**SPECIAL ARTICLE**

# Cardiac fibrosis in the ageing heart: Contributors and mechanisms

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## Summary

Cardiac fibrosis refers to an excessive deposition of extracellular matrix (ECM) in cardiac tissue. Fibrotic tissue is stiffer and less compliant, resulting in subsequent cardiac dysfunction and heart failure. Cardiac fibrosis in the ageing heart may involve activation of fibrogenic signalling and inhibition of anti-fibrotic signalling, leading to an imbalance of ECM turnover. Excessive accumulation of ECM such as collagen in older patients contributes to progressive ventricular dysfunction. Overexpression of collagen is derived from various sources, including higher levels of fibrogenic growth factors, proliferation of fibroblasts and cellular transdifferentiation. These may be triggered by factors, such as oxidative stress, inflammation, hypertension, cellular senescence and cell death, contributing to age-related fibrotic cardiac remodelling. In this review, we will discuss the fibrogenic contributors in age-related cardiac fibrosis, and the potential mechanisms by which fibrogenic processes can be interrupted for therapeutic intent.

**KEYWORDS**
ageing, cardiac fibrosis, extracellular matrix turnover, fibrogenic factors, heart failure

## 1 | INTRODUCTION

Ageing is a major independent risk factor for cardiovascular-related morbidity and mortality. The ageing heart exhibits different biological features and processes compared with young hearts, which include increased apoptosis, sustained low grade inflammation, hemodynamic changes and cardiomyocyte senescence.$^{1}$ Most ageing-dependent changes result in the accumulation of collagen, leading to cardiac fibrosis and subsequent progression to heart failure. In this review, we will summarise current knowledge about the contributing factors for age-related cardiac fibrosis and the potential mechanisms responsible for fibrosis development in the ageing heart. Fully understanding these factors and mechanisms of ageing may provide insight into potential novel anti-fibrotic therapeutics for ageing-related cardiovascular diseases such as heart failure within the ageing population.

## 2 | THE PROCESS OF CARDIAC FIBROSIS

Cardiac fibrosis due to excessive deposition of extracellular matrix (ECM), including collagen and fibronectin, results in excessive accumulation of fibrous connective tissue. The ECM is normally regulated
by resident fibroblasts which modulate the balance between synthesis and degradation of collagen and provides structural support and tissue repair for the heart. However, excessive of ECM deposition leads to pathological changes that include chamber dilation and hypertrophy, eventually leading to failure.  

There are two main causes for overexpression of collagen: fibrogenic growth factors and increase of cellular population. ECM deposition is regulated by proteases and their inhibitors, such as matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs). MMPs are members of proteases family, which play an important role in collagen degradation. In contrast, TIMPs acts as an inhibitor of MMPs by decreasing collagen degradation.  

The levels of MMPs and TIMPs are balanced by several cytokines, such as platelet-derived growth factor (PDGF), heparin-binding EGF-like growth factor (HB-EGF), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and transforming growth factor β (TGFβ). These factors induce fibroblast proliferation, indicating their fibrogenic activity. Fibroblasts proliferation and transformation are another key cellular events in the fibrotic process. In the fibrotic heart, increased myofibroblasts are derived from proliferation and transformation of the local resident populations of fibroblasts and transdifferentiation of intrinsic cells. This is enhanced in the process of tissue repair when there is a pressure overload or myocardial infarction.  

Other known cell type trans-differentiations include epithelial cells undergoing epithelial to mesenchymal transition (EMT) and endothelial cells undergoing endothelial to mesenchymal transdifferentiation (EndMT). The cell transdifferentiation process is characterised by expression of the contractile protein α-smooth muscle actin (αSMA). Cell transformation and the fibrogenic factors also interact with each other, as intrinsic cells transdifferentiation is followed by increasing levels of fibrogenic factors (such as TGF-β1 and ED-A fibronectin). Pericytes may also be an additional source of myofibroblasts in the fibrotic heart. However, their role in fibrotic remodelling of the ventricle is still unknown. Proliferating myofibroblasts are also commonly found in many damaged hearts. Therefore, targeting fibrogenic growth factors and cellular transdifferentiation may be of therapeutic benefit for cardiac fibrosis.

