that Tet2 inactivation in hematopoietic cells worsened late-stage cardiac remodeling through effects on IL-1β/NLRP3 inflammasome activity, and reduced cardiac function in mice with HF induced by permanent left anterior descending artery ligation or TAC.[185] Given that CHIP has been found to be relatively common in asymptomatic, cancer-free older individuals,[183,186] the association between CHIP and cardiac disease in the elderly provides a potential causal link between somatic mutation and aging-related cardiovascular disease. CHIP-associated mutations may provide useful markers for assessing cardiovascular risk in aging populations independent of traditional cardiometabolic risk factors. Moreover the link to inflammatory signaling raises the possibility that therapies directed at specific mediators of inflammation, such as antibodies to IL-1β,[187] might be particularly beneficial in subjects with a high burden of CHIP.

While all organs are subject to accumulation of somatic mutations over time, the cells of the cardiovascular system may be particularly prone to DNA damage due to the hemodynamic forces and mechanical strain these cells experience. In a process known as mechanosignaling, physical stresses can modulate intracellular signaling pathways, including pathways that protect the cell from DNA damage, and the activity of these mechanosensitive protective pathways may change over time. Lamin A is a mechanosensitive nuclear structural protein that promotes DNA damage control in cardiomyocytes by preventing strain-induced breaches in the nuclear membrane.[188] Genetic perturbations of lamin A in human patients result in dilated cardiomyopathy, likely reflecting excessive activation of the platelet-derived growth factor pathway, and are also associated with a premature aging phenotype similar to that resulting from disruption of DNA repair enzymes.[189,190] Lamin A levels are greatest in cell types that experience a high degree of physical strain, and physical strain is required to maintain lamin A levels in cardiomyocytes by blocking its MMP-dependent degradation.[190] Notably, accumulation of the lamin A precursor, prelamin A, increases with age in arterial vascular smooth muscle cells, and results in DNA damage and senescence in these cells, suggesting that this protective mechanosignaling mechanism may become pathologically dysregulated in the aging cardiovascular system.[191] In addition to its protective structural role, lamin A levels also regulate histone methylation in lamin A-associated domains near the nuclear membrane in iPSC-derived cardiomyocytes, raising the interesting possibility that declining lamin A may also contribute to epigenetic changes observed with age.[190]

Conclusions and Perspectives

Given the aging of populations around the world and the associated increase in HF prevalence, there is a compelling need to develop therapeutic interventions that mitigate age-related HF. New candidates for intervention have emerged as our knowledge of the biology of aging and HF has progressed in recent years. Moreover, exercise studies have provided complementary insights in the search for new targets.[21,52,91,94,96–100,102,103,192–194] We can anticipate that as a deeper understanding of the fundamental biology of aging develops, there will be additional opportunities for translation in the future. Since biological aging and HF are complex and multifactorial systemic processes, it seems unlikely that any single pathway or intervention will fully mitigate age-related cardiac phenotypes. However, we are optimistic that insights gained through studies of aging biology and its interplay with cardiovascular pathophysiology will lay a foundation for new therapeutic strategies that can at least mitigate some features of age-related heart disease and may even be generalizable to other forms of heart failure.

Nonstandard Abbreviations And Acronyms

ANGPTL2	**angiopoietin-like protein 2**
BET	**bromodomain and extraterminal domain**
CHIP	**clonal hematopoiesis of indeterminate potential**
Chk2	**checkpoint kinase 2**
DNMT	**DNA methyltransferase**
Edn3	**endothelin 3**
GDF	**growth/differentiation factor**
HDACs	**histone deacetylases**
HF	**eart failure**

lncRNA	**long noncoding RNA**
mtDNA	**mitochondrial DNA**
ncRNAs	**noncoding RNAs**
PGC-1α	**proliferator-activated receptor γ coactivator 1α**
Polg	**polymerase γ**
ROS	**reactive oxygen species**
SASP	**senescence-associated secretory phenotype**
SCOT	**succinyl-CoA:3-oxoacid CoA transferase**
TAC	**transverse aortic constriction**
TERT	**telomerase reverse transcriptase**
Tgfβ2	**transforming growth factor β 2**
TRF2	**telomeric repeat-binding factor 2**

Sources of Funding

This work was supported by the NIH (AG061034, HL122987, HL135886, K08HL140200, K76AG064328), AHA (16SFRN31720000, 16FTF29630016, 14FTF20440012), the Fred and Ines Yeatts Fund for Innovative Research, the Foundation for Anesthesia Education and Research (FAER), and the Sarnoff Cardiovascular Research Foundation Fellowship.

Disclosures

J.D.R. and A.R. are inventors on a pending patent (PCT/US2018/023390; Methods for Preventing and Treating Heart Disease; WIPO) submitted by BIDMC and Novartis that covers methods for preventing and treating heart disease with activin receptor inhibition.

Footnotes

For Sources of Funding and Disclosures, see page 546.

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References

1. ↵ Mosterd A, Hoes AW. Clinical epidemiology of heart failure. **Heart**. 2007; 93:1137–1146. doi: 10.1136/hrt.2003.025270 Crossref | Medline | Google Scholar

2. ↵ Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. **Circulation**. 2019; 139:e56–e528. doi: 10.1161/CIR.0000000000000659 Link | Google Scholar

3. ↵ Fleg JL, Cooper LS, Borlaug BA, Haykowsky MJ, Kraus WE, Levine BD, Pfeffer MA, Piña IL, Poole DC, Reeves GR, et al.; National Heart, Lung, and Blood Institute Working Group. Exercise training as therapy for heart failure: current status and future directions. **Circ Heart Fail**. 2015; 8:209–220. doi: 10.1161/CIRCHEARTFAILURE.113.001420 Link | Google Scholar

4. ↵ Lakatta EG. So! What's aging? Is cardiovascular aging a disease? **J Mol Cell Cardiol**. 2015; 83:1–13. doi: 10.1016/j.yjmcc.2015.04.005 Crossref | Medline | Google Scholar

5. ↵ Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. **Circulation**. 2003; 107:139–146. doi: 10.1161/01.cir.0000048892.83521.58 Link | Google Scholar

6. ↵ Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham Study: an Echocardiographic Study Over 3 Decades. **JACC Cardiovasc Imaging**. 2018; 11:1–11. doi: 10.1016/j.jcmg.2017.08.007 Crossref | Medline | Google Scholar

7. ↵ Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. **Circ Res**. 2019; 124:1598–1617. doi: 10.1161/CIRCRESAHA.119.313572 Link | Google Scholar

8. ↵ Pandey A, Kraus WE, Brubaker PH, Kitzman DW. Healthy aging and cardiovascular function: Invasive hemodynamics during rest and exercise in 104 healthy volunteers. **JACC Heart Fail**. 2019; pii:S2213–1779. doi: 10.1016/j.jchf.2019.08.020 Google Scholar

9. ↵ Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated longitudinal decline of aerobic capacity in healthy older adults. **Circulation**. 2005; 112:674–682. doi: 10.1161/CIRCULATIONAHA.105.545459 Link | Google Scholar

10. ↵ Fleg JL, O'Connor F, Gerstenblith G, Becker LC, Clulow J, Schulman SP, Lakatta EG. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. **J Appl Physiol (1985)**. 1995; 78:890–900. doi: 10.1152/jappl.1995.78.3.890 Crossref | Medline | Google Scholar

11. ↵ Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. **J Am Coll Cardiol**. 2010; 56:845–854. doi: 10.1016/j.jacc.2010.03.077 Crossref | Medline | Google Scholar

12. ↵ Upadhya B, Rocco M, Lewis CE, Oparil S, Lovato LC, Cushman WC, Bates JT, Bello NA, Aurigemma G, Fine LJ, et al.. Effect of intensive blood pressure treatment on heart failure events in the systolic blood pressure reduction intervention trial. **Circ Heart Fail**. 2017; 10:e003613. doi: 10.1161/CIRCHEARTFAILURE.116.003613 Link | Google Scholar

13. ↵ Aviv A. Chronology versus biology: telomeres, essential hypertension, and vascular aging. **Hypertension**. 2002; 40:229–232. doi: 10.1161/01.hyp.0000027280.91984.1b Link | Google Scholar

14. ↵ Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. **Nature**. 2019; 571:183–192. doi: 10.1038/s41586-019-1365-2 Crossref | Medline | Google Scholar

15. ↵ Roh JD, Hobson R, Chaudhari V, Quintero P, Yeri A, Benson M, Xiao C, Zlotoff D, Bezzerides V, Houstis N, et al.. Activin type ii receptor signaling in cardiac aging and heart failure. **Sci Transl Med**. 2019; 11:eaau8680. doi: 10.1126/scitranslmed.aau8680 Crossref | Medline | Google Scholar

