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Trajectories in Cardiac Aging: Journey to the Crossroads of Inflammation and Metabolism

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Cardiac aging is a natural process that involves a gradual decline in cardiovascular function and leads to increased vulnerability to injury such as ischemia, hypertension, and metabolic stress. Accumulated age-related damage to cardiac cells is aggravated by abnormal metabolism, inflammation and senescence, and results in interstitial fibrosis, cardiac hypertrophy, vascular remodeling, and loss of cardiac compliance.[1]

Modifiable risk factors (eg, sedentary lifestyle and calorie-dense diet), accelerate trajectory towards cardiac aging through dysregulated inflammation, oxidative stress, epigenetic modifications, and metabolic imbalances. They synergistically act as the "four horsemen of the apocalypse" to affect the heart at multiple levels in an intercellular and inter-organ crosstalk. Obesity and diabetes expose to premature cardiac aging, whilst exercise and caloric restriction can slow the aging process and protect the heart from damage. Understanding the underpinnings of cardiac aging is important to design novel preventive and curative strategies.

Cellular senescence, an attractive target for age-related disease, has been understudied in cardiac aging, but recently nonproliferative senescence in postmitotic cells (eg, cardiomyocytes) has been appreciated. Senescent-like cardiomyocytes are characterized by multiple distinctive hallmarks, such as depleted intracellular nicotinamide adenine dinucleotide (NAD^+), dysfunctional mitochondria, metabolic reprogramming, overproduction of reactive oxygen species, DNA damage, and defective genomic DNA repair. Additionally, persistent DNA damage in telomere regions without change in telomere length activates senescent pathways with induction of cyclin-dependent kinase inhibitors $p16^{Ink4a}$, $p15^{Ink4b}$, and $p21^{CIP}$.[1,2] Senescent cardiomyocytes exhibit a profibrotic and prohypertrophic SASP (senescent-associated secretory phenotype), featuring Tgfb2 (transforming growth factor beta-2), Edn3 (endothelin 3) and Gdf15 (Growth Differentiation Factor-15), which propagates senescence to the neighboring cardiac cells[3] and attracts bone marrow–derived macrophages. These autocrine-polarized, bone marrow–recruited macrophages secrete profibrotic factors that promote myofibroblast activation and myocardial fibrosis.[4]

Inflammation is intertwined with cellular senescence, oxidative stress, and metabolic dysregulation, with adverse consequences for cardiac function. Adipose tissue, the largest energy reservoir and endocrine organ, plays a central role in developing chronic low-grade inflammation, ultimately leading to immuno-senescence and energy dysregulation. Inflammaging is particularly pronounced in obesity and diabetes, evidenced by activity of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and the NLRP3 (NLR family pyrin domain containing 3) inflammasome, driving adipose tissue macrophage-derived secretion of proinflammatory and profibrotic cytokines. Moreover, the senescent adipose microenvironment promotes insulin resistance and aberrant adipokine production with a profibrotic shift towards elevated circulating levels of TGFβ, osteopontin, activin, and leptin.[5] Evidence for a key contribution of adipose tissue to cardiac aging is provided by the ability

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of visceral lipectomy in old mice to rejuvenate the heart.[5] Therefore, strategies to block adipose tissue senescence may delay or reverse cardiac aging. Given the role of inflammaging in cardiac aging, cytokine blockade may mitigate cardiac aging but has not been clearly demonstrated as in coronary artery disease. Clonal hematopoiesis of indeterminate potential, referring to clonally expanded hematopoietic stem cells, has also been linked to inflammaging. Specifically, clonal hematopoiesis of indeterminate potential induced by specific mutations in preleukemia genes is associated with accelerated cardiovascular diseases, higher incidence of diabetes, increased inflammatory properties of leukocytes, and increased risk of all-cause mortality.