3 | CONTRIBUTORS OF CARDIAC FIBROSIS IN AGEING

In contrast to conventional cardiac fibrosis which is accompanied by inappropriate proliferation of cardiac cells and excessive deposition of ECM, ageing-related cardiac fibrosis is characterised by degenerative changes, such as progressive loss of myocytes due to necrotic and apoptotic cell death with increase in myocardial collagen content. This means the absolute number of myocytes decreases in ageing hearts, and the remaining cardiomyocytes undergo hypertrophy and myocardium fibrosis. With ageing, the levels of MMP-1, MMP-2, MMP-3, and MMP-14 decreases significantly. MMPs primarily serve as collagenases, playing an important role in the degradation of aggrecan (by

![FIGURE 1 A schematic depiction of the fibrosis process in ageing. Increase/activation of fibrogenic contributors (blue) and decrease/inhibition of anti-fibrogenic contributors (red) promote collagen deposition and/or fibroblast proliferation, and eventually leading to cardiac fibrosis in the ageing heart.](image)

MMP-1, MMP-2, and MMP-3, fibronectin (by MMP-2, MMP-3, and MMP-14), laminin (by MMP-2, MMP-3, and MMP-14), and gelatin (by MMP-1, MMP-2, MMP-3, and MMP-14). On the other hand, ageing increases pro-fibrotic MMPs inhibitors, TIMP-1 and TIMP-4, in the human heart leading to unbalance of ECM turnover and cardiac fibrosis. The key contributing factors related to cardiac ageing and the roles they play are summarised in Figure 1.

3.1 | Inflammation

The relationship between inflammation and cardiac fibrosis is well established. Inflammatory cells release fibrogenic cytokines and growth factors stimulating the reparative process. A series of cytokines (IL-1, TNFα, and IL-18) promote DNA damage, senescence and even apoptosis in the myocardium, followed by fibroblasts undergoing proliferation to replace lost cardiomyocytes. In addition, cardiac fibroblasts exhibit dynamic phenotypic changes to the proliferative phase due inflammation. Of these, TGFβ serves as the master switch, regulating the transition from inflammation to fibrosis.
factors (TIMP-1, osteopontin and periostin), down-regulating anti-fibrotic factors (MMP-2 and MMP-13), and inducing fibroblast proliferation and/or differentiation. In the mouse model, aged cardiactrophin 1/-/- mice demonstrate reduced arterial fibrosis and greater longevity. Therefore, inflammatory factors may be one of the key contributors in age-related cardiac fibrosis through collagen turnover and cellular proliferation/differentiation.

3.2 | Haemodynamic factors

Hypertension is commonly found in older persons. With ageing, vasculature undergoes structural and functional changes, characterised by endothelial dysfunction, wall thickening, reduced contractility, and arterial stiffening. Current evidence demonstrates a close relationship between hypertension and cardiac fibrosis. A previous study found that the accumulation of collagen during natural ageing, chronic hypertension, and in vitro myofibroblast senescence, share many common protein profiles, suggesting that fibrosis arising from ageing may have common underlying mechanisms with hypertension. On the other hand, there are a series of hemodynamic factors possessing fibrogenic effects, independent of the influences by blood pressure, including the hormone factors from renin–angiotensin–aldosterone system (RAAS) and endothelin-1.