16. ↵ Jeong MY, Lin YH, Wennersten SA, Demos-Davies KM, Cavasin MA, Mahaffey JH, Monzani V, Saripalli C, Mascagni P, Reece TB, et al.. Histone deacetylase activity governs diastolic dysfunction through a nongenomic mechanism. **Sci Transl Med**. 2018; 10:eaao0144. doi: 10.1126/scitranslmed.aao0144 Crossref | Medline | Google Scholar

17. ↵ Safdar A, Annis S, Kraytsberg Y, Laverack C, Saleem A, Popadin K, Woods DC, Tilly JL, Khrapko K. Amelioration of premature aging in mtDNA mutator mouse by exercise: the interplay of oxidative stress, PGC-1α, p53, and DNA damage. A hypothesis. **Curr Opin Genet Dev**. 2016; 38:127–132. doi: 10.1016/j.gde.2016.06.011 Crossref | Medline | Google Scholar

18. ↵ Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly medicare beneficiaries. **Circulation**. 2010; 121:63–70. doi: 10.1161/CIRCULATIONAHA.109.876383 Link | Google Scholar

19. ↵ Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. **JAMA**. 2016; 315:36–46. doi: 10.1001/jama.2015.17346 Crossref | Medline | Google Scholar

20. ↵ O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, et al.; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. **JAMA**. 2009; 301:1439–1450. doi: 10.1001/jama.2009.454 Crossref | Medline | Google Scholar

21. ↵ Roh J, Rhee J, Chaudhari V, Rosenzweig A. The role of exercise in cardiac aging: from physiology to molecular mechanisms. **Circ Res**. 2016; 118:279–295. doi: 10.1161/CIRCRESAHA.115.305250 Link | Google Scholar

22. ↵ Werner C, Hanhoun M, Widmann T, Kazakov A, Semenov A, Pöss J, Bauersachs J, Thum T, Pfreundschuh M, Müller P, et al.. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. **J Am Coll Cardiol**. 2008; 52:470–482. doi: 10.1016/j.jacc.2008.04.034 Crossref | Medline | Google Scholar

23. ↵ Werner C, Fürster T, Widmann T, Pöss J, Roggia C, Hanhoun M, Scharhag J, Büchner N, Meyer T, Kindermann W, et al.. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. **Circulation**. 2009; 120:2438–2447. doi: 10.1161/CIRCULATIONAHA.109.861005 Link | Google Scholar

24. ↵ Kraigher-Krainer E, Lyass A, Massaro JM, Lee DS, Ho JE, Levy D, Kannel WB, Vasan RS. Association of physical activity and heart failure with preserved vs. reduced ejection fraction in the elderly: the Framingham Heart Study. **Eur J Heart Fail**. 2013; 15:742–746. doi: 10.1093/eurjhf/hft025 Crossref | Medline | Google Scholar

25. ↵ Pandey A, Patel M, Gao A, Willis BL, Das SR, Leonard D, Drazner MH, de Lemos JA, DeFina L, Berry JD. Changes in mid-life fitness predicts heart failure risk at a later age independent of interval development of cardiac and noncardiac risk factors: the Cooper Center Longitudinal Study. **Am Heart J**. 2015; 169:290–297.e1. doi: 10.1016/j.ahj.2014.10.017 Crossref | Medline | Google Scholar

26. ↵ Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. **Circulation**. 2010; 122:1797–1805. doi: 10.1161/CIRCULATIONAHA.110.973784 Link | Google Scholar

27. ↵ Spina RJ, Ogawa T, Kohrt WM, Martin WH, Holloszy JO, Ehsani AA. Differences in cardiovascular adaptations to endurance exercise training between older men and women. **J Appl Physiol (1985)**. 1993; 75:849–855. doi: 10.1152/jappl.1993.75.2.849 Crossref | Medline | Google Scholar

28. ↵ Kohrt WM, Malley MT, Coggan AR, Spina RJ, Ogawa T, Ehsani AA, Bourey RE, Martin WH, Hollos zy JO. Effects of gender, age, and fitness level on response of VO2max to training in 60-71 yr olds. **J Appl Physiol (1985)**. 1991; 71:2004–2011. doi: 10.1152/jappl.1991.71.5.2004 Crossref | Medline | Google Scholar

29. ↵ Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB. Cardiovascular responses to exer cise. Effects of aging and exercise training in healthy men. **Circulation**. 1994; 89:1648–1655. doi: 1 0.1161/01.cir.89.4.1648 Crossref | Medline | Google Scholar

30. ↵ Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, Sadek HA. Transient re generative potential of the neonatal mouse heart. **Science**. 2011; 331:1078–1080. doi: 10.1126/scie nce.1200708 Crossref | Medline | Google Scholar

31. ↵ Senyo SE, Steinhauser ML, Pizzimenti CL, Yang VK, Cai L, Wang M, Wu TD, Guerquin-Kern JL, Le chene CP, Lee RT. Mammalian heart renewal by pre-existing cardiomyocytes. **Nature**. 2013; 493:433 –436. doi: 10.1038/nature11682 Crossref | Medline | Google Scholar

32. ↵ Bergmann O, Zdunek S, Felker A, Salehpour M, Alkass K, Bernard S, Sjostrom SL, Szewczykows ka M, Jackowska T, Dos Remedios C, et al.. Dynamics of cell generation and turnover in the human h eart. **Cell**. 2015; 161:1566–1575. doi: 10.1016/j.cell.2015.05.026 Crossref | Medline | Google Schol ar

33. ↵ Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, et al.. Evidence for cardiomyocyte renewal in humans. **Science**. 2009; 324:9 8–102. doi: 10.1126/science.1164680 Crossref | Medline | Google Scholar

34. ↵ Wencker D, Chandra M, Nguyen K, Miao W, Garantziotis S, Factor SM, Shirani J, Armstrong RC, Kitsis RN. A mechanistic role for cardiac myocyte apoptosis in heart failure. **J Clin Invest**. 2003; 111: 1497–1504. doi: 10.1172/JCI17664 Crossref | Medline | Google Scholar

35. ↵ James TN. Normal and abnormal consequences of apoptosis in the human heart. From postn atal morphogenesis to paroxysmal arrhythmias. **Circulation**. 1994; 90:556–573. doi.org/10.1161/0 1.cir.90.1.556 Link | Google Scholar

36. ↵ Mallat Z, Fornes P, Costagliola R, Esposito B, Belmin J, Lecomte D, Tedgui A. Age and gender effects on cardiomyocyte apoptosis in the normal human heart. **J Gerontol A Biol Sci Med Sci**. 2001; 56:M719–M723. doi: 10.1093/gerona/56.11.m719 Crossref | Medline | Google Scholar

37. ↵ Eschenhagen T, Bolli R, Braun T, Field LJ, Fleischmann BK, Frisén J, Giacca M, Hare JM, Houser S, Lee RT, et al.. Cardiomyocyte regeneration: a consensus statement. **Circulation**. 2017; 136:680–686. doi: 10.1161/CIRCULATIONAHA.117.029343 Link | Google Scholar

38. ↵ Vicinanza C, Aquila I, Scalise M, Cristiano F, Marino F, Cianflone E, Mancuso T, Marotta P, Sacco W, Lewis FC, et al.. Adult cardiac stem cells are multipotent and robustly myogenic: c-kit expression is necessary but not sufficient for their identification. **Cell Death Differ**. 2017; 24:2101–2116. doi: 10.1038/cdd.2017.130 Crossref | Medline | Google Scholar

39. ↵ Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, Pasumarthi KB, Virag JI, Bartelmez SH, Poppa V, et al.. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. **Nature**. 2004; 428:664–668. doi: 10.1038/nature02446 Crossref | Medline | Google Scholar

40. ↵ Liu Q, Yang R, Huang X, Zhang H, He L, Zhang L, Tian X, Nie Y, Hu S, Yan Y, et al.. Genetic lineage tracing identifies in situ Kit-expressing cardiomyocytes. **Cell Res**. 2016; 26:119–130. doi: 10.1038/cr.2015.143 Crossref | Medline | Google Scholar

41. ↵ Sultana N, Zhang L, Yan J, Chen J, Cai W, Razzaque S, Jeong D, Sheng W, Bu L, Xu M, et al.. Resident c-kit(+) cells in the heart are not cardiac stem cells. **Nat Commun**. 2015; 6:8701. doi: 10.1038/ncomms9701 Crossref | Medline | Google Scholar