Metabolism is heavily influenced by age. For instance, mitochondrial dysfunction is a critical hallmark of aging further enhanced by obesity and diabetes. In both aging and metabolic disorders, changes in fission/fusion, mitochondrial DNA damage, and p53-linked senescence inhibit mitochondrial turnover. This can induce senescence, promote apoptosis, impair autophagy, and alter cellular metabolism. Thus, mitochondrial dysfunction and its consequences are important targets in mitigating cardiac aging. For example, reducing the rate of mitochondrial DNA mutations and reactive oxygen species production, enhancing mitophagy, promoting autophagy (via mTOR [mammalian target of rapamycin] inhibition) have shown promising results. Boosting de novo NAD^+ synthesis, or supplementing with NAD^+ precursors to restore the NAD^+:NADH ratio are other antiaging strategies. Better understanding the role of mitokines such as FGF21 (fibroblast growth factor 21) and GDF15 in interorgan crosstalk might help fight aging by improving systemic metabolism and cardiac metabolic flexibility. The use of mitochondrial miRNA could also be explored to rejuvenate mitochondrial machinery.

Epigenetic alterations represent another sign of aging controlled by metabolism. Epigenetic clocks based on DNA methylation at specific genomic sites can estimate biological age. Histone variants have specialized functions in transcriptional regulation and genome stability. SIRTs (sirtuins), a family of NAD^+-dependent histone deacetylases, protect against senescence. For example, SIRT1 (NAD-dependent deacetylase sirtuin-1) suppresses the transcription of SASP through histone deacetylation in cardiomyocytes, while reducing oxidative stress through recoupling endothelial nitric oxide synthase in endothelial cells. Interestingly, epigenetic manipulation through miRNA modulators and histone modification have yielded promising results in suppressing SASP.

Senotherapy reprograming (senostatics or senomorphics) or eliminating (senolytics) senescent cells hold therapeutic promise. The accumulation of cellular senescence in the heart may undermine adaptation to stress, potentially promoting heart failure, yet elucidating whether long-term beneficial effects of senotherapy are specifically linked to removal of senescent cardiac cells or systemic effects is needed. As an additional concern, recent reports highlighted detrimental effects of senotherapy in cardiovascular diseases, as suppression of senescence in cardiac fibroblasts promotes cardiac fibrosis in myocardial infarction, and removal of senescent vascular cells aggravates pulmonary hypertension. Therefore, it is critical to evaluate the underlying molecular mechanisms, design and test drugs targeting the implicated pathways in cardiac aging, and deliver senotherapy in a cell-specific manner to provide geroprotection against cardiac aging.

Nonpharmacologic approaches may be another area of promise. Because of limited regenerative capacity in the aged heart, strategies may aim to reactivate telomerase through endothelial progenitor cell–targeted gene transfer to enforce endothelial barrier function, manipulate the epigenetic landscape of cardiomyocytes, and reduce mitochondrial-dependent oxidative stress, or reprogram human fibroblasts into cardiomyocytes in vivo. Furthermore, engineered heart tissue transplantation represents a potential strategy for patients with heart failure. Additionally, it may deliver compounds targeting pathways involved in cardiomyocyte proliferation to drive regenerative programs. Finally, it is helpful to distinguish between modifiable versus nonmodifiable effects of aging; modifiable effects include lifestyle changes such as exercise, a healthy diet, and targeted therapies to promote healthier cardiac aging trajectories.

Considering the current disease trends in our aging society, we predict that research into cardiac aging will become increasingly important. A key question in the next centennial is whether cardiac aging is a precursor to cardiac syndromes such as heart failure with preserved ejection fraction? If so, it is vital to understand how and why cardiac aging leads to heart failure with preserved ejection fraction, and which factors contribute to this transition.

From a broader perspective, it is crucial to understand molecular mechanisms underlying cardiac aging as a precursor to other cardiac diseases. This may involve identifying direct and indirect triggers of cardiac aging, key pathogenic nodes, and how the aged myocardium becomes more susceptible to disease. In today's data-rich *-omics* era, we must identify the critical pathways within complex networks and distinguish causal relationships from epiphenomena to manage cardiac vulnerability effectively.

To improve diagnostic accuracy, we need to identify reliable and specific biomarkers to track the development of age-related cardiac disorders from the early to advanced stages. Diagnostic markers may come from deep cardiac imaging phenotyping or -omics technologies focusing on parallel heart and plasma changes. An exciting possibility is to identify new cardiokines that would quantitatively report on cardiac-aging trajectories.

Ultimately, our goal is to reduce the burden of human cardiovascular disease, so we must move from preclinical models to humans to better model the trajectories of chronologic and premature cardiac aging. This phase will implement drug development and clinical studies to delay natural and premature cardiac aging.

ARTICLE INFORMATION

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Disclosures

None.

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