Several haemodynamic factors are closely linked with age-dependent cardiac fibrosis. Of these, the hormonal factors of the RAAS attracted the most attention, and are the most important contributor. RAAS is a hormone system that is involved in the regulation of the plasma sodium concentration and blood pressure. When the plasma sodium concentration is lower than normal or the renal blood flow is reduced, pro-renin is converted into renin. Plasma renin then cleaves angiotensinogen to a short chain amino acid peptide known as angiotensin I (Ang I). Ang I is then converted to form an octa-peptide known as angiotensin II (Ang II), by the enzyme angiotensin-converting enzyme (ACE) found in the endothelium. Ang II results in increased arterial blood pressure and also stimulates the secretion of aldosterone, which causes the tubular epithelial cells to increase the reabsorption of sodium. Increased activation of the RAAS has been demonstrated in the ageing population by a previous study, which can result in hypertension-related fibrosis.

In ageing, apart from its hypertensive effect, RAAS activation directly affects progressive ageing-related organ fibrosis specifically in the heart and kidney. AngII alone can promote myofibroblast proliferation and stimulate ECM synthesis. Age-dependent stimulation of local RAAS in the myocardium drives cardiac hypertrophy and fibrosis, a feature that can be replicated in young rats chronically infused with Ang II. As another important vasoconstriction factor, endothelin-1, enhances fibronectin and collagen expression in an ageing model, suggesting that ageing-related cardiac fibrosis is, at least in part, dependent on the upregulation of endothelin-1. Currently, several targeted inhibitors of RAAS have been shown to inhibit the development of cardiac fibrosis in various experimental models of pathological cardiac remodelling.

On the other hand, some vasodilator factors have been shown to have beneficial effects for fibrosis. They include relaxin and natriuretic peptides (ANP, BNP and CNP) which play important roles in ageing-dependent processes. Relaxin possesses various cardio-protective biological functions and reverses cardiac and renal fibrosis in spontaneously hypertensive rats. In ageing, the physiological endothelium-dependent and -independent vasodilator response to relaxin are blunted, which could induce fibrosis. The recombinant form of relaxin-2 showed potential clinical benefits for ageing-related atrial fibrillation by reversing atrial fibrosis and modulating cardiac ionic currents. Natriuretic peptides functions to decrease blood pressure by suppressing the RAAS and increasing sodium and water excretion.

In ageing, the levels of serum ANP and BNP are increased and serum CNP is decreased. ANP and CNP have been shown to inhibit collagen synthesis and fibroblast proliferation. In animal experimentation, plasma CNP in older rats was less than one-third of the level of younger rats. The fall in CNP was reciprocated by concurrent increases in left ventricular fibrosis. A progressive decline in circulating CNP was also noted in another study and was strongly associated with a reciprocal increase in cardiac fibrosis. The natriuretic peptides have been proven to possess potent cardio-renal actions and are beginning to be regarded as a therapeutic target with clinical development underway.

3.3 | Cellular senescence and death

Cellular senescence is the phenomenon by which normal diploid cells cease to divide. It is characterised by a large flattened morphology, upregulation of senescence-associated β-galactosidase (SA-β-gal) activity and proteins (such as p16, p19, p21 and p53). It is accompanied with ageing and ascribed to an accumulation of age-related damage, involving either myocytes or fibroblasts. More than 600 genes have been identified for cellular senescence, and of them, the p53/p21 pathway has been identified to play a key role. Heart intrinsic cellular senescence closely relates to cardiac fibrosis, making cardiomyocytes vulnerable to certain stresses. Furthermore, senescence at a molecular level results in an accumulation of reactive oxygen species (ROS), generated from dysfunctional mitochondria, leading to inflammation, inducing apoptosis of cardiac myocytes and fibroblasts, and resulting in remodelling and fibrosis.

p53 knockdown in cardiac fibroblasts in vivo, results in inhibition of senescence accompanied by reduced collagen production. This mechanism may be a result of suppressing inflammatory cytokines. As an anti-ageing factor, senescence marker protein 30 shows cardio-protective effects through anti-oxidative effects and could be a novel therapeutic target to prevent ageing-related cardiac fibrosis.

During ageing, cardiac myocyte death is often the initial event responsible for activation of fibrogenic signals in the myocardium. Cardiac myocyte death causes stress, prompting the fibrotic response in cardiac tissues by a series of signalling cross-talk. Inflammatory cytokines and ROS promote cell death by activating both death receptor pathways (activated by TNFα) and mitochondrial apoptotic pathways (activated by ROS) causing further exacerbation of cardiac dysfunction. Current therapies for cardiac fibrosis usually focus on blocking the fibrosis pathway. However, these cannot eliminate the sustained...
FIGURE 2. Enrichment analysis for different expression of genes in the heart of old mice show that biological processes mostly involve cellular cycle, adaptive immunity, metabolic shift, and cellular death. The genes involved in stress signalling and adaptive protection are differentially expressed. The data was derived from the GEO public database (GSE8146) and figures are draw by ReactomePA package in R/Bioconductor.
fibrotic response activated by cell senescence and death. Therefore, in addition to targeting the initial triggers, anti-fibrosis treatment should also focus on interrupting the cycle of cell death to prevent further fibrosis.51

3.4 | Reactive oxygen species

Reactive oxygen species are reactive chemical species containing oxygen, derived from NADPH oxidase, located within cell membranes, mitochondria, peroxisomes, and endoplasmic reticulum, all of which play important roles in immune defences.52 However, overexpression of ROS can potentially cause cellular damage by impairing DNA/RNA synthesis and protein functions, and accelerating the ageing process. In fibrosis, fibroblasts and epithelial cells have been well documented to utilise mitochondrial ROS as second messengers to facilitate diverse signal transduction pathways.53 Some cytokines are involved in ROS-induced differentiation of fibroblasts such as TGFβ, which has been reported to require ROS for the induction of differentiation.54,55 Accumulating evidence suggests that Nox4 NADPH oxidase may be an important downstream effector in mediating TGFβ-induced fibrosis, while NADPH oxidase-dependent redox signalling may in turn regulate TGFβ/Smad signalling in a feed-forward manner.56,57 ROS may also play an important role in the RAAS-dependent ageing fibrosis process, since RAAS inhibition reduces cardiac expression of NADPH oxidative components p22phox, p47phox, and gp91phox.34 In addition, accumulation of ROS induces cell apoptosis through a mitochondria-dependent pathway, which promotes stress and fibrosis.51

Interestingly, under certain conditions like hyperglycaemia, the hydrogen peroxide-producing NADPH oxidase subtype shows anti-fibrotic effects. A previous study found that NOX4 inhibits smooth muscle cells pathophysiological proliferation in diabetic ApoE-/- mice in vivo through PDGF and NOX1 activation.58 Further investigation is needed to provide more evidence for the role of ROS in ageing-related cardiac fibrosis.

3.5 | Other factors

In addition to the aforementioned factors, there are other age-related mechanisms that promote cardiac fibrosis including plasminogen activator inhibitor-1 (PAI-1), and cathepsin K. PAI-1 is a principal inhibitor of fibrinolysis, which can regulate the dissolution of fibrin and also inhibit the degradation of the ECM by reducing plasmin generation. PAI-1 is significantly upregulated in a variety of pathologies associated with the procession of ageing.59 The lysosomal cysteine protease, cathepsin K, has been shown to attenuate ageing-related cardiac fibrosis via suppression of cellular apoptosis.48

4 | MOLECULAR MECHANISMS

Upon comprehensive analysis of the GEO public database (GSE8146),50 which documents the differential expression of genes of the heart between old and young mice, the results show that the old heart is characterised by changes in the cellular cycle, adaptive immunity, metabolic shift and cell death cycle as shown with GO(BP) enrichment (Figure 2A) and pathway enrichment (Figure 2B). These show that the ageing process involves a series of important cellular signalling events, such as the mitogen-activated protein kinase (MAPK) signalling pathway, TGF-β/Smad signalling pathway, and a series of noncoding RNA and autophagy pathways.

4.1 | MAPK signalling pathway

The MAPK signalling pathways may be the key signalling modulator linking a multitude of adverse contributors to detrimental effects on cardiac function, including fibrosis in ageing. Mammals express at least four distinctly regulated groups of MAPKs including extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38MAPK proteins (p38MAPK has α/β/δ/γ isomers) and ERK5 which are activated by specific upstream MAPK Kinases (MAPKKs, or MEKs). MAPK signalling activates at least 20 transcription factors, and is involved in a series of other signalling pathways.62,63

The MAPK signalling pathway is responsible for various cellular functions, including cellular apoptosis, proliferation, differentiation and migration. It is suggested that MAPK signalling is increased during ageing.65-67 The activation of p38MAPK due to endoplasmic reticulum stress has been found to promote cardiac myocytes apoptosis in ageing mice, which in turn promotes cardiac stress and induces fibrosis.68 Activation of ERK1/2 MAPK signalling has been shown to contribute to cardiac fibrosis through TGFβ/Smad signalling in aged PAI-1 deficient mice.69 Recently, Inhibition of the MAPK signalling pathway has been regarded as a potential therapeutic target for ageing-related fibrosis and other degenerative changes, such as the inhibition of apoptosis signal regulated kinase 1 (ASK1) (a ROS sensitive kinase belongs to MAKKK family) to alleviate oxidative stress by blocking downstream p38MAPK signalling.70 Cardiac fibrosis can also be alleviated by other small molecules, including scutellarin, rosmarinic acid and phosphocreatine, through inhibition of MAPK signalling.71-73

4.2 | TGFβ/Smad signalling pathway

In TGFβ/Smad signalling, the Smad complex, made up of TGFβ phosphorylated receptor-activated Smads (R-Smads: Smad1, Smad2, Smad3, Smad5, and Smad8) that have associate with the co-mediator Smad. Then the Smad complexes activate specific gene transcription through cooperative interactions with other DNA-binding and coactivator proteins.74 In fibrosis, TGF-β not only directly stimulates ECM expression, but also exerts its potent matrix-preserving actions by suppressing the activity of MMPs and inducing synthesis of protease inhibitors, such as PAI-1 and TIMPs.5,75 It also plays a key role in the process of EMT and EndMT when Smad2/3/4 complex recruits EMT-promoting transcription factors as co-activators, such as TWISTs.76

Even though, others have observed higher levels of TGFβ and phosphorylation of Smad2 in ageing hearts.77 Our previous studies showed no major variations in mRNA levels of TGFβ in myocardium during ageing.78,79 However, higher levels of TGFβ and phosphorylation of
Smad2 have been observed in ageing hearts.\textsuperscript{80} This disparity may be due to the levels of TGFβ being increased in heart connective tissue, and not in myocytes.\textsuperscript{77} Furthermore, some ageing-related factors such as MMP-9 can activate latent TGFβ, leading to further activation of Smad signalling.\textsuperscript{80}

Interventions directly targeting this pathway have been shown to have undesired systemic side effects due to the pleiotropic physiological functions of TGFβ.\textsuperscript{81} Therefore, targeting downstream signalling pathways involved in TGFβ-induced processes may be a better option to prevent fibrosis in ageing.\textsuperscript{82,83}

### 4.3 | Noncoding RNA

Currently it is estimated that nearly a quarter of the human genome can be transcribed into RNA, whereas protein-coding genes make up only 1%-2% of the genome.\textsuperscript{84} Noncoding RNA transcriptions are a class of the RNA species and are categorised into small noncoding microRNAs (miRNAs) and long noncoding RNAs (lncRNAs).\textsuperscript{85} These have various effects in regulating gene expression, including transcriptional regulation IncRNA by recruiting chromatin regulatory proteins to specific genomic locations, genomic imprinting, organisation of protein complexes, and shaping distinct nuclear structures.\textsuperscript{86}

To date, many miRNAs have been confirmed to be involved in cardiac fibrosis. The targets of these miRNAs (miR-21, miR-29, miR-15, miR-101, miR-132, miR-1, miR-133, miR-208a and miR-34) are mostly involved in collagen synthesis proteins (Elastin, Fibrