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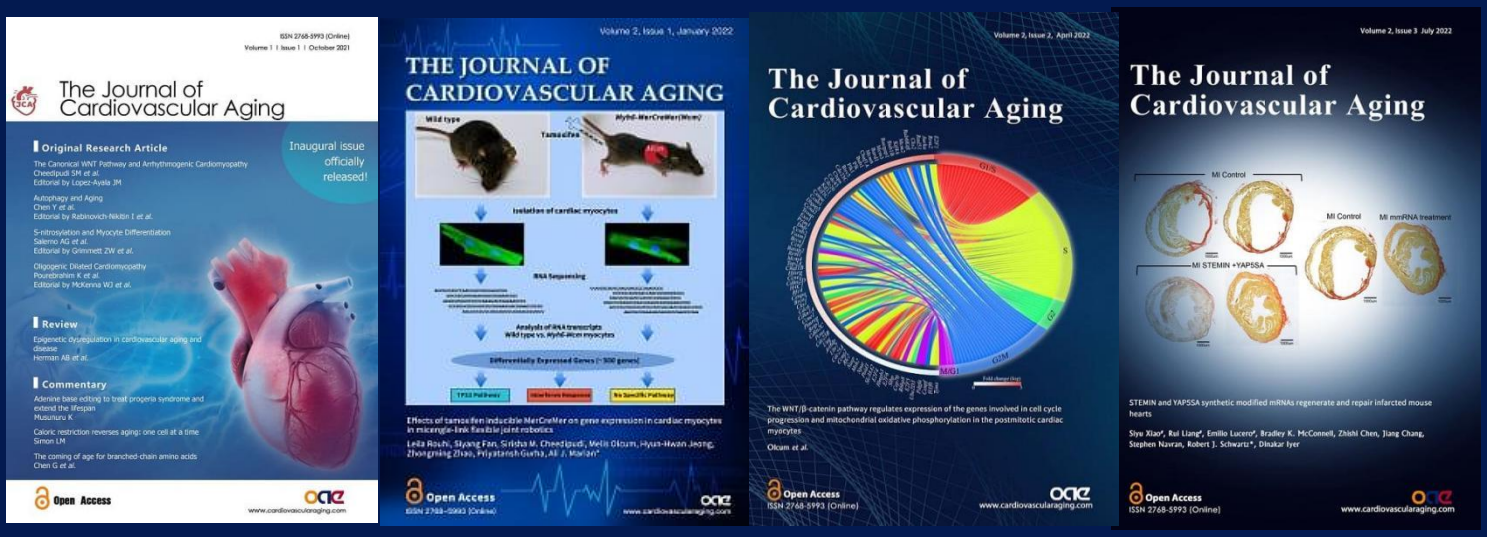

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Contents

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Original Research Article

1. Pharmacological suppression of the WNT signaling pathway attenuates age-dependent expression of the phenotype in a mouse model of arrhythmogenic cardiomyopathy

Sirisha M. Cheedipudi, Siyang Fan, Leila Rouhi, Ali J. Marian*

Read
Full-text PDF PMID: 34447973 PMCID: PMC8386676 DOI: 10.20517/jca.2021.04
Citation
RIS Plain text

Abstract

Introduction: Arrhythmogenic cardiomyopathy (ACM) is a genetic disease of the myocardium, characterized by cardiac arrhythmias, dysfunction, and sudden cardiac death. The pathological hallmark of ACM is fibro-adipocytes replacing cardiac myocytes. The canonical WNT pathway is implicated in the pathogenesis of ACM.

Aim: The study aimed to determine the effects of the suppression of the WNT pathway on cardiac phenotype in a mouse model of ACM.

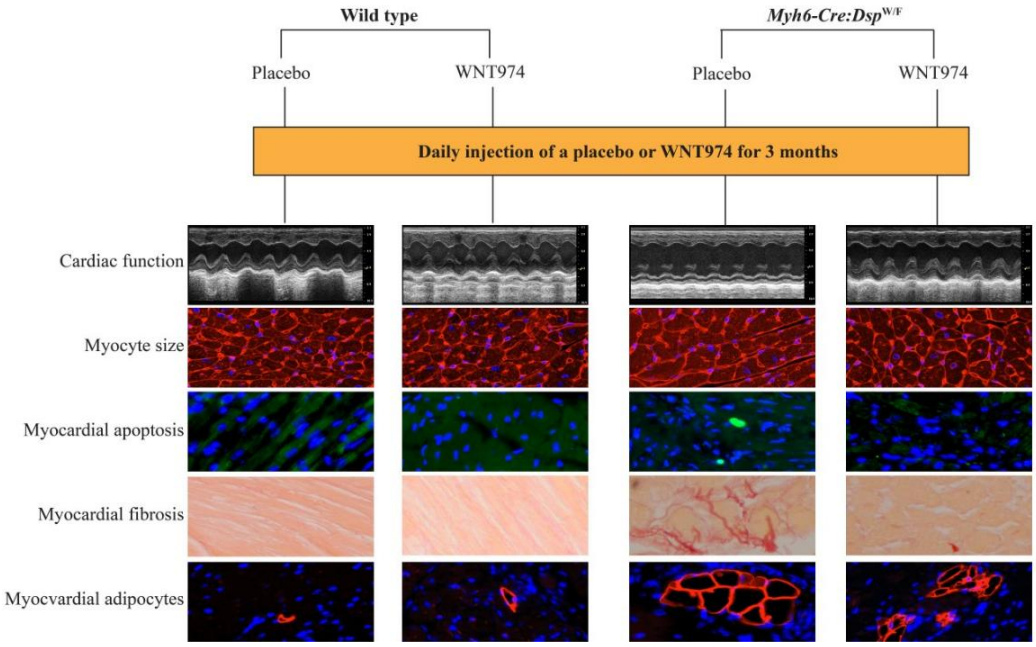
Methods and Results: One copy of the Dsp gene, a known cause of ACM in humans, was deleted specifically in cardiac myocytes (*Myh6-Cre-Dsp*$^{W/F}$). Three-month-old wild type and *Myh6-Cre-Dsp*$^{W/F}$ mice, without a discernible phenotype, were randomized to either untreated or daily administration of a vehicle (placebo), or WNT974, the latter an established inhibitor of the WNT pathway, for three months. The *Myh6-Cre-Dsp*$^{W/F}$ mice in the untreated or placebo-treated groups exhibited cardiac dilatation and dysfunction, increased myocardial fibrosis, and apoptosis upon completion of the study, which was verified by complementary methods. Daily administration of WNT974 prevented and/or attenuated evolving cardiac dilatation and dysfunction, normalized myocardial fibrosis, and reduced apoptosis, compared to the untreated or placebo-treated groups. However, administration of WNT974 increased the number of adipocytes only in the *Myh6-Cre-Dsp*$^{W/F}$ hearts. There were no differences in the incidence of cardiac arrhythmias and survival rates.

Conclusion: Suppression of the WNT pathway imparts salutary phenotypic effects by preventing or attenuating age-dependent expression of cardiac dilatation and dysfunction, myocardial fibrosis, and apoptosis in a mouse model of ACM. The findings set the stage for large-scale studies and studies in larger animal models to test the beneficial effects of the suppression of the WNT pathway in ACM.

Keywords

Cardiomyopathy, WNT signaling, fibrosis, apoptosis, heart failure

Graphical abstract



Cite this article

Cheedipudi SM, Fan S, Rouhi L, Marian AJ. Pharmacological suppression of the WNT signaling pathway attenuates age-dependent expression of the phenotype in a mouse model of arrhythmogenic cardiomyopathy. *J Cardiovasc Aging* 2021;1:3. http://dx.doi.org/10.20517/jca.2021.04

2. Ser9 phosphorylation of GSK-3β promotes aging in the heart through suppression of autophagy

Yanbin Chen, Yasuhiro Maejima, Akihiro Shirakabe, Takanobu Yamamoto, Yoshiyuki Ikeda, Junichi Sadoshima*, Peiyong Zhai*

Read
Full-text PDF PMID: 34778891 PMCID: PMC8589323 DOI: 10.20517/jca.2021.13
Citation
RIS Plain text

Abstract

Introduction: Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase and a negative regulator of cardiac hypertrophy. Phosphorylation of GSK-3β at Ser9 negatively regulates its kinase activity. The role of GSK-3β in cardiac aging remains poorly understood.

Aim: The study aimed to elucidate the role of GSK-3β Ser9 phosphorylation in mediating cardiac aging and the underlying mechanism.

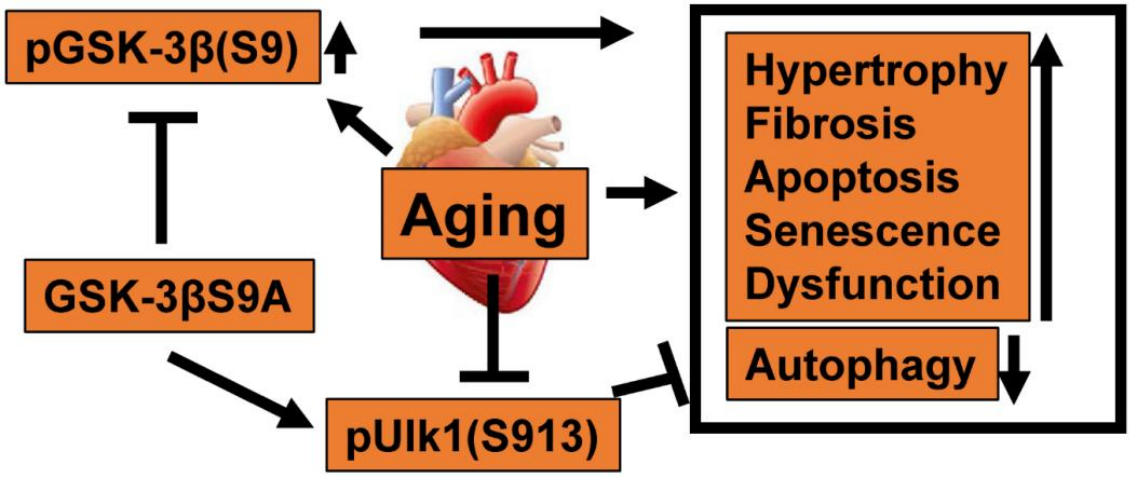
Methods and Results: Phosphorylation of GSK-3β at Ser9 and the levels of β-catenin and Mcl-1 were

increased in the mouse heart during aging, suggesting that GSK-3β is inactivated during aging in the heart. Age-induced cardiac hypertrophy, fibrosis, left ventricular dysfunction, and increases in cardiomyocyte apoptosis and senescence were all attenuated in constitutively active GSK-3β^{S9A} knock-in (KI) mice compared to littermate wild type mice. Although autophagy is inhibited in the heart during aging, KI of GSK-3β^{S9A} reversed the age-associated decline in autophagy in the mouse heart. GSK-3β directly phosphorylates Ulk1, a regulator of autophagy, at Ser913, thereby stimulating autophagy in cardiomyocytes. Ulk1Ser913A KI mice exhibited decreased autophagic flux and increased senescence in cardiomyocytes.

Conclusion: Our results suggest that GSK-3β is inactivated during aging through Ser9 phosphorylation, which in turn plays an important role in mediating cardiac aging. GSK-3β promotes autophagy through phosphorylation of Ulk1 at Ser913, which in turn prevents aging in the heart.

Keywords
GSK-3β, autophagy, Ulk1, aging, senescence

Graphical abstract



Cite this article

Chen Y, Maejima Y, Shirakabe A, Yamamoto T, Ikeda Y, Sadoshima J, Zhai P. Ser9 phosphorylation of GSK-3β promotes aging in the heart through suppression of autophagy. *J Cardiovasc Aging* 2021;1:9.
http://dx.doi.org/10.20517/jca.2021.13

3. A combinatorial oligogenic basis for the phenotypic plasticity between late-onset dilated and arrhythmogenic cardiomyopathy in a single family

Kimia Pourebrahim, John Garrity Marian, Yanli Tan, Jeffrey T. Chang, Ali J. Marian*

Read
Full-text PDF PMID: 34790974 PMCID: PMC8594872 DOI: 10.20517/jca.2021.15

Abstract

Introduction: Primary dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are the two common and distinct forms of hereditary cardiomyopathies caused by defined pathogenic variants (PVs) typically in different sets of genes. DCM is characterized by left ventricular dilatation, dysfunction, and failure, whereas ARVC classically involves the right ventricle and is characterized by fibrofatty infiltration of the myocardium. DCM is caused primarily by the PVs in genes encoding sarcomere and cytoskeletal protein, while ARVC is mainly a disease of the desmosome proteins. DCM and ARVC exhibit partial phenotypic and genetic overlaps.

Aim: To analyze the genetic basis of the phenotypic heterogeneity of cardiomyopathy in members of a single family.

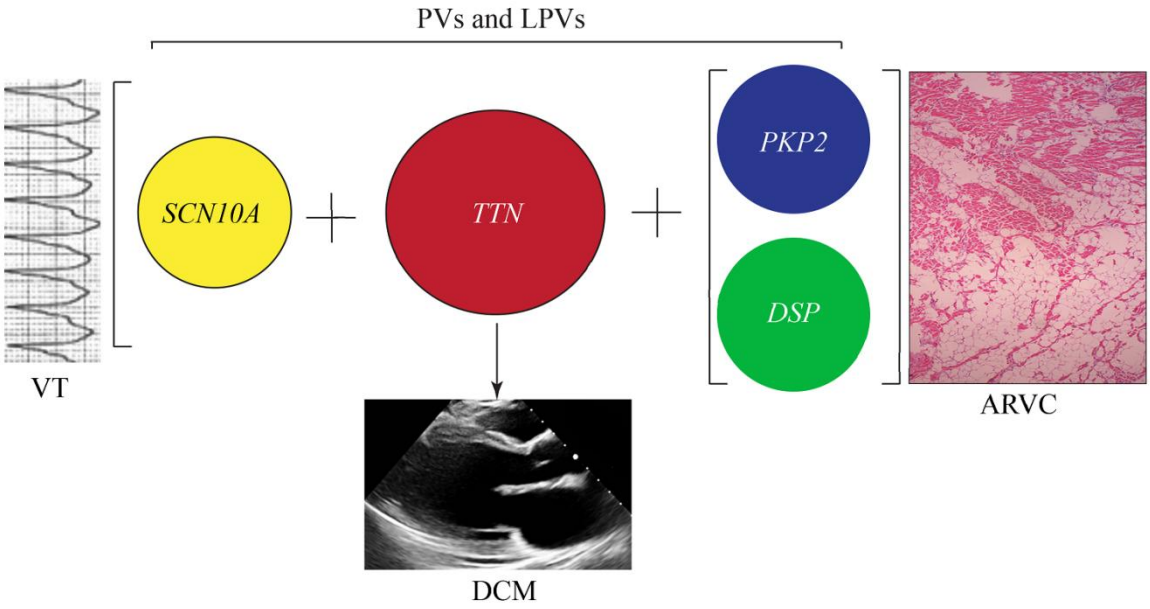
Methods and Results: We recruited, clinically characterized, and performed whole-exome sequencing in five affected, three probably affected, and two clinically unaffected members of a single family. The family members mainly exhibited late-onset DCM associated with conduction defects and arrhythmias. One family member who died suddenly was diagnosed with the classic ARVC at autopsy and another presented with isolated ventricular tachycardia. A novel splicing (truncating) and a rare missense variant in the *TTN* gene, likely in cis, co-segregated with the phenotype in all affected and probably affected family members and were likely the causal variants. Several PVs and LPVs in other genes involved in cardiomyopathies and arrhythmias were also identified that seem to modify the expression of the phenotype. Notably, LPVs in the *DSP* and *PKP2* genes, which are known genes for ARVC, were identified in the family member who also carried the *TTN* variants but developed the classic ARVC.

Conclusion: The findings indicate the causal role of the *TTN* variants, exhibiting an age-dependent penetrance in late-onset DCM, and highlight the potential modifying role of the concomitant LPVs in additional genes on the expression of the phenotype, including a phenotypic switch from the anticipated DCM to ARVC. The findings support an oligogenic basis of the cardiac phenotype in hereditary cardiomyopathies. A comprehensive genetic analysis involving all PVs and LPVs along with detailed phenotypic characterization is necessary to gain insights into the molecular pathogenesis of hereditary cardiomyopathies.
graphical abstract

Keywords

Titin, plakophilin 2, desmoplakin, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, genetic, pathogenic variant, sudden death, mutation

Graphical abstract



Cite this article

Pourebrahim K, Marian JG, Tan Y, Chang JT, Marian AJ. A combinatorial oligogenic basis for the phenotypic plasticity between late-onset dilated and arrhythmogenic cardiomyopathy in a single family. *J Cardiovasc Aging* 2021;1:12. http://dx.doi.org/10.20517/jca.2021.15

4. S-nitrosoglutathione reductase (GSNOR) deficiency accelerates cardiomyocyte differentiation of induced pluripotent stem cells

Alessandro G. Salerno, Amarylis C. B. A. Wanschel, Raul A. Dulce, Konstantinos E. Hatzistergos, Wayne Balkan, Joshua M. Hare*

Read
Full-text PDF PMID: 34790975 PMCID: PMC8594875 DOI: 10.20517/jca.2021.19
Citation
RIS Plain text

Abstract

Introduction: Induced pluripotent stem cells (iPSCs) provide a model of cardiomyocyte (CM) maturation. Nitric oxide signaling promotes CM differentiation and maturation, although the mechanisms remain controversial.

Aim: The study tested the hypothesis that in the absence of S-nitrosoglutathione reductase (GSNOR), a denitrosylase regulating protein S-nitrosylation, the resultant increased S-nitrosylation accelerates the differentiation and maturation of iPSC-derived cardiomyocytes (CMs).

Methods and Results: iPSCs derived from mice lacking GSNOR (iPSC$^{GSNOR-/-}$) matured faster than wildtype

iPSCs (iPS^{CWT}) and demonstrated transient increases in expression of murine Snail Family Transcriptional Repressor 1 gene (*Snail*), murine Snail Family Transcriptional Repressor 2 gene (*Slug*) and murine Twist Family BHLH Transcription Factor 1 gene *(Twist*), transcription factors that promote epithelial-to-mesenchymal transition (EMT) and that are regulated by Glycogen Synthase Kinase 3 Beta (GSK3β). Murine Glycogen Synthase Kinase 3 Beta (*Gsk3β*) gene exhibited much greater S-nitrosylation, but lower expression in iPSC$^{GSNOR-/-}$. S-nitrosoglutathione (GSNO)-treated iPSC^{WT} and human (h)iPSCs also demonstrated reduced expression of GSK3β. *Nkx2.5* expression, a CM marker, was increased in iPSC$^{GSNOR-/-}$ upon directed differentiation toward CMs on Day 4, whereas murine Brachyury (*t*), *Isl1*, and GATA Binding Protein (*Gata4*) mRNA were decreased, compared to iPSC^{WT}, suggesting that GSNOR deficiency promotes CM differentiation beginning immediately following cell adherence to the culture dish-transitioning from mesoderm to cardiac progenitor.

Conclusion: Together these findings suggest that increased S-nitrosylation of Gsk3β promotes CM differentiation and maturation from iPSCs. Manipulating the post-translational modification of GSK3β may provide an important translational target and offers new insight into understanding of CM differentiation from pluripotent stem cells.

Keywords
GSNOR, GSK3β, differentiation, EMT, cardiomyocytes, iPSCs

Cite this article

Salerno AG, Wanschel ACBA, Dulce RA, Hatzistergos KE, Balkan W, Hare JM. S-nitrosoglutathione reductase (GSNOR) deficiency accelerates cardiomyocyte differentiation of induced pluripotent stem cells. *J Cardiovasc Aging* 2021;1:13. http://dx.doi.org/10.20517/jca.2021.19

5. Systemic delivery of large-scale manufactured Wharton's Jelly mesenchymal stem cell-derived extracellular vesicles improves cardiac function after myocardial infarction

Michael A. Bellio, Rosemeire M. Kanashiro-Takeuchi, Lauro Takeuchi , Shathiyah Kulandavelu, Yee-Shuan Lee, Wayne Balkan, Karen C. Young, Joshua M. Hare, Aisha Khan*

Read
Full-text PDF PMID: 35112111 PMCID: PMC8804674 DOI: 10.20517/jca.2021.21
Citations
RIS Plain text

Abstract
Introduction: Cardiovascular disease and myocardial infarction are leading causes of morbidity and mortality in aged populations. Mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) are under evaluation as a therapeutic option for the treatment of myocardial infarction.

Aim: This study aimed to develop a large-scale manufacturing procedure to harvest clinical-grade EVs required for the translation of EVs to the clinic.

Methods and Results: We compared the efficiency of large scale MSC-derived EV production and characterized EV miRNA cargo using the Quantum bioreactor with either fetal bovine serum or human platelet lysate (PLT)-containing expansion media. We tested the potency of the EV products in a murine model of acute myocardial infarction. Our results demonstrate an advantage of the Quantum bioreactor as a large-scale platform for EV production using PLT media; however, both media produced EVs with similar effects *in vivo*. The systemic delivery of EV products improved cardiac function following myocardial infarctions as indicated by a significant improvement in ejection fraction as well as parameters of cardiac performance, afterload, contractility and lusitropy.

Conclusion: These findings have important implications for scale-up strategies of EVs and will facilitate clinical trials for their clinical evaluation.

Keywords
Extracellular vesicles, Wharton's Jelly, mesenchymal stem cells, manufacturing, myocardial infarction

Cite this article

Bellio MA, Kanashiro-Takeuchi RM, Takeuchi L, Kulandavelu S, Lee YS, Balkan W, Young KC, Hare JM, Khan A. Systemic delivery of large-scale manufactured Wharton's Jelly mesenchymal stem cell-derived extracellular vesicles improves cardiac function after myocardial infarction. *J Cardiovasc Aging* 2022;2:9.
http://dx.doi.org/10.20517/jca.2021.21

6. Associations between estimated and measured carotid-femoral pulse wave velocity in older Black and White adults: the atherosclerosis risk in communities (ARIC) study

Kevin Heffernan, Lee Stoner*, Michelle L. Meyer, Adam Keifer, Lauren Bates, Patricia Pagan Lassalle, Erik D. Hanson, Masahiro Horiuchi, Erin D. Michos, Anna Kucharska-Newton, Kunihiro Matsushita, Timothy M. Hughes, Hirofumi Tanaka

Read
Full-text PDF PMCID:PMC9934460 DOI: 10.20517/jca.2021.22
Citation
RIS Plain text

Abstract
Introduction: Aortic stiffness offers important insight into vascular aging and cardiovascular disease (CVD) risk. The referent measure of aortic stiffness is carotid-femoral pulse wave velocity (cfPWV). cfPWV can be estimated (ePWV) from age and mean arterial pressure. Few studies have directly compared the association of ePWV to measured cfPWV, particularly in non-White adults. Moreover, whether ePWV and cfPWV correlate similarly with CVD risk remains unexplored.

Aim: (1) To estimate the strength of the agreement between ePWV and cfPWV in both Black and White older adults; and (2) to compare the associations of ePWV and cfPWV with CVD risk factors and determine

whether these associations were consistent across races.

Methods and Results: We evaluated 4478 [75.2 (SD 5.0) years] Black and White older adults in the Atherosclerosis Risk in Communities (ARIC) Study. cfPWV was measured using an automated pulse waveform analyzer. ePWV was derived from an equation based on age and mean arterial pressure. Association and agreement between the two measurements were determined using Pearson's correlation coefficient (r), standard error of estimate (SEE), and Bland-Altman analysis. Associations between traditional risk factors with ePWV and cfPWV were evaluated using linear mixed regression models. We observed weak correlations between ePWV and cfPWV within White adults ($r = 0.36$) and Black adults ($r = 0.31$). The mean bias for Bland-Altman analysis was low at -0.17 m/s (95%CI: -0.25 to -0.09). However, the inspection of the Bland-Altman plots indicated systematic bias ($P < 0.001$), which was consistent across race strata. The SEE, or typical absolute error, was 2.8 m/s suggesting high variability across measures. In models adjusted for sex, prevalent diabetes, the number of prevalent cardiovascular diseases, and medication count, both cfPWV and ePWV were positively associated with heart rate, triglycerides, and fasting glucose, and negatively associated with body mass index (BMI) and smoking status in White adults ($P < 0.05$). cfPWV and ePWV were not associated with heart rate, triglycerides, and fasting glucose in Black adults, while both measures were negatively associated with BMI in Black adults.

Conclusions: Findings suggest a weak association between ePWV and cfPWV in older White and Black adults from ARIC. There were similar weak associations between CVD risk factors with ePWV and cfPWV in White adults with subtle differences in associations in Black adults.

Keywords
Vascular stiffness, measurement, health disparities, pulse wave velocity, blood pressure

Cite this article

Heffernan K, Stoner L, Meyer ML, Keifer A, Bates L, Lassalle PP, Hanson ED, Horiuchi M, Michos ED, Kucharska-Newton A, Matsushita K, Hughes TM, Tanaka H. Associations between estimated and measured carotid-femoral pulse wave velocity in older Black and White adults: the atherosclerosis risk in communities (ARIC) study. *J Cardiovasc Aging* 2022;2:7. http://dx.doi.org/10.20517/jca.2021.22

7. The WNT/β-catenin pathway regulates expression of the genes involved in cell cycle progression and mitochondrial oxidative phosphorylation in the postmitotic cardiac myocytes

Melis Olcum1, Sirisha M. Cheedipudi, Leila Rouhi, Siyang Fan, Hyun-Hwan Jeong, Zhongming Zhao, Priyatansh Gurha, Ali J. Marian*

Read
Full-text PDF PMID: 35224561 PMCID: PMC8874274 DOI: 10.20517/jca.2021.35
Citations
RIS Plain text

Abstract
Introduction: Aging is associated with cardiac myocyte loss, sarcopenia, and cardiac dysfunction. Adult cardiac myocytes are postmitotic cells with an insufficient proliferative capacity to compensate for myocyte

loss. The canonical WNT (cWNT) pathway is involved in the regulation of cell cycle reentry in various cell types. The effects of the cWNT pathway on the expression of genes involved in cell cycle reentry in the postmitotic cardiac myocytes are unknown.

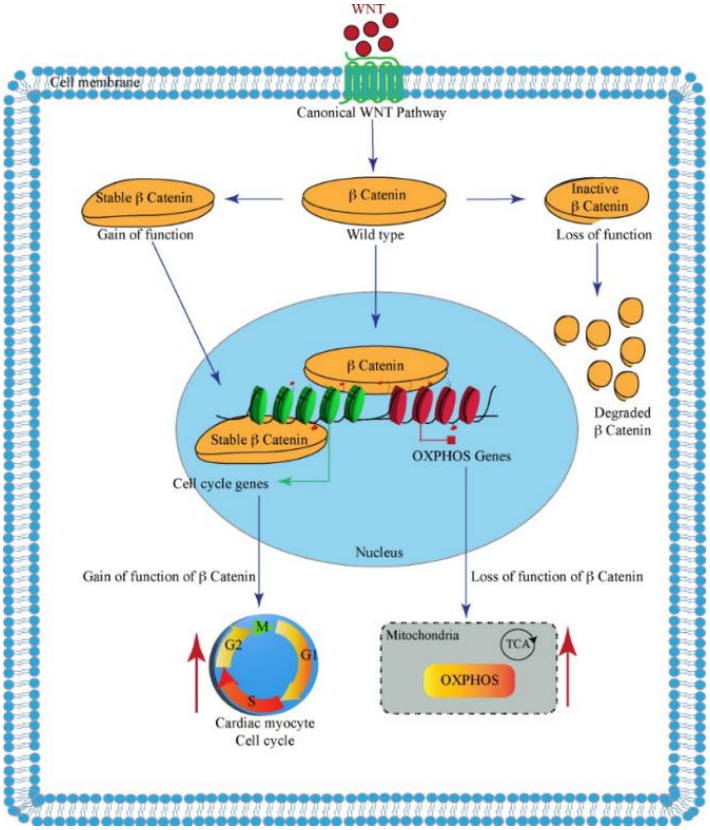
Aim: The aim of the study was to identify genes whose expression is regulated by the β-catenin, the indispensable component to the cWNT signaling, in the postmitotic myocytes.

Methods and Results: Cardiac myocyte-specific tamoxifen-inducible MerCreMer (*Myh6-Mcm*) mice were used to delete the floxed exon 3 or exons 8 to 13 of the *Ctnnb1* gene to induce gain-of-function (GoF) or loss-of-function (LoF) the β-catenin, respectively. Deletion of exon 3 leads to the expression of a stable β-catenin. In contrast, deletion of exons 8-13 leads to the expression of transcriptionally inactive truncated β-catenin, which is typically degraded. GoF or LoF of the β-catenin was verified by reverse transcription-polymerase chain reaction (RT-PCR), immunoblotting, and immunofluorescence. Myocyte transcripts were analyzed by RNA-Sequencing (RNA-Seq) at 4 weeks of age. The GoF of β-catenin was associated with differential expression of ~1700 genes, whereas its LoF altered expression of ~400 genes. The differentially expressed genes in the GoF myocytes were enriched in pathways regulating the cell cycle, including karyokinesis and cytokinesis, whereas the LoF was associated with increased expression of genes involved in mitochondrial oxidative phosphorylation. These findings were validated by RT-PCR in independent samples. Short-term GoF nor LoF of β-catenin did not affect the number of cardiac myocytes, cardiac function, myocardial fibrosis, myocardial apoptosis, or adipogenesis at 4 weeks of age.

Conclusion: Activation of the β-catenin of the cWNT pathway in postmitotic myocytes leads to cell cycle reentry and expression of genes involved in cytokinesis without leading to an increase in the number of myocytes. In contrast, suppression of the β-catenin modestly increases the expression of genes involved in oxidative phosphorylation. The findings provide insights into the role of β-catenin of the cWNT pathway in the regulation of cell cycle reentry and oxidative phosphorylation in the postmitotic cardiac myocytes.

Keywords
Myocyte proliferation, WNT signaling, beta-catenin, cytokinesis, cell cycle, oxidative phosphorylation, mitochondria

Graphical abstract



Cite this article

Olcum M, Cheedipudi SM, Rouhi L, Fan S, Jeong HH, Zhao Z, Gurha P, Marian AJ. The WNT/β-catenin pathway regulates expression of the genes involved in cell cycle progression and mitochondrial oxidative phosphorylation in the postmitotic cardiac myocytes. *J Cardiovasc Aging* 2022;2:15. http://dx.doi.org/10.20517/jca.2021.35

8. Mutant SRF and YAP synthetic modified mRNAs drive cardiomyocyte nuclear replication

Siyu Xiao, Rui Liang, Azeez B. Muili , Xuanye Cao, Stephen Navran, Robert J. Schwartz*, Dinakar Iyer

Read
Full-text PDF DOI: 10.20517/jca.2022.17
Citations
RIS Plain text

Abstract

Introduction: Aging is associated with sarcopenia, myocyte loss, and dysfunction. The problem is compounded as the adult heart lacks the regenerative capacity to self-repair. Serum response factor's (SRF's) dual activity is essential for cell replication and heart cell differentiation. SRF interacts with cofactors, such as NKX2-5 and GATA4, which give cardiac-specific gene activity, and ETS factors such as ELK1 drive cell replication. Recently, the mutant YAP-5SA of the Hippo pathway was implicated in cardiomyocyte proliferation and growth.

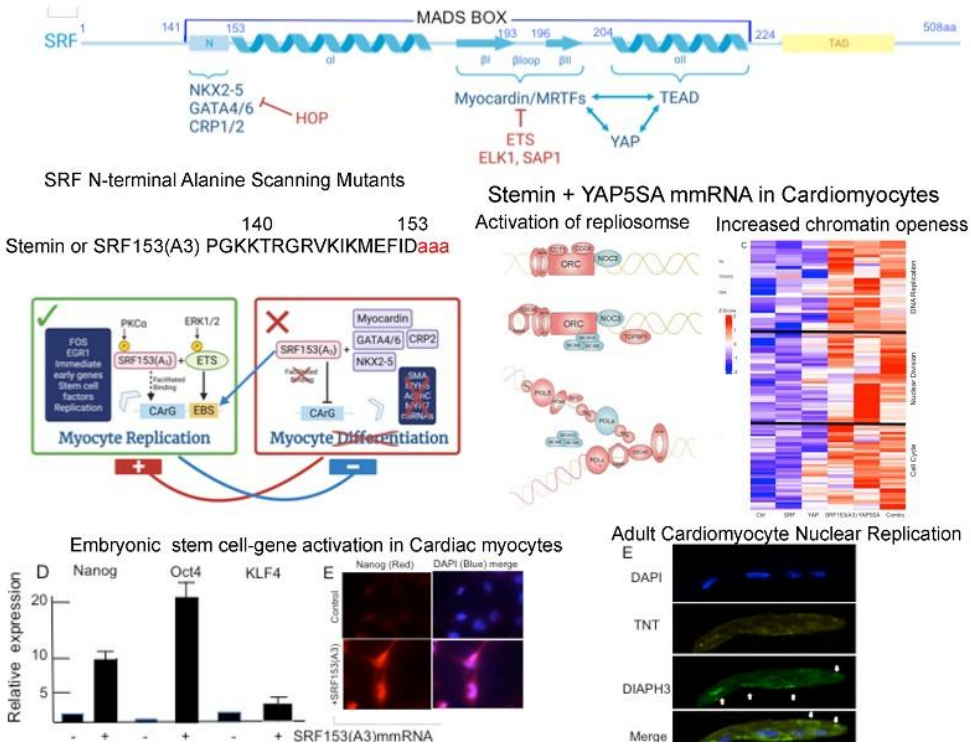
Aim: We hypothesized that disruption of interactions of SRF with NKX2-5 and GATA4 would lead to dedifferentiation of cardiomyocytes to a proliferative stem cell state and complement YAP-5SA to generate undifferentiated cardiomyocytes in a more primitive replicative state.

Methods and results: To weaken SRF interactions with NKX2-5 and GATA4, alanine scanning mutations were generated across the SRF N-terminus of the MADS-box. One SRF mutant, SRF153(A3), was tested along with the YAP-5SA mutant, as degradable synthetic modified mRNAs (mmRNAs), in rat primary cardiomyocytes. To measure cell replication, adult cardiomyocytes were pulsed with alpha-EdU and then DAPI stained, while gene activity was assayed by RNA sequencing. To measure chromatin remodeling, Transposon 5 was used in ATAC sequencing. We observed that single and triple alanine substitutions of mutants centering over SRF-Lys154 essentially blocked myocyte differentiation, and NKX2-5 and GATA4 failed to stabilize mutated SRF DNA binding. Instead, many stem cell factors including NANOG and OCT4 were induced. SRF153(A3) does not recognize SRF response elements per ATAC sequencing and consequently induces stem cell factors such as NANOG and OCT4, cardiomyocyte dedifferentiation, and cell cycle reentry. SRF153(A3) and YAP5SA mmRNA led to alpha-EDU incorporation in ~35% of the cardiomyocytes. DIAPH 3, a marker of the contractile ring during anaphase, appeared between and around replicated nuclei in three-month-old adult mouse cardiac myocytes. The combination of these synthetic mRNA increased nuclei replication with the expression of origin of replication genes, while genes associated with cardiomyocyte differentiation were down-regulated. ATAC sequencing revealed SRF153(A3) and YAP5SA mmRNA-induced chromatin remodeling of cell cycle, spindle, and growth factor genes by additive and synergistic activities.

Conclusion: SRF153(A3) synthetic mmRNA and the mutant YAP-5SA mmRNA induced cardiomyocyte dedifferentiation, to nuclear replication in adult cardiac myocytes. The combinatorial use of mmRNA encoding SRF153(A3) and YAP-5SA has the potential to become a powerful clinical strategy for treating human heart disease.

Keywords
Cardiac regeneration, synthetic mRNA, heart delivery, serum response factor, SRF153(A3), hippo pathway, YAP

Graphical abstract



Cite this article

Xiao S, Liang R, Muili AB, Cao X, Navran S, Schwartz RJ, Iyer D. Mutant SRF and YAP synthetic modified mRNAs drive cardiomyocyte nuclear replication. *J Cardiovasc Aging* 2022;2:29. http://dx.doi.org/10.20517/jca.2022.17

9. Deletion of the Lmna gene in fibroblasts causes senescence-associated dilated cardiomyopathy by activating the double-stranded DNA damage response and induction of senescence-associated secretory phenotype

Leila Rouhi, Gaelle Auguste, Qiong Zhou, Raffaella Lombardi, Melis Olcum, Kimia Pourebrahim, Sirisha M. Cheedipudi, Saman Asghar, Kui Hong, Matthew J. Robertson, Cristian Coarfa, Priyatansh Gurha, Ali J. Marian*

Read
Full-text PDF PMID: 35891706 PMCID: PMC9311325 DOI: 10.20517/jca.2022.14
Citations
RIS Plain text

Abstract

Introduction: Mutations in the *LMNA* gene, encoding Lamin A/C (LMNA), are established causes of dilated cardiomyopathy (DCM). The phenotype is typically characterized by progressive cardiac conduction defects, arrhythmias, heart failure, and premature death. DCM is primarily considered a disease of cardiac myocytes. However, LMNA is also expressed in other cardiac cell types, including fibroblasts.

Aim: The purpose of the study was to determine the contribution of the fibroblasts to DCM caused by LMNA deficiency.

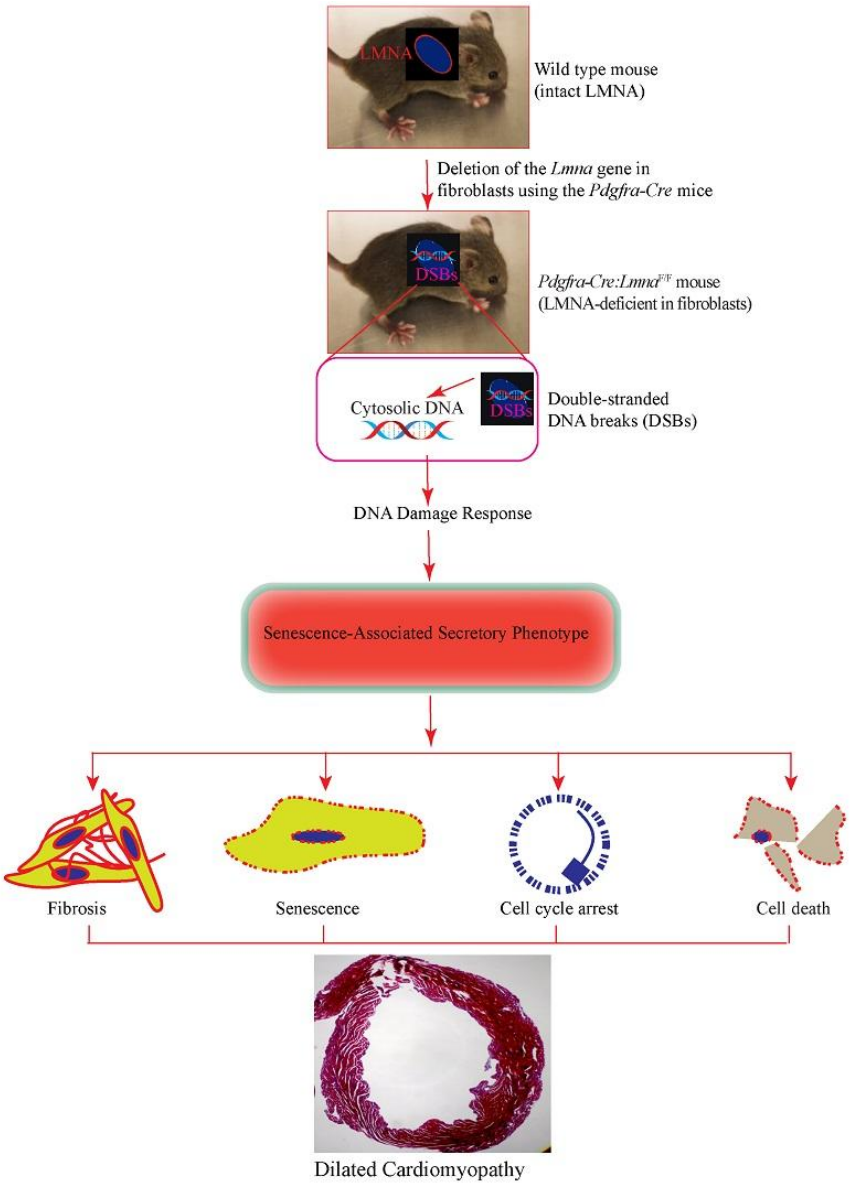
Methods and Results: The *Lmna* gene was deleted by crossing the platelet-derived growth factor receptor α - Cre recombinase (*Pdgfra-Cre*) and floxed *Lmna* ($Lmna^{F/F}$) mice. The LMNA protein was nearly absent in ~80% of the cardiac fibroblasts and ~25% of cardiac myocytes in the *Pdgfra-Cre:*$Lmna^{F/F}$ mice. The *Pdgfra-Cre:*$Lmna^{F/F}$ mice showed an early phenotype characterized by cardiac conduction defects, arrhythmias, cardiac dysfunction, myocardial fibrosis, apoptosis, and premature death within the first six weeks of life. The *Pdgfra-Cre:*$Lmna^{Wild\ type/F}$ ($Lmna^{W/F}$) mice also showed a similar but slowly evolving phenotype that was expressed within one year of age. RNA sequencing of LMNA-deficient and wild-type cardiac fibroblasts identified differential expression of ~410 genes, which predicted activation of the TP53 and TNFA/NF κ B and suppression of the cell cycle pathways. In agreement with these findings, levels of phospho-H2AFX, ATM, phospho-TP53, and CDKN1A, markers of the DNA damage response (DDR) pathway, were increased in the *Pdgfra-Cre:*$Lmna^{F/F}$ mouse hearts. Moreover, expression of senescence-associated beta-galactosidase was induced and levels of the senescence-associated secretory phenotype (SASP) proteins TGFβ1, CTGF (CCN2), and LGLAS3 were increased as well as the transcript levels of additional genes encoding SASP proteins in the *Pdgfra-Cre:LmnaF/F* mouse hearts. Finally, expression of pH2AFX, a bonafide marker of the double-stranded DNA breaks, was increased in cardiac fibroblasts isolated from the *Pdgfra-Cre:*$Lmna^{F/F}$ mouse hearts.

Conclusion: Deletion of the *Lmna* gene in fibroblasts partially recapitulates the phenotype of the LMNA-associated DCM, likely through induction of double-stranded DNA breaks, activation of the DDR pathway, and induction of expression of the SASP proteins. The findings indicate that the phenotype in the LMNA-associated DCM is the aggregate consequence of the LMNA deficiency in multiple cardiac cells, including cardiac fibroblasts.

One sentence summary: Cardiac fibroblasts contribute to the pathogenesis of DCM - associated with LMNA deficiency through activation of the senescence-associated secretory phenotype.

Keywords
Fibroblasts, senescence, fibrosis, apoptosis, lamin A/C, heart failure, cardiomyopathy

Graphical abstract



Cite this article

Rouhi L, Auguste G, Zhou Q, Lombardi R, Olcum M, Pourebrahim K, Cheedipudi SM, Asghar S, Hong K, Robertson MJ, Coarfa C, Gurha P, Marian AJ. Deletion of the *Lmna* gene in fibroblasts causes senescence-associated dilated cardiomyopathy by activating the double-stranded DNA damage response and induction of senescence-associated secretory phenotype. *J Cardiovasc Aging* 2022;2:30. http://dx.doi.org/10.20517/jca.2022.14

10. STEMIN and YAP5SA synthetic modified mRNAs regenerate and repair infarcted mouse hearts

Siyu Xiao, Rui Liang, Emilio Lucero, Bradley K. McConnell, Zhishi Chen, Jiang Chang, Stephen Navran, Robert J. Schwartz*, Dinakar Iyer

Read
Full-text PDF PMID: 35891703 PMCID: PMC9311335 DOI: 10.20517/jca.2022.20
Citation
RIS Plain text

Abstract

Introduction: The adult heart lacks the regenerative capacity to self-repair. Serum response factor (SRF) is essential for heart organogenesis, sarcomerogenesis, and contractility. SRF interacts with co-factors, such as NKX2.5 and GATA4, required for cardiac specified gene activity. ETS factors such as ELK1 interact with SRF and drive cell replication. To weaken SRF interactions with NKX2.5 and GATA4, one mutant, SRF153(A3) named STEMIN, did not bind CArG boxes, yet induced stem cell factors such as NANOG and OCT4, cardiomyocyte dedifferentiation, and cell cycle reentry. The mutant YAP5SA of the Hippo pathway also promotes cardiomyocyte proliferation and growth.

Aim: Infarcted adult mouse hearts were injected with translatable STEMIN and YAP5SA mmRNA to evaluate their clinical potential,

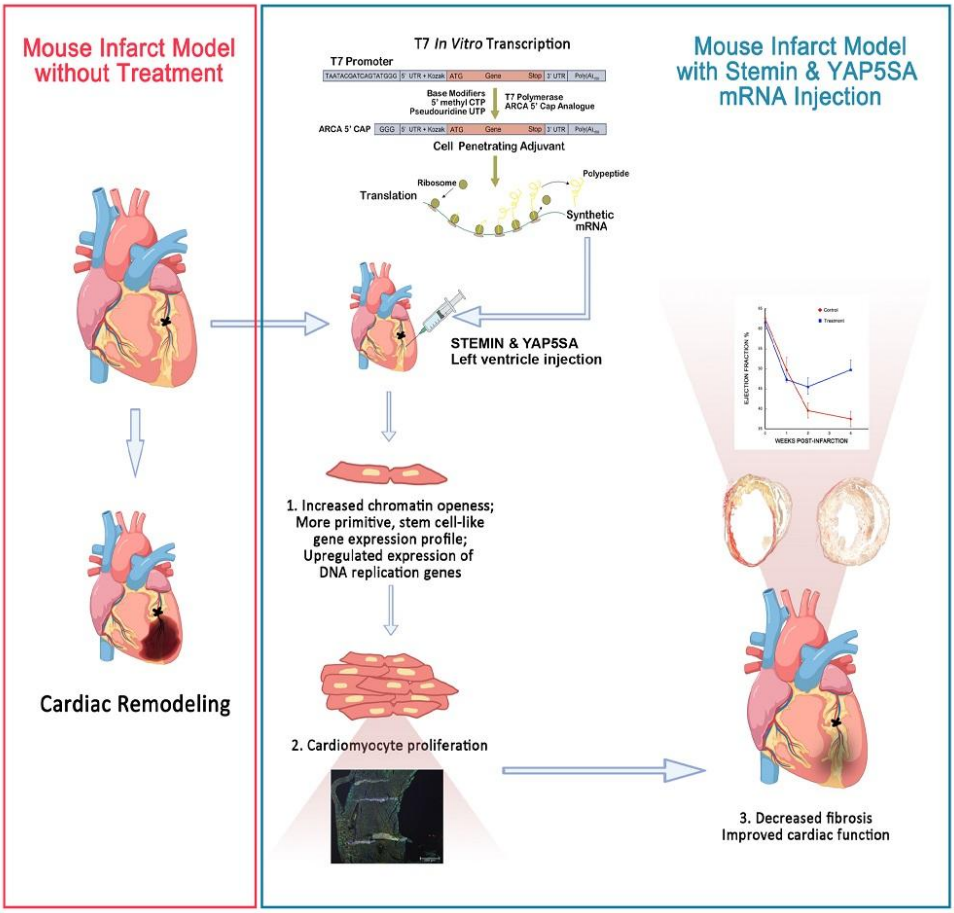
Methods and Results: Mice were pulsed one day later with alpha-EDU and then heart sections were DAPI stained. Replicating cells were identified by immuno-staining against members of the DNA replisome pathway that mark entry to S phase of the cell cycle. Echocardiography was used to determine cardiac function following infarcts and mRNA treatment. To monitor cardiac wall repair, microscopic analysis was performed, and the extent of myocardial fibrosis was analyzed for immune cell infiltration. Injections of STEMIN and YAP5SA mmRNA into the left ventricles of infarcted adult mice promoted a greater than 17-fold increase in the DAPI stained and alpha-EDU marked cardiomyocyte nuclei, within a day. We observed de novo expression of phospho-histone H3, ORC2, MCM2, and CLASPIN. Cardiac function was significantly improved by four weeks post-infarct, and fibrosis and immune cell infiltration were diminished in hearts treated with STEMIN and YAP5SA mmRNA than each alone.

Conclusion: STEMIN and YAP5SA mmRNA improved cardiac function and myocardial fibrosis in left ventricles of infarcted adult mice. The combinatorial use of mmRNA encoding STEMIN and YAP5SA has the potential to become a powerful clinical strategy to treat human heart disease.

Keywords

Cardiac regeneration, synthetic mRNA, heart delivery, serum response factor, STEMIN, hippo pathway, YAP5SA

Graphical abstract



Cite this article

Xiao S, Liang R, Lucero E, McConnell BK, Chen Z, Chang J, Navran S, Schwartz RJ, Iyer D. STEMIN and YAP5SA synthetic modified mRNAs regenerate and repair infarcted mouse hearts. *J Cardiovasc Aging* 2022;2:31. http://dx.doi.org/10.20517/jca.2022.20

11. In-depth characterization of a mouse model of postoperative atrial fibrillation

Joshua A. Keefe, Jose Alberto Navarro-Garcia, Li Ni, Svetlana Reilly, Dobromir Dobrev, Xander H.T. Wehrens*

Read
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Citation
RIS Plain text

Abstract

Introduction: Postoperative atrial fibrillation (POAF), characterized as AF that arises 1-3 days after surgery, occurs after 30%-40% of cardiac and 10%-20% of non-cardiac surgeries, and is thought to arise due to

transient surgery-induced triggers acting on a preexisting vulnerable atrial substrate often associated with inflammation and autonomic nervous system dysfunction. Current experimental studies often rely on human atrial tissue samples, collected during surgery prior to arrhythmia development, or animal models such as sterile pericarditis and atriotomy, which have not been robustly characterized.

Aim: To characterize the demographic, electrophysiologic, and inflammatory properties of a POAF mouse model.

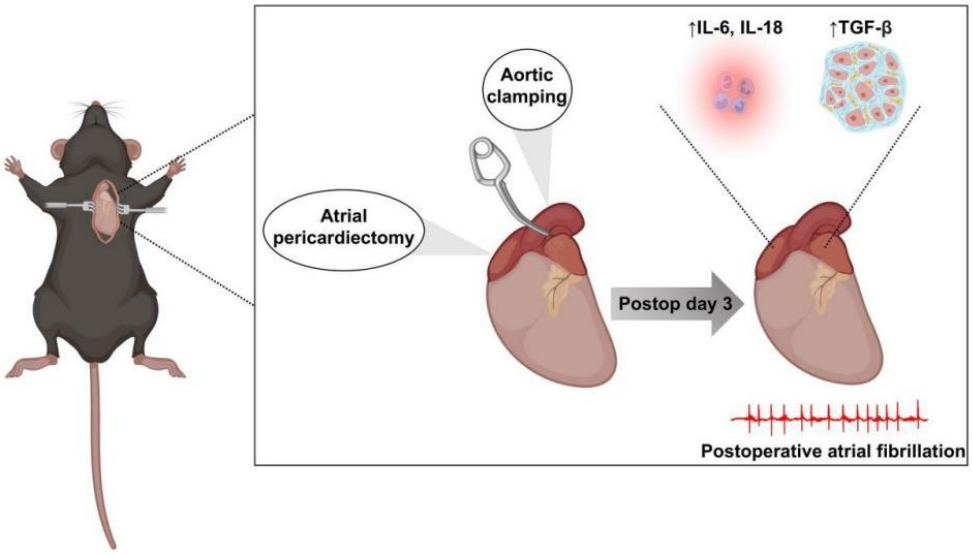
Methods and Results: A total of 131 wild-type C57BL/6J mice were included in this study. A total of 86 (65.6%) mice underwent cardiothoracic surgery (THOR), which consisted of bi-atrial pericardiectomy with 20 s of aortic cross-clamping; 45 (34.3%) mice underwent a sham procedure consisting of dissection down to but not into the thoracic cavity. Intracardiac pacing, performed 72 h after surgery, was used to assess AF inducibility. THOR mice showed greater AF inducibility (38.4%) compared to Sham mice (17.8%, P = 0.027). Stratifying the cohort by tertiles of age showed that the greatest risk of POAF after THOR compared to Sham occurred in the 12-19-week age group. Stratifying by sex showed that cardiothoracic (CT) surgery increased POAF risk in females but had no significant effect in males. Quantitative polymerase chain reaction of atrial samples revealed upregulation of transforming growth factor beta 1 (*TGF-β1*) and interleukin 6 (IL6) and 18 (IL18) expression in THOR compared to Sham mice.

Conclusion: Here, we demonstrate that the increased POAF risk associated with CT surgery is most pronounced in female and 12-19-week-old mice, and that the expression of inflammatory cytokines is upregulated in the atria of THOR mice prone to inducible AF.

One sentence summary: We developed a mouse model of POAF that replicates key features of this condition in humans in terms of incidence and inflammatory indices. We demonstrated that female mice have a greater POAF risk than males, highlighting the importance of considering biological sex in future POAF mouse studies.

Keywords
Atrial fibrillation, cardiothoracic surgery, biological sex, inflammation, fibrosis

Graphical abstract



Cite this article

Keefe JA, Navarro-Garcia JA, Ni L, Reilly S, Dobrev D, Wehrens XHT. In-depth characterization of a mouse model of postoperative atrial fibrillation. *J Cardiovasc Aging* 2022;2:40. http://dx.doi.org/10.20517/jca.2022.21

12. Mitochondrial DAMPs-dependent inflammasome activation during aging induces vascular smooth muscle cell dysfunction and aortic stiffness in low aerobic capacity rats

Chandrika Canugovi, Mark D. Stevenson, Aleksandr E. Vendrov, Andrey Lozhkin, Steven L. Britton, Lauren G. Koch, Marschall S. Runge, Nageswara R. Madamanchi*

Read
Full-text PDF DOI: 10.20517/jca.2022.35
Citation
RIS Plain text

Abstract

Introduction: Low aerobic exercise capacity is an independent risk factor for cardiovascular disease (CVD) and a predictor of premature death. In combination with aging, low aerobic capacity lowers the threshold for CVD.

Aim: Since low aerobic capacity and aging have been linked to mitochondrial oxidative stress and dysfunction, we investigated whether aged Low-Capacity Runner (LCR) rats (27 months) had vascular dysfunction compared to High-Capacity Runner (HCR) rats.

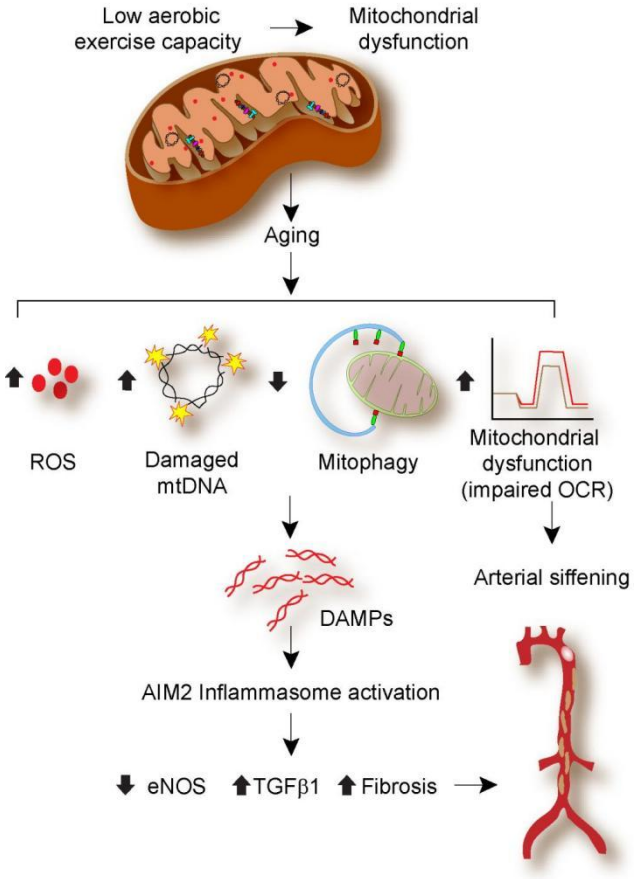
Methods and Results: A significant decrease in aortic eNOS levels and vasodilation as well as an increase in aortic collagen and stiffness were observed in aged LCR rats compared to age and sex-matched HCR rats.

There was a correlation between age-related vascular dysfunction and increased levels of ROS and DNA damage in aortas of LCR rats. Moreover, mitochondrial oxygen consumption, membrane potential, ATP levels, and mitophagy were lower in VSMCs of aged LCR rats. VSMCs from older LCR rats showed AIM2 inflammasome activation. VSMCs of young (4 months old) LCR rats treated with purified mitochondrial damage-associated molecular patterns (DAMP) recapitulated an inflammasome activation phenotype similar to that seen in aged rat VSMCs. Rapamycin, a potent immunosuppressant, induced mitophagy, stimulated electron transport chain activity, reduced inflammasome activity, mitochondrial ROS and DAMP levels in VSMCs from aged LCR rats. MitoTEMPO, a mitochondrial ROS scavenger, was similarly effective on VSMCs from aged rats.

Conclusion: The findings suggest that impaired mitophagy and inflammasome activation in the vasculature under conditions of low aerobic exercise capacity during aging results in arterial dysfunction and aortic stiffness. In older adults with reduced aerobic capacity, mitochondrial antioxidants, mitophagy induction, and inflammasome inhibition may be effective therapeutic strategies for enhancing vascular health.

Keywords
Oxidative stress, DNA damage, AIM2 inflammasome, mitophagy, mitochondrial bioenergetics, VSMC

Graphical abstract



Video abstract
https://v1.oaepublish.com/files/talkvideo/5208.mp4

Cite this article

Canugovi C, Stevenson MD, Vendrov AE, Lozhkin A, Britton SL, Koch LG, Runge MS, Madamanchi NR. Mitochondrial DAMPs-dependent inflammasome activation during aging induces vascular smooth muscle cell dysfunction and aortic stiffness in low aerobic capacity rats. *J Cardiovasc Aging* 2022;2:47.
http://dx.doi.org/10.20517/jca.2022.35

13. PANoptosis is a prominent feature of desmoplakin cardiomyopathy

Melis Olcum, Leila Rouhi, Siyang Fan, Maya M. Gonzales, Hyun-Hwan Jeong, Zhongming Zhao, Priyatansh Gurha, Ali J. Marian*

Read
Full-text PDF PMCID: PMC9933912 DOI: 10.20517/jca.2022.34
Citation
RIS Plain text

Abstract

Introduction: Arrhythmogenic cardiomyopathy (ACM) is hereditary cardiomyopathy caused by pathogenic variants (mutations) in genes encoding the intercalated disc (ID), particularly desmosome proteins. ACM caused by mutations in the DSP gene encoding desmoplakin (DSP) is characterized by the prominence of cell death, myocardial fibrosis, and inflammation, and is referred to as desmoplakin cardiomyopathy.

Aim: The aim of this article was to gain insight into the pathogenesis of DSP cardiomyopathy.

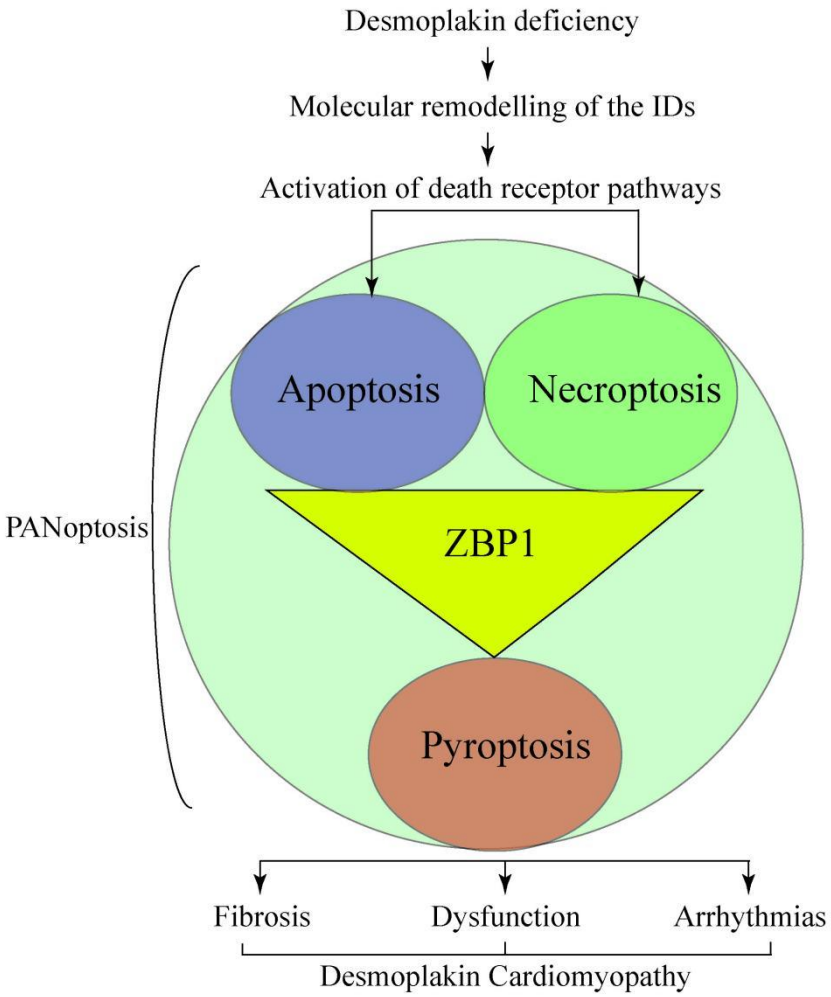
Methods and Results: The Dsp gene was exclusively deleted in cardiac myocytes using tamoxifen-inducible MerCreMer (*Myh6-Mcm*^{Tam}) and floxed *Dsp* (*Dsp*$^{F/F}$) mice (*Myh6-Mcm*^{Tam}:*Dsp*$^{F/F}$). Recombination was induced upon subcutaneous injection of tamoxifen (30 mg/kg/d) for 5 days starting post-natal day 14. Survival was analyzed by Kaplan-Meier plots, cardiac function by echocardiography, arrhythmias by rhythm monitoring, and gene expression by RNA-Seq, immunoblotting, and immunofluorescence techniques. Cell death was analyzed by the TUNEL assay and the expression levels of specific markers were by RT-PCR and immunoblotting. Myocardial fibrosis was assessed by picrosirius red staining of the myocardial sections, RT-PCR, and immunoblotting. The *Myh6-Mcm*^{Tam}:*Dsp*$^{F/F}$ mice showed extensive molecular remodeling of the IDs and the differential expression of ~10,000 genes, which predicted activation of KDM5A, IRFs, and NFκB and suppression of PPARGC1A and RB1, among others in the DSP-deficient myocytes. Gene set enrichment analysis predicted activation of the TNFα/NFκB pathway, inflammation, cell death programs, and fibrosis. Analysis of cell death markers indicated PANoptosis, comprised of apoptosis (increased CASP3, CASP8, BAD and reduced BCL2), necroptosis (increased RIPK1, RIPK3, and MLKL), and pyroptosis (increased GSDMD and ASC or PYCARD) in the DSP-deficient myocytes. Transcript levels of the pro-inflammatory and pro-fibrotic genes were increased and myocardial fibrosis comprised ~25% of the myocardium in the DSP-deficient hearts. The *Myh6-Mcm*^{Tam}:*Dsp*$^{F/F}$ mice showed severe cardiac systolic dysfunction and ventricular arrhythmias, and died prematurely with a median survival rate of ~2 months.

Conclusion: The findings identify PANoptosis as a prominent phenotypic feature of DSP cardiomyopathy and set the stage for delineating the specific molecular mechanisms involved in its pathogenesis. The model also provides the opportunity to test the effects of pharmacological and genetic interventions on myocardial fibrosis and cell death.

One sentence summary: Post-natal homozygous deletion of the *Dsp* gene leads to fulminant PANoptosis and severe myocardial fibrosis, cardiac dysfunction, arrhythmias, and premature death in mice.

Keywords
Desmoplakin cardiomyopathy, PANoptosis, apoptosis, necroptosis, pyroptosis, inflammation, fibrosis

Graphical abstract



Video abstract
https://v1.oaepublish.com/files/talkvideo/5252.mp4

Cite this article

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14. The *TNNI3* p.R186Q mutation is responsible for hypertrophic cardiomyopathy via promoting FASN-stimulated abnormal fatty acid metabolism

Linjuan Guo[#], Yuhao Su[#], Chen Chen, Qiongqiong Zhou, Yang Shen, Zhenhong Jiang, Xia Yan, Xiaoqing Li, Wen Zhuo, Xiaogang Peng, Rong Wan*, Kui Hong*

Read
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Citation
RIS Plain text

Abstract

Introduction: The *TNNI3* gene encodes the protein of cardiac troponin I (cTnI), which is an inhibitory subunit of sarcomeres. Mutations in this gene account for 3% of hypertrophic cardiomyopathy (HCM) and the molecular mechanism is complex. Recently, lipid metabolism has been revealed to be involved in HCM.

Aim: The purpose of this work is to identify whether the pathological mechanism of the hotspot mutation *TNNI3* p.R186Q in HCM is related to abnormal lipid metabolism.

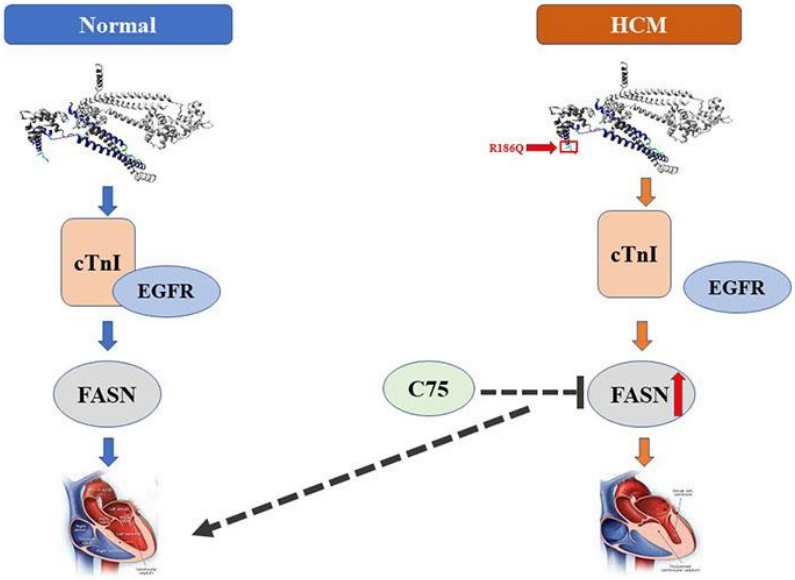
Methods and Results: A knock-in (KI) mouse model carrying the *Tnni3* p.R186Q homozygous mutation (*Tnni3*$^{R186Q/R186Q}$) was novelty generated by *CRISPR/Cas9* technology and successfully constructed a typical phenotype of cardiac-myopathy. Likewise, neonatal rat cardiomyocytes (NRCMs) transfected with a mutant plasmid with the *TNNI3* p.R186Q mutation showed the same phenomenon. In-depth experiments on related functions and molecular mechanisms were conducted, and *Tnni3*$^{R186Q/R186Q}$ mice exhibited abnormal fatty acid metabolism, which was induced by the activation of epidermal growth factor receptor (EGFR)-dependent high expression of fatty acid synthase (FASN) *in vivo* and *in vitro*. Specifically, the direct binding of EGFR and cTnI was destroyed by *TNNI3* p.R186Q mutation, as observed through bioinformatics, Co-IP and GST-pull down analysis.

Conclusion: In the present study, we successfully engineered *Tnni3*$^{R186Q/R186Q}$ mice with the typical phenotype of myocardial hypertrophy. We demonstrated that the *TNNI3* p.R186Q mutation could induce HCM by the dissociation of EGFR and cTnI, which further led to EGFR-dependent increased expression of FASN and abnormal lipid metabolism.

Keywords

TNNI3, gene mutation, FASN, hypertrophic cardiomyopathy, abnormal fatty acid metabolism

Graphical abstract



Cite this article

Guo L, Su Y, Chen C, Zhou Q, Shen Y, Jiang Z, Yan X, Li X, Zhuo W, Peng X, Wan R, Hong K. The TNNI3 p.R186Q mutation is responsible for hypertrophic cardiomyopathy via promoting FASN-stimulated abnormal fatty acid metabolism. *J Cardiovasc Aging* 2023;3:6. http://dx.doi.org/10.20517/jca.2022.29

15. Reassessment of genes associated with dilated and hypertrophic cardiomyopathy in a Chinese Han population

Yang Sun[#], Hong Wang[#], Man Huang, Ke Li, Xiuli Song, Lei Xiao, Jiaqi Dai, Linlin Wang, Yanghui Chen, Dongyang Wu, Ting Yu, Rui Li, Fei Ma, Zongzhe Li, Peng Chen, Hong Wang, Yan Wang, Zhongsheng Sun, Li Jin, Dao Wu Wang, Guangzhi Chen*, Dao Wen Wang*

Read
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Citation
RIS Plain text

Abstract

Introduction: More than 100 genes are reportedly associated with dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). However, the situation that many genes lack of reassessment in a large population hinders the interpretations of these genes in genetic diagnostic testing. Moreover, limited genetic data for cardiomyopathy in Chinese patients was reported.

Aim: Therefore, here we reassessed an estimated 500 putative genes in the Chinese Han population by whole exome sequencing (WES) to describe the landscape of variants in these genes and to confirm their genetic

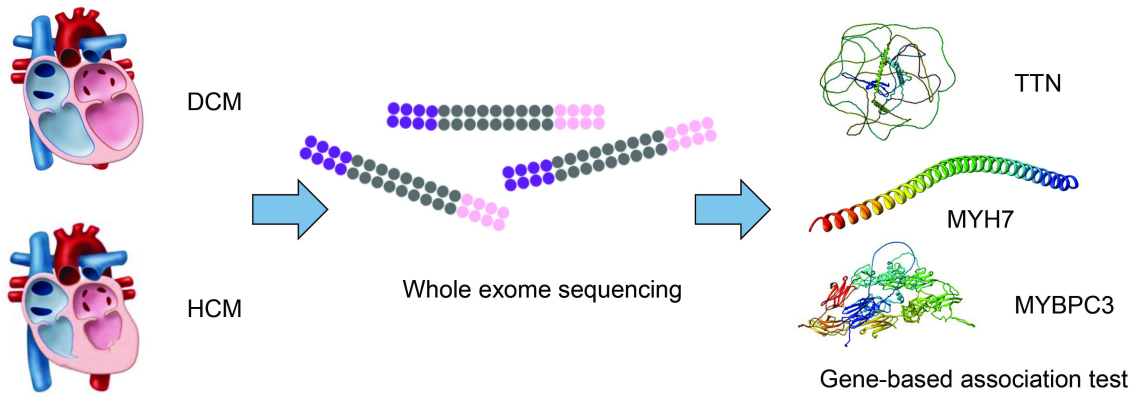
contribution to DCM and HCM.

Methods and Results: WES was performed in 1059 DCM patients, 1175 HCM patients and 514 controls. Approximately 500 candidate genes were selected for evaluation. Truncating variants of TTN and MYBPC3 were the most burdensome for both groups. Gene-based association tests identified 35 and 35 genes associated with DCM and HCM, respectively. Except for the known genes of cardiomyopathy, the top three genes associated with DCM were MUC16, KMT2C, and FBN1, while the top three genes associated with HCM were KMT2C, RYR2, and SCN5A. After filtering for pathogenicity, FBN1 is still significantly associated with DCM and SCN5A and RYR2 remains significantly enriched in HCM patients. However, after adjustment, only TTN with DCM and MYBPC3 and MYH7 with HCM remains significant.

Conclusion: We described the genetic landscape of Chinese patients with DCM and HCM and developed a website (www.cardioexome.cn) to enable open access to this information. Furthermore, the gene-based association test confirmed the contribution of TTN to DCM and MYBPC3 and MYH7 to HCM in Chinese Han. In addition, the website, www.cardioexome.cn, was developed to store these sequencing results.

Keywords
Dilated Cardiomyopathy, hypertrophic cardiomyopathy, whole exome sequencing, gene-based association, case-control study

Graphical abstract



CardioExomes
https://www.cardioexome.cn/

Cite this article

Sun Y, Wang H, Huang M, Li K, Song X, Xiao L, Dai J, Wang L, Chen Y, Wu D, Yu T, Li R, Ma F, Li Z, Chen P, Wang H,

Wang Y, Sun Z, Jin L, Wang DW, Chen G, Wang DW. Reassessment of genes associated with dilated and hypertrophic cardiomyopathy in a Chinese Han population. *J Cardiovasc Aging* 2023;3:12. http://dx.doi.org/10.20517/jca.2022.44

16. Senolytics rejuvenate the reparative activity of human cardiomyocytes and endothelial cells

Piotr Sunderland, Lulwah Alshammari, Emily Ambrose, Daniele Torella, Georgina M. Ellison-Hughes*

Read
Full-text PDF DOI: 10.20517/jca.2023.07
Citation
RIS Plain text

Abstract

Introduction: Senescent cells have emerged as bona fide drivers of ageing and age-related cardiovascular disease, with senescent cells accumulating in the aged heart and following damage/injury. We have shown that the removal of senescent cells using senolytics can rejuvenate the regenerative capacity of the aged heart.

Aim: To investigate the effects of cell senescence and the action of the senolytics, Dasatinib (D) and Quercetin (Q) on human iPSC-derived cardiomyocyte survival and cell cycle, and endothelial cell survival, cell cycle, migration and tube formation in vitro.

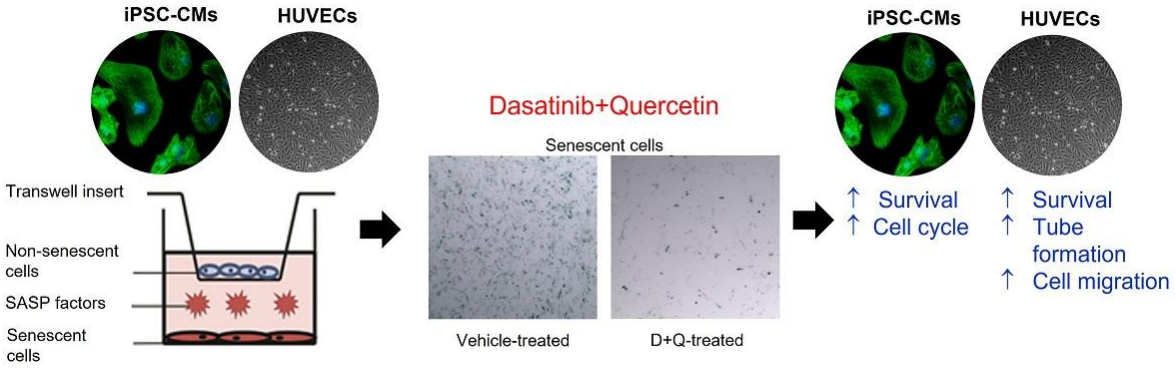
Methods and Results: We developed a transwell insert co-culture stress-induced premature senescence human cell model system to test the effects of senolytics D+Q in vitro. Co-culture of iPSC-derived cardiomyocytes (iPSC-CMs) with senescent cardiac stromal progenitor cells (senCPCs) led to decreased number and DNA-synthesising activity of iPSC-CMs. Treatment with senolytics D+Q led to the elimination of senCPCs in the co-culture and the rescue of iPSC-CM number and DNA synthesis. Treatment of HUVECs with senCPC conditioned media decreased HUVEC number, cell cycle activity, migration, and tube formation. Treatment of HUVECs with D+Q conditioned media rescued HUVEC number, migration and tube formation. Next, we investigated the effects of co-culture of senescent HUVECs (senHUVECs) with HUVECs and showed decreased HUVEC number and DNA synthesis. Treatment with senolytics D+Q led to the elimination of senHUVECs in the co-culture and ameliorated HUVEC number, but not DNA synthesis. Treatment of HUVECs with conditioned media from senHUVECs led to decreased HUVEC migration and tube formation. Treatment of HUVECs with D+Q conditioned media improved HUVEC tube formation but not migration. Luminex analysis of the conditioned media from iPSC-CM and HUVEC co-cultures revealed upregulation of senescence-associated secretory phenotype (SASP) factors, but the level of SASP factors was reduced with the application of D+Q.

Conclusion: Senescent cell removal by senolytics D+Q shows therapeutic potential in rejuvenating the reparative activity of human cardiomyocytes and endothelial cells. These results open the path to further studies on using senolytic therapy in age-related cardiac deterioration and rejuvenation.

Potential impact of the findings: Senescent cells and their SASP present a promising therapeutic target to rejuvenate the heart's reparative potential. Clinical trials using senolytics D+Q are already underway and thus far have shown promising results. Further pre-clinical studies are warranted for evidence-based clinical trials using senolytics in age-related cardiovascular diseases.

Keywords
Cell senescence, senolytics, iPSC-derived cardiomyocytes, endothelial cells, cardiovascular

Graphical abstract



Cite this article

Sunderland P, Alshammari L, Ambrose E, Torella D, Ellison-Hughes GM. Senolytics rejuvenate the reparative activity of human cardiomyocytes and endothelial cells. *J Cardiovasc Aging* 2023;3:21. http://dx.doi.org/10.20517/jca.2023.07

17. Rare variants in the *FBN1* gene are associated with sporadic dilated cardiomyopathy in a Chinese Han population

Dongyang Wu, Yang Sun, Chenze Li, Lei Xiao, Jiaqi Dai, Yanghui Chen, Peng Chen, Hong Wang, Bo Yu, Haoran Wei, Rui Li, Xiuli Song, Ting Yu, Leming Shi, Dao Wen Wang*

Read
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Citation
RIS Plain text

Abstract
Introduction: Dilated cardiomyopathy (DCM) represents a diverse set of myocardial diseases characterized by notable genetic heterogeneity. Although over 50 genes have been associated with DCM, these collectively explain 35% of idiopathic DCM cases. Variants in the *FBN1* gene encoding fibrillin-1 are primarily linked to connective tissue disorders. Considering the potential of these disorders to impact myocardial tissue, this study probes into the possible association between *FBN1* variants and DCM.

Aim: The objective of this study was to investigate the association between *FBN1* variants and DCM in a Chinese Han population.

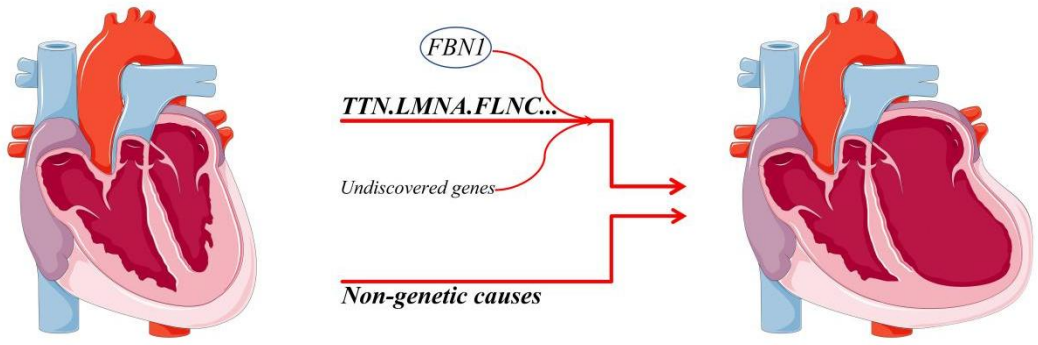
Methods and Results: We performed whole-exome sequencing (WES) to identify rare *FBN1* variants among 1,059 DCM cases and 514 controls. Utilizing a case-control strategy and the optimal sequence kernel association test (SKAT-O), we found a significant enrichment of rare deleterious *FBN1* variants in DCM patients (19 of 1,059 *vs.* 0 of 514, $P_{SKAT\text{-}O}$ = 7.49E-04). Clinical characteristics analysis indicated a higher occurrence of atrial fibrillation and a higher rate of implantable cardioverter-defibrillator (ICD) implantation among DCM patients carrying *FBN1* variants (*FBN1*$^{+}$) compared to non-carriers (*FBN1*$^{-}$). However, these *FBN1* variants did not significantly affect primary endpoints, defined as cardiac mortality or heart transplantation, yet appeared to increase the risk of secondary endpoints, including all-cause mortality or heart failure recurrence.

Conclusion: The findings suggest an association between rare deleterious variants in the *FBN1* gene and DCM in a Chinese Han population. Our findings underline the importance of further research to validate these results and elucidate the role of *FBN1* in DCM.

Potential impact of the findings: This research provides fresh insights into the potential role of *FBN1* rare variants in DCM, pointing to new directions for future genetic studies and potential therapeutic strategies in DCM management.

Keywords
Dilated cardiomyopathy, whole-exome sequencing, gene-based association test, case-control study

Graphical abstract



Cite this article

Wu D, Sun Y, Li C, Xiao L, Dai J, Chen Y, Chen P, Wang H, Yu B, Wei H, Li R, Song X, Yu T, Shi L, Wang DW. Rare variants in the *FBN1* gene are associated with sporadic dilated cardiomyopathy in a Chinese Han population. *J Cardiovasc Aging* 2023;3:30. http://dx.doi.org/10.20517/jca.2023.12

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging

18. Characterization of atrial and ventricular remodeling in an improved minimally invasive mouse model of transverse aortic constriction

Jose Alberto Navarro-Garcia[#], Satadru K. Lahiri[#], Yuriana Aguilar-Sanchez, Anilkumar K. Reddy, Xander H. T. Wehrens*

Read
Full-text PDF DOI: 10.20517/jca.2023.18
Citation
RIS Plain text

Abstract

Introduction: Heart failure (HF) is the leading cause of death worldwide. Most large and small animal disease models of HF are based on surgical procedures. A common surgical technique to induce HF is transverse aortic constriction (TAC), which induces pressure overload. The conventional TAC (cTAC) procedure is a highly invasive surgery that is associated with severe inflammation and excessive perioperative deaths.

Aim: To establish an improved, minimally invasive TAC (mTAC) procedure that does not require thoracotomy.

Methods and Results: Following anesthesia, mice were intubated, and a small incision was made at the neck and chest. After cutting the sternum about 4 mm, the aortic arch was approached without opening the pleural cavity. A suture was placed between the brachiocephalic artery and the left common carotid artery. This model was associated with low perioperative mortality and a highly reproducible constriction evidenced by an increased right-to-left carotid blood flow velocity ratio in mTAC mice (5.9 ± 0.2) *vs.* sham controls (1.2 ± 0.1; $P < 0.001$). mTAC mice exhibited progressive cardiac remodeling during the 8 weeks post-TAC, resulting in reduced left ventricular (LV) contractility, increased LV end-systolic diameter, left atrial enlargement and diastolic dysfunction, and an increased heart weight to tibia length ratio (mTAC: 15.0 ± 0.8 *vs.* sham: 10.1 ± 0.6; $P < 0.01$).

Conclusion: Our data show that the mTAC procedure yields a highly reproducible phenotype consisting of LV contractile dysfunction and enlargement, combined with left atrial enlargement and diastolic dysfunction.

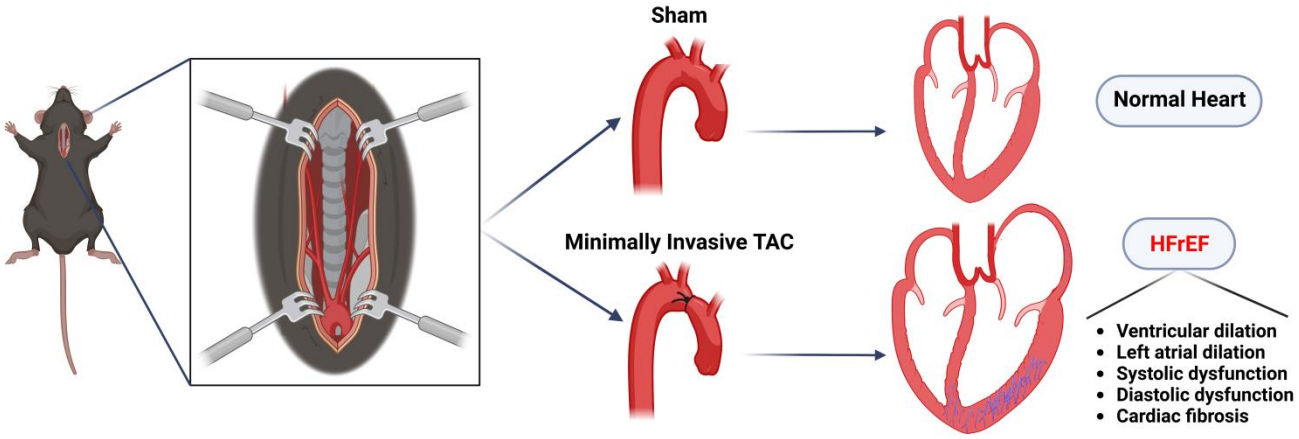
Potential impact of the findings: This model may be used to test the molecular mechanisms underlying atrial remodeling associated with HF development or to evaluate therapeutic strategies to treat these conditions.

Keywords

Atrial remodeling, atrial fibrillation, heart failure, mouse model, transverse aortic constriction

Graphical abstract

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging



Cite this article

Navarro-Garcia JA, Lahiri SK, Aguilar-Sanchez Y, Reddy AK, Wehrens XHT. Characterization of atrial and ventricular remodeling in an improved minimally invasive mouse model of transverse aortic constriction. *J Cardiovasc Aging* 2023;3:31. http://dx.doi.org/10.20517/jca.2023.18

Review

1. Epigenetic dysregulation in cardiovascular aging and disease

Allison B. Herman*, James R. Occean, Payel Sen*

Read
Full-text PDF PMID: 34790973 PMCID: PMC8594871 DOI: 10.20517/jca.2021.16
Citation
RIS Plain text

Abstract
Cardiovascular disease (CVD) is the leading cause of mortality and morbidity for all sexes, racial and ethnic groups. Age, and its associated physiological and pathological consequences, exacerbate CVD incidence and progression, while modulation of biological age with interventions track with cardiovascular health. Despite the strong link between aging and CVD, surprisingly few studies have directly investigated heart failure and vascular dysfunction in aged models and subjects. Nevertheless, strong correlations have been found between heart disease, atherosclerosis, hypertension, fibrosis, and regeneration efficiency with senescent cell burden and its proinflammatory sequelae. In agreement, senotherapeutics have had success in reducing the detrimental effects in experimental models of cardiovascular aging and disease. Aside from senotherapeutics, cellular reprogramming strategies targeting epigenetic enzymes remain an unexplored yet viable option for reversing or delaying CVD. Epigenetic alterations comprising local and global changes in DNA and histone modifications, transcription factor binding, disorganization of the nuclear lamina, and misfolding of the genome are hallmarks of aging. Limited studies in the aging cardiovascular system of murine models or human patient samples have identified strong correlations between the epigenome, age, and senescence. Here, we compile the findings in published studies linking epigenetic changes to CVD and identify clear themes of epigenetic deregulation during aging. Pending direct investigation of these general mechanisms in aged tissues, this review predicts that future work will establish epigenetic rejuvenation as a potent method to delay CVD.

Keywords
Epigenetics, chromatin, cardiovascular, senescence, aging

Cite this article

Herman AB, Occean JR, Sen P. Epigenetic dysregulation in cardiovascular aging and disease. *J Cardiovasc Aging* 2021;1:10. http://dx.doi.org/10.20517/jca.2021.16

2. Cellular aging and rejuvenation in ischemic heart disease: a translation from basic science to clinical therapy

Rosalinda Madonna*

Read
Full-text PDF DOI: 10.20517/jca.2021.34
Citation
RIS Plain text

Abstract
Ischemic heart disease and heart failure (HF) remain the leading causes of death worldwide. The inability of the adult heart to regenerate itself following ischemic injury and subsequent scar formation may explain the poor prognosis in these patients, especially when necrosis is extensive and leads to severe left ventricular dysfunction. Under physiological conditions, the crosstalk between cardiomyocytes and cardiac interstitial/vascular cells plays a pivotal role in cardiac processes by limiting ischemic damage or promoting repair processes, such as angiogenesis, regulation of cardiac metabolism, and the release of soluble paracrine or endocrine factors. Cardiovascular risk factors are the main cause of accelerated senescence of cardiomyocytes and cardiac stromal cells (CSCs), causing the loss of their cardioprotective and repairing functions. CSCs are supportive cells found in the heart. Among these, the pericytes/mural cells have the propensity to differentiate, under appropriate stimuli in vitro, into adipocytes, smooth muscle cells, osteoblasts, and chondroblasts, as well as other cell types. They contribute to normal cardiac function and have an antifibrotic effect after ischemia. Diabetes represents a condition of accelerated senescence. Among the new pharmacological armamentarium with hypoglycemic effect, gliflozins have been shown to reduce the incidence of HF and re-hospitalization, probably through the anti-remodeling and anti-senescent effect on the heart, regardless of diabetes. Therefore, either reducing the senescence of CSC or removing senescent cells from the infarcted heart could represent future antisenescence strategies capable of preventing the deterioration of heart function leading to HF.

Keywords
Aging, ischemic heart disease, rejuvenation, omics, experimental studies

Cite this article

Madonna R. Cellular aging and rejuvenation in ischemic heart disease: a translation from basic science to clinical therapy. *J Cardiovasc Aging* 2022;2:12. http://dx.doi.org/10.20517/jca.2021.34

3. Changes in cardiac structure and function with aging

Tanushree Agrawal , Sherif F. Nagueh*

Read
Full-text PDF DOI: 10.20517/jca.2021.40
Citations
RIS Plain text

Abstract
Aging is associated with progressive changes in cardiac structure and function. The prevalence of cardiovascular risk factors and disease also increases profoundly with advancing age. Therefore, understanding the spectrum of physiological changes in the aging heart is crucial for the identification and risk stratification of cardiovascular disease. In this review, we discuss echocardiographic features of age-related cardiac remodeling.

Keywords
Aging, cardiovascular imaging, echocardiography, systolic, diastolic

Cite this article

Agrawal T, Nagueh SF. Changes in cardiac structure and function with aging. *J Cardiovasc Aging* 2022;2:13. http://dx.doi.org/10.20517/jca.2021.40

4. Mechanisms and implications of sex differences in cardiac aging

Aykhan Yusifov, Kathleen C. Woulfe, Danielle R. Bruns*

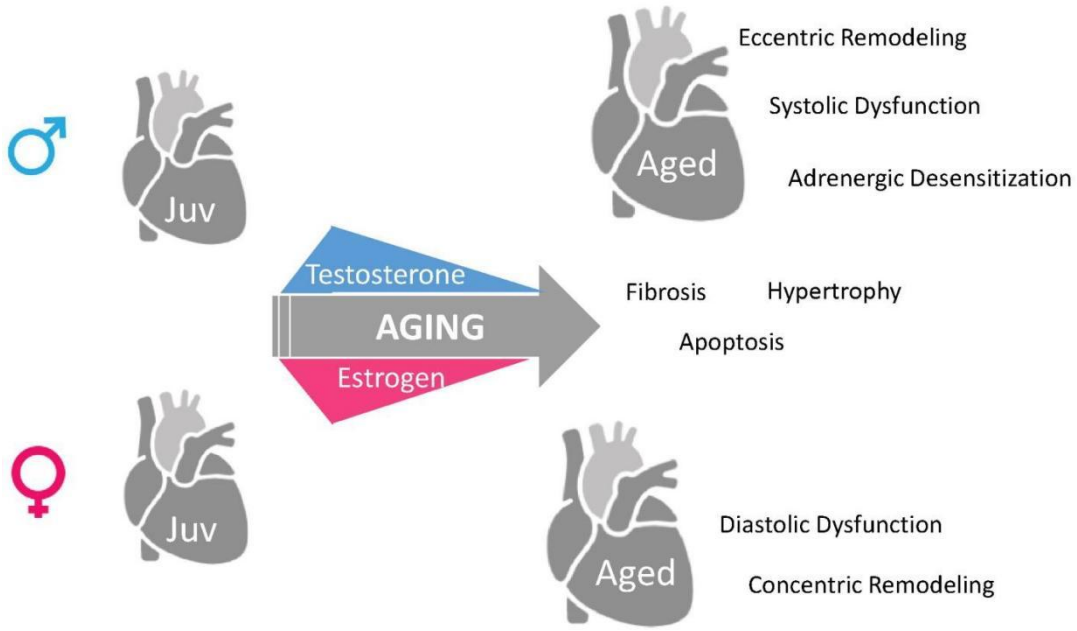
Read
Full-text PDF PMID: 35419571 PMCID: PMC9004711 DOI: 10.20517/jca.2022.01
Citation
RIS Plain text

Abstract
Aging promotes structural and functional remodeling of the heart, even in the absence of external factors. There is growing clinical and experimental evidence supporting the existence of sex-specific patterns of cardiac aging, and in some cases, these sex differences emerge early in life. Despite efforts to identify sex-specific differences in cardiac aging, understanding how these differences are established and regulated remains limited. In addition to contributing to sex differences in age-related heart disease, sex differences also appear to underlie differential responses to cardiac stress such as adrenergic activation. Identifying the underlying mechanisms of sex-specific differences may facilitate the characterization of underlying heart disease phenotypes, with the ultimate goal of utilizing sex-specific therapeutic approaches for cardiac disease.

The purpose of this review is to discuss the mechanisms and implications of sex-specific cardiac aging, how these changes render the heart more susceptible to disease, and how we can target age- and sex-specific differences to advance therapies for both male and female patients.

Keywords
Cardiac, aging, sex differences, fibrosis, adrenergic desensitization

Graphical abstract



Cite this article

Yusifov A, Woulfe KC, Bruns DR. Mechanisms and implications of sex differences in cardiac aging. *J Cardiovasc Aging* 2022;2:20. http://dx.doi.org/10.20517/jca.2022.01

5. Genetic basis of cardiovascular aging is at the core of human longevity

Ali J. Marian*

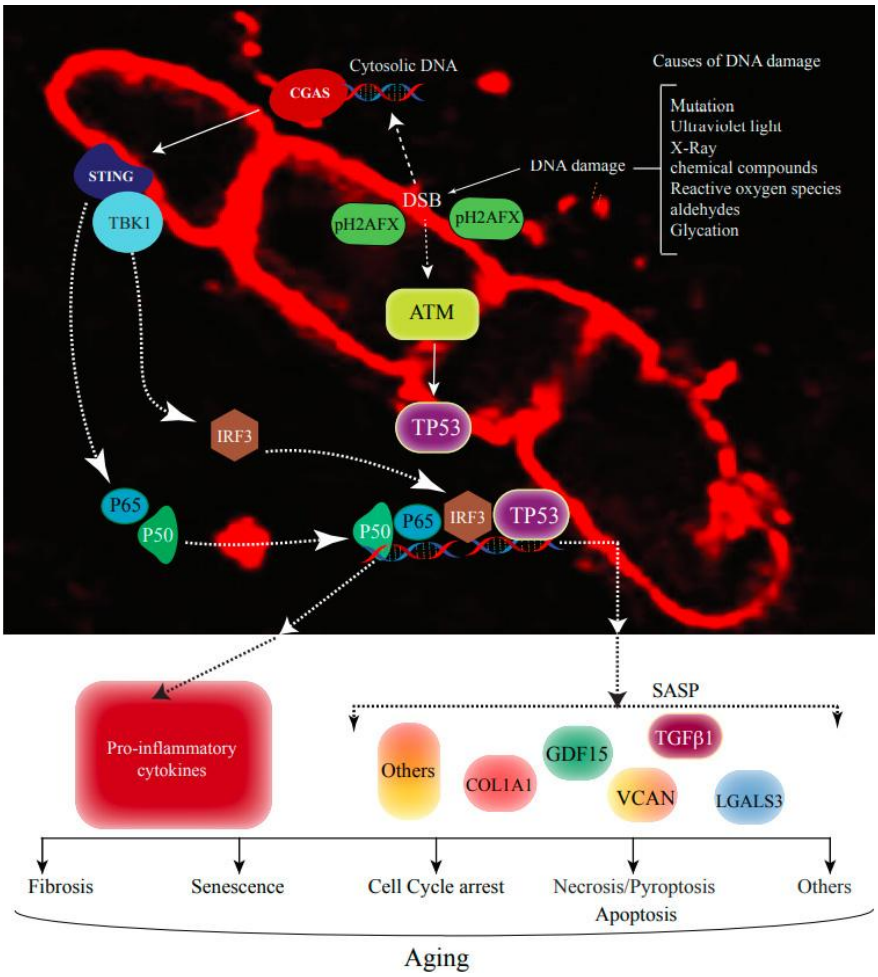
Read
Full-text PDF PMID: 35531366 PMCID: PMC9075051 DOI: 10.20517/jca.2022.06
Citation
RIS Plain text

Abstract
Aging is an archetypical complex process influenced by genetic and environmental factors. Genetic variants impart a gradient of effect sizes, albeit the effect sizes seem to be skewed toward those with small effect sizes. On one end of the spectrum are the rare monogenic premature aging syndromes, such as Hutchinson Gilford

Progeria Syndrome, whereby single nucleotide changes lead to rapidly progressive premature aging. On the end of the spectrum is the complex, slowly progressive process of living to an arbitrary-defined old age, i.e., longevity. Whereas the genetic basis of rare premature aging syndromes has been elucidated, only a small fraction of the genetic determinants of longevity and life span, time from birth to death, have been identified. The latter point to the complexity of the process and involvement of myriad of genetic and non-genetic factors and hence, the diluted effect of each determinant on longevity. The genetic discoveries point to the involvement of the DNA damage and activation of the DNA damage response pathway, particularly in the premature aging syndromes. Likewise, the insulin/insulin-like growth factor 1/mTOR/FOXO pathways have emerged as major regulators of life span. A notable fraction of the genetic variants that are associated with life span is also associated with age-related cardiovascular diseases, such as coronary artery disease and dyslipidemia, which places cardiovascular aging at the core of human life span. The clinical impact of the discoveries pertains to the identification of the pathways that are involved in life span, which might serve as targets of interventions to prevent, slow, and even possibly reverse aging.

Keywords
Longevity, life span, health span, genetics, progeria, APOE4, FOXO3, mTOR, DNA damage

Graphical abstract



Cite this article

Marian AJ. Genetic basis of cardiovascular aging is at the core of human longevity. *J Cardiovasc Aging* 2022;2:25. http://dx.doi.org/10.20517/jca.2022.06

6. Cancer treatment-induced NAD+ depletion in premature senescence and late cardiovascular complications

Priyanka Banerjee, Elizabeth A. Olmsted-Davis, Anita Deswa, Minh TH. Nguyen, Efstratios Koutroumpakis, Nicholas L. Palaskas, Steven H. Lin, Sivareddy Kotla, Cielito Reyes-Gibby, Sai-Ching J. Yeung, Syed Wamique Yusuf, Momoko Yoshimoto, Michihiro Kobayashi, Bing Yu, Keri Schadler, Joerg Herrmann, John P. Cooke, Abhishek Jain, Eduardo Chini, Nhat-Tu Le*, Jun-Ichi Abe*

Read
Full-text PDF PMID: 35801078 PMCID: PMC9258520 DOI: 10.20517/jca.2022.13
Citation
RIS Plain text

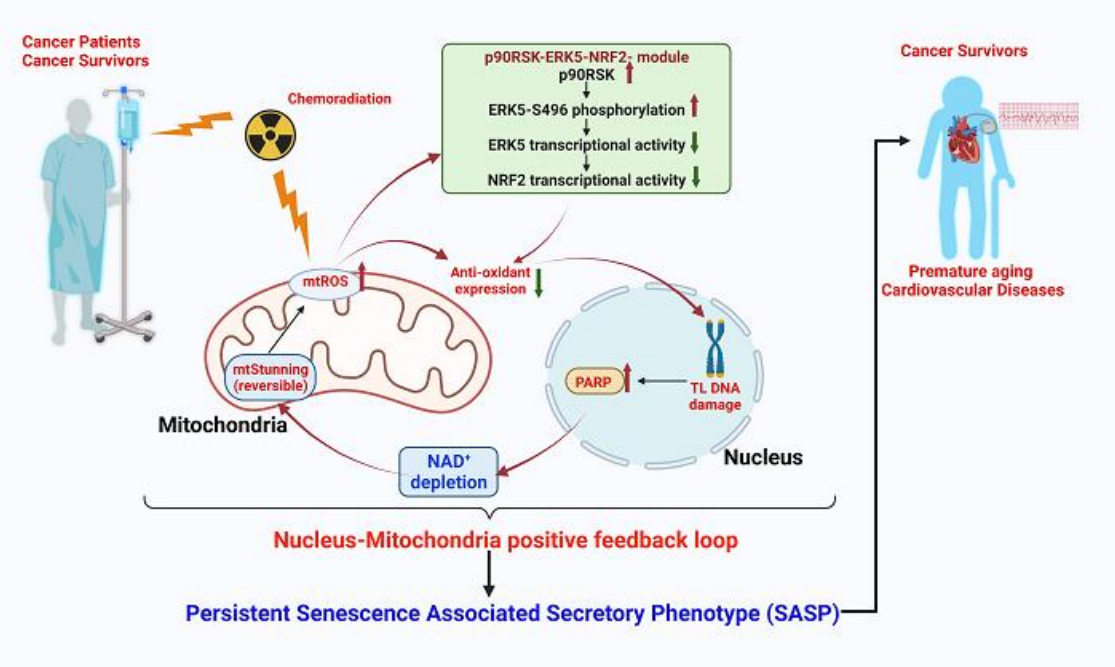
Abstract

Numerous studies have revealed the critical role of premature senescence induced by various cancer treatment modalities in the pathogenesis of aging-related diseases. Senescence-associated secretory phenotype (SASP) can be induced by telomere dysfunction. Telomeric DNA damage response induced by some cancer treatments can persist for months, possibly accounting for long-term sequelae of cancer treatments. Telomeric DNA damage-induced mitochondrial dysfunction and increased reactive oxygen species production are hallmarks of premature senescence. Recently, we reported that the nucleus-mitochondria positive feedback loop formed by p90 ribosomal S6 kinase (p90RSK) and phosphorylation of S496 on ERK5 (a unique member of the mitogen-activated protein kinase family that is not only a kinase but also a transcriptional co-activator) were vital signaling events that played crucial roles in linking mitochondrial dysfunction, nuclear telomere dysfunction, persistent SASP induction, and atherosclerosis. In this review, we will discuss the role of NAD^+ depletion in instigating SASP and its downstream signaling and regulatory mechanisms that lead to the premature onset of atherosclerotic cardiovascular diseases in cancer survivors.

Keywords

NAD^+, senescence-associated secretory phenotype (SASP), cardiovascular diseases, p90RSK, ERK5

Graphical abstract



Cite this article

Banerjee P, Olmsted-Davis EA, Deswal A, Nguyen MTH, Koutroumpakis E, Palaskas NL, Lin SH, Kotla S, Reyes-Gibby C, Yeung SCJ, Yusuf SW, Yoshimoto M, Kobayashi M, Yu B, Schadler K, Herrmann J, Cooke JP, Jain A, Chini E, Le NT, Abe JI. Cancer treatment-induced NAD$^+$ depletion in premature senescence and late cardiovascular complications. *J Cardiovasc Aging* 2022;2:28. http://dx.doi.org/10.20517/jca.2022.13

7. Gut microbiota in sarcopenia and heart failure

Chia-Feng Liu, W. H. Wilson Tang*

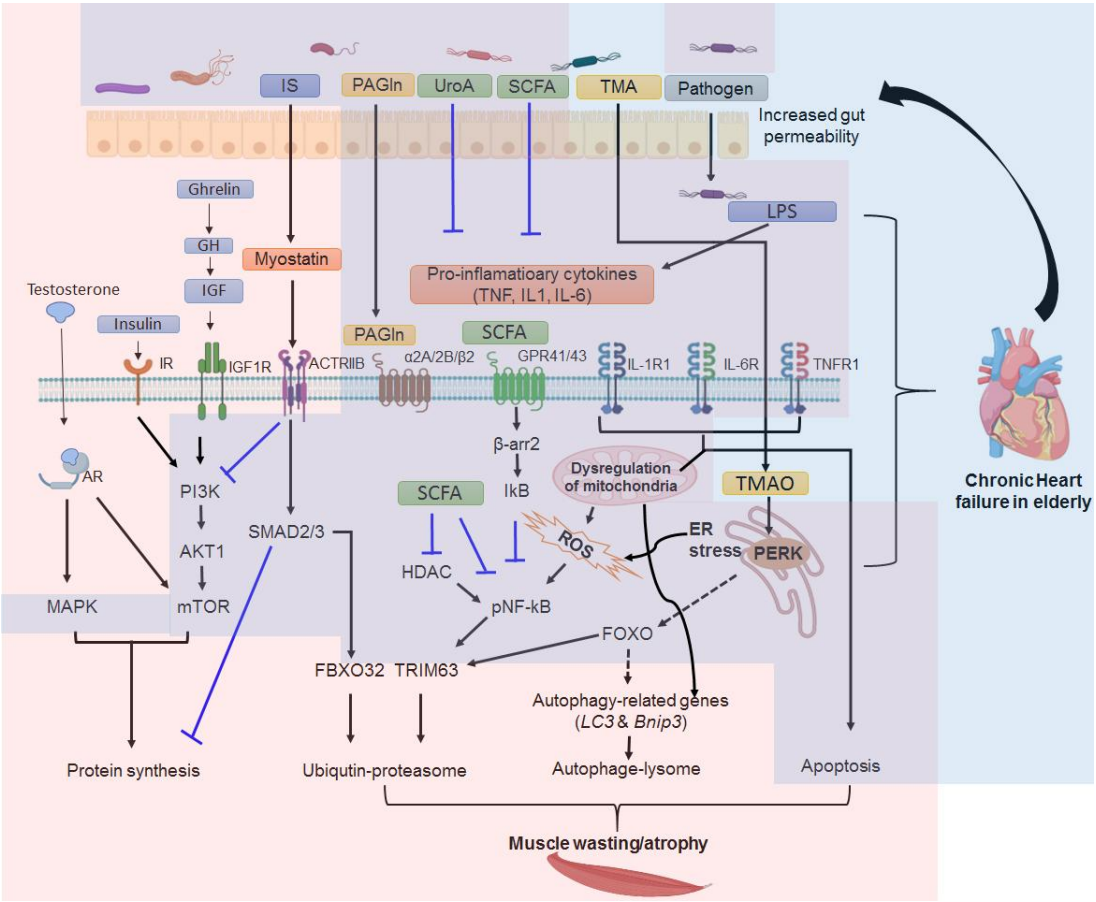
Read
Full-text PDF PMID: 35891702 PMCID: PMC9311382 DOI: 10.20517/jca.2022.07
Citation
RIS Plain text

Abstract
Sarcopenia is common in aging and in patients with heart failure (HF) who may experience worse outcomes. Patients with muscle wasting are more likely to experience falls and can have serious complications when undergoing cardiac procedures. While intensive nutritional support and exercise rehabilitation can help reverse some of these changes, they are often under-prescribed in a timely manner, and we have limited insights into who would benefit. Mechanistic links between gut microbial metabolites (GMM) have been identified and may contribute to adverse clinical outcomes in patients with cardio-renal diseases and aging. This review will examine the emerging evidence for the influence of the gut microbiome-derived metabolites and notable signaling pathways involved in both sarcopenia and HF, especially those linked to dietary intake

and mitochondrial metabolism. This provides a unique opportunity to gain mechanistic and clinical insights into developing novel therapeutic strategies that target these GMM pathways or through tailored nutritional modulation to prevent progressive muscle wasting in elderly patients with heart failure.

Keywords
Gut microbiota, sarcopenia, heart failure, aging

Graphical abstract



Cite this article

Liu CF, Tang WHW. Gut microbiota in sarcopenia and heart failure. *J Cardiovasc Aging* 2022;2:35.
http://dx.doi.org/10.20517/jca.2022.07

8. Promoting healthy cardiovascular aging: emerging topics

Zachary S. Clayton, Daniel H. Craighead, Sanna Darvish, McKinley Coppock, Katelyn R. Ludwig, Vienna E. Brunt, Douglas R. Seals, Matthew J. Rossman*

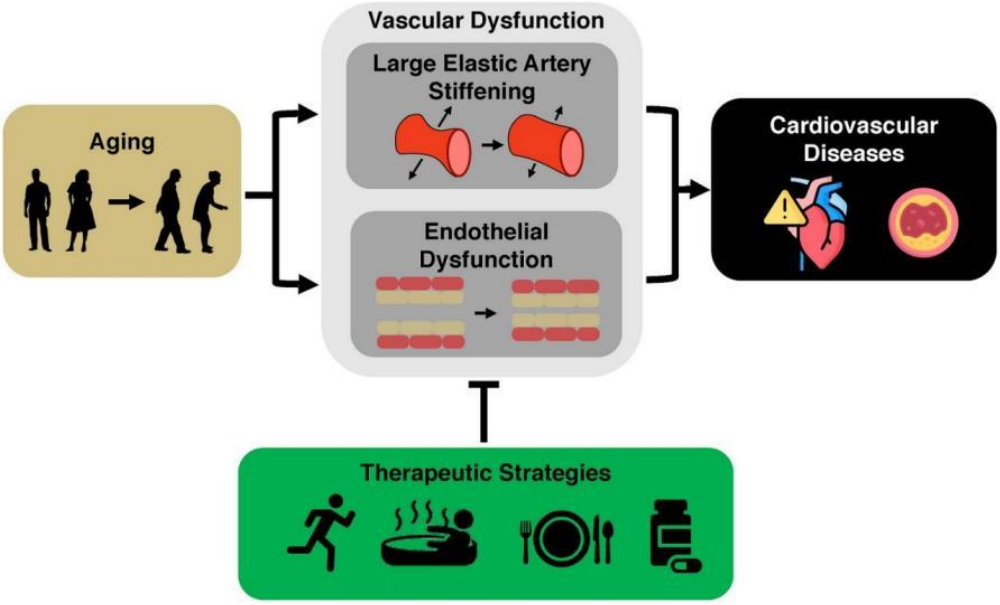
Read
Full-text PDF DOI: 10.20517/jca.2022.27

Citation
RIS Plain text

Abstract
The development of age-related cardiovascular (CV) dysfunction increases the risk of CV disease as well as other chronic age-associated disorders, including chronic kidney disease, and Alzheimer's disease and related dementias. Major manifestations of age-associated CV dysfunction that increase disease risk are vascular dysfunction, primarily vascular endothelial dysfunction and arterial stiffening, and elevated systolic blood pressure. Declines in nitric oxide bioavailability secondary to increased oxidative stress and inflammation are established mechanisms of CV dysfunction with aging. Moreover, fundamental mechanisms of aging, termed the "hallmarks of aging" extend to the CV system and, as such, may be considered "hallmarks of CV aging". These mechanisms represent viable therapeutic targets for treating CV dysfunction with aging. Healthy lifestyle behaviors, such as regular aerobic exercise and certain dietary patterns, are considered "first-line" strategies to prevent and/or treat age-associated CV dysfunction. Despite the well-established benefits of these strategies, many older adults do not meet the recommended guidelines for exercise or consume a healthy diet. Therefore, it is important to establish alternative and/or complementary evidence-based approaches to prevent or reverse age-related CV dysfunction. Targeting fundamental mechanisms of CV aging with interventions such as time-efficient exercise training, food-derived molecules, termed nutraceuticals, or select synthetic pharmacological agents represents a promising approach. In the present review, we will highlight emerging topics in the field of healthy CV aging with a specific focus on how exercise, nutrition/dietary patterns, nutraceuticals and select synthetic pharmacological compounds may promote healthy CV aging, in part, by targeting the hallmarks of CV aging.

Keywords
Hallmarks of aging, exercise, nutrition, oxidative stress, inflammation, endothelial function, arterial stiffness

Graphical abstract



Cite this article

Clayton ZS, Craighead DH, Darvish S, Coppock MK, Ludwig KR, Brunt VE, Seals DR, Rossman MJ. Promoting healthy cardiovascular aging: emerging topics. *J Cardiovasc Aging* 2022;2:43. http://dx.doi.org/10.20517/jca.2022.27

9. Metabolic targets in cardiac aging and rejuvenation

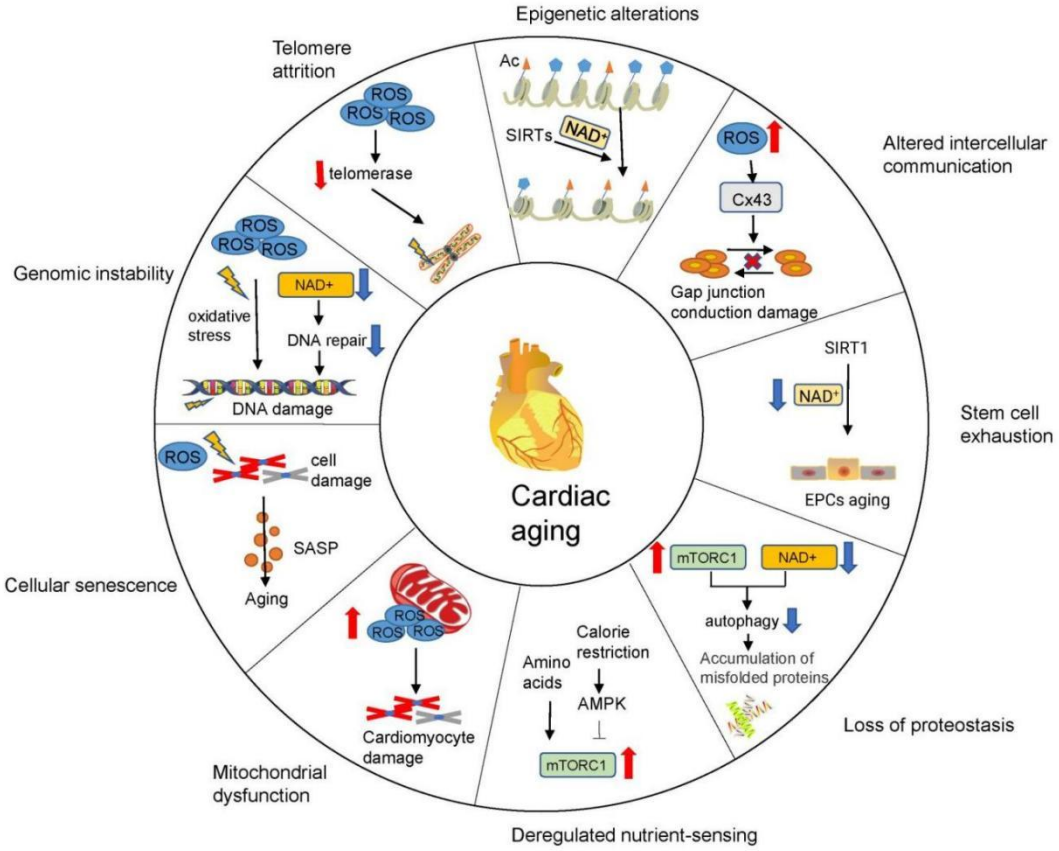
Chang Liu, Xiao Zhang, Meiyu Hu, Yi Lu, Priyanka Gokulnath, Gururaja Vulugundam, Junjie Xiao*

Read
Full-text PDF DOI: 10.20517/jca.2022.31
Citation
RIS Plain text

Abstract
Cardiac aging is accompanied by progressive loss of cellular function, leading to impaired heart function and heart failure. There is an urgent need for efficient strategies to combat this age-related cardiac dysfunction. A growing number of events suggest that age-related cardiac diseases are tightly related to metabolic imbalance. This review summarizes recent findings concerning metabolic changes during cardiac aging and highlights the therapeutic approaches that target metabolic pathways in cardiac aging.

Keywords
Cardiac aging, metabolic imbalance, mitochondria dysfunction, anti-aging therapy

Graphical abstract



Cite this article

Liu C, Zhang X, Hu M, Lu Y, Gokulnath P, Vulugundam G, Xiao J. Metabolic targets in cardiac aging and rejuvenation. *J Cardiovasc Aging* 2022;2:46. http://dx.doi.org/10.20517/jca.2022.31

10. Thrombosis and myocardial infarction: the role of bioresorbable scaffolds

Massoud A. Leesar*, Marc D. Feldman

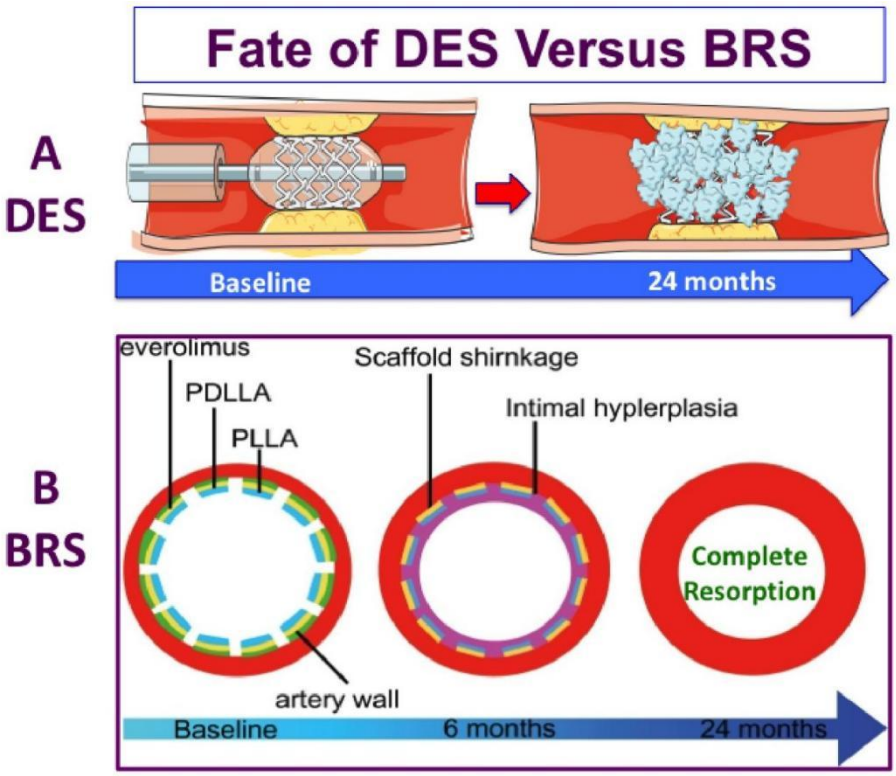
Read
Full-text PDF DOI: 10.20517/jca.2022.41
Citation
RIS Plain text

Abstract
Coronary atherosclerosis is a leading cause of death as a result of coronary thrombosis and acute myocardial infarction. Drug-eluting stents (DES) have dramatically improved the treatment of coronary artery stenosis. However, stent thrombosis (ST) and in-stent-restenosis (ISR) have remained a vexing limitation of the DES. After DES implantation, despite taking dual antiplatelet (DAPT) therapy, very late ST results in myocardial infarction and death. This occurs regardless of the type of polymer or antiproliferative agent used in the contemporary DES. Such adverse events occur at a rate of approximately 2% to 3% per year after the first

year, which have been attributed to strut fractures, loss of vessel compliance, and neoatherosclerosis. Bioresorbable scaffolds (BRS) have been introduced to overcome the above shortfalls and to a “leave nothing behind” approach. While BRS are novel and interesting, the initial experience with BRS was hampered by the increased rate of thrombosis compared with DES. Accordingly, in this review, we summarized underlying mechanisms leading to BRS failure and provided insights into optimizing BRS deployment with intravascular imaging. In addition, we outlined the perspectives of new generations of BRS with thinner struts and new designs as well as alternative materials to improve outcomes.

Keywords
Bioresorbable scaffolds, coronary artery disease, intravascular imaging, scaffold thrombosis

Graphical abstract



Cite this article

Leesar MA, Feldman MD. Thrombosis and myocardial infarction: the role of bioresorbable scaffolds. *J Cardiovasc Aging* 2023;3:7. http://dx.doi.org/10.20517/jca.2022.41

11. The dynamic interplay between cardiac mitochondrial health and myocardial structural remodeling in metabolic heart disease, aging, and heart failure

Benjamin Werbner, Omid Mohammad Tavakoli-Rouzbehani, Amir Nima Fatahian, Sihem Boudina*

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging

Read
Full-text PDF PMID: 36742465 PMCID: PMC9894375 DOI: 10.20517/jca.2022.42
Citation
RIS Plain text

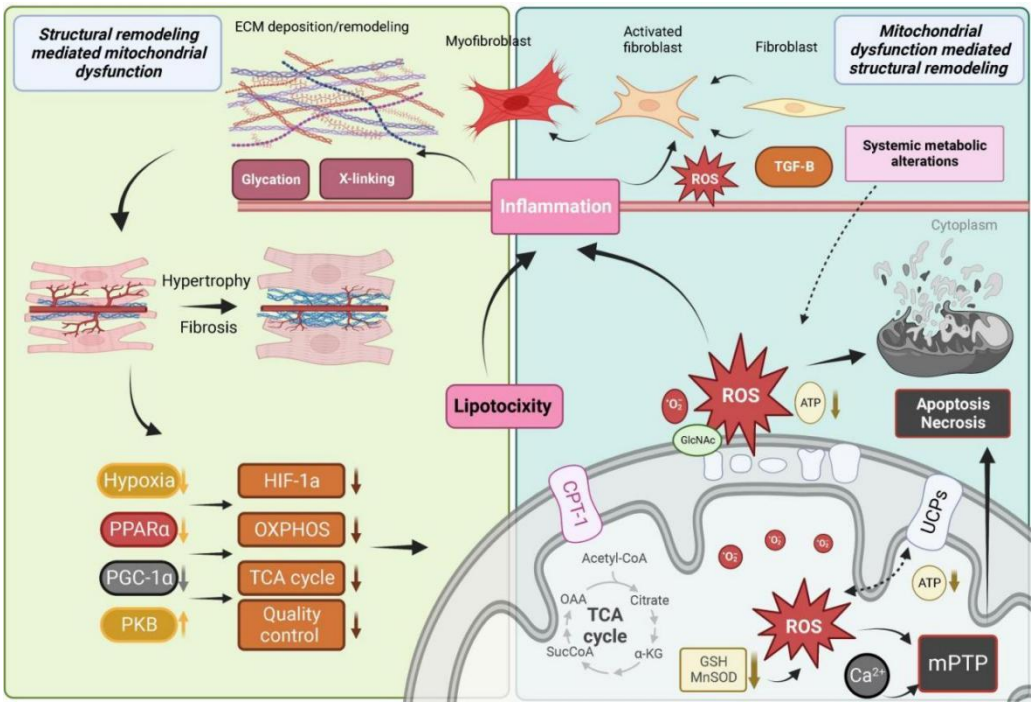
Abstract

This review provides a holistic perspective on the bi-directional relationship between cardiac mitochondrial dysfunction and myocardial structural remodeling in the context of metabolic heart disease, natural cardiac aging, and heart failure. First, a review of the physiologic and molecular drivers of cardiac mitochondrial dysfunction across a range of increasingly prevalent conditions such as metabolic syndrome and cardiac aging is presented, followed by a general review of the mechanisms of mitochondrial quality control (QC) in the heart. Several important mechanisms by which cardiac mitochondrial dysfunction triggers or contributes to structural remodeling of the heart are discussed: accumulated metabolic byproducts, oxidative damage, impaired mitochondrial QC, and mitochondrial-mediated cell death identified as substantial mechanistic contributors to cardiac structural remodeling such as hypertrophy and myocardial fibrosis. Subsequently, the less studied but nevertheless important reverse relationship is explored: the mechanisms by which cardiac structural remodeling feeds back to further alter mitochondrial bioenergetic function. We then provide a condensed pathogenesis of several increasingly important clinical conditions in which these relationships are central: diabetic cardiomyopathy, age-associated declines in cardiac function, and the progression to heart failure, with or without preserved ejection fraction. Finally, we identify promising therapeutic opportunities targeting mitochondrial function in these conditions.

Keywords

Mitochondria, mitophagy, fibrosis, fibroblasts, remodeling, cardiac

Graphical abstract



Cite this article

Werbner B, Tavakoli-Rouzbehani OM, Fatahian AN, Boudina S. The dynamic interplay between cardiac mitochondrial health and myocardial structural remodeling in metabolic heart disease, aging, and heart failure. *J Cardiovasc Aging* *2023*;3:9. http://dx.doi.org/10.20517/jca.2022.42

12. Can age be a modifiable risk factor? the impact of dietary patterns on the molecular mechanisms that underlie cardiovascular aging

Steven A. Lewis, William M. Britt, Rachel L. Koch, Alexander C. Razavi, Parth Patel, Laurence S. Sperling, Melroy S. D'Souza*

Read
Full-text PDF DOI: 10.20517/jca.2023.1
Citation
RIS Plain text

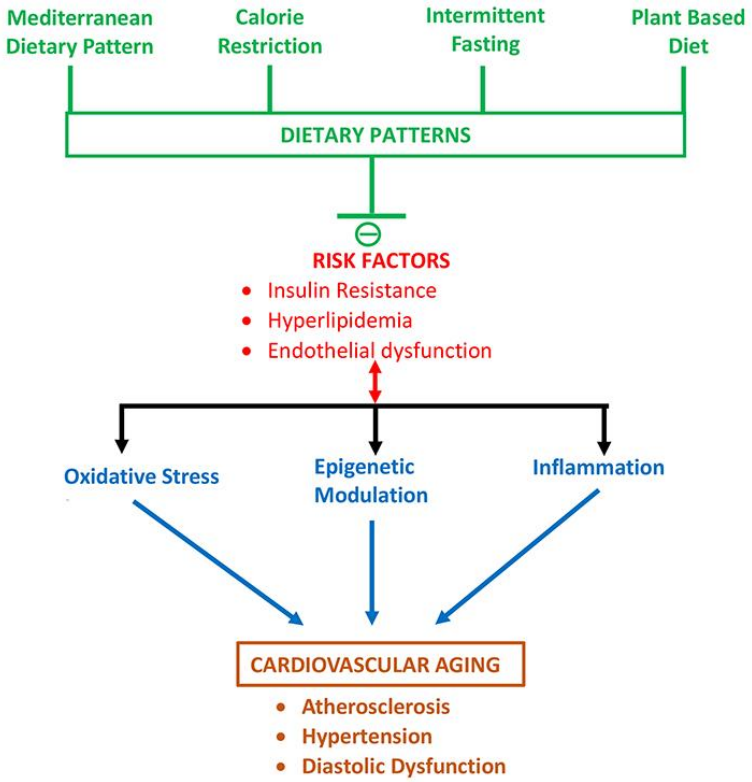
Abstract

Aging is the number one risk factor for the development of cardiovascular disease (CVD). Therefore, an evaluation of therapies for the prevention of CVD should focus on factors that slow down aging, particularly cardiovascular aging. There are various proposed mechanisms that advance cardiovascular age; in this review, we focus on chronic inflammation, oxidative stress and epigenetics as the primary drivers of aging. Furthermore, we will evaluate several dietary patterns on their impact on these aging mechanisms. The traditional "heart-healthy" dietary patterns such as the Mediterranean diet, plant-based diet and intermittent fasting will be evaluated for their performance to slow down the aforementioned aging mechanisms. The aim of this review will be to guide practitioners and patients on the dietary components that can slow down the effects of aging to prevent CVD.

Keywords

Cardiovascular aging, dietary patterns, chronic inflammation, epigenetics, oxidative stress

Graphical abstract



Cite this article

Lewis SA, Britt WM, Koch RL, Razavi AC, Patel P, Sperling LS, D'Souza MS. Can age be a modifiable risk factor? the impact of dietary patterns on the molecular mechanisms that underlie cardiovascular aging. *J Cardiovasc Aging* 2023;3:14. http://dx.doi.org/10.20517/jca.2023.1

13. Protein homeostasis in the aged and diseased heart

Nirjal Mainali, Srinivas Ayyadevara*, Akshatha Ganne, Robert J. Shmookler Reis*, Jawahar L. Mehta*

Read
Full-text PDF PMID: 37092014 PMCID: PMC10121184 DOI: 10.20517/jca.2023.4
Citation
RIS Plain text

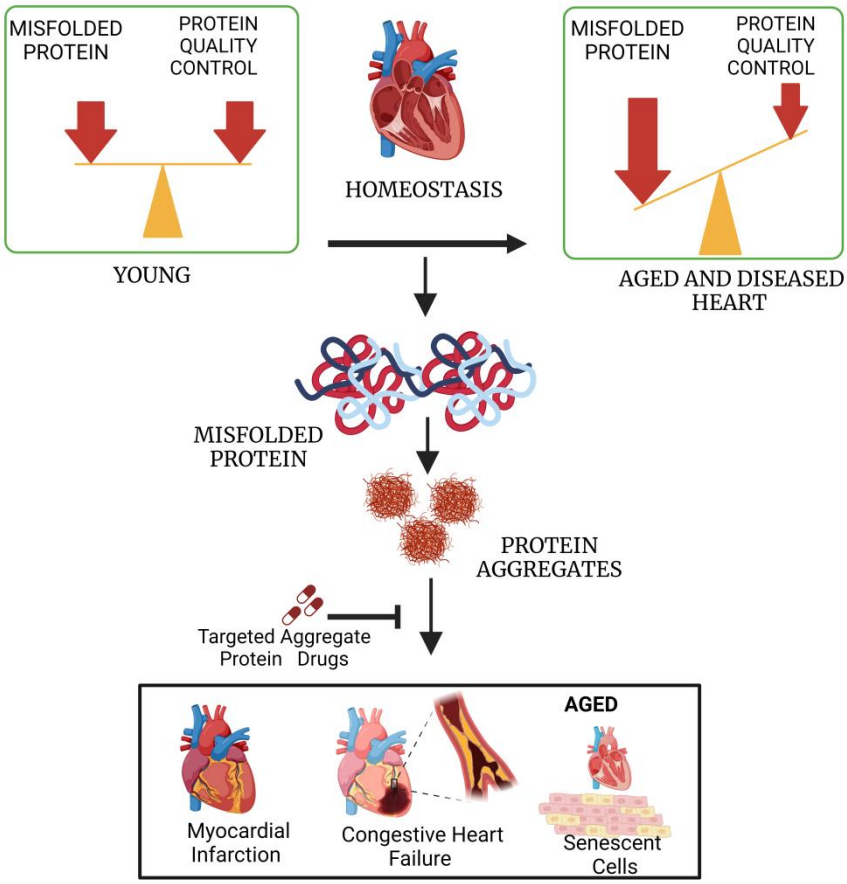
Abstract

Protein homeostasis, the balance between protein synthesis and degradation, requires the clearance of misfolded and aggregated proteins and is therefore considered to be an essential aspect of establishing a physiologically effective proteome. Aging alters this balance, termed "proteostasis", resulting in the progressive accumulation of misfolded and aggregated proteins. Defective proteostasis leads to the functional deterioration of diverse regulatory processes during aging and is implicated in the etiology of multiple

pathological conditions underlying a variety of neurodegenerative diseases and in age-dependent cardiovascular disease. Detergent-insoluble protein aggregates have been reported by us in both aged and hypertensive hearts. The protein constituents were found to overlap with protein aggregates seen in neurodegenerative diseases such as Alzheimer's disease. Therefore, targeting these protein components of aggregates may be a promising therapeutic strategy for cardiovascular pathologies associated with aging, ischemia, and/or hypertension.

Keywords
Protein aggregation, cardiovascular disease, aging, myocardial ischemia, hypertension

Graphical abstract



Cite this article

Mainali N, Ayyadevara S, Ganne A, Shmookler Reis RJ, Mehta JL. Protein homeostasis in the aged and diseased heart. *J Cardiovasc Aging* 2023;3:16. http://dx.doi.org/10.20517/jca.2023.4

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging

14. Immune mechanisms of cardiac aging

Daniel R. Goldstein*, Ahmed Abdel-Latif

Read
Full-text PDF PMID: 37092016 DOI: 10.20517/jca.2023.02
Citation
RIS Plain text

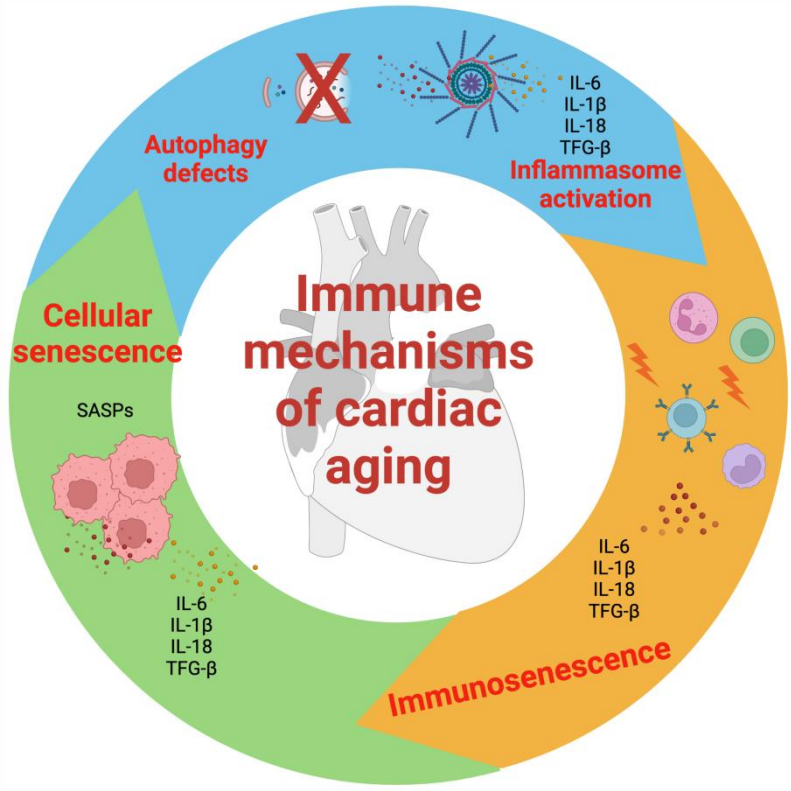
Abstract

Advances in healthcare and improvements in living conditions have led to rising life expectancy worldwide. Aging is associated with excessive oxidative stress, a chronic inflammatory state, and limited tissue healing, all of which result in an increased risk of heart failure. In fact, the prevalence of heart failure approaches 40% in the ninth decade of life, with the majority of these cases suffering from heart failure with preserved ejection fraction (HFpEF). In cardiomyocytes (CMs), age-related mitochondrial dysfunction results in disrupted calcium signaling and covalent protein-linked aggregates, which cause cardiomyocyte functional disturbances, resulting in increased stiffness and diastolic dysfunction. Importantly, aging is also associated with chronic low-grade, sterile inflammation, which alters the function of interstitial cardiac cells and leads to cardiac fibrosis. Taken together, cardiac aging is associated with cellular, structural, and functional changes in the heart that contribute to the rising prevalence of heart failure in older people.

Keywords

Aging, cardiac fibrosis, heart failure with preserved ejection fraction

Graphical abstract



Cite this article

Goldstein DR, Abdel-Latif A. Immune mechanisms of cardiac aging. *J Cardiovasc Aging* 2023;3:17.
http://dx.doi.org/10.20517/jca.2023.02

15. Cadiovascular aging: from cellular and molecular changes to therapeutic interventions

Angeliki Vakka, Junco S. Warren, Konstantinos Drosatos*

Read
Full-text PDF DOI: 10.20517/jca.2023.09
Citation
RIS Plain text

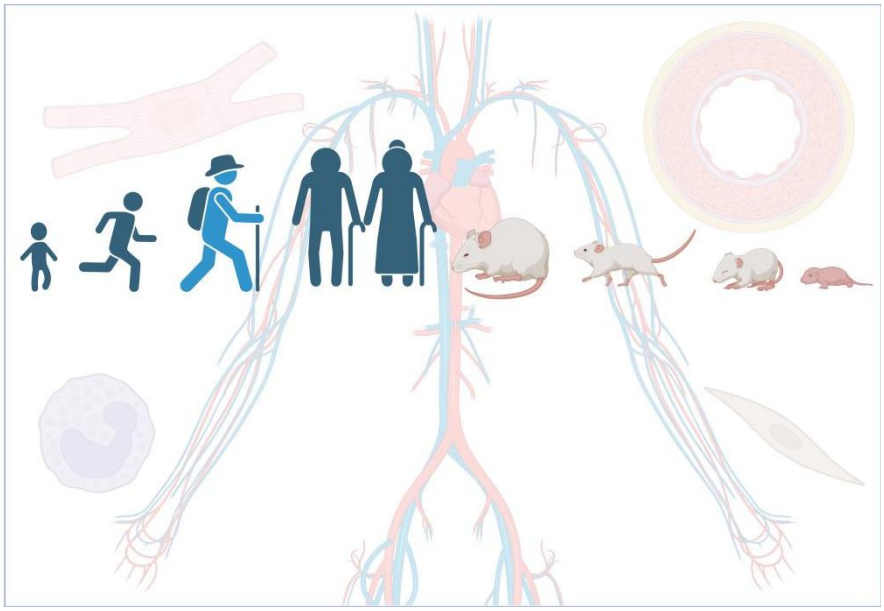
Abstract

Progressive age-induced deterioration in the structure and function of the cardiovascular system involves cardiac hypertrophy, diastolic dysfunction, myocardial fibrosis, arterial stiffness, and endothelial dysfunction. These changes are driven by complex processes that are interconnected, such as oxidative stress, mitochondrial dysfunction, autophagy, inflammation, fibrosis, and telomere dysfunction. In recent years, the advances in research of cardiovascular aging, including the wide use of animal models of cardiovascular aging, elucidated an abundance of cell signaling pathways involved in these processes and brought into sight possible interventions, which span from pharmacological agents, such as metformin, sodium-glucose cotransporter 2-inhibitors, rapamycin, dasatinib and quercetin, to lifestyle changes.

Keywords

Cardiovascular aging, oxidative stress, mitochondrial dysfunction, autophagy, inflammaging, fibrosis

Graphical abstract



Cite this article

Vakka A, Warren JS, Drosatos K. Cardiovascular aging: from cellular and molecular changes to therapeutic interventions. *J Cardiovasc Aging* 2023;3:23. http://dx.doi.org/10.20517/jca.2023.09

16. The mTOR signaling pathway in cardiac aging

Dao-Fu Dai*, Ping Kang, Hua Bai

Read
Full-text PDF DOI: 10.20517/jca.2023.10
Citation
RIS Plain text

Abstract

The mammalian target of rapamycin (mTOR) is one of the most important signaling pathways that regulate nutrient sensing, cell growth, metabolism, and aging. The mTOR pathway, particularly mTOR complex 1 (mTORC1), has been shown to control aging, lifespan, and healthspan through the regulation of protein synthesis, autophagy, mitochondrial function, and metabolic health. The mTOR pathway also plays critical roles in the heart, from cardiac development, growth and maturation, and maintenance of cardiac homeostasis. Hyperactivation of mTORC1 signaling is well documented in aging and many age-related pathologies, including age-related cardiac dysfunction and heart failure. Suppression of mTORC1 by calorie restriction or rapamycin not only extends lifespan but also restores youthful phenotypes in the heart. In this article, we review model organisms of cardiac aging and highlight recent advances in the impact of the mTORC1 pathway on organismal and cardiac aging, particularly in *Drosophila* and mice. We focus on the downstream signaling pathways S6 kinase and 4EBP1, which regulates protein synthesis, as well as ULK1 and its related pathway that regulates autophagy. The interaction with mTOR complex 2 (mTORC2) and its potential role in cardiac aging are also discussed.

Keywords
mTOR, aging, cardiac aging, heart failure, rapamycin, caloric restriction

Cite this article

Dai DF, Kang P, Bai H. The mTOR signaling pathway in cardiac aging . *J Cardiovasc Aging* 2023;3:24. http://dx.doi.org/10.20517/jca.2023.10

17. The secretome as a biomarker and functional agent in heart failure

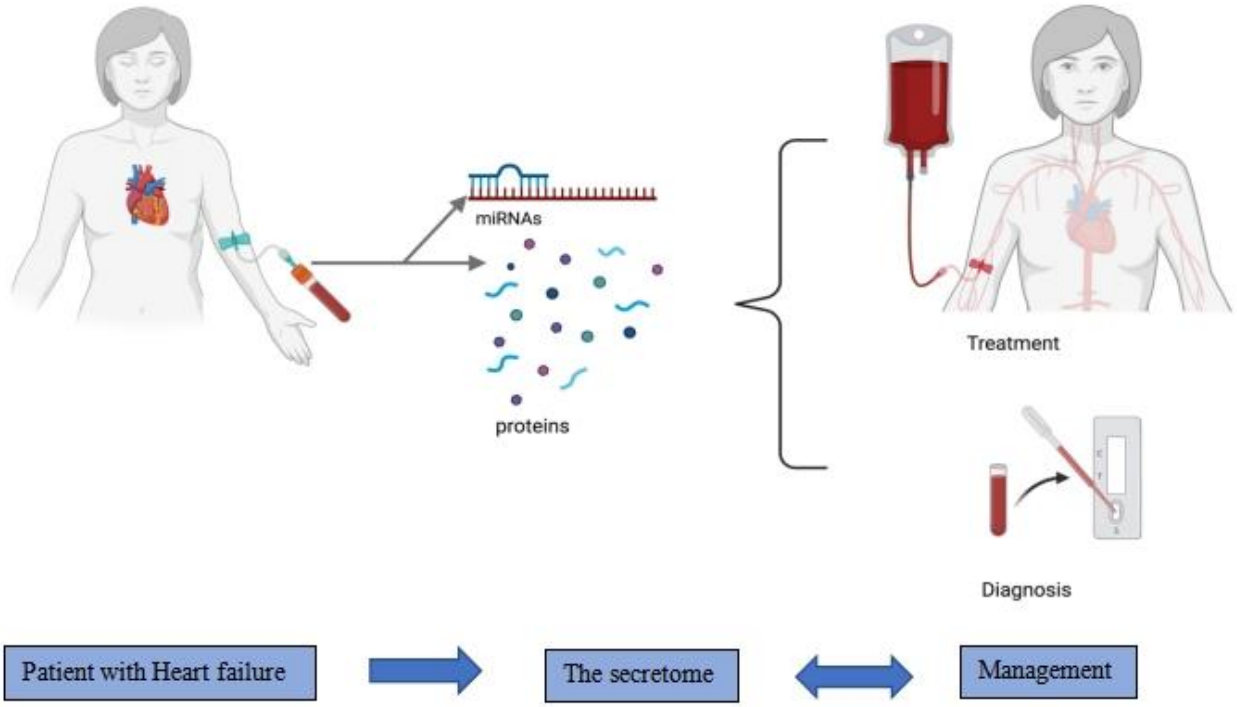
Obed O. Nyarko, Carmen C. Sucharov*

Read
Full-text PDF PMID: 37484982 PMCID: PMC10361342 DOI: 10.20517/jca.2023.15
Citation
RIS Plain text

Abstract
Heart failure (HF) is a complex and multifactorial disease. Recent advances have been made in understanding the underlying molecular processes involved in HF pathogenesis. These scientific advancements have brought to light the importance of the secretome. This paper presents a thorough overview of the state of science regarding the secretome's involvement in the onset, progression, and possibility of improved diagnosis and therapeutic interventions in HF. We explore the various types of secreted factors, including novel proteins, growth factors, cytokines, and microRNAs. We also discuss how they affect cellular signaling, angiogenesis, fibrosis, pathological cardiac remodeling, and inflammation in HF. Furthermore, we examine the role of the secretome in cardioprotection and cardiotoxicity. This review emphasizes the potential of the secretome for biomarker discovery. This might enable better HF diagnosis, risk stratification, monitoring and treatment. The review also discusses the difficulties on investigating the role of secreted factors and novel directions on secretome research. It highlights its potential as a target for novel therapeutic approaches and biomarker development.

Keywords
Secretome, circulating protein, circulating microRNA, heart failure, biomarker

Graphical abstract



Cite this article

Nyarko OO, Sucharov CC. The secretome as a biomarker and functional agent in heart failure. *J Cardiovasc Aging* 2023;3:27. http://dx.doi.org/10.20517/jca.2023.15

18. Cardiovascular aging: the mitochondrial influence

Shakti Sagar, Asa B. Gustafsson*

Read
Full-text PDF DOI: 10.20517/jca.2023.22
Citation
RIS Plain text

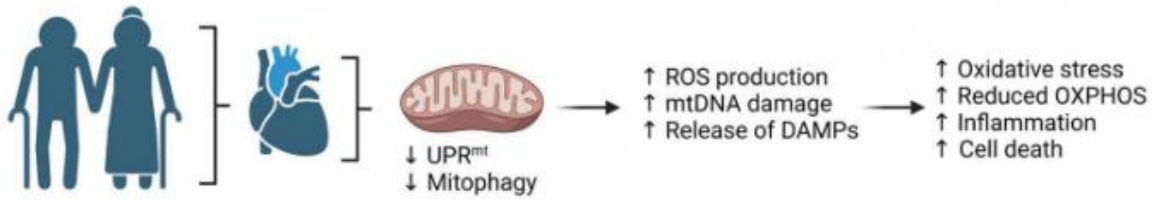
Abstract

Age-associated cardiovascular disease is becoming progressively prevalent due to the increased lifespan of the population. However, the fundamental mechanisms underlying the aging process and the corresponding decline in tissue functions are still poorly understood. The heart has a very high energy demand and the cellular energy needed to sustain contraction is primarily generated by mitochondrial oxidative phosphorylation. Mitochondria are also involved in supporting various metabolic processes, as well as activation of the innate immune response and cell death pathways. Given the central role of mitochondria in energy metabolism and cell survival, the heart is highly susceptible to the effects of mitochondrial dysfunction. These key organelles have been implicated as underlying drivers of cardiac aging. Here, we review the

evidence demonstrating the mitochondrial contribution to the cardiac aging process and disease susceptibility. We also discuss the potential mechanisms responsible for the age-related decline in mitochondrial function.

Keywords
Aging, mitochondria, heart disease

Graphical abstract



Cite this article

Sagar S, Gustafsson AB. Cardiovascular aging: the mitochondrial influence. *J Cardiovasc Aging* 2023;3:33. http://dx.doi.org/10.20517/jca.2023.22

Resource Report

1. Effects of tamoxifen inducible MerCreMer on gene expression in cardiac myocytes in mice

Leila Rouhi, Siyang Fan, Sirisha M. Cheedipudi, Melis Olcum , Hyun-Hwan Jeong, Zhongming Zhao, Priyatansh Gurha, Ali J. Marian*

Read
Full-text PDF PMID: 35079750 PMCID: PMC8785140 DOI: 10.20517/jca.2021.30
Citation
RIS Plain text

Abstract
The Cre-LoxP technology, including the tamoxifen (TAM) inducible MerCreMer (MCM), is increasingly used to delineate gene function, understand the disease mechanisms, and test therapeutic interventions. We set to determine the effects of TAM-MCM on cardiac myocyte transcriptome.

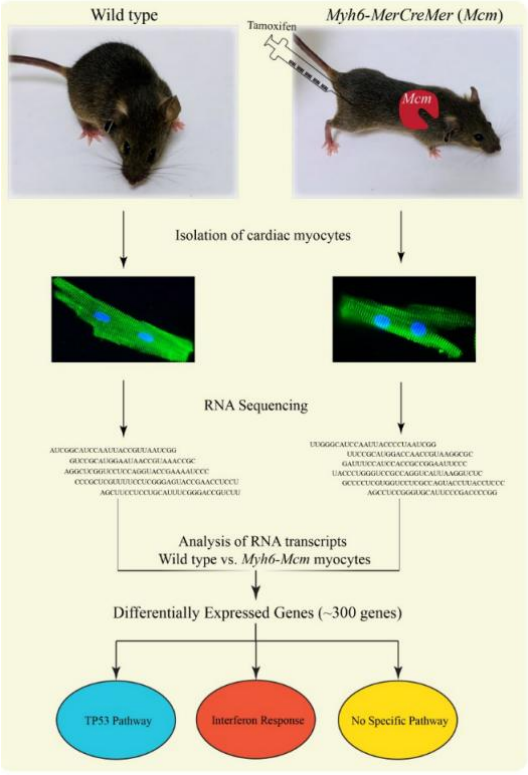
Expression of the MCM was induced specifically in cardiac myocytes upon injection of TAM to myosin

heavy chain 6-MCM (*Myh6-Mcm*) mice for 5 consecutive days. Cardiac function, myocardial histology, and gene expression (RNA-sequencing) were analyzed 2 weeks after TAM injection. A total of 346 protein coding genes (168 up- and 178 down-regulated) were differentially expressed. Transcript levels of 85 genes, analyzed by a reverse transcription-polymerase chain reaction in independent samples, correlated with changes in the RNA-sequencing data. The differentially expressed genes were modestly enriched for genes involved in the interferon response and the tumor protein 53 (TP53) pathways. The changes in gene expression were relatively small and mostly transient and had no discernible effects on cardiac function, myocardial fibrosis, and apoptosis or induction of double-stranded DNA breaks.

Thus, TAM-inducible activation of MCM alters cardiac myocytes gene expression, provoking modest and transient interferon and DNA damage responses without exerting other discernible phenotypic effects. Thus, the effects of TAM-MCM on gene expression should be considered in discerning the bona fide changes that result from the targeting of the gene of interest.

Keywords
Transcriptome, gene expression, tamoxifen, Cre recombinase, MerCreMer, interferon, inflammation, TP53

Graphical abstract



Cite this article

Rouhi L, Fan S, Cheedipudi SM, Olcum M, Jeong HH, Zhao Z, Gurha P, Marian AJ. Effects of tamoxifen inducible MerCreMer on gene expression in cardiac myocytes in mice. *J Cardiovasc Aging* 2022;2:8.
http://dx.doi.org/10.20517/jca.2021.30

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging

Brief Report

1. Male carriers of HLA-C*04:01 have increased risk of cardiac injury in COVID-19

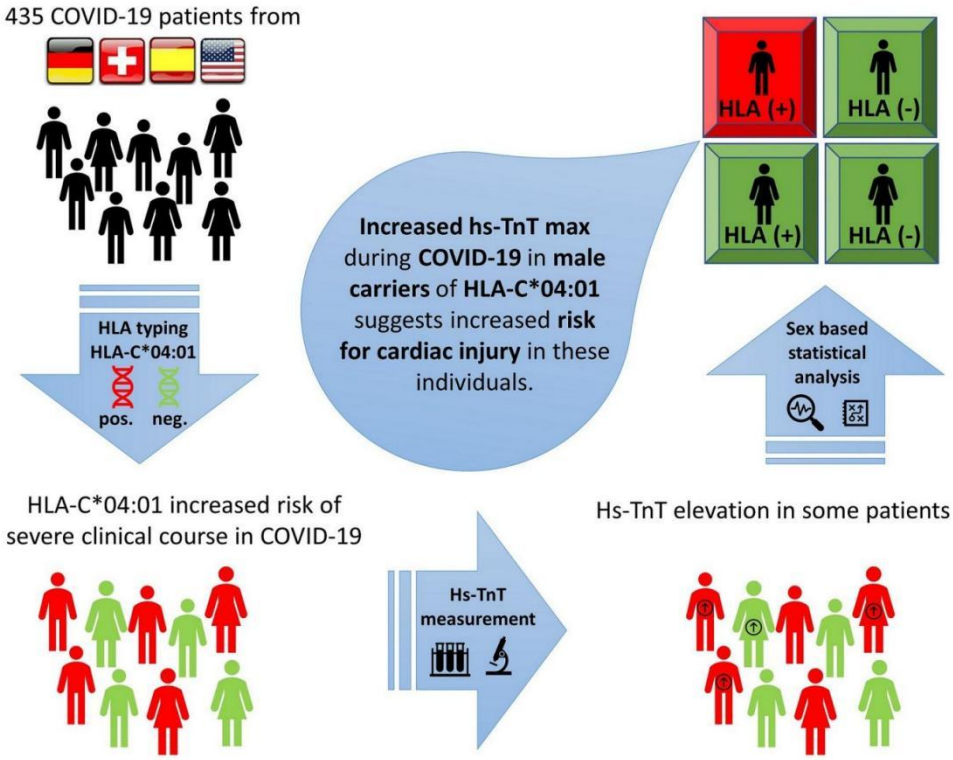
Phillip Suwalski, Michele Violano, Melina Müller, Dimitri Patriki, Charlotte Thibeault, Claudia Quedenau, Xiaomin Wang, Zehra Karadeniz, Jacopo Saccomanno, Jan-Moritz Doehn, Ralf-Harto Hübner, Bernd Hinzmann, H. Juerg Beer, Benedikt Wiggli, Sandra Siemann, Norbert Suttorp, Martin Witzenrath, Stefan Hippenstiel, Carsten Skurk, Wolfgang Poller, Pa-COVID Study Group, Leif E. Sander, Florian Kurth, Tatiana Borodina, Toumy Guettouche, Ulf Landmesser, Bettina Heidecker*

Read
Full-text PDF DOI: 10.20517/jca.2022.19
Citation
RIS Plain text

Abstract
Identification of factors that lead to the severe clinical course of COVID-19 is crucial for timely allocation of resources. The purpose of this study was to evaluate possible sex differences in cardiac injury associated with HLA-C*04:01. High sensitivity troponin T on admission (hs-TnTa) and maximum high sensitivity troponin T (hs-TnTmax) were used to assess for cardiac injury in patients with COVID-19 (n = 435). We tested for the association of elevated hs-TnT with HLA-C* 04:01 and evaluated for potential sex-specific differences. An association between hs-TnTa and the severity of clinical course was identified. In addition, our study revealed that hs-TnTmax was higher in men who were carriers of HLA-C*04:01 compared to men without the risk allele. Male carriers of HLA-C*04:01 with COVID-19 developed higher hs-TnTmax, suggesting a larger extent of cardiac injury. This association suggests the presence of different pathomechanisms in COVID-19 based on sex.

Keywords
Genetic, HLA, HLA-C, HLA-C*04:01, COVID-19, troponin T, hs-TnT

Graphical abstract



Cite this article

Suwalski P, Violano M, Müller M, Patriki D, Thibeault C, Quedenau C, Wang X, Karadeniz Z, Saccomanno J, Doehn JM, Hübner RH, Hinzmann B, Beer HJ, Wiggli B, Siemann S, Suttorp N, Witzenrath M, Hippenstiel S, Skurk C, Poller W, Pa-COVID Study Group , Sander LE, Kurth F, Borodina T, Guettouche T, Landmesser U, Heidecker B. Male carriers of HLA-C*04:01 have increased risk of cardiac injury in COVID-19. *J Cardiovasc Aging* 2022;2:33. http://dx.doi.org/10.20517/jca.2022.19

2. Cytosolic DNA sensing protein pathway is activated in human hearts with dilated cardiomyopathy

Leila Rouhi, Sirisha M. Cheedipudi, Benjamin Cathcart, Priyatansh Gurha, Ali J. Marian*

Read
Full-text PDF DOI: 10.20517/jca.2023.20
Citation
RIS Plain text

Abstract

Introduction: The genome is constantly exposed to numerous stressors, which induce DNA lesions, including double-stranded DNA breaks (DSBs). DSBs are the most dangerous, as they induce genomic instability. In response to DNA damage, the cell activates nuclear DNA damage response (DDR) and the cytosolic DNA sensing protein (CDSP) pathways, the latter upon release of the DSBs to the cytosol. The CDSP pathway

activates NF κ B and IRF3, which induce the expression of the pro-inflammatory genes. There is scant data on the activation of the CDSP pathway in human hearts with dilated cardiomyopathy (DCM).

Aim: We aimed to determine expression levels of selected components of the CDSP pathway in human hearts with DCM.

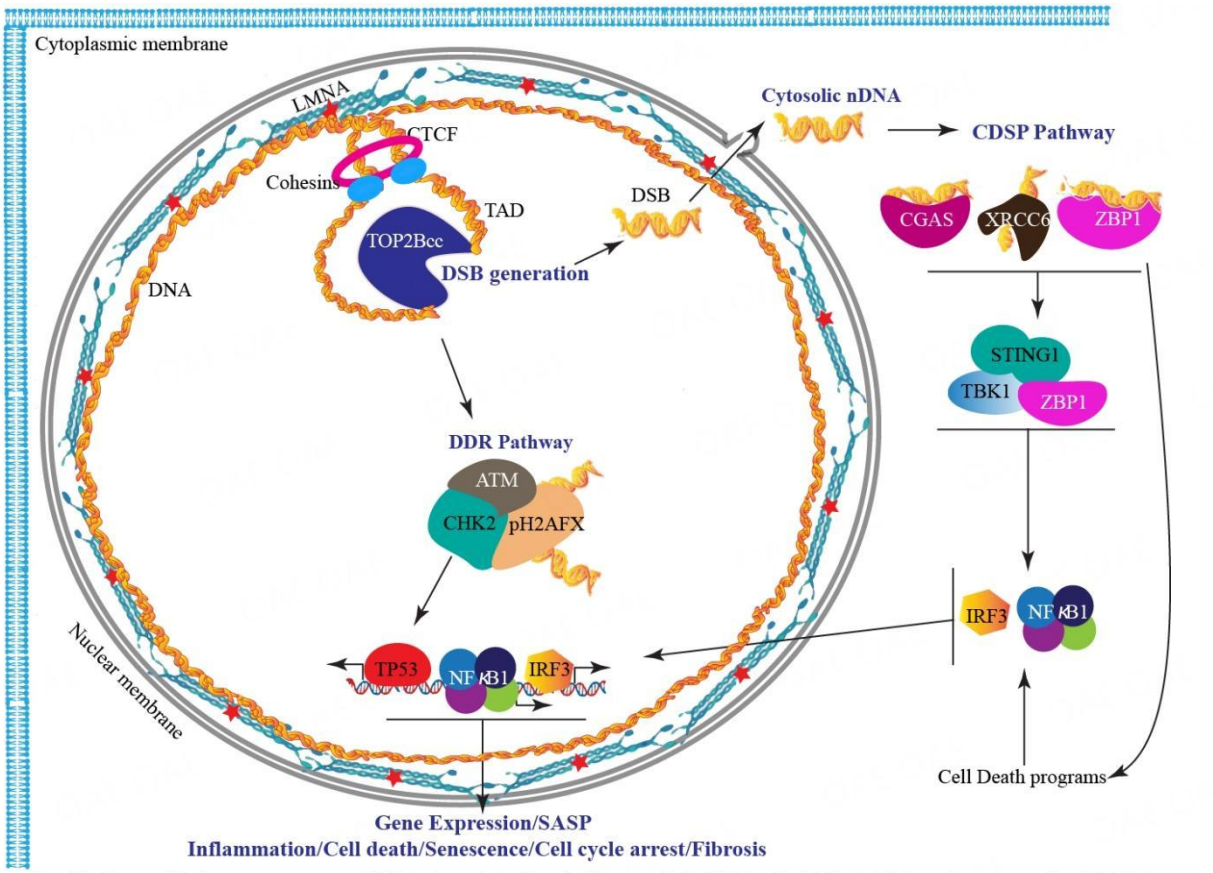
Methods: The DNA strand breaks were detected by the single-cell gel electrophoresis or the comet assay and expression of selected proteins by immunoblotting. Transcript levels were quantified in the RNA-Seq data.

Results: Single-cell gel electrophoresis showed an approximately 2-fold increase in the number of COMET cells in the DCM hearts. Immunoblotting showed increased levels of cyclic GMP-AMP synthase (CGAS), the canonical CDSP; TANK-binding kinase 1 (TBK1), an intermediary kinase in the pathway; and RELB, P52, and P50 components of the NF κ B pathway in human heart samples from patients with DCM. Likewise, transcript levels of over 2 dozen genes involved in inflammatory responses were increased.

Conclusions: The findings provide the first set of evidence for the activation of the CDSP pathway in human hearts with DCM. The data in conjunction with the previous evidence of activation of the DDR pathway implicate the DSBs in the pathogenesis of human DCM.

Keywords
DNA damage, double-stranded DNA breaks, cardiomyopathy, heart failure

Graphical abstract



Graphic abstract: Various stressors cause DNA lesions, including double-stranded DNA breaks (DSBs). DSBs activate the nuclear DNA Damage Response (DDR) pathway, comprised of H2AFX, ATM, CHK2, and TP53. The latter induces expression of genes involved in cell cycle arrest, cell death, senescence, and DNA repair among others.
DSBs are also released into the cytosol where the DNA activated the cytosolic DNA sensing proteins, such as CGAS, leading to the activation of a cascade of proteins that merge into activating NFkB and IRF3. These transcription factors induce the expression of pro-inflammatory genes and senescence-associated secretory phenotype (SASP).

Cite this article

Rouhi L, Cheedipudi SM, Cathcart B, Gurha P, Marian AJ. Cytosolic DNA sensing protein pathway is activated in human hearts with dilated cardiomyopathy. *J Cardiovasc Aging* 2023;3:32. http://dx.doi.org/10.20517/jca.2023.20

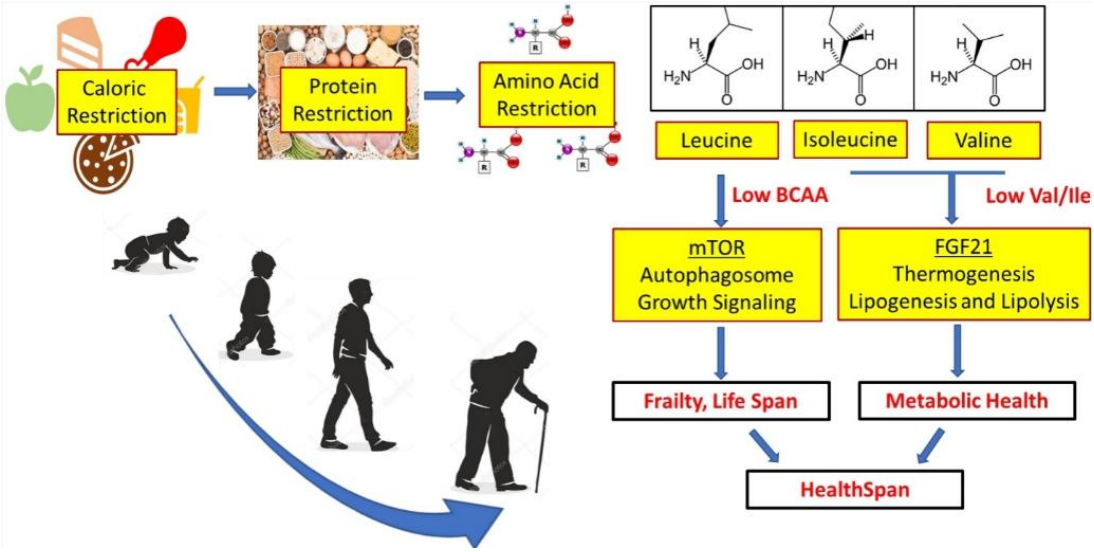
Commentary

1. The coming of age for branched-chain amino acids

Chen Gao, Nancy Cao, Yibin Wang*

Read
Full-text PDF PMID: 34568877 PMCID: PMC8459750 DOI: 10.20517/jca.2021.02
Citation
RIS Plain text

Graphical abstract



Cite this article

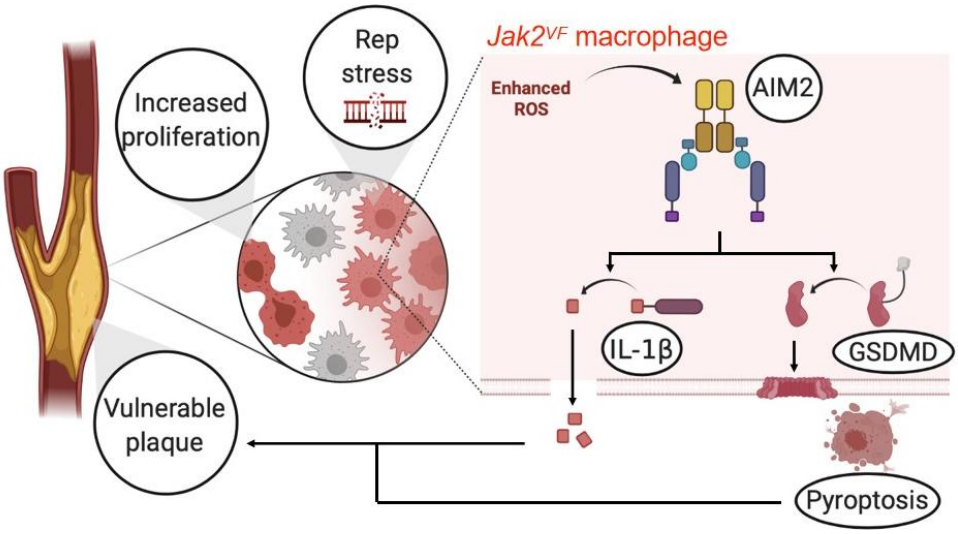
Gao C, Cao N, Wang Y. The coming of age for branched-chain amino acids. *J Cardiovasc Aging* 2021;1:2.
http://dx.doi.org/10.20517/jca.2021.02

2. Hematopoietic JAK2V617F-mediated clonal hematopoiesis: AIM2 understand mechanisms of atherogenesis

Soichi Sano, Kenneth Walsh*

Read
Full-text PDF PMID: 34396370 PMCID: PMC8360421 DOI: 10.20517/jca.2021.06
Citation
RIS Plain text

Graphical abstract



Cite this article

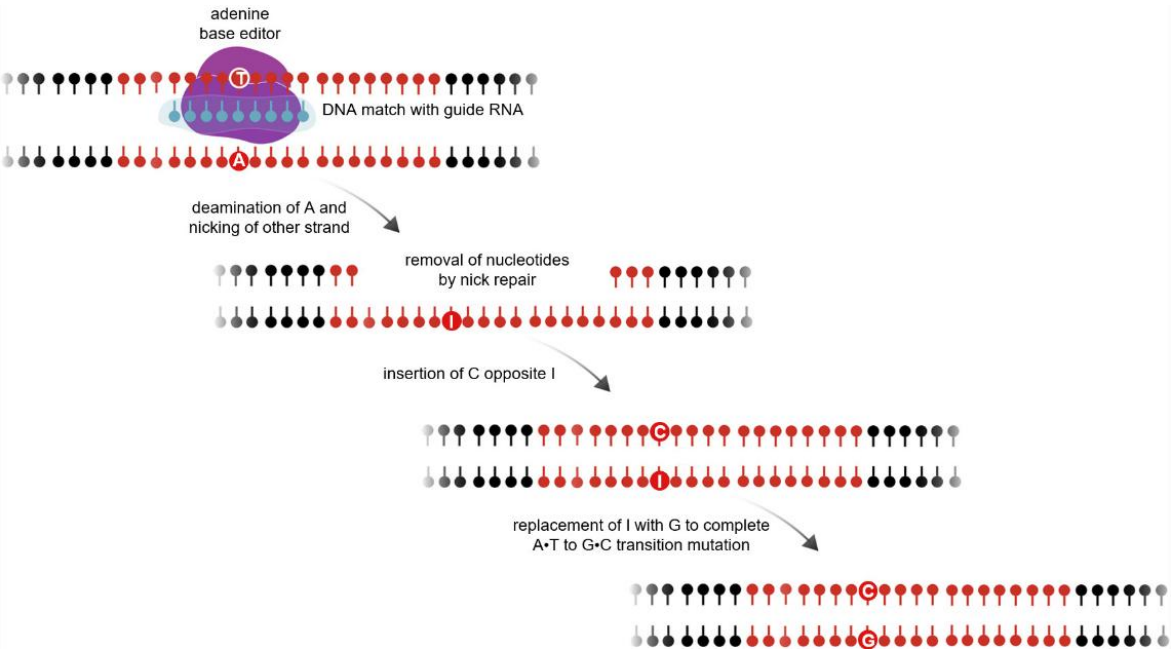
Sano S, Walsh K. Hematopoietic JAK2^{V617F}-mediated clonal hematopoiesis: AIM2 understand mechanisms of atherogenesis. *J Cardiovasc Aging* 2021;1:5. http://dx.doi.org/10.20517/jca.2021.06

3. Adenine base editing to treat progeria syndrome and extend the lifespan

Kiran Musunuru*

Read
Full-text PDF PMID: 34308436 PMCID: PMC8302045 DOI: 10.20517/jca.2021.10
Citations
RIS Plain text

Graphical abstract



Cite this article

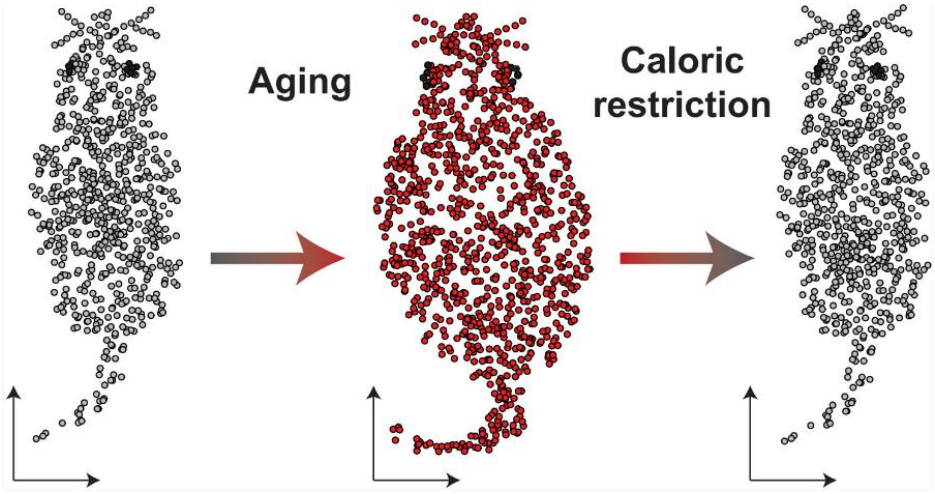
Musunuru K. Adenine base editing to treat progeria syndrome and extend the lifespan. *J Cardiovasc Aging* 2021;1:8. http://dx.doi.org/10.20517/jca.2021.10

4. Caloric restriction reverses aging: one cell at a time

Lukas M. Simon*

Read
Full-text PDF DOI: 10.20517/jca.2021.12
Citation
RIS Plain text

Graphical abstract



Cite this article

Simon LM. Caloric restriction reverses aging: one cell at a time. *J Cardiovasc Aging* 2021;1:7.
http://dx.doi.org/10.20517/jca.2021.12

5. COVID-19 and BRD4: a stormy and cardiotoxic bromo-romance

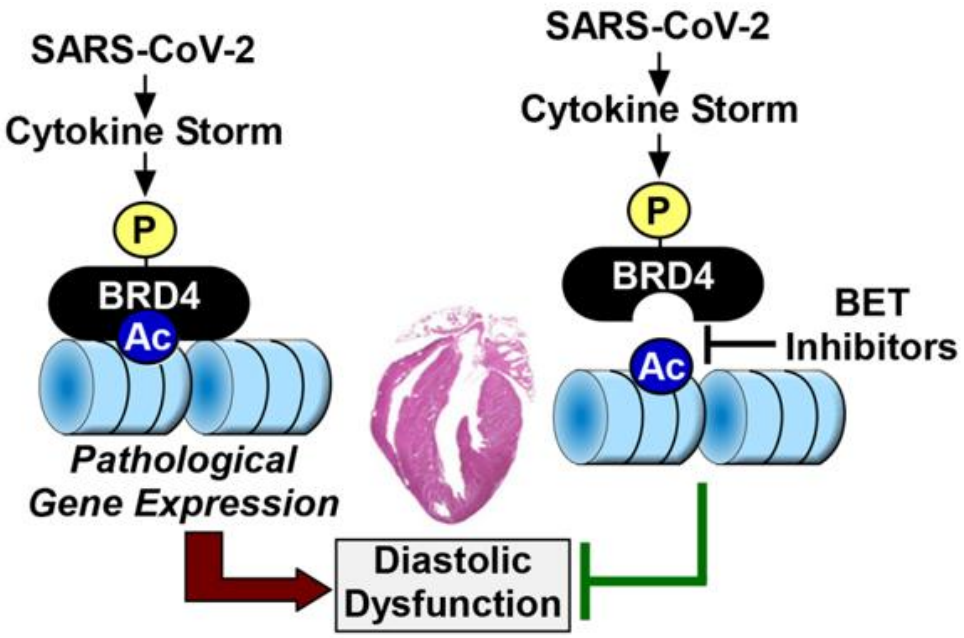
Emma L. Robinson , Timothy A. McKinsey*

Read
Full-text PDF PMID: 34901955 PMCID: PMC8664241 DOI: 10.20517/jca.2021.20
Citation
RIS Plain text

Abstract
Severe systemic inflammation in COVID-19 patients can lead to dysfunction of multiple organs, including the heart. Using an ex vivo cardiac organoid system, Mills et al discovered that inhibitors of the chromatin reader protein, bromodomain-containing protein 4, protect cardiomyocytes from COVID-associated “cytokine storm”. We briefly review these important findings and highlight the translational significance of the work.

Keywords
SARS-CoV-2, COVID-19, cytokine storm, bromodomain-containing protein 4, diastolic dysfunction

Graphical abstract



Cite this article

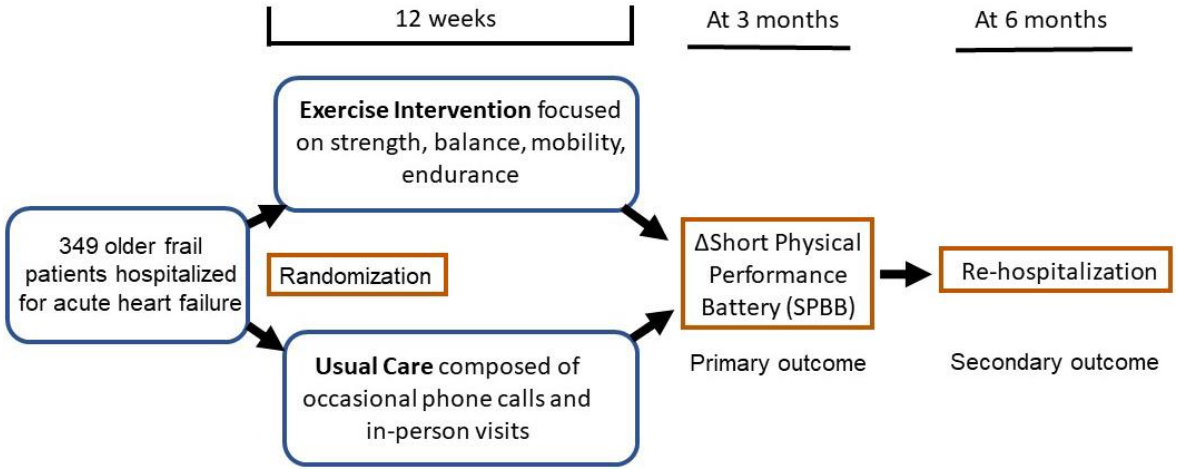
Robinson EL, McKinsey TA. COVID-19 and BRD4: a stormy and cardiotoxic bromo-romance. *J Cardiovasc Aging* 2022;2:1. http://dx.doi.org/10.20517/jca.2021.20

6. Physical exercise in older patients with heart failure

Hirofumi Tanaka*

Read
Full-text PDF DOI: 10.20517/jca.2021.23
Citations
RIS Plain text

Graphical abstract



Cite this article

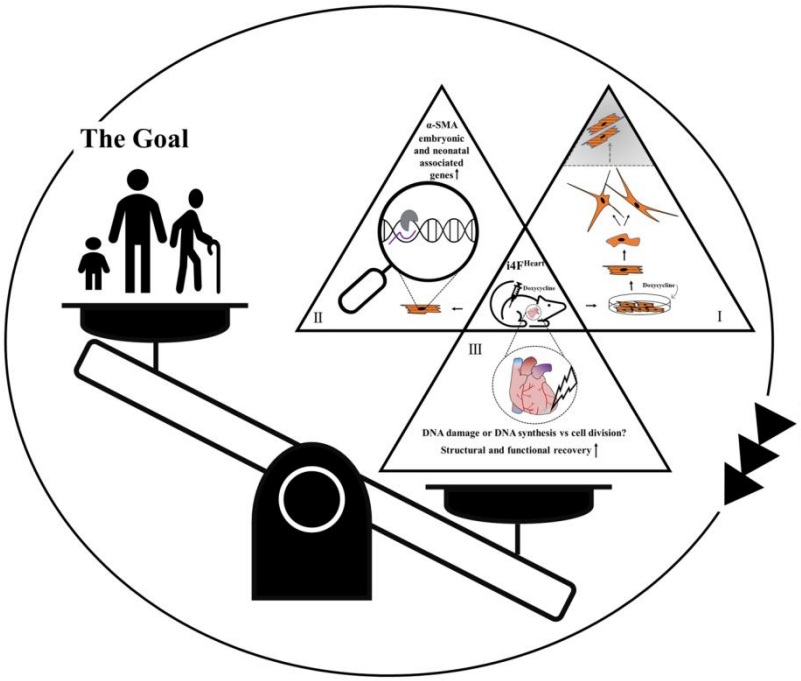
Tanaka H. Physical exercise in older patients with heart failure. *J Cardiovasc Aging* 2022;2:2.
http://dx.doi.org/10.20517/jca.2021.23

7. Transient reprogramming primes the heart for repair

Natalie A. Gude , Fareheh Firouzi , Mark A. Sussman*

Read
Full-text PDF PMID: 34901956 PMCID: PMC8664274 DOI: 10.20517/jca.2021.31
Citation
RIS Plain text

Graphical abstract



Cite this article

Gude NA, Firouzi F, Sussman MA. Transient reprogramming primes the heart for repair. *J Cardiovasc Aging* 2022;2:4.
http://dx.doi.org/10.20517/jca.2021.31

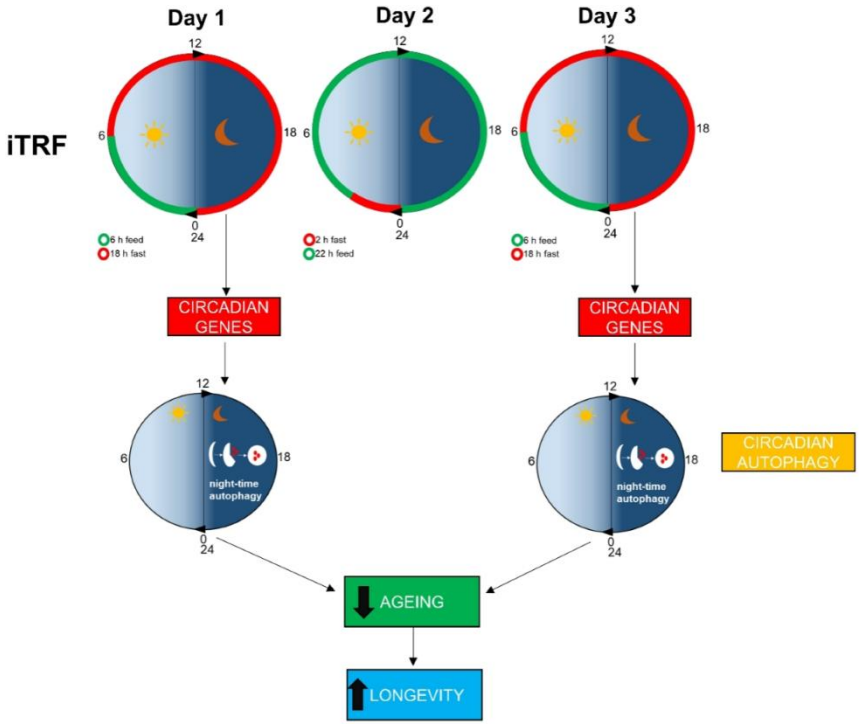
8. Boosting circadian autophagy by means of intermittent time-restricted feeding: a novel anti-ageing strategy?

Sebastiano Sciarretta, Maurizio Forte, Junichi Sadoshima*

Read
Full-text PDF PMID: 35083475 PMCID: PMC8785976 DOI: 10.20517/jca.2021.33

Citation
RIS Plain text

Graphical abstract



Cite this article

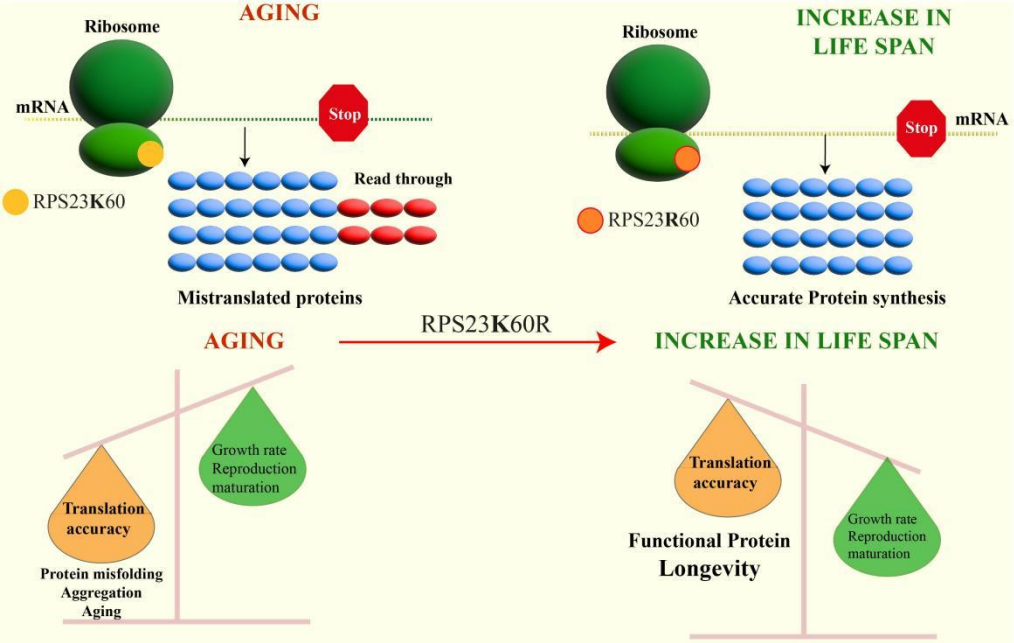
Sciarretta S, Forte M, Sadoshima J. Boosting circadian autophagy by means of intermittent time-restricted feeding: a novel anti-ageing strategy?. *J Cardiovasc Aging* 2022;2:5. http://dx.doi.org/10.20517/jca.2021.33

9. Thermophiles reveal the clues to longevity: precise protein synthesis

Manisha Deogharia, Priyatansh Gurha*

Read
Full-text PDF PMID: 36778790 PMCID: PMC9912815 DOI: 10.20517/jca.2021.38
Citation
RIS Plain text

Graphical abstract



Cite this article

Deogharia M, Gurha P. Thermophiles reveal the clues to longevity: precise protein synthesis. *J Cardiovasc Aging* 2022;2:14. http://dx.doi.org/10.20517/jca.2021.38

10. Senolytic vaccination: a new mandate for cardiovascular health?

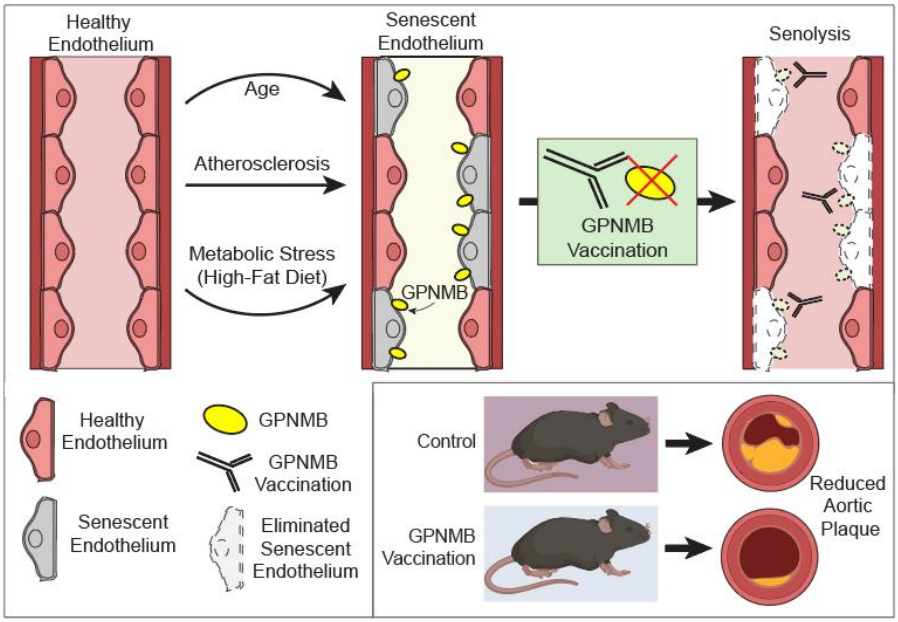
Travis B. Lear, Toren Finkel*

Read
Full-text PDF PMCID:PMC9937554 DOI: 10.20517/jca.2022.03
Citation
RIS Plain text

Abstract
Senescent cell accumulation is increasingly associated with a number of age-related cardiovascular diseases. Now, a new manuscript in *Nature Aging* suggests that a novel vaccine-based strategy might provide a targeted method to eliminate the senescent cell population.

Keywords
Senolytic vaccination, aging, GPNMB

Graphical abstract



Cite this article

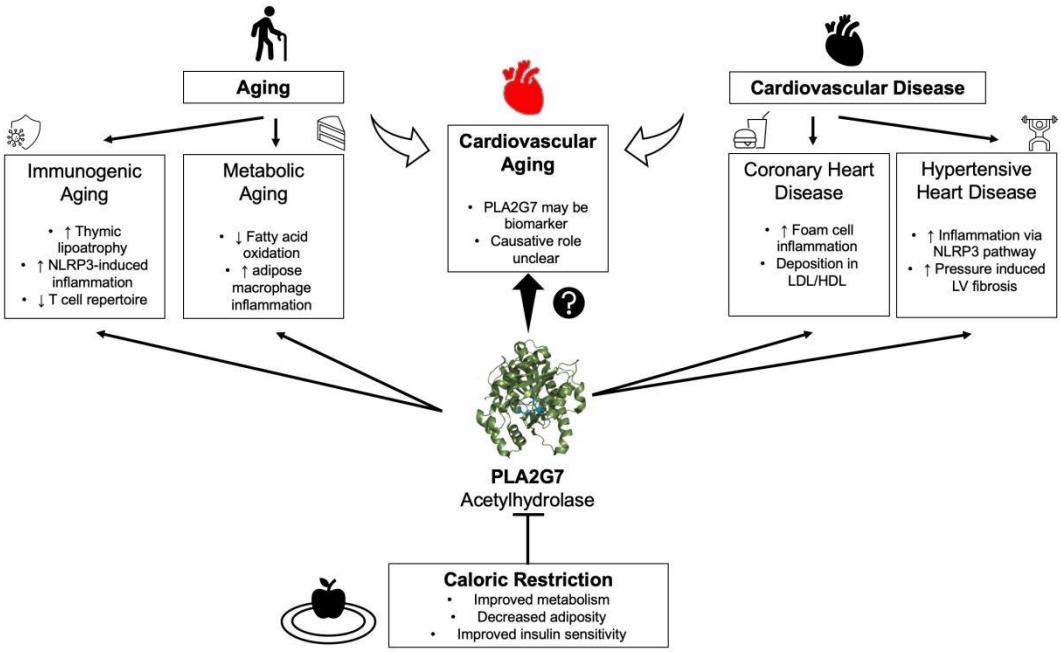
Lear TB, Finkel T. Senolytic vaccination: a new mandate for cardiovascular health?. *J Cardiovasc Aging* 2022;2:17. http://dx.doi.org/10.20517/jca.2022.03

11. PLA2G7, caloric restriction and cardiovascular aging

Fang Cao, Richard T. Lee*

Read
Full-text PDF PMID: 35497092 PMCID: PMC9053108 DOI: 10.20517/jca.2022.08
Citations
RIS Plain text

Graphical abstract



Cite this article

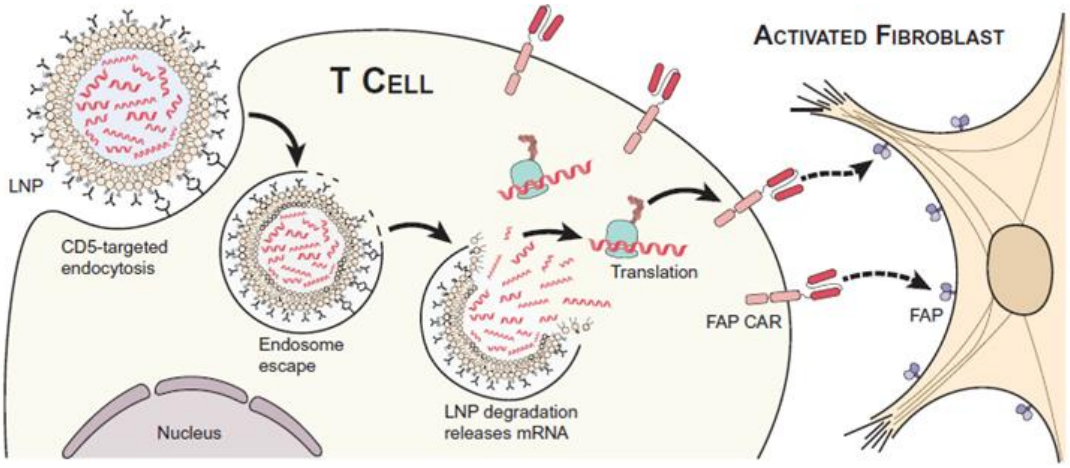
Cao F, Lee RT. PLA2G7, caloric restriction and cardiovascular aging. *J Cardiovasc Aging* 2022;2:19.
http://dx.doi.org/10.20517/jca.2022.08

12. The use of targeted LNP/mRNA technology to generate functional, transient CAR T cells and treat cardiac injury in vivo

Georgina M. Ellison-Hughes*

Read
Full-text PDF DOI: 10.20517/jca.2022.05
Citation
RIS Plain text

Graphical abstract



Cite this article

Ellison-Hughes GM. The use of targeted LNP/mRNA technology to generate functional, transient CAR T cells and treat cardiac injury *in vivo*. *J Cardiovasc Aging* 2022;2:23. http://dx.doi.org/10.20517/jca.2022.05

13. Towards a BETter understanding of cardiac fibrosis

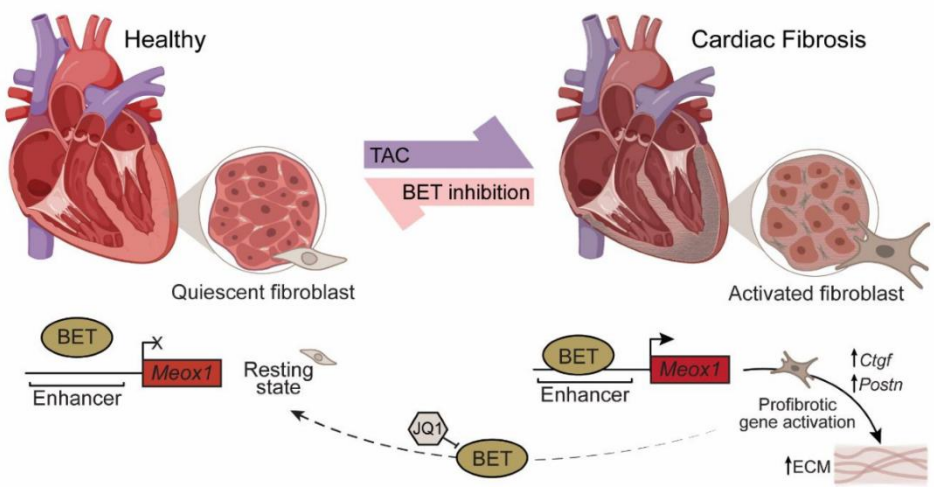
Elizabeth S. Stout, David A. Elliott*, Enzo R. Porrello*

Read
Full-text PDF DOI: 10.20517/jca.2022.15
Citation
RIS Plain text

Abstract
Fibroblast activation is a hallmark feature of pathological remodeling of the heart and represents an attractive target for therapeutic intervention. Pharmacological inhibition of chromatin remodeling enzymes reduces cardiac fibrosis, but the underlying transcriptional regulatory mechanisms remain poorly understood. Using single-cell genomics to profile alterations in the transcriptional and chromatin landscape during stress-induced cardiac remodeling, Alexanian *et al.* discovered a critical role for Mesenchyme Homeobox 1 in the regulation of myofibroblast activation and cardiac fibrosis. We briefly review these important findings and comment on the significance of their work.

Keywords
Cardiac fibrosis, chromatin, fibroblast activation, heart failure

Graphical abstract



Cite this article

Stout ES, Elliott DA, Porrello ER. Towards a BETter understanding of cardiac fibrosis. *J Cardiovasc Aging* 2022;2:24. http://dx.doi.org/10.20517/jca.2022.15

14. Hydrogen sulfide: the gas that fuels longevity

Erik A. Blackwood, Christopher C. Glembotski*

Read
Full-text PDF PMID: 36776272 PMCID: PMC9912355 DOI: 10.20517/jca.2022.16
Citation
RIS Plain text

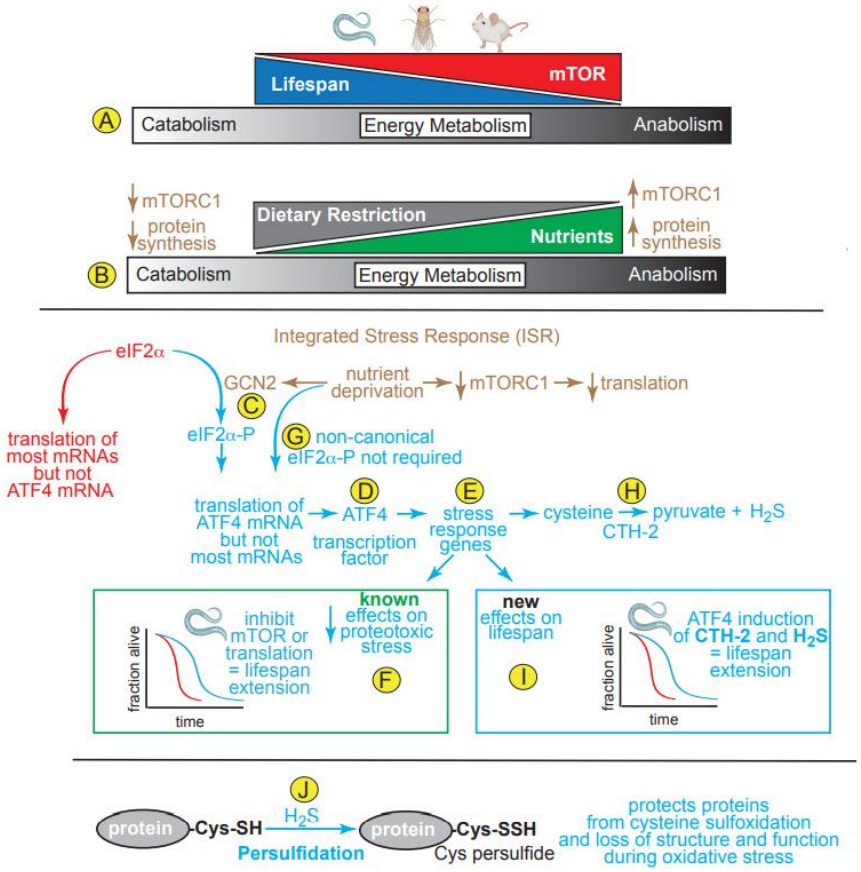
Abstract

The molecular determinants of lifespan can be examined in animal models with the long-term objective of applying what is learned to the development of strategies to enhance longevity in humans. Here, we comment on a recent publication examining the molecular mechanisms that determine lifespan in worms, *Caenorhabditis elegans* (*C. elegans*), where it was shown that inhibiting protein synthesis increased levels of the transcription factor, ATF4. Gene expression analyses showed that ATF4 increased the expression of genes responsible for the formation of the gas, hydrogen sulfide (H_2S). Further examination showed that H_2S increased longevity in *C. elegans* by modifying proteins in ways that stabilize their structures and enhance their functions. H_2S has been shown to improve cardiovascular performance in mouse models of heart disease, and clinical trials are underway to test the effects of H_2S on cardiovascular health in humans. These findings support the concept that nutrient deprivation, which slows protein synthesis and leads to ATF4-mediated H_2S production, may extend lifespan by improving the function of the cardiovascular system and other systems that influence longevity in humans.

Keywords

ATF4, mTORC1, protein synthesis, hydrogen sulfide, longevity

Graphical abstract



Cite this article

Blackwood EA, Glembotski CC. Hydrogen sulfide: the gas that fuels longevity. *J Cardiovasc Aging* 2022;2:26. http://dx.doi.org/10.20517/jca.2022.16

15. Fasting confers stress resistance to skeletal muscle stem cells through non-metabolic actions of β-hydroxybutyrate: implications in cardioprotection and aging

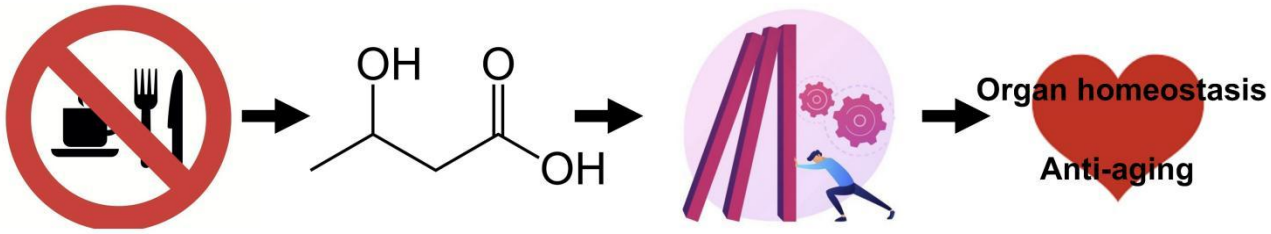
Junichi Sadoshima*

Read
Full-text PDF PMID: 35891705 PMCID: PMC9311383 DOI: 10.20517/jca.2022.24
Citation
RIS Plain text

Graphical abstract

Fasting may induce stress resistance in cardiac cells through increases in beta-hydroxybutyrate. This may

enhance the ability of the heart to regenerate against stress and prevent aging. This remains hypothetical. The image of stress resistance was obtained from https://enkhtuul092811.medium.com/resilience-stress-tolerance-and-flexibility-skills-4bcce544c301.



Cite this article

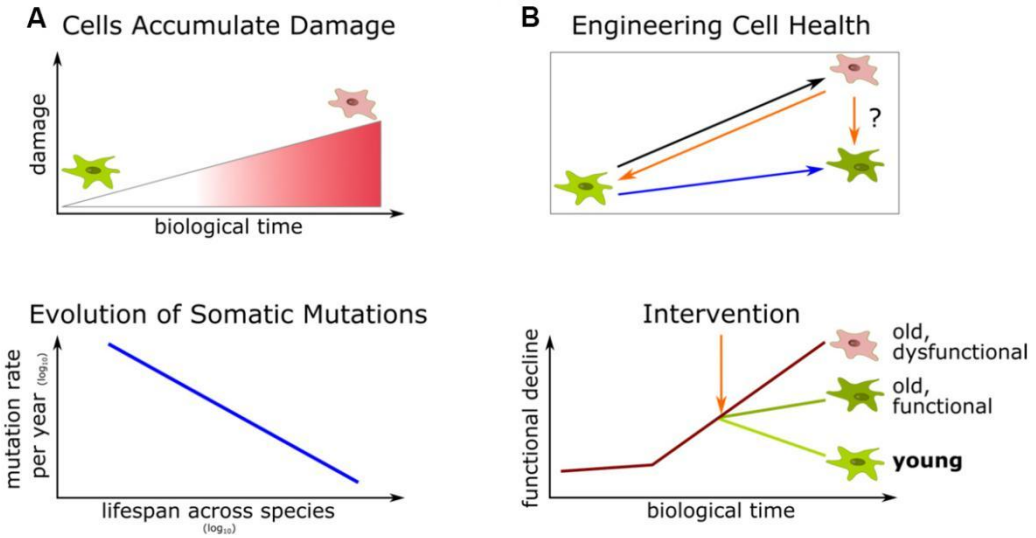
Sadoshima J. Fasting confers stress resistance to skeletal muscle stem cells through non-metabolic actions of β-hydroxybutyrate: implications in cardioprotection and aging. *J Cardiovasc Aging* 2022;2:34. http://dx.doi.org/10.20517/jca.2022.24

16. A role for somatic mutations in the evolution of lifespan

Sebastian Memczak, Juan Carlos Izpisua Belmonte*

Read
Full-text PDF DOI: 10.20517/jca.2022.28
Citation
RIS Plain text

Graphical abstract



Cite this article

Memczak S, Izpisua Belmonte JC. A role for somatic mutations in the evolution of lifespan. *J Cardiovasc Aging* 2022;2:39. http://dx.doi.org/10.20517/jca.2022.28

17. SGLT2 inhibitors in patients with HFpEF: how old is too old?

Dan Tong*

Read
Full-text PDF PMID: 35935281 PMCID: PMC9354734 DOI: 10.20517/jca.2022.30
Citation
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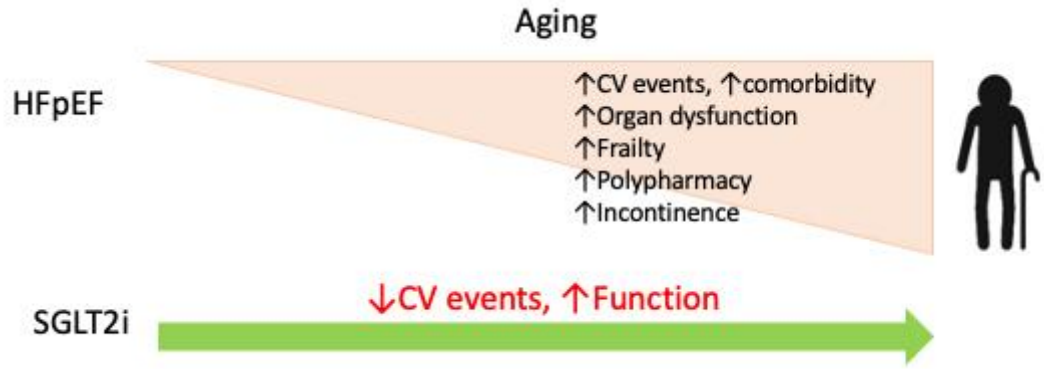
Graphical abstract



Cite this article

Tong D. SGLT2 inhibitors in patients with HFpEF: how old is too old?. *J Cardiovasc Aging* 2022;2:41. http://dx.doi.org/10.20517/jca.2022.30

18. YAP/TAZ dull the STING of aging

Jamie Francisco, Dominic P. Del Re*

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Full-text PDF PMID: 36337727 PMCID: PMC9632523 DOI: 10.20517/jca.2022.33
Citation
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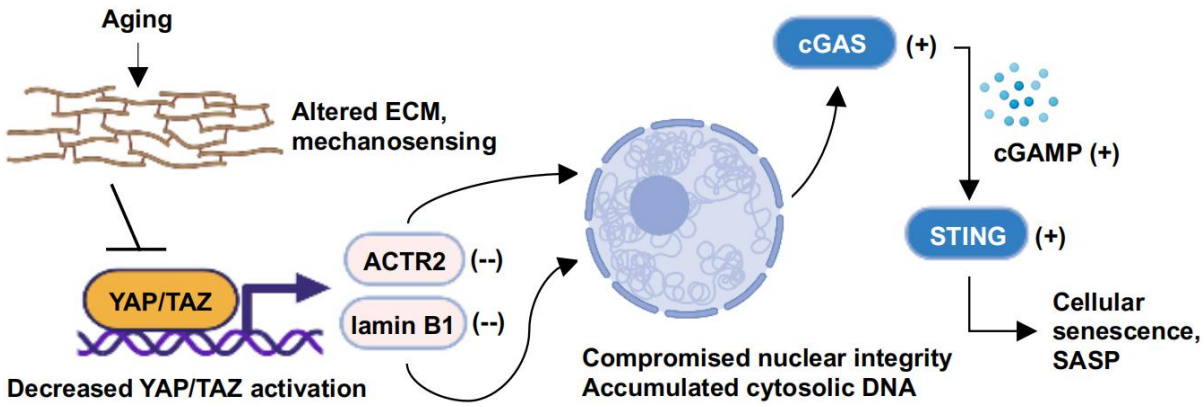
Graphical abstract



Cite this article

Francisco J, Del Re DP. YAP/TAZ dull the STING of aging. *J Cardiovasc Aging* 2022;2:44.
http://dx.doi.org/10.20517/jca.2022.33

19. Small molecules that enhance mitophagy to delay aging and neurodegeneration

Gerald W. Dorn II*

Read
Full-text PDF DOI: 10.20517/jca.2022.36
Citation
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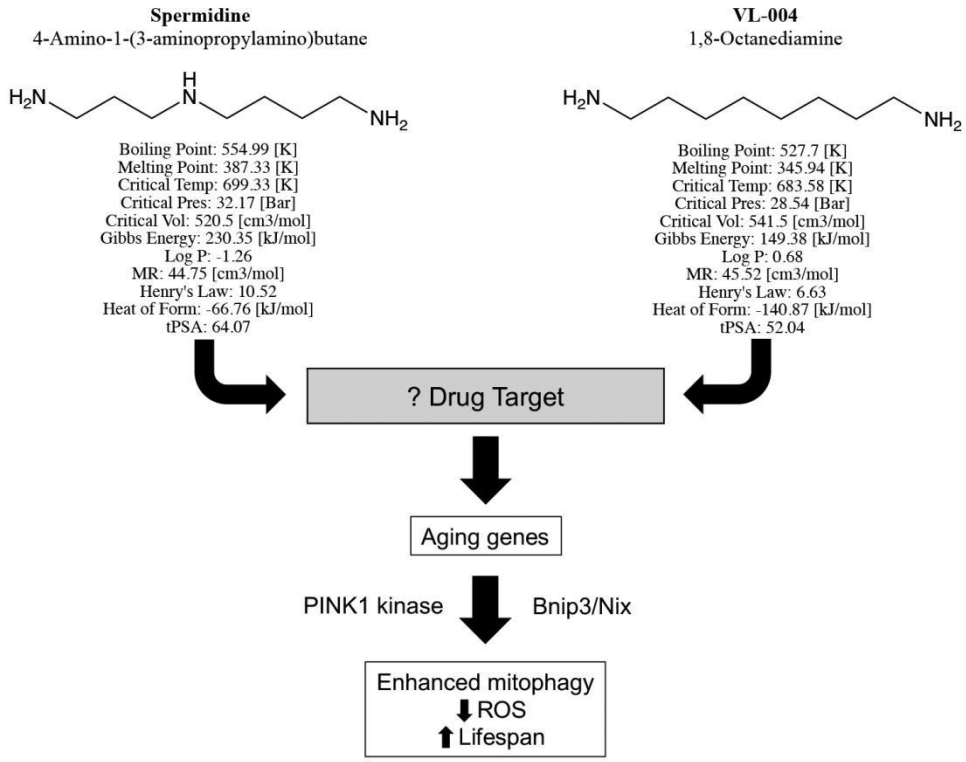
Graphical abstract



Cite this article

Dorn GW II. Small molecules that enhance mitophagy to delay aging and neurodegeneration. *J Cardiovasc Aging* 2022;2:45. http://dx.doi.org/10.20517/jca.2022.36

20. The role of paracrine crosstalk between myeloid and endothelial cells in myocardial angiogenesis and infarcted heart repair

Kyu-Won Cho, Seongho Bae, Young-sup Yoon*

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Full-text PDF PMID: 36544808 PMCID: PMC9762688 DOI: 10.20517/jca.2022.37
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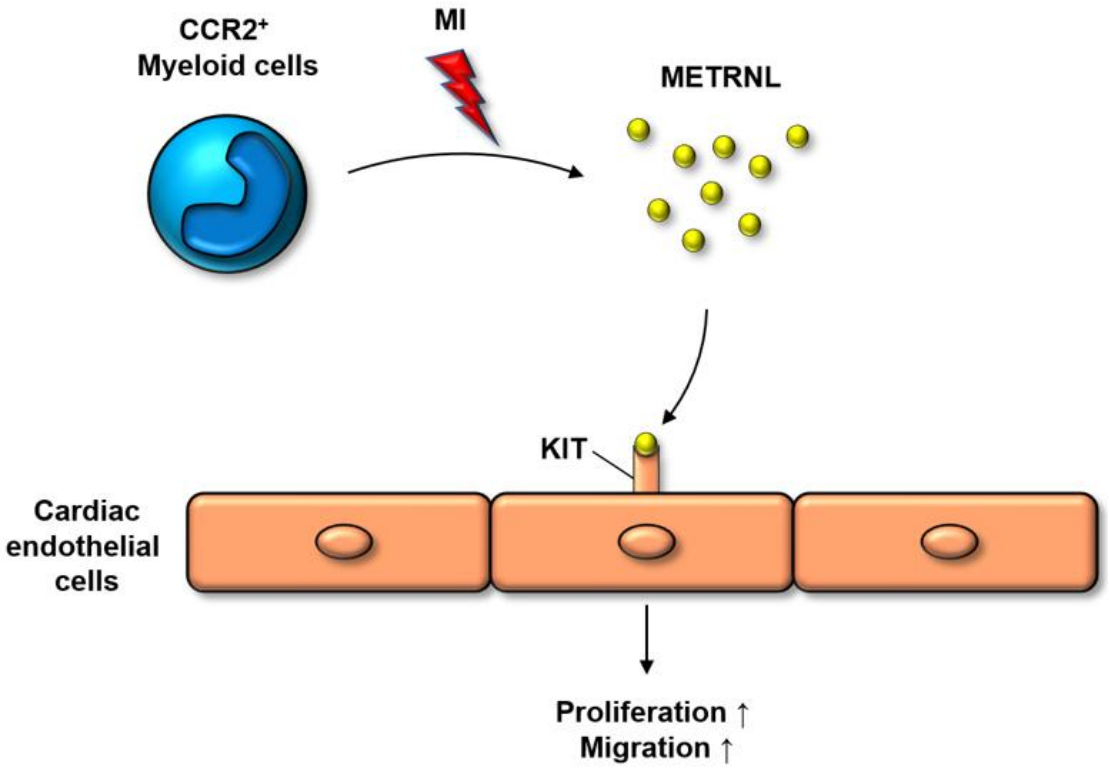
Graphical abstract



Cite this article

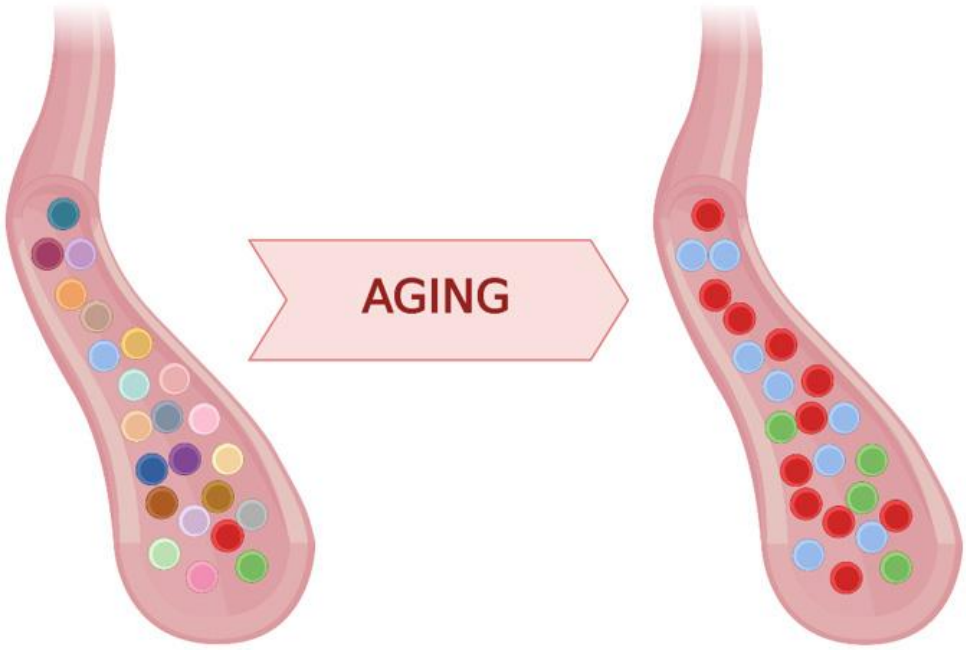
Cho KW, Bae S, Yoon Y. The role of paracrine crosstalk between myeloid and endothelial cells in myocardial angiogenesis and infarcted heart repair. *J Cardiovasc Aging* 2023;3:1. http://dx.doi.org/10.20517/jca.2022.37

21. New insights into the dynamics of age-related clonal hematopoiesis

María A. Zuriaga, José J. Fuster*

Read
Full-text PDF DOI: 10.20517/jca.2022.38
Citation
RIS Plain text

Graphical abstract



Cite this article

Zuriaga MA, Fuster JJ. New insights into the dynamics of age-related clonal hematopoiesis. *J Cardiovasc Aging* 2023;3:2. http://dx.doi.org/10.20517/jca.2022.38

22. The importance of “when” in calorie restriction-induced lifespan extension

Kristin Eckel-Mahan*

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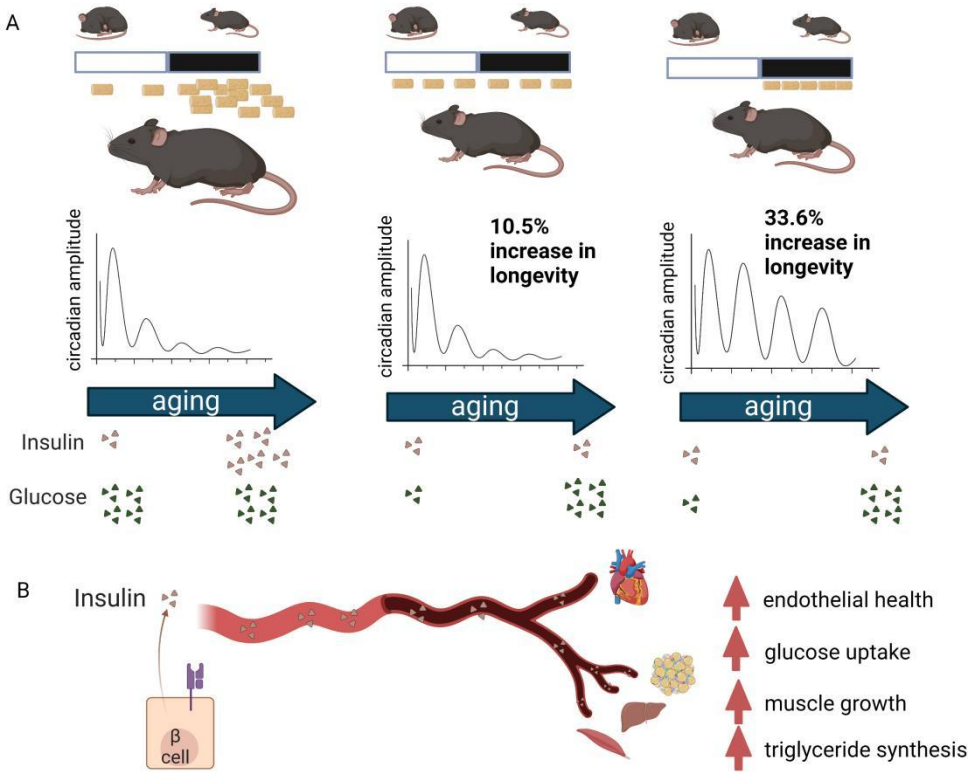
Full-text PDF PMID: 36544807 PMCID: PMC9762686 DOI: 10.20517/jca.2022.40
Citation
RIS Plain text

Graphical abstract



Cite this article

Eckel-Mahan K. The importance of "when" in calorie restriction-induced lifespan extension. *J Cardiovasc Aging* 2023;3:5. http://dx.doi.org/10.20517/jca.2022.40

23. ASGR1 and cholesterol: connecting the dots

Hilma Holm*

Read
Full-text PDF DOI: 10.20517/jca.2023.8
Citation
RIS Plain text

Cite this article

Holm H. ASGR1 and cholesterol: connecting the dots. *J Cardiovasc Aging* 2023;3:15. http://dx.doi.org/10.20517/jca.2023.8

24. Exercise induces cardiomyogenesis in the aged heart

Waleed Elhelaly, Hesham Sadek*

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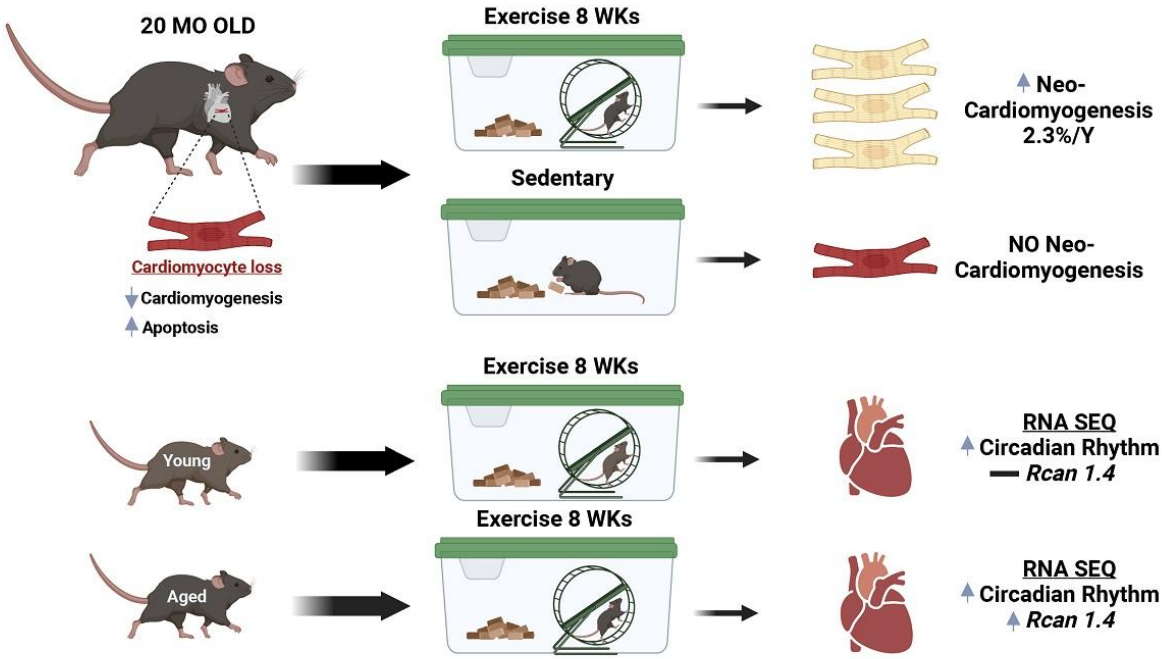
Full-text PDF DOI: 10.20517/jca.2023.06
Citation
RIS Plain text

Graphical abstract



Cite this article

Elhelaly W, Sadek H. Exercise induces cardiomyogenesis in the aged heart . *J Cardiovasc Aging* 2023;3:18. http://dx.doi.org/10.20517/jca.2023.06

25. CaMKII δ gene editing- A base hit for the heart

Christopher J. Walkey, William R. Lagor*

Read
Full-text PDF PMID: 37065676 PMCID: PMC10104458 DOI: 10.20517/jca.2023.11
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Cite this article

Walkey CJ, Lagor WR. CaMKIIδ gene editing - A base hit for the heart. *J Cardiovasc Aging* 2023;3:19. http://dx.doi.org/10.20517/jca.2023.11

26. A worm's life: AMPK links muscle mitochondrial dynamics to phesical fitness and healthy aging in *Caenorhabditis elegans*

Vihang A. Narkar*

Read
Full-text PDF DOI: 10.20517/jca.2023.14
Citation
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Cite this article

Narkar VA. A worm's life: AMPK links muscle mitochondrial dynamics to physical fitness and healthy aging in Caenorhabditis elegans. *J Cardiovasc Aging* 2023;3:25. http://dx.doi.org/10.20517/jca.2023.14

27. Editing the trajectory of hypertrophic cardiomyopathy

Mason E. Sweat, William T. Pu*

Read
Full-text PDF PMID: 37484981 PMCID: PMC10361709 DOI: 10.20517/jca.2023.19
Citation
RIS Plain text

Cite this article

Sweat ME, Pu WT. Editing the trajectory of hypertrophic cardiomyopathy. *J Cardiovasc Aging* 2023;3:28. http://dx.doi.org/10.20517/jca.2023.19

28. The burden of somatic mutations in the aging heart

Brenda Gerull*, Ruping Chen

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Full-text PDF DOI: 10.20517/jca.2023.24
Citation
RIS Plain text

Cite this article

Gerull B, Chen R. The burden of somatic mutations in the aging heart. *J Cardiovasc Aging* 2023;3:34. http://dx.doi.org/10.20517/jca.2023.24

29. The newborn heart GLAdly benefits from maternal milk

Caitlyn E. Bowman, Zoltan Arany*

Read
Full-text PDF DOI: 10.20517/jca.2023.25
Citation
RIS Plain text

Cite this article

Bowman CE, Arany Z. The newborn heart GLAdly benefits from maternal milk. *J Cardiovasc Aging* 2023;3:35. http://dx.doi.org/10.20517/jca.2023.25

Perspective

1. Genetic risk stratification, pivotal to precluding the CAD pandemic

Robert Roberts*

Read
Full-text PDF DOI: 10.20517/jca.2021.05
Citation
RIS Plain text

Cite this article

Roberts R. Genetic risk stratification, pivotal to precluding the CAD pandemic. *J Cardiovasc Aging* 2021;1:4. http://dx.doi.org/10.20517/jca.2021.05

J Cardiovasc Aging
Online ISSN: 2768-5993
The Journal of Cardiovascular Aging

2. Principles of scientific research conduct, peer review, and publication: an editor's perspective

Ali J. Marian*

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Full-text PDF PMID: 35037003 PMCID: PMC8756452 DOI: 10.20517/jca.2021.37
Citation
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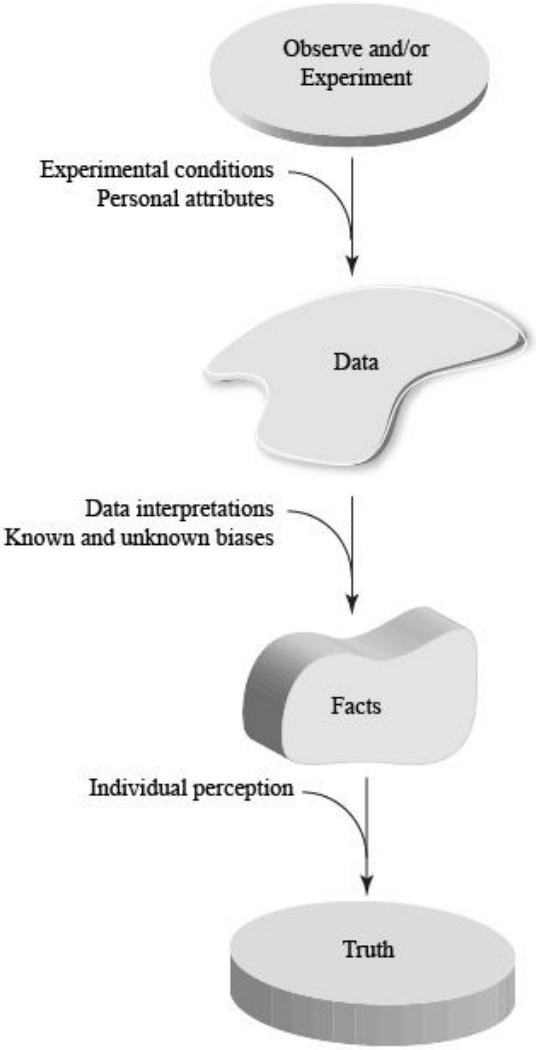
Graphical abstract



Cite this article

Marian AJ. Principles of scientific research conduct, peer review, and publication: an editor's perspective. *J Cardiovasc Aging* 2022;2:6. http://dx.doi.org/10.20517/jca.2021.37

3. The sad plight of cell therapy for heart failure: causes and consequences

Roberto Bolli*, Xian-Liang Tang

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Full-text PDF PMID: 35373217 PMCID: PMC8974963 DOI: 10.20517/jca.2022.02
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RIS Plain text

Cite this article

Bolli R, Tang XL. The sad plight of cell therapy for heart failure: causes and consequences. *J Cardiovasc Aging* 2022;2:16. http://dx.doi.org/10.20517/jca.2022.02

4. Why animal model studies are lost in translation

Nikolaos G. Frangogiannis*

Read
Full-text PDF PMID: 35497093 PMCID: PMC9052957 DOI: 10.20517/jca.2022.10
Citations
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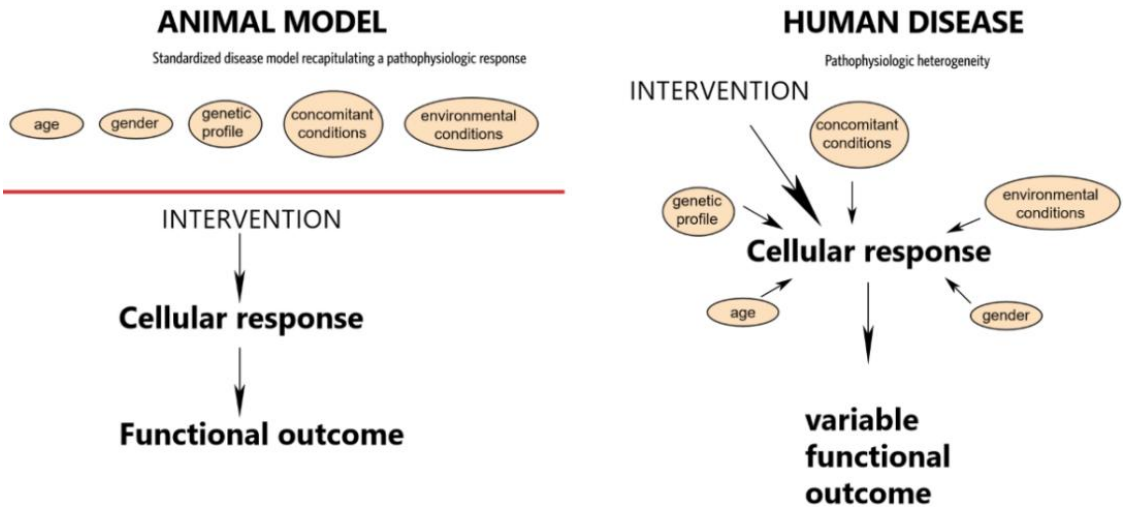
Abstract
The development of novel therapies based on understanding the pathophysiologic basis of disease is a major goal of biomedical research. Despite an explosion in new knowledge on the molecular mechanisms of disease derived from animal model investigations, translation into effective treatment for human patients has been disappointingly slow. Several fundamental problems may explain the translational failures. First, the emphasis on novel and highly significant findings selectively rewards implausible, low-probability observations and high-magnitude effects, providing a biased perspective of the pathophysiology of disease that underappreciates the complexity and redundancy of biological systems. Second, even when a sound targetable mechanism is identified, animal models cannot recapitulate the pathophysiologic heterogeneity of the human disease, and are poor predictors of therapeutic success. Third, traditional classifications of most complex diseases are based primarily on clinical criteria and do not reflect the diverse pathophysiologic mechanisms that may be involved. The development of a flexible and dynamic conceptual paradigm that takes into account the totality of the evidence on the mechanisms of disease, and pathophysiologic stratification of patients to identify subpopulations with distinct pathogenetic mechanisms, are crucial for the development of new therapeutics.

Keywords
Animal model, translation, pathophysiology, human disease

Graphical abstract



Cite this article

Frangogiannis NG. Why animal model studies are lost in translation. *J Cardiovasc Aging* 2022;2:22.
http://dx.doi.org/10.20517/jca.2022.10

5. What ails the NIH peer review study sections and how to fix the review process of the grant applications

Ali J. Marian*

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Full-text PDF PMCID: PMC9933949 DOI: 10.20517/jca.2023.3
Citations
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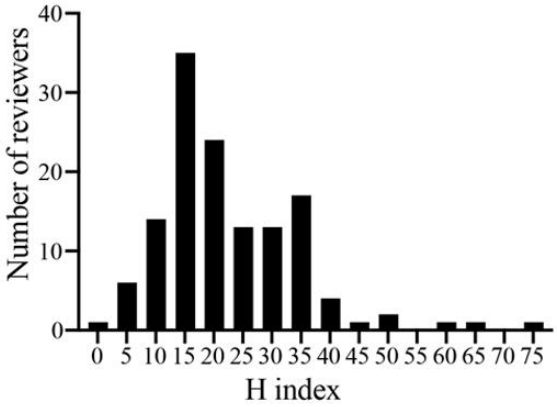
Keywords
Peer review, NIH, Study section, Grant application

Graphical abstract



Cite this article

Marian AJ. What ails the NIH peer review study sections and how to fix the review process of the grant applications. *J Cardiovasc Aging* 2023;3:11. http://dx.doi.org/10.20517/jca.2023.3

6. Why the bee in our bonnets about Beethoven's hair?

Peter Libby*

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Full-text PDF DOI: 10.20517/jca.2023.17
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Cite this article

Libby P. Why the bee in our bonnets about Beethoven's hair?. *J Cardiovasc Aging* 2023;3:26. http://dx.doi.org/10.20517/jca.2023.17

Editorial

1. Editors' Preamble to *The Journal of Cardiovascular Aging*

Ali J. Marian*, Babken Asatryan, Roberto Bolli, Sirisha M. Cheedipudi, Naranjan S. Dhalla, Toren Finkel, Nikolaos G. Frangogiannis, Priyatansh Gurha1, Juan Carlos Izpisua Belmonte, Joshua M. Hare, Kui Hong, Lorrie A. Kirshenbaum, Richard T. Lee, Massoud A. Leesar, Peter Libby, Rosalinda Madonna, Sherif F. Nagueh, Robert Roberts, Anthony Rosenzweig, Leila Rouhi, Junichi Sadoshima, Mark A. Sussman, George E. Taffet, Hirofumi Tanaka, Daniele Torella, Yibin Wang, Dao Wen Wang

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Cite this article

Marian AJ, Asatryan B, Bolli R, Cheedipudi SM, Dhalla NS, Finkel T, Frangogiannis NG, Gurha P, Izpisua Belmonte JC, Hare JM, Hong K, Kirshenbaum LA, Lee RT, Leesar MA, Libby P, Madonna R, Nagueh SF, Roberts R, Rosenzweig A, Rouhi L, Sadoshima J, Sussman MA, Taffet GE, Tanaka H, Torella D, Wang Y, Wang DW. Editors' Preamble to The Journal of Cardiovascular Aging. *J Cardiovasc Aging* 2021;1:1. http://dx.doi.org/10.20517/jca.2021.01

2. Porcupine inhibition: a novel disease-modifier target in arrhythmogenic cardiomyopathy

Jose M. Lopez-Ayala*

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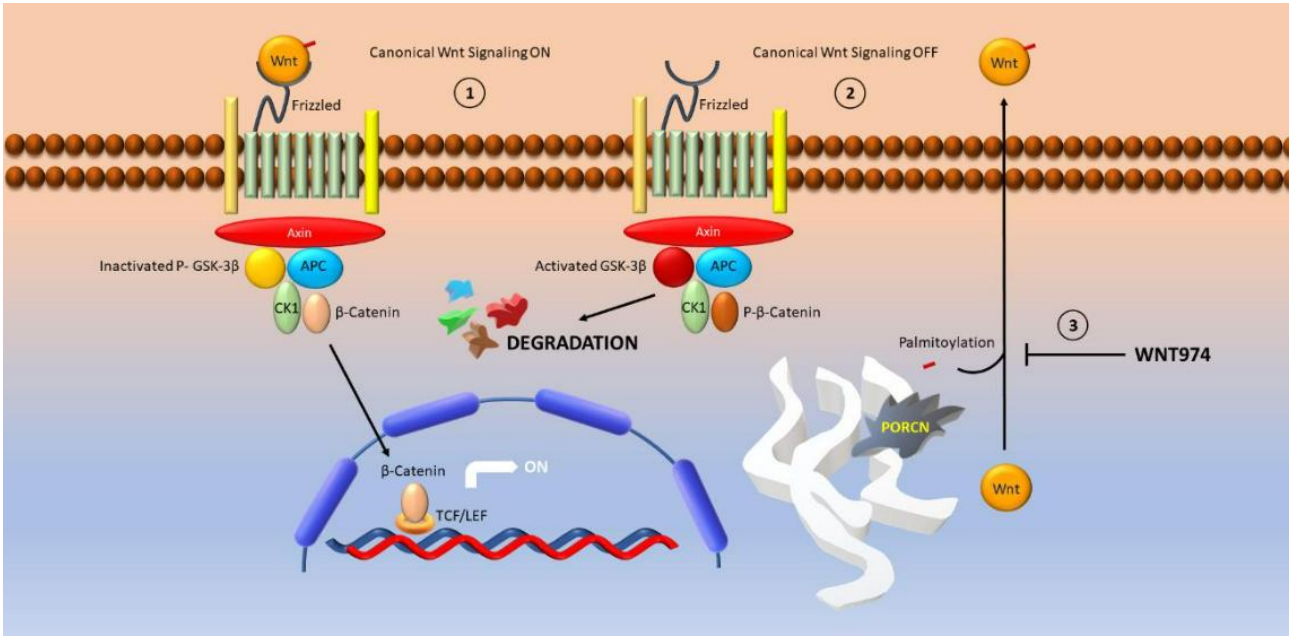
Graphical abstract



Cite this article

Lopez-Ayala JM. Porcupine inhibition: a novel disease-modifier target in arrhythmogenic cardiomyopathy. *J Cardiovasc Aging* 2021;1:11. http://dx.doi.org/10.20517/jca.2021.14

3. GSK-3β mediates cardiac senescence through inhibition of ULK1 directed autophagy

Inna Rabinovich-Nikitin, Lorrie A. Kirshenbaum*

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Citations
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Abstract
Cardiac senescence is the progressive decline in cardiac performance resulting from decline in age related structural and metabolic processes. Aging cardiac myocytes exhibit alterations in fatty acid and glucose oxidation metabolism, activation of innate immune signaling, enhanced fibrosis, mitochondrial dysfunction, endoplasmic reticulum stress, DNA damage, senescence-associated secreting phenotype and impaired autophagy. GSK-3β is an upstream regulator of autophagy through its interaction with ULK1 which regulates the initiation step of autophagy and formation of the autophagosme. Herein, we highlight a novel putative molecular mechanism that functionally links cardiac senescence, hypertrophy and autophagy regulation. Ser9 phosphorylation of GSK-3β is critical for promoting cardiac senescence via reduction in ULK1 phosphorylation at Ser913 and inhibition of autophagy.

Keywords
GSK-3β, senescence, aging, autophagy, ULK1

Cite this article

Rabinovich-Nikitin I, Kirshenbaum LA. GSK-3β mediates cardiac senescence through inhibition of ULK1 directed autophagy. *J Cardiovasc Aging* 2021;1:14. http://dx.doi.org/10.20517/jca.2021.24

4. Value of clinical and genetic evaluation in inherited cardiomyopathy: insights and challenges

William J. McKenna*, Luis de la Higuera Romero, Soledad Garcia Hernandez, Juan Pablo Ochoa

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Full-text PDF DOI: 10.20517/jca.2021.26
Citation
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Cite this article

McKenna WJ, de la Higuera Romero L, Garcia Hernandez S, Ochoa JP. Value of clinical and genetic evaluation in inherited cardiomyopathy: insights and challenges. *J Cardiovasc Aging* 2021;1:15.
http://dx.doi.org/10.20517/jca.2021.26

5. GSNOR regulates cardiomyocyte differentiation and maturation through protein S-nitrosylation

Zachary W. Grimmett, Nicholas M. Venetos, Richard T. Premont, Jonathan S. Stamler*

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Full-text PDF PMID: 34790976 PMCID: PMC8594876 DOI: 10.20517/jca.2021.25
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Grimmett ZW, Venetos NM, Premont RT, Stamler JS. GSNOR regulates cardiomyocyte differentiation and maturation through protein S-nitrosylation. *J Cardiovasc Aging* 2021;1:16. http://dx.doi.org/10.20517/jca.2021.25

6. Taking in the trash: bioreactors for the mass production of clinical-grade extracellular vesicles

Matthew J. Robeson, Michael E. Davis*

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Full-text PDF DOI: 10.20517/jca.2021.32
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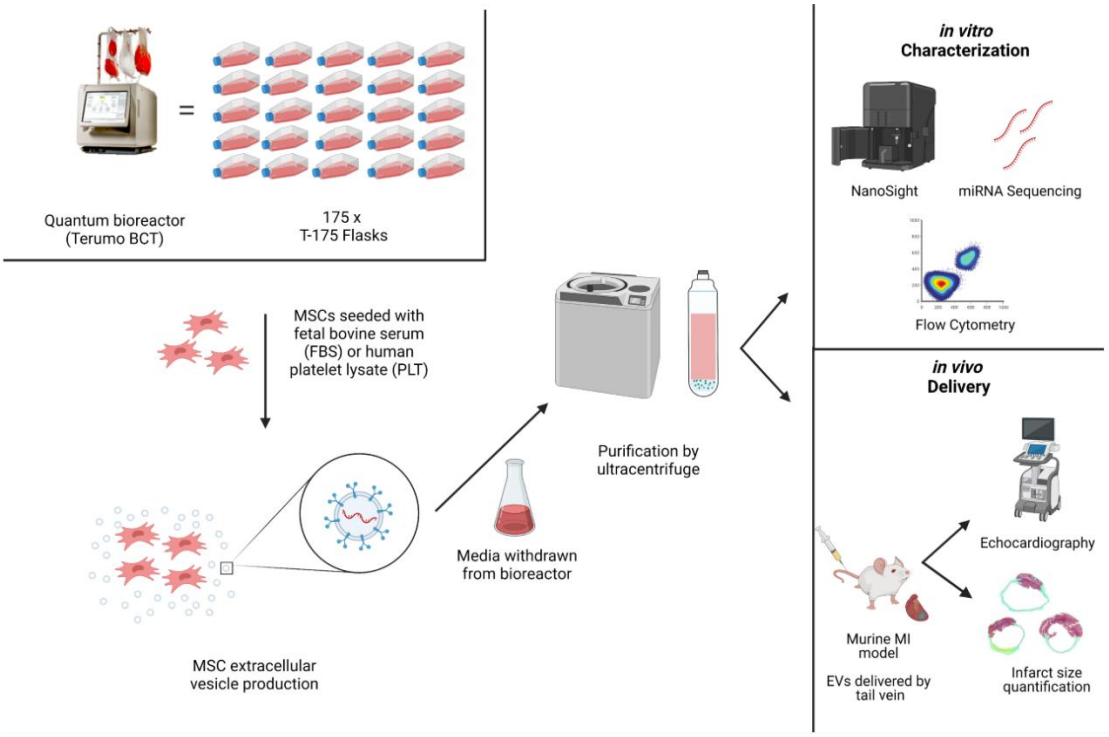
Graphical abstract



Cite this article

Robeson MJ, Davis ME. Taking in the trash: bioreactors for the mass production of clinical-grade extracellular vesicles. *J Cardiovasc Aging* 2022;2:11. http://dx.doi.org/10.20517/jca.2021.32

7. Pulse wave velocity: why is it important to know to estimate?

Anilkumar K. Reddy*, George E. Taffet*

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Full-text PDF DOI: 10.20517/jca.2021.36
Citation
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Reddy AK, Taffet GE. Pulse wave velocity: why is it important to know to estimate?. *J Cardiovasc Aging* 2022;2:10. http://dx.doi.org/10.20517/jca.2021.36

8. Optimization of tamoxifen-induced gene regulation in cardiovascular research

Abitha Sukumaran*, Sakthivel Sadayappan*

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Full-text PDF PMID: 35463869 PMCID: PMC9022678 DOI: 10.20517/jca.2022.12
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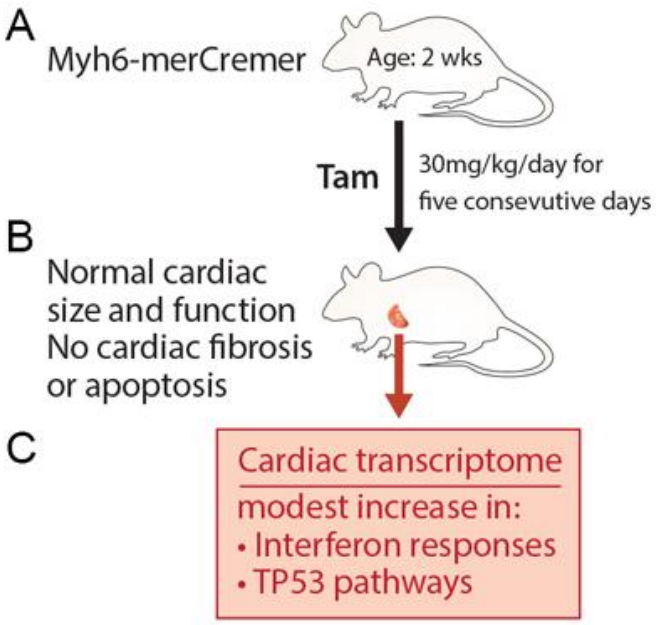
Graphical abstract



Cite this article

Sukumaran A, Sadayappan S. Optimization of tamoxifen-induced gene regulation in cardiovascular research. *J Cardiovasc Aging* 2022;2:21. http://dx.doi.org/10.20517/jca.2022.12

9. WNT links metabolism and cell cycle in postnatal cardiomyocytes

Ivan Menendez-Montes, Hesham A. Sadek*

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Citation
RIS Plain text

Keywords
WNT, cell cycle, metabolism, cardiomyocytes

Cite this article

Menendez-Montes I, Sadek HA. WNT links metabolism and cell cycle in postnatal cardiomyocytes. *J Cardiovasc Aging* 2022;2:27. http://dx.doi.org/10.20517/jca.2022.18

10. SRF and Yap1, partners in cardiac repair

Maha Abdellatif*

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Full-text PDF PMID: 36330199 PMCID: PMC9629335 DOI: 10.20517/jca.2022.23
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Abdellatif M. SRF and Yap1, partners in cardiac repair. *J Cardiovasc Aging* 2022;2:36.
http://dx.doi.org/10.20517/jca.2022.23

11. Mutant SRF and YAP1 remodel the chromatin to entice cardiac myocyte nuclear division

Ali J. Marian*

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Full-text PDF PMID: 35891704 PMCID: PMC9311337 DOI: 10.20517/jca.2022.25
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Keywords
Myocyte replication, transcription factor, hippo, regenerative medicine

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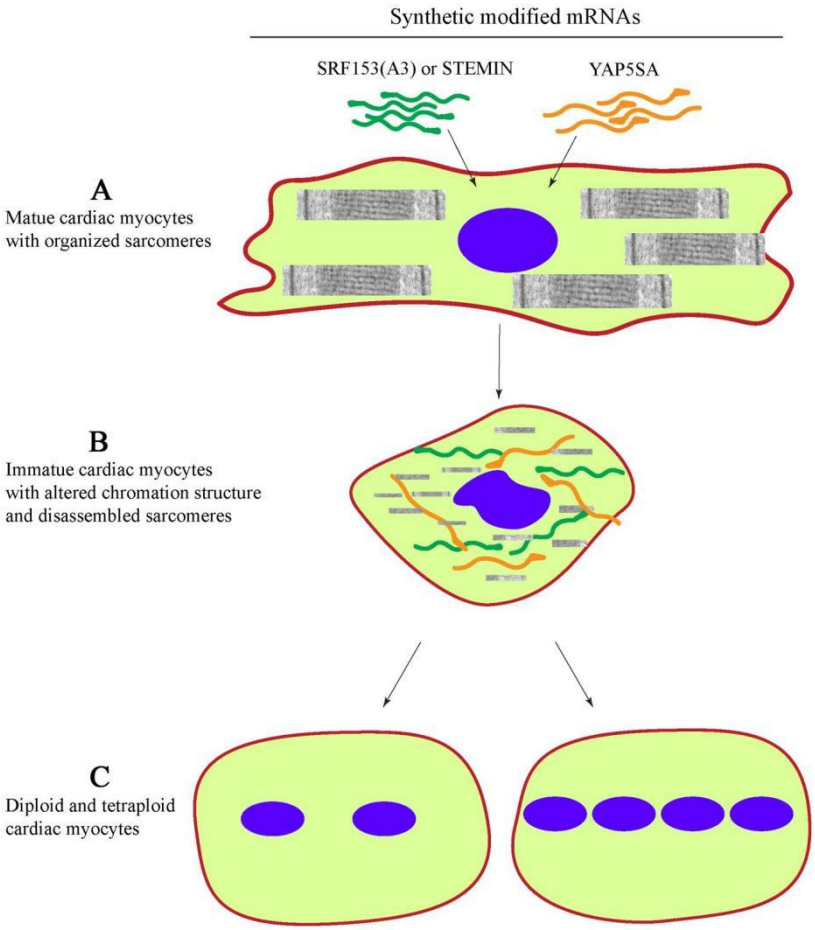

Cite this article

Marian AJ. Mutant SRF and YAP1 remodel the chromatin to entice cardiac myocyte nuclear division. *J Cardiovasc Aging* 2022;2:37. http://dx.doi.org/10.20517/jca.2022.25

12. Deficient *Lmna* in fibroblasts: an emerging role of non-cardiomyocytes in DCM

Xinjie Wang, Weijia Luo, Jiang Chang*

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Full-text PDF PMID: 36082133 PMCID: PMC9450693 DOI: 10.20517/jca.2022.26
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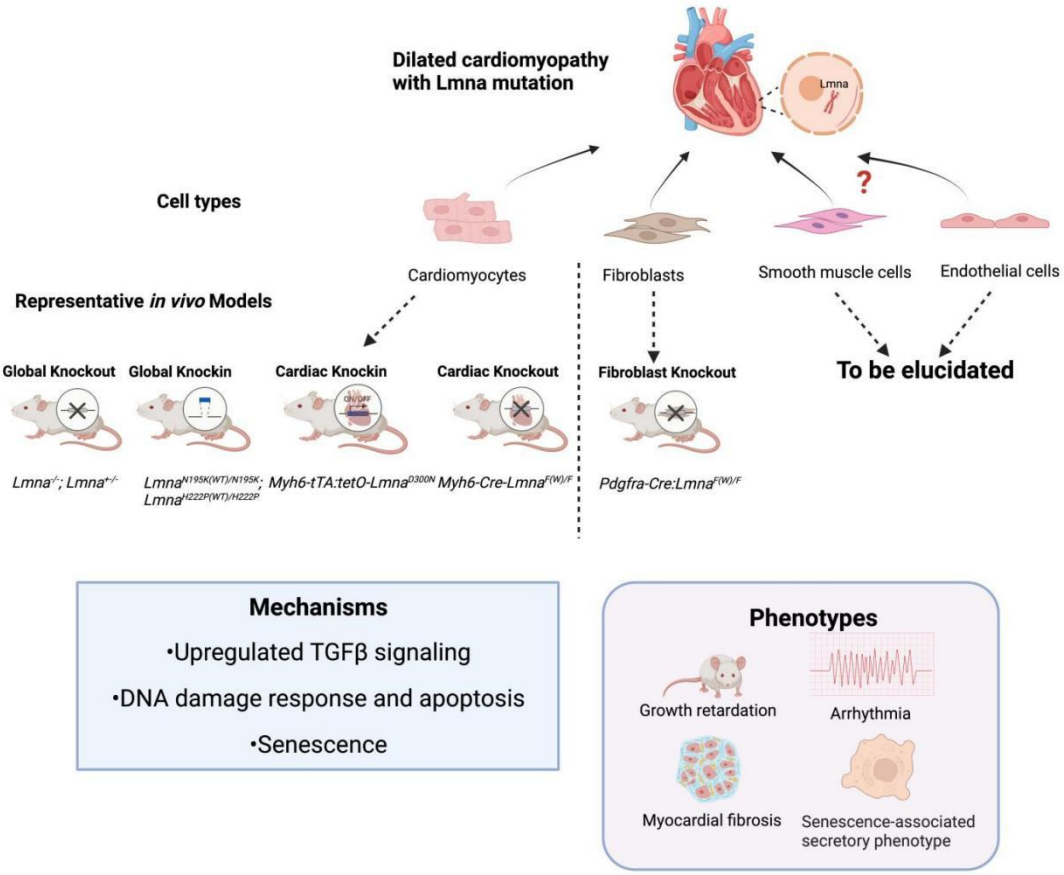
Graphical abstract



Cite this article

Wang X, Luo W, Chang J. Deficient *Lmna* in fibroblasts: an emerging role of non-cardiomyocytes in DCM. *J Cardiovasc Aging* 2022;2:38. http://dx.doi.org/10.20517/jca.2022.26

13. Lipid overload - a culprit for hypertrophic cardiomyopathy?

Lilei Zhang, Na Li*

Read
Full-text PDF PMCID: PMC9933935 DOI: 10.20517/jca.2022.43
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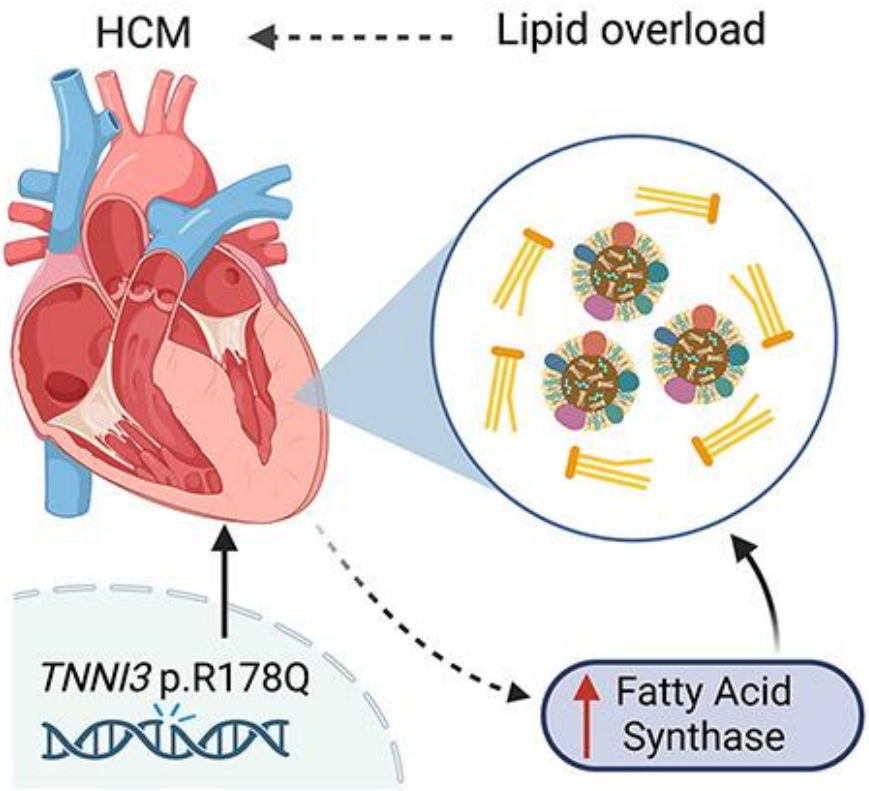
Graphical abstract



Cite this article

Zhang L, Li N. Lipid overload - a culprit for hypertrophic cardiomyopathy?. *J Cardiovasc Aging* 2023;3:8. http://dx.doi.org/10.20517/jca.2022.43

14. Parsing cell death in arrhythmogenic cardiomyopathy: PANoptosis

Calum A. MacRae*

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Full-text PDF DOI: 10.20517/jca.2022.45
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Cite this article

MacRae CA. Parsing cell death in arrhythmogenic cardiomyopathy: PANoptosis. *J Cardiovasc Aging* 2023;3:10. http://dx.doi.org/10.20517/jca.2022.45

15. ChatGPT and other artificial intelligence chatbots and biomedical writing

Priyatansh Gurha, Nadeem Ishaq, Ali J. Marian*

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Full-text PDF DOI: 10.20517/jca.2023.13
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Gurha P, Ishaq N, Marian AJ. ChatGPT and other artificial intelligence chatbots and biomedical writing. *J Cardiovasc Aging* 2023;3:20. http://dx.doi.org/10.20517/jca.2023.13

16. Understanding cardiac senescence one cell type at a time

Payel Sen, Priyatansh Gurha*

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Full-text PDF PMID: 37273661 PMCID: PMC10237624 DOI: 10.20517/jca.2023.16
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Cite this article

Sen P, Gurha P. Understanding cardiac senescence one cell type at a time. *J Cardiovasc Aging* 2023;3:22. http://dx.doi.org/10.20517/jca.2023.16

Letter to Editor

1. Oligogenic cardiomyopathy

Ali J. Marian*

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Full-text PDF PMID: 34841425 PMCID: PMC8623865 DOI: 10.20517/jca.2021.27
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Cite this article

Marian AJ. Oligogenic cardiomyopathy. *J Cardiovasc Aging* 2022;2:3. http://dx.doi.org/10.20517/jca.2021.27

Early Career Investigators Forum

1. Hard work takes you where luck can find you

Leila Rouhi*

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Interviewee

Tamer M. A. Mohamed, PhD

Cite this article

Rouhi L. Hard work takes you where luck can find you. *J Cardiovasc Aging* 2021;1:6.
http://dx.doi.org/10.20517/jca.2021.03

2. Find Your Ikigai in Science

Leila Rouhi*

Read
Full-text PDF DOI: 10.20517/jca.2022.04
Citation
RIS Plain text

Interviewee

Sean M. Wu, MD, PhD.

Cite this article

Rouhi L. Find Your Ikigai in Science. *J Cardiovasc Aging* 2022;2:18. http://dx.doi.org/10.20517/jca.2022.04

3. On being a scientist and a mom; successfully walking a tightrope

Leila Rouhi*

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Full-text PDF DOI: 10.20517/jca.2022.32
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Interviewee

Inna Rabinovich-Nikitin, PhD.

Cite this article

Rouhi L. On being a scientist and a mom; successfully walking a tightrope. *J Cardiovasc Aging* 2022;2:42. http://dx.doi.org/10.20517/jca.2022.32

4. To live in your growth zone, you need to leave your comfort zone

Leila Rouhi*

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Full-text PDF DOI: 10.20517/jca.2022.22
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Interviewee

Melis Olcum Uzan, PhD.

Cite this article

Rouhi L. To live in your growth zone, you need to leave your comfort zone. *J Cardiovasc Aging* 2022;2:32. http://dx.doi.org/10.20517/jca.2022.22

5. Pursuing the physician-scientist path to satisfy research curiosity and passion for patient care

Leila Rouhi*

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Full-text PDF DOI: 10.20517/jca.2022.39
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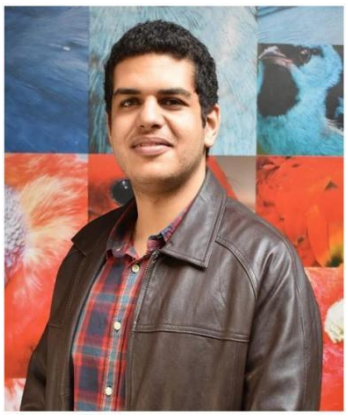
Interviewee



Anis Hanna, M.D.

Cite this article

Rouhi L. Pursuing the physician-scientist path to satisfy research curiosity and passion for patient care. *J Cardiovasc Aging* 2023;3:4. http://dx.doi.org/10.20517/jca.2022.39

6. Every day is an opportunity to learn something new

Leila Rouhi*

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Full-text PDF DOI: 10.20517/jca.2023.05
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Interviewee

Mahmoud Abdellatif, M.D., Ph.D.

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Rouhi L. Every day is an opportunity to learn something new. *J Cardiovasc Aging* 2023;3:13.
http://dx.doi.org/10.20517/jca.2023.05

7. Passion for science: a journey of inspiration and dedication

Leila Rouh*

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Full-text PDF DOI: 10.20517/jca.2023.21
Citation
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Interviewee

Mohit Hulsurkar, Ph.D.

Cite this article

Rouhi L. Passion for science: a journey of inspiration and dedication. *J Cardiovasc Aging* 2023;3:29. http://dx.doi.org/10.20517/jca.2023.21