42. ↵ van Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, Middleton RC, Marbán E, Molkentin JD. c-kit+ cells minimally contribute cardiomyocytes to the heart. **Nature**. 2014; 509:337–341. doi: 10.1038/nature13309 Crossref | Medline | Google Scholar

43. ↵ He L, Li Y, Li Y, Pu W, Huang X, Tian X, Wang Y, Zhang H, Liu Q, Zhang L, et al.. Enhancing the precision of genetic lineage tracing using dual recombinases. **Nat Med**. 2017; 23:1488–1498. doi: 10.1038/nm.4437 Crossref | Medline | Google Scholar

44. ↵ Maliken BD, Kanisicak O, Karch J, Khalil H, Fu X, Boyer JG, Prasad V, Zheng Y, Molkentin JD. Gata4-Dependent differentiation of c-Kit+-derived endothelial cells underlies artefactual cardiomyocyte regeneration in the heart. **Circulation**. 2018; 138:1012–1024. doi: 10.1161/CIRCULATIONAHA.118.033703 Link | Google Scholar

45. ↵ Ali SR, Hippenmeyer S, Saadat LV, Luo L, Weissman IL, Ardehali R. Existing cardiomyocytes generate cardiomyocytes at a low rate after birth in mice. **Proc Natl Acad Sci U S A**. 2014; 111:8850–8855. doi: 10.1073/pnas.1408233111 Crossref | Medline | Google Scholar

46. ↵ Hsieh PC, Segers VF, Davis ME, MacGillivray C, Gannon J, Molkentin JD, Robbins J, Lee RT. Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury. **Nat Med**. 2007; 13:970–974. doi: 10.1038/nm1618 Crossref | Medline | Google Scholar

47. ↵ Wang L, Luo JY, Li B, Tian XY, Chen LJ, Huang Y, Liu J, Deng D, Lau CW, Wan S, et al.. Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow. **Nature**. 2016; 540:579–582. doi: 10.1038/nature20602 Crossref | Medline | Google Scholar

48. ↵ Picca A, Mankowski RT, Burman JL, Donisi L, Kim JS, Marzetti E, Leeuwenburgh C. Mitochondrial quality control mechanisms as molecular targets in cardiac ageing. **Nat Rev Cardiol**. 2018; 15:543–554. doi: 10.1038/s41569-018-0059-z Crossref | Medline | Google Scholar

49. ↵ Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H, et al.. Extension of murine life span by overexpression of catalase targeted to mitochondria. **Science**. 2005; 308:1909–1911. doi: 10.1126/science.1106653 Crossref | Medline | Google Scholar

50. ↵ Dai DF, Santana LF, Vermulst M, Tomazela DM, Emond MJ, MacCoss MJ, Gollahon K, Martin GM, Loeb LA, Ladiges WC, et al.. Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging. **Circulation**. 2009; 119:2789–2797. doi: 10.1161/CIRCULATIONAHA.108.822403 Link | Google Scholar

51. ↵ Arany Z, He H, Lin J, Hoyer K, Handschin C, Toka O, Ahmad F, Matsui T, Chin S, Wu PH, et al.. Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac

muscle. **Cell Metab**. 2005; 1:259–271. doi: 10.1016/j.cmet.2005.03.002 Crossref | Medline | Google Scholar

52. ↵ Arany Z, Novikov M, Chin S, Ma Y, Rosenzweig A, Spiegelman BM. Transverse aortic constriction leads to accelerated heart failure in mice lacking PPAR-gamma coactivator 1alpha. **Proc Natl Acad Sci U S A**. 2006; 103:10086–10091. doi: 10.1073/pnas.0603615103 Crossref | Medline | Google Scholar

53. ↵ Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, Stumvoll M, Kahn CR, Blüher M. Antioxidants prevent health-promoting effects of physical exercise in humans. **Proc Natl Acad Sci U S A**. 2009; 106:8665–8670. doi: 10.1073/pnas.0903485106 Crossref | Medline | Google Scholar

54. ↵ Yun J, Finkel T. Mitohormesis. **Cell Metab**. 2014; 19:757–766. doi: 10.1016/j.cmet.2014.01.011 Crossref | Medline | Google Scholar

55. ↵ Ristow M, Schmeisser S. Extending life span by increasing oxidative stress. **Free Radic Biol Med**. 2011; 51:327–336. doi: 10.1016/j.freeradbiomed.2011.05.010 Crossref | Medline | Google Scholar

56. ↵ Zhu X, Shen W, Yao K, Wang H, Liu B, Li T, Song L, Diao D, Mao G, Huang P, et al.. Fine-Tuning of PGC1α expression regulates cardiac function and longevity. **Circ Res**. 2019; 125:707–719. doi: 10.1161/CIRCRESAHA.119.315529 Link | Google Scholar

57. ↵ Bedi KC, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, Wang LL, Javaheri A, Blair IA, Margulies KB, et al.. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. **Circulation**. 2016; 133:706–716. doi: 10.1161/CIRCULATIONAHA.115.017545 Link | Google Scholar

58. ↵ Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC, Koves T, Gardell SJ, Krüger M, Hoppel CL, et al.. The failing heart relies on ketone bodies as a fuel. **Circulation**. 2016; 133:698–705. doi: 10.1161/CIRCULATIONAHA.115.017355 Link | Google Scholar

59. ↵ Kolwicz SC, Airhart S, Tian R. Ketones step to the plate: a game changer for metabolic remodeling in heart failure? **Circulation**. 2016; 133:689–691. doi: 10.1161/CIRCULATIONAHA.116.021230 Link | Google Scholar

60. ↵ Taegtmeyer H. Failing heart and starving brain: ketone bodies to the rescue. **Circulation**. 2016; 134:265–266. doi: 10.1161/CIRCULATIONAHA.116.022141 Link | Google Scholar

61. ↵ Schugar RC, Moll AR, André d'Avignon D, Weinheimer CJ, Kovacs A, Crawford PA. Cardiomyocyte-specific deficiency of ketone body metabolism promotes accelerated pathological remodeling. **Mol Metab**. 2014; 3:754–769. doi: 10.1016/j.molmet.2014.07.010 Crossref | Medline | Google Scholar

62. ↵ Lee CF, Chavez JD, Garcia-Menendez L, Choi Y, Roe ND, Chiao YA, Edgar JS, Goo YA, Goodlett DR, Bruce JE, et al.. Normalization of NAD+ redox balance as a therapy for heart failure. **Circulation**. 2016; 134:883–894. doi: 10.1161/CIRCULATIONAHA.116.022495 Link | Google Scholar

63. ↵ Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, Sinclair DA. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. **Aging (Albany NY)**. 2010; 2:914–923. doi: 10.18632/aging.100252 Crossref | Medline | Google Scholar

64. ↵ Yang H, Yang T, Baur JA, Perez E, Matsui T, Carmona JJ, Lamming DW, Souza-Pinto NC, Bohr VA, Rosenzweig A, et al.. Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. **Cell**. 2007; 130:1095–1107. doi: 10.1016/j.cell.2007.07.035 Crossref | Medline | Google Scholar

65. ↵ Airhart SE, Shireman LM, Risler LJ, Anderson GD, Nagana Gowda GA, Raftery D, Tian R, Shen DD, O'Brien KD. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. **PLoS One**. 2017; 12:e0186459. doi: 10.1371/journal.pone.0186459 Crossref | Medline | Google Scholar

66. ↵ Hayflick L. The limited in vitro lifetime of human diploid cell strains. **Exp Cell Res**. 1965; 37:614–636. doi: 10.1016/0014-4827(65)90211-9 Crossref | Medline | Google Scholar

67. ↵ Yun MH. Cellular senescence in tissue repair: every cloud has a silver lining. **Int J Dev Biol**. 2018; 62:591–604. doi: 10.1387/ijdb.180081my Crossref | Medline | Google Scholar

68. ↵ Wang M, Shah AM. Age-associated pro-inflammatory remodeling and functional phenotype in the heart and large arteries. **J Mol Cell Cardiol**. 2015; 83:101–111. doi: 10.1016/j.yjmcc.2015.02.004 Crossref | Medline | Google Scholar

69. ↵ Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, Palmer AK, Ikeno Y, Hubbard GB, Lenburg M, et al.. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. **Aging Cell**. 2015; 14:644–658. doi: 10.1111/acel.12344 Crossref | Medline | Google Scholar

70. ↵ Anderson R, Lagnado A, Maggiorani D, Walaszczyk A, Dookun E, Chapman J, Birch J, Salmonowicz H, Ogrodnik M, Jurk D, et al.. Length-independent telomere damage drives post-mitotic cardiomyocyte senescence. **EMBO J**. 2019;38 Google Scholar

71. ↵ Shimizu I, Minamino T. Cellular senescence in cardiac diseases. **J Cardiol**. 2019; 74:313–319. doi: 10.1016/j.jjcc.2019.05.002 Crossref | Medline | Google Scholar

72. ↵ Leri A, Franco S, Zacheo A, Barlucchi L, Chimenti S, Limana F, Nadal-Ginard B, Kajstura J, Anversa P, Blasco MA. Ablation of telomerase and telomere loss leads to cardiac dilatation and heart failure associated with p53 upregulation. **EMBO J**. 2003; 22:131–139. doi: 10.1093/emboj/cdg013 Crossref | Medline | Google Scholar

73. ↵ Gevaert AB, Shakeri H, Leloup AJ, Van Hove CE, De Meyer GRY, Vrints CJ, Lemmens K, Van Craenenbroeck EM. Endothelial senescence contributes to heart failure with preserved ejection fraction in an aging mouse model. **Circ Heart Fail**. 2017; 10:e003806. doi: 10.1161/CIRCHEARTFAILURE.116.003806 Link | Google Scholar

74. ↵ Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, et al.. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. **Nature**. 2016; 530:184–189. doi: 10.1038/nature16932 Crossref | Medline | Google Scholar

75. ↵ Meyer K, Hodwin B, Ramanujam D, Engelhardt S, Sarikas A. Essential role for premature senescence of myofibroblasts in myocardial fibrosis. **J Am Coll Cardiol**. 2016; 67:2018–2028. doi: 10.1016/j.jacc.2016.02.047 Crossref | Medline | Google Scholar

76. ↵ Lewis-McDougall FC, Ruchaya PJ, Domenjo-Vila E, Shin Teoh T, Prata L, Cottle BJ, Clark JE, Punjabi PP, Awad W, Torella D, et al.. Aged-senescent cells contribute to impaired heart regeneration. **Aging Cell**. 2019; 18:e12931. doi: 10.1111/acel.12931 Crossref | Medline | Google Scholar

77. ↵ Campisi J. Cellular senescence: putting the paradoxes in perspective. **Curr Opin Genet Dev**. 2011; 21:107–112. doi: 10.1016/j.gde.2010.10.005 Crossref | Medline | Google Scholar

78. ↵ Walaszczyk A, Dookun E, Redgrave R, Tual-Chalot S, Victorelli S, Spyridopoulos I, Owens A, Arthur HM, Passos JF, Richardson GD. Pharmacological clearance of senescent cells improves survival and recovery in aged mice following acute myocardial infarction. **Aging Cell**. 2019; 18:e12945. doi: 10.1111/acel.12945 Crossref | Medline | Google Scholar

79. ↵ Parikh P, Wicher S, Khandalavala K, Pabelick CM, Britt RD, Prakash YS. Cellular senescence in the lung across the age spectrum. **Am J Physiol Lung Cell Mol Physiol**. 2019; 316:L826–L842. doi: 10.1152/ajplung.00424.2018 Crossref | Medline | Google Scholar

80. ↵ Triana-Martínez F, Picallos-Rabina P, Da Silva-Álvarez S, Pietrocola F, Llanos S, Rodilla V, Sopranzo E, Pedrosa P, Ferreirós A, Barradas M, et al.. Identification and characterization of Cardiac Glycosides as senolytic compounds. **Nat Commun**. 2019; 10:4731. doi: 10.1038/s41467-019-12888-x Crossref | Medline | Google Scholar

81. ↵ Prata L, Ovsyannikova IG, Tchkonia T, Kirkland JL. Senescent cell clearance by the immune system: Emerging therapeutic opportunities. **Semin Immunol**. 2019; 40:101275. doi: 10.1016/j.smim.2019.04.003 Crossref | Google Scholar

82. ↵ Feng T, Meng J, Kou S, Jiang Z, Huang X, Lu Z, Zhao H, Lau LF, Zhou B, Zhang H. CCN1-induced cellular senescence promotes heart regeneration. **Circulation**. 2019; 139:2495–2498. doi: 10.1161/CIRCULATIONAHA.119.039530 Link | Google Scholar

83. ↵ Woo JS, Derleth C, Stratton JR, Levy WC. The influence of age, gender, and training on exercise efficiency. **J Am Coll Cardiol**. 2006; 47:1049–1057. doi: 10.1016/j.jacc.2005.09.066 Crossref | Medline | Google Scholar

84. ↵ Linke A, Adams V, Schulze PC, Erbs S, Gielen S, Fiehn E, Möbius-Winkler S, Schubert A, Schuler G, Hambrecht R. Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. **Circulation**. 2005; 111:1763–1770. doi: 10.1161/01.CIR.0000165503.08661.E5 Link | Google Scholar

85. ↵ Liao PH, Hsieh DJ, Kuo CH, Day CH, Shen CY, Lai CH, Chen RJ, Padma VV, Kuo WW, Huang CY. Moderate exercise training attenuates aging-induced cardiac inflammation, hypertrophy and fibrosis injuries of rat hearts. **Oncotarget**. 2015; 6:35383–35394. doi: 10.18632/oncotarget.6168 Crossref | Medline | Google Scholar

86. ↵ Eisele JC, Schaefer IM, Randel Nyengaard J, Post H, Liebetanz D, Brüel A, Mühlfeld C. Effect of voluntary exercise on number and volume of cardiomyocytes and their mitochondria in the mouse left ventricle. **Basic Res Cardiol**. 2008; 103:12–21. doi: 10.1007/s00395-007-0684-x Crossref | Medline | Google Scholar

87. ↵ Safdar A, Little JP, Stokl AJ, Hettinga BP, Akhtar M, Tarnopolsky MA. Exercise increases mitochondrial PGC-1alpha content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis. **J Biol Chem**. 2011; 286:10605–10617. doi: 10.1074/jbc.M110.211466 Crossref | Medline | Google Scholar

88. ↵ Kang KW, Lee SJ, Kim SG. Molecular mechanism of nrf2 activation by oxidative stress. **Antioxid Redox Signal**. 2005; 7:1664–1673. doi: 10.1089/ars.2005.7.1664 Crossref | Medline | Google Scholar

89. ↵ Kwak HB, Song W, Lawler JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. **FASEB J**. 2006; 20:791–793. doi: 10.1096/fj.05-5116fje Crossref | Medline | Google Scholar

90. ↵ Quindry J, French J, Hamilton K, Lee Y, Mehta JL, Powers S. Exercise training provides cardiopr otection against ischemia-reperfusion induced apoptosis in young and old animals. **Exp Gerontol**. 2 005; 40:416–425. doi: 10.1016/j.exger.2005.03.010 Crossref | Medline | Google Scholar

91. ↵ Boström P, Mann N, Wu J, Quintero PA, Plovie ER, Panáková D, Gupta RK, Xiao C, MacRae CA, R osenzweig A, et al.. C/EBPβ controls exercise-induced cardiac growth and protects against patholog ical cardiac remodeling. **Cell**. 2010; 143:1072–1083. doi: 10.1016/j.cell.2010.11.036 Crossref | Me dline | Google Scholar

92. ↵ Steinhauser ML, Bailey AP, Senyo SE, Guillermier C, Perlstein TS, Gould AP, Lee RT, Lechene CP. Multi-isotope imaging mass spectrometry quantifies stem cell division and metabolism. **Nature**. 201 2; 481:516–519. doi: 10.1038/nature10734 Crossref | Medline | Google Scholar

93. ↵ Vujic A, Lerchenmüller C, Wu TD, Guillermier C, Rabolli CP, Gonzalez E, Senyo SE, Liu X, Guerqui n-Kern JL, Steinhauser ML, et al.. Exercise induces new cardiomyocyte generation in the adult mam malian heart. **Nat Commun**. 2018; 9:1659. doi: 10.1038/s41467-018-04083-1 Crossref | Medline | Google Scholar

94. ↵ Liu X, Xiao J, Zhu H, Wei X, Platt C, Damilano F, Xiao C, Bezzerides V, Boström P, Che L, et al.. mi R-222 is necessary for exercise-induced cardiac growth and protects against pathological cardiac re modeling. **Cell Metab**. 2015; 21:584–595. doi: 10.1016/j.cmet.2015.02.014 Crossref | Medline | Go ogle Scholar

95. ↵ Wei X, Liu X, Rosenzweig A. What do we know about the cardiac benefits of exercise? **Trends C ardiovasc Med**. 2015; 25:529–536. doi: 10.1016/j.tcm.2014.12.014 Crossref | Medline | Google Sc holar

96. ↵ McMullen JR, Shioi T, Zhang L, Tarnavski O, Sherwood MC, Kang PM, Izumo S. Phosphoinositid e 3-kinase(p110alpha) plays a critical role for the induction of physiological, but not pathological, car diac hypertrophy. **Proc Natl Acad Sci U S A**. 2003; 100:12355–12360. doi: 10.1073/pnas.193465410 0 Crossref | Medline | Google Scholar

97. ↵ Weeks KL, Gao X, Du XJ, Boey EJ, Matsumoto A, Bernardo BC, Kiriazis H, Cemerlang N, Tan JW, Tham YK, et al.. Phosphoinositide 3-kinase p110α is a master regulator of exercise-induced cardiopr otection and PI3K gene therapy rescues cardiac dysfunction. **Circ Heart Fail**. 2012; 5:523–534. doi: 10.1161/CIRCHEARTFAILURE.112.966622 Link | Google Scholar

98. ↵ Matsui T, Li L, del MonteF Fukui Y, Franke TF, Hajjar RJ, Rosenzweig A. Adenoviral gene transfer of activated phosphatidylinositol 3'-kinase and Akt inhibits apoptosis of hypoxic cardiomyocytes in v itro. **Circulation**. 1999; 100:2373–2379. doi: 10.1161/01.cir.100.23.2373 Crossref | Medline | Googl e Scholar

99. ↵ Matsui T, Tao J, del Monte F, Lee KH, Li L, Picard M, Force TL, Franke TF, Hajjar RJ, Rosenzweig A. Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in vi vo. **Circulation**. 2001; 104:330–335. doi: 10.1161/01.cir.104.3.330 Crossref | Medline | Google Sch olar

100. ↵ DeBosch B, Treskov I, Lupu TS, Weinheimer C, Kovacs A, Courtois M, Muslin AJ. Akt1 is requir ed for physiological cardiac growth. **Circulation**. 2006; 113:2097–2104. doi: 10.1161/CIRCULATION AHA.105.595231 Link | Google Scholar

101. ↵ Calvert JW, Condit ME, Aragón JP, Nicholson CK, Moody BF, Hood RL, Sindler AL, Gundewar S, Seals DR, Barouch LA, et al.. Exercise protects against myocardial ischemia-reperfusion injury via sti mulation of β(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosot hiols. **Circ Res**. 2011; 108:1448–1458. doi: 10.1161/CIRCRESAHA.111.241117 Link | Google Schol ar

102. ↵ Arany Z, Foo SY, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G, Cooper M, Laznik D, Chinsomboon J, Rangwala SM, et al.. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. **Nature**. 2008; 451:1008–1012. doi: 10.1038/nature06613 Crossref | Medli ne | Google Scholar

103. ↵ Bezzerides VJ, Platt C, Lerchenmuller C, Paruchuri K, Oh NL, Xiao C, Cao Y, Mann N, Spiegelma n BM, Rosenzweig A. Cited4 induces physiologic hypertrophy and promotes functional recovery afte

r ischemic injury. **JCI Insight**. 2016; 1:e85904. doi: 10.1172/jci.insight.85904 Crossref | Medline | Google Scholar

104. ↵ Martínez P, Blasco MA. Heart-breaking telomeres. **Circ Res**. 2018; 123:787–802. doi: 10.1161/CIRCRESAHA.118.312202 Link | Google Scholar

105. ↵ Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. **Science**. 2015; 350:1193–1198. doi: 10.1126/science.aab3389 Crossref | Medline | Google Scholar

106. ↵ López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. **Cell**. 2013; 153:1194–1217. doi: 10.1016/j.cell.2013.05.039 Crossref | Medline | Google Scholar

107. ↵ Matsumoto C, Jiang Y, Emathinger J, Quijada P, Nguyen N, De La Torre A, Moshref M, Nguyen J, Levinson AB, Shin M, et al.. Short telomeres induce p53 and autophagy and modulate age-associated changes in cardiac progenitor cell fate. **Stem Cells**. 2018; 36:868–880. doi: 10.1002/stem.2793 Crossref | Medline | Google Scholar

108. ↵ Wong LS, Oeseburg H, de Boer RA, van Gilst WH, van Veldhuisen DJ, van der Harst P. Telomere biology in cardiovascular disease: the TERC-/- mouse as a model for heart failure and ageing. **Cardiovasc Res**. 2009; 81:244–252. doi: 10.1093/cvr/cvn337 Crossref | Medline | Google Scholar

109. ↵ Aix E, Gutiérrez-Gutiérrez Ó, Sánchez-Ferrer C, Aguado T, Flores I. Postnatal telomere dysfunction induces cardiomyocyte cell-cycle arrest through p21 activation. **J Cell Biol**. 2016; 213:571–583. doi: 10.1083/jcb.201510091 Crossref | Medline | Google Scholar

110. ↵ Chang ACY, Chang ACH, Kirillova A, Sasagawa K, Su W, Weber G, Lin J, Termglinchan V, Karakikes I, Seeger T, et al.. Telomere shortening is a hallmark of genetic cardiomyopathies. **Proc Natl Acad Sci U S A**. 2018; 115:9276–9281. doi: 10.1073/pnas.1714538115 Crossref | Medline | Google Scholar

111. ↵ Mourkioti F, Kustan J, Kraft P, Day JW, Zhao MM, Kost-Alimova M, Protopopov A, DePinho RA, Bernstein D, Meeker AK, et al.. Role of telomere dysfunction in cardiac failure in Duchenne muscular

dystrophy. **Nat Cell Biol**. 2013; 15:895–904. doi: 10.1038/ncb2790 Crossref | Medline | Google Scholar

112. ↵ Oh H, Wang SC, Prahash A, Sano M, Moravec CS, Taffet GE, Michael LH, Youker KA, Entman ML, Schneider MD. Telomere attrition and Chk2 activation in human heart failure. **Proc Natl Acad Sci U S A**. 2003; 100:5378–5383. doi: 10.1073/pnas.0836098100 Crossref | Medline | Google Scholar

113. ↵ Oh H, Taffet GE, Youker KA, Entman ML, Overbeek PA, Michael LH, Schneider MD. Telomerase reverse transcriptase promotes cardiac muscle cell proliferation, hypertrophy, and survival. **Proc Natl Acad Sci U S A**. 2001; 98:10308–10313. doi: 10.1073/pnas.191169098 Crossref | Medline | Google Scholar

114. ↵ Rudolph KL, Chang S, Lee HW, Blasco M, Gottlieb GJ, Greider C, DePinho RA. Longevity, stress response, and cancer in aging telomerase-deficient mice. **Cell**. 1999; 96:701–712. doi: 10.1016/s0092-8674(00)80580-2 Crossref | Medline | Google Scholar

115. ↵ Terai M, Izumiyama-Shimomura N, Aida J, Ishikawa N, Sawabe M, Arai T, Fujiwara M, Ishii A, Nakamura K, Takubo K. Association of telomere shortening in myocardium with heart weight gain and cause of death. **Sci Rep**. 2013; 3:2401. doi: 10.1038/srep02401 Crossref | Medline | Google Scholar

116. ↵ Sharifi-Sanjani M, Oyster NM, Tichy ED, Bedi KC, Harel O, Margulies KB, Mourkioti F. Cardiomyocyte-specific telomere shortening is a distinct signature of heart failure in humans. **J Am Heart Assoc**. 2017; 6:e005086. doi: 10.1161/JAHA.116.005086 Link | Google Scholar

117. ↵ Childs BG, Li H, van Deursen JM. Senescent cells: a therapeutic target for cardiovascular disease. **J Clin Invest**. 2018; 128:1217–1228. doi: 10.1172/JCI95146 Crossref | Medline | Google Scholar

118. ↵ Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. **Nature**. 2005; 433:760–764. doi: 10.1038/nature03260 Crossref | Medline | Google Scholar

119. ↵ Loffredo FS, Steinhauser ML, Jay SM, Gannon J, Pancoast JR, Yalamanchi P, Sinha M, Dall'Osso C, Khong D, Shadrach JL, et al.. Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. **Cell**. 2013; 153:828–839. doi: 10.1016/j.cell.2013.04.015 Crossref | Medline | Google Scholar

120. ↵ Sinha M, Jang YC, Oh J, Khong D, Wu EY, Manohar R, Miller C, Regalado SG, Loffredo FS, Pancoast JR, et al.. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. **Science**. 2014; 344:649–652. doi: 10.1126/science.1251152 Crossref | Medline | Google Scholar

121. ↵ Katsimpardi L, Litterman NK, Schein PA, Miller CM, Loffredo FS, Wojtkiewicz GR, Chen JW, Lee RT, Wagers AJ, Rubin LL. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. **Science**. 2014; 344:630–634. doi: 10.1126/science.1251141 Crossref | Medline | Google Scholar

122. ↵ Schafer MJ, Atkinson EJ, Vanderboom PM, Kotajarvi B, White TA, Moore MM, Bruce CJ, Greason KL, Suri RM, Khosla S, et al.. Quantification of GDF11 and myostatin in human aging and cardiovascular disease. **Cell Metab**. 2016; 23:1207–1215. doi: 10.1016/j.cmet.2016.05.023 Crossref | Medline | Google Scholar

123. ↵ Morissette MR, Stricker JC, Rosenberg MA, Buranasombati C, Levitan EB, Mittleman MA, Rosenzweig A. Effects of myostatin deletion in aging mice. **Aging Cell**. 2009; 8:573–583. doi: 10.1111/j.1474-9726.2009.00508.x Crossref | Medline | Google Scholar

124. ↵ Egerman MA, Cadena SM, Gilbert JA, Meyer A, Nelson HN, Swalley SE, Mallozzi C, Jacobi C, Jennings LL, Clay I, et al.. GDF11 increases with age and inhibits skeletal muscle regeneration. **Cell Metab**. 2015; 22:164–174. doi: 10.1016/j.cmet.2015.05.010 Crossref | Medline | Google Scholar

125. ↵ Smith SC, Zhang X, Zhang X, Gross P, Starosta T, Mohsin S, Franti M, Gupta P, Hayes D, Myzithras M, et al.. GDF11 does not rescue aging-related pathological hypertrophy. **Circ Res**. 2015; 117:926–932. doi: 10.1161/CIRCRESAHA.115.307527 Link | Google Scholar

126. ↵ Tian Z, Miyata K, Kadomatsu T, Horiguchi H, Fukushima H, Tohyama S, Ujihara Y, Okumura T, Yamaguchi S, Zhao J, et al.. ANGPTL2 activity in cardiac pathologies accelerates heart failure by perturbing cardiac function and energy metabolism. **Nat Commun**. 2016; 7:13016. doi: 10.1038/ncomms13016 Crossref | Medline | Google Scholar

127. ↵ Shimamoto A, Kagawa H, Zensho K, Sera Y, Kazuki Y, Osaki M, Oshimura M, Ishigaki Y, Hamasaki K, Kodama Y, et al.. Reprogramming suppresses premature senescence phenotypes of Werner syndrome cells and maintains chromosomal stability over long-term culture. **PLoS One**. 2014; 9:e112900. doi: 10.1371/journal.pone.0112900 Crossref | Medline | Google Scholar

128. ↵ Tian Z, Miyata K, Morinaga J, Horiguchi H, Kadomatsu T, Endo M, Zhao J, Zhu S, Sugizaki T, Sato M, et al.. Circulating ANGPTL2 levels increase in humans and mice exhibiting cardiac dysfunction. **Circ J**. 2018; 82:437–447. doi: 10.1253/circj.CJ-17-0327 Crossref | Medline | Google Scholar

129. ↵ Lenk K, Erbs S, Höllriegel R, Beck E, Linke A, Gielen S, Winkler SM, Sandri M, Hambrecht R, Schuler G, et al.. Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. **Eur J Prev Cardiol**. 2012; 19:404–411. doi: 10.1177/1741826711402735 Crossref | Medline | Google Scholar

130. ↵ Lenk K, Schur R, Linke A, Erbs S, Matsumoto Y, Adams V, Schuler G. Impact of exercise training on myostatin expression in the myocardium and skeletal muscle in a chronic heart failure model. **Eur J Heart Fail**. 2009; 11:342–348. doi: 10.1093/eurjhf/hfp020 Crossref | Medline | Google Scholar

131. ↵ McIntyre RL, Daniels EG, Molenaars M, Houtkooper RH, Janssens GE. From molecular promise to preclinical results: HDAC inhibitors in the race for healthy aging drugs. **EMBO Mol Med**. 2019; 11:e9854. doi: 10.15252/emmm.201809854 Crossref | Medline | Google Scholar

132. ↵ Zhang W, Song M, Qu J, Liu GH. Epigenetic modifications in cardiovascular aging and diseases. **Circ Res**. 2018; 123:773–786. doi: 10.1161/CIRCRESAHA.118.312497 Link | Google Scholar

133. ↵ Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. **Cell**. 1999; 99:247–257. doi: 10.1016/s0092-8674(00)81656-6 Crossref | Medline | Google Scholar

134. ↵ Heyn H, Moran S, Esteller M. Aberrant DNA methylation profiles in the premature aging disorders hutchinson-gilford progeria and werner syndrome. **Epigenetics**. 2013; 8:28–33. doi: 10.4161/epi.23366 Crossref | Medline | Google Scholar

135. ↵ Issa JP. Aging and epigenetic drift: a vicious cycle. **J Clin Invest**. 2014; 124:24–29. doi: 10.1172/JCI69735 Crossref | Medline | Google Scholar

136. ↵ Wang W, Zhang Y, Wang R, Shrestha Y, Xu Y, Peng L, Zhang J, Li J, Zhang L. Risk factors and epigenetic markers of left ventricular diastolic dysfunction with preserved ejection fraction in a community-based elderly Chinese population. **Clin Interv Aging**. 2019; 14:1719–1728. doi: 10.2147/CIA.S219748 Crossref | Medline | Google Scholar

137. ↵ Gilsbach R, Preissl S, Grüning BA, Schnick T, Burger L, Benes V, Würch A, Bönisch U, Günther S, Backofen R, et al.. Dynamic DNA methylation orchestrates cardiomyocyte development, maturation and disease. **Nat Commun**. 2014; 5:5288. doi: 10.1038/ncomms6288 Crossref | Medline | Google Scholar

138. ↵ Movassagh M, Choy MK, Knowles DA, Cordeddu L, Haider S, Down T, Siggens L, Vujic A, Simeoni I, Penkett C, et al.. Distinct epigenomic features in end-stage failing human hearts. **Circulation**. 2011; 124:2411–2422. doi: 10.1161/CIRCULATIONAHA.111.040071 Link | Google Scholar

139. ↵ Xiao D, Dasgupta C, Chen M, Zhang K, Buchholz J, Xu Z, Zhang L. Inhibition of DNA methylation reverses norepinephrine-induced cardiac hypertrophy in rats. **Cardiovasc Res**. 2014; 101:373–382. doi: 10.1093/cvr/cvt264 Crossref | Medline | Google Scholar

140. ↵ Dorn LE, Lasman L, Chen J, Xu X, Hund TJ, Medvedovic M, Hanna JH, van Berlo JH, Accornero F. The N6-methyladenosine mRNA methylase METTL3 controls cardiac homeostasis and hypertrophy. **Circulation**. 2019; 139:533–545. doi: 10.1161/CIRCULATIONAHA.118.036146 Link | Google Scholar

141. ↵ O'Sullivan RJ, Kubicek S, Schreiber SL, Karlseder J. Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. **Nat Struct Mol Biol**. 2010; 17:1218–1225. doi: 10.1038/nsmb.1897 Crossref | Medline | Google Scholar

142. ↵ Piazzesi A, Papić D, Bertan F, Salomoni P, Nicotera P, Bano D. Replication-independent histone variant H3.3 controls animal lifespan through the regulation of pro-longevity transcriptional programs. **Cell Rep**. 2016; 17:987–996. doi: 10.1016/j.celrep.2016.09.074 Crossref | Medline | Google Scholar

143. ↵ Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. **Nat Rev Genet**. 2009; 10:32–42. doi: 10.1038/nrg2485 Crossref | Medline | Google Scholar

144. ↵ Montgomery RL, Potthoff MJ, Haberland M, Qi X, Matsuzaki S, Humphries KM, Richardson JA, Bassel-Duby R, Olson EN. Maintenance of cardiac energy metabolism by histone deacetylase 3 in mice. **J Clin Invest**. 2008; 118:3588–3597. doi: 10.1172/JCI35847 Crossref | Medline | Google Scholar

145. ↵ Montgomery RL, Davis CA, Potthoff MJ, Haberland M, Fielitz J, Qi X, Hill JA, Richardson JA, Olson EN. Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. **Genes Dev**. 2007; 21:1790–1802. doi: 10.1101/gad.1563807 Crossref | Medline | Google Scholar

146. ↵ Wang L, Quan N, Sun W, Chen X, Cates C, Rousselle T, Zhou X, Zhao X, Li J. Cardiomyocyte-specific deletion of Sirt1 gene sensitizes myocardium to ischaemia and reperfusion injury. **Cardiovasc Res**. 2018; 114:805–821. doi: 10.1093/cvr/cvy033 Crossref | Medline | Google Scholar

147. ↵ Lyu G, Guan Y, Zhang C, Zong L, Sun L, Huang X, Huang L, Zhang L, Tian XL, Zhou Z, et al.. TGF-β signaling alters H4K20me3 status via miR-29 and contributes to cellular senescence and cardiac aging. **Nat Commun**. 2018; 9:2560. doi: 10.1038/s41467-018-04994-z Crossref | Medline | Google Scholar

148. ↵ Soci UPR, Fernandes T, Barauna VG, Hashimoto NY, de Fátima Alves Mota G, Rosa KT, Irigoyen MC, Philips MI, de Oliveira EM. Epigenetic control of exercise training-induced cardiac hypertrophy by miR-208. **Clin Sci (Lond)**. 2016; 130:2005–2015. doi: 10.1042/CS20160480 Crossref | Medline | Google Scholar

149. ↵ Zhao D, Sun Y, Tan Y, Zhang Z, Hou Z, Gao C, Feng P, Zhang X, Yi W, Gao F. Short-duration swi mming exercise after myocardial infarction attenuates cardiac dysfunction and regulates mitochond rial quality control in aged mice. **Oxid Med Cell Longev**. 2018; 2018:4079041. doi: 10.1155/2018/40 79041 Crossref | Medline | Google Scholar

150. ↵ Pillai VB, Sundaresan NR, Gupta MP. Regulation of Akt signaling by sirtuins: its implication in cardiac hypertrophy and aging. **Circ Res**. 2014; 114:368–378. doi: 10.1161/CIRCRESAHA.113.30053 6 Link | Google Scholar

151. ↵ Jiang YW, Veschambre P, Erdjument-Bromage H, Tempst P, Conaway JW, Conaway RC, Kornbe rg RD. Mammalian mediator of transcriptional regulation and its possible role as an end-point of sig nal transduction pathways. **Proc Natl Acad Sci U S A**. 1998; 95:8538–8543. doi: 10.1073/pnas.95.1 5.8538 Crossref | Medline | Google Scholar

152. ↵ Anand P, Brown JD, Lin CY, Qi J, Zhang R, Artero PC, Alaiti MA, Bullard J, Alazem K, Margulies KB, et al.. BET bromodomains mediate transcriptional pause release in heart failure. **Cell**. 2013; 154: 569–582. doi: 10.1016/j.cell.2013.07.013 Crossref | Medline | Google Scholar

153. ↵ Duan Q, McMahon S, Anand P, Shah H, Thomas S, Salunga HT, Huang Y, Zhang R, Sahadevan A, Lemieux ME, et al.. Bet bromodomain inhibition suppresses innate inflammatory and profibrotic tr anscriptional networks in heart failure. **Sci Transl Med**. 2017; 9: eaah5084. doi: 10.1126/scitranslme d.aah5084 Crossref | Medline | Google Scholar

154. ↵ Zamore PD, Haley B. Ribo-gnome: the big world of small RNAs. **Science**. 2005; 309:1519–152 4. doi: 10.1126/science.1111444 Crossref | Medline | Google Scholar

155. ↵ Gupta SK, Foinquinos A, Thum S, Remke J, Zimmer K, Bauters C, de Groote P, Boon RA, de Win dt LJ, Preissl S, et al.. Preclinical development of a microRNA-based therapy for elderly patients with myocardial infarction. **J Am Coll Cardiol**. 2016; 68:1557–1571. doi: 10.1016/j.jacc.2016.07.739 Cro ssref | Medline | Google Scholar

156. ↵ Boon RA, Iekushi K, Lechner S, Seeger T, Fischer A, Heydt S, Kaluza D, Tréguer K, Carmona G, B onauer A, et al.. MicroRNA-34a regulates cardiac ageing and function. **Nature**. 2013; 495:107–110. d

oi: 10.1038/nature11919 Crossref | Medline | Google Scholar

157. ↵ Huang W, Feng Y, Liang J, Yu H, Wang C, Wang B, Wang M, Jiang L, Meng W, Cai W, et al.. Loss of microRNA-128 promotes cardiomyocyte proliferation and heart regeneration. **Nat Commun**. 2018; 9:700. doi: 10.1038/s41467-018-03019-z Crossref | Medline | Google Scholar

158. ↵ Elmén J, Lindow M, Schütz S, Lawrence M, Petri A, Obad S, Lindholm M, Hedtjärn M, Hansen H F, Berger U, et al.. LNA-mediated microRNA silencing in non-human primates. **Nature**. 2008; 452:896 –899. doi: 10.1038/nature06783 Crossref | Medline | Google Scholar

159. ↵ Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, et al.. Treatment of HCV infection by targeting microRNA. **N Engl J Med**. 2013; 368:1685–1694. doi: 10.1056/NEJMoa1209026 Crossref | Medline | Google Scholar

160. ↵ van Almen GC, Verhesen W, van Leeuwen RE, van de Vrie M, Eurlings C, Schellings MW, Swinn en M, Cleutjens JP, van Zandvoort MA, Heymans S, et al.. MicroRNA-18 and microRNA-19 regulate C TGF and TSP-1 expression in age-related heart failure. **Aging Cell**. 2011; 10:769–779. doi: 10.1111/j. 1474-9726.2011.00714.x Crossref | Medline | Google Scholar

161. ↵ Eulalio A, Mano M, Dal Ferro M, Zentilin L, Sinagra G, Zacchigna S, Giacca M. Functional scree ning identifies miRNAs inducing cardiac regeneration. **Nature**. 2012; 492:376–381. doi: 10.1038/nat ure11739 Crossref | Medline | Google Scholar

162. ↵ Hou Z, Qin X, Hu Y, Zhang X, Li G, Wu J, Li J, Sha J, Chen J, Xia J, et al.. Longterm exercise-deri ved exosomal miR-342-5p. **Circ Res**. 2019; 124:1386–1400. doi: 10.1161/CIRCRESAHA.118.314635 Link | Google Scholar

163. ↵ Zhang X, Cheng L, Xu L, Zhang Y, Yang Y, Fu Q, Mi W, Li H. The lncRNA, H19 mediates the prote ctive effect of hypoxia postconditioning against hypoxia-reoxygenation injury to senescent cardiomy ocytes by targeting microRNA-29b-3p. **Shock**. 2019; 52:249–256. doi: 10.1097/SHK.000000000000 1213 Crossref | Medline | Google Scholar

164. ↵ Zhu B, Zhang L, Liang C, Liu B, Pan X, Wang Y, Zhang Y, Zhang Y, Xie W, Yan B, et al.. Stem cell-derived exosomes prevent aging-induced cardiac dysfunction through a novel exosome/lncRNA MA

LAT1/NF-κB/TNF-α signaling pathway. **Oxid Med Cell Longev**. 2019; 2019:9739258. doi: 10.1155/2019/9739258 Crossref | Medline | Google Scholar

165. ↵ Chun Yang X, Hui Zhao D, Bond Lau W, Qiang Liu K, Yu Tian J, Chao Cheng Z, Liang Ma X, Hua Liu J, Fan Q. lncRNA ENSMUST00000134285 increases MAPK11 activity, regulating aging-related myocardial apoptosis. **J Gerontol A Biol Sci Med Sci**. 2018; 73:1010–1017. doi: 10.1093/gerona/gly020 Crossref | Medline | Google Scholar

166. ↵ Huang S, Li X, Zheng H, Si X, Li B, Wei G, Li C, Chen Y, Chen Y, Liao W, et al.. Loss of super-enhancer-regulated circRNA Nfix induces cardiac regeneration after myocardial infarction in adult mice. **Circulation**. 2019; 139:2857–2876. doi: 10.1161/CIRCULATIONAHA.118.038361 Link | Google Scholar

167. ↵ Garikipati VNS, Verma SK, Cheng Z, Liang D, Truongcao MM, Cimini M, Yue Y, Huang G, Wang C, Benedict C, et al.. Circular RNA CircFndc3b modulates cardiac repair after myocardial infarction via FUS/VEGF-A axis. **Nat Commun**. 2019; 10:4317. doi: 10.1038/s41467-019-11777-7 Crossref | Medline | Google Scholar

168. ↵ Gruner H, Cortés-López M, Cooper DA, Bauer M, Miura P. CircRNA accumulation in the aging mouse brain. **Sci Rep**. 2016; 6:38907. doi: 10.1038/srep38907 Crossref | Medline | Google Scholar

169. ↵ Gude NA, Broughton KM, Firouzi F, Sussman MA. Cardiac ageing: extrinsic and intrinsic factors in cellular renewal and senescence. **Nat Rev Cardiol**. 2018; 15:523–542. doi: 10.1038/s41569-018-0061-5 Crossref | Medline | Google Scholar

170. ↵ Linnane AW, Marzuki S, Ozawa T, Tanaka M. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. **Lancet**. 1989; 1:642–645. doi: 10.1016/s0140-6736(89)92145-4 Crossref | Medline | Google Scholar

171. ↵ Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA, Loeb LA. DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. **Nat Genet**. 2008; 40:392–394. doi: 10.1038/ng.95 Crossref | Medline | Google Scholar

172. ↵ Baris OR, Ederer S, Neuhaus JF, von Kleist-Retzow JC, Wunderlich CM, Pal M, Wunderlich FT, Peeva V, Zsurka G, Kunz WS, et al.. Mosaic deficiency in mitochondrial oxidative metabolism promotes cardiac arrhythmia during aging. **Cell Metab**. 2015; 21:667–677. doi: 10.1016/j.cmet.2015.04.005 Crossref | Medline | Google Scholar

173. ↵ Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly-Y M, Gidlöf S, Oldfors A, Wibom R, et al.. Premature ageing in mice expressing defective mitochondrial DNA polymerase. **Nature**. 2004; 429:417–423. doi: 10.1038/nature02517 Crossref | Medline | Google Scholar

174. ↵ Dai DF, Chen T, Wanagat J, Laflamme M, Marcinek DJ, Emond MJ, Ngo CP, Prolla TA, Rabinovitch PS. Age-dependent cardiomyopathy in mitochondrial mutator mice is attenuated by overexpression of catalase targeted to mitochondria. **Aging Cell**. 2010; 9:536–544. doi: 10.1111/j.1474-9726.2010.00581.x Crossref | Medline | Google Scholar

175. ↵ Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, et al.. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. **Science**. 2005; 309:481–484. doi: 10.1126/science.1112125 Crossref | Medline | Google Scholar

176. ↵ Trifunovic A, Hansson A, Wredenberg A, Rovio AT, Dufour E, Khvorostov I, Spelbrink JN, Wibom R, Jacobs HT, Larsson NG. Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production. **Proc Natl Acad Sci U S A**. 2005; 102:17993–17998. doi: 10.1073/pnas.0508886102 Crossref | Medline | Google Scholar

177. ↵ Migliaccio E, Giorgio M, Mele S, Pelicci G, Reboldi P, Pandolfi PP, Lanfrancone L, Pelicci PG. The p66shc adaptor protein controls oxidative stress response and life span in mammals. **Nature**. 1999; 402:309–313. doi: 10.1038/46311 Crossref | Medline | Google Scholar

178. ↵ Rota M, LeCapitaine N, Hosoda T, Boni A, De Angelis A, Padin-Iruegas ME, Esposito G, Vitale S, Urbanek K, Casarsa C, et al.. Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene. **Circ Res**. 2006; 99:42–52. doi: 10.1161/01.RES.0000231289.63468.08 Link | Google Scholar

179. ↵ Camici GG, Schiavoni M, Francia P, Bachschmid M, Martin-Padura I, Hersberger M, Tanner FC, Pelicci P, Volpe M, Anversa P, et al.. Genetic deletion of p66(Shc) adaptor protein prevents hyperglycemia-induced endothelial dysfunction and oxidative stress. **Proc Natl Acad Sci U S A**. 2007; 104:5217–5222. doi: 10.1073/pnas.0609656104 Crossref | Medline | Google Scholar

180. ↵ Francia P, Cosentino F, Schiavoni M, Huang Y, Perna E, Camici GG, Lüscher TF, Volpe M. p66(Shc) protein, oxidative stress, and cardiovascular complications of diabetes: the missing link. **J Mol Med (Berl)**. 2009; 87:885–891. doi: 10.1007/s00109-009-0499-3 Crossref | Medline | Google Scholar

181. ↵ Safdar A, Khrapko K, Flynn JM, Saleem A, De Lisio M, Johnston AP, Kratysberg Y, Samjoo IA, Kitaoka Y, Ogborn DI, et al.. Exercise-induced mitochondrial p53 repairs mtDNA mutations in mutator mice. **Skelet Muscle**. 2016; 6:7. doi: 10.1186/s13395-016-0075-9 Crossref | Medline | Google Scholar

182. ↵ Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burtt N, Chavez A, et al.. Age-related clonal hematopoiesis associated with adverse outcomes. **N Engl J Med**. 2014; 371:2488–2498. doi: 10.1056/NEJMoa1408617 Crossref | Medline | Google Scholar

183. ↵ Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, McConkey M, Gupta N, Gabriel S, Ardissino D, et al.. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. **N Engl J Med**. 2017; 377:111–121. doi: 10.1056/NEJMoa1701719 Crossref | Medline | Google Scholar

184. ↵ Sano S, Oshima K, Wang Y, Katanasaka Y, Sano M, Walsh K. CRISPR-mediated gene editing to assess the roles of Tet2 and Dnmt3a in clonal hematopoiesis and cardiovascular disease. **Circ Res**. 2018; 123:335–341. doi: 10.1161/CIRCRESAHA.118.313225 Link | Google Scholar

185. ↵ Sano S, Oshima K, Wang Y, MacLauchlan S, Katanasaka Y, Sano M, Zuriaga MA, Yoshiyama M, Goukassian D, Cooper MA, et al.. Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. **J Am Coll Cardiol**. 2018; 71:875–886. doi: 10.1016/j.jacc.2017.12.037 Crossref | Medline | Google Scholar

186. ↵ Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, McMichael JF, Schmidt HK, Yellapantula V, Miller CA, et al.. Age-related mutations associated with clonal hematopoietic expansion and malignancies. **Nat Med**. 2014; 20:1472–1478. doi: 10.1038/nm.3733 Crossref | Medline | Google Scholar

187. ↵ Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al.; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. **N Engl J Med**. 2017; 377:1119–1131. doi: 10.1056/NEJMoa1707914 Crossref | Medline | Google Scholar

188. ↵ Cho S, Vashisth M, Abbas A, Majkut S, Vogel K, Xia Y, Ivanovska IL, Irianto J, Tewari M, Zhu K, et al.. Mechanosensing by the lamina protects against nuclear rupture, DNA damage, and cell-cycle arrest. **Dev Cell**. 2019; 49:920–935.e5. doi: 10.1016/j.devcel.2019.04.020 Crossref | Medline | Google Scholar

189. ↵ Brayson D, Shanahan CM. Current insights into LMNA cardiomyopathies: Existing models and missing LINCs. **Nucleus**. 2017; 8:17–33. doi: 10.1080/19491034.2016.1260798 Crossref | Medline | Google Scholar

190. ↵ Lee J, Termglinchan V, Diecke S, Itzhaki I, Lam CK, Garg P, Lau E, Greenhaw M, Seeger T, Wu H, et al.. Activation of PDGF pathway links LMNA mutation to dilated cardiomyopathy. **Nature**. 2019; 572:335–340. doi: 10.1038/s41586-019-1406-x Crossref | Medline | Google Scholar

191. ↵ Ragnauth CD, Warren DT, Liu Y, McNair R, Tajsic T, Figg N, Shroff R, Skepper J, Shanahan CM. Prelamin A acts to accelerate smooth muscle cell senescence and is a novel biomarker of human vascular aging. **Circulation**. 2010; 121:2200–2210. doi: 10.1161/CIRCULATIONAHA.109.902056 Link | Google Scholar

192. ↵ Wei X, Liu X, Rosenzweig A. What do we know about the cardiac benefits of exercise? **Trends Cardiovasc Med**. 2015; 25:529–536. doi: 10.1016/j.tcm.2014.12.014 Crossref | Medline | Google Scholar

193. ↵ Calvert JW, Condit ME, Aragón JP, Nicholson CK, Moody BF, Hood RL, Sindler AL, Gundewar S, Seals DR, Barouch LA, et al.. Exercise protects against myocardial ischemia-reperfusion injury via stimulation of β(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. **Circ Res**. 2011; 108:1448–1458. doi: 10.1161/CIRCRESAHA.111.241117 Link | Google Scholar

194. ↵ Platt C, Houstis N, Rosenzweig A. Using exercise to measure and modify cardiac function. **Cell Metab**. 2015; 21:227–236. doi: 10.1016/j.cmet.2015.01.014 Crossref | Medline | Google Scholar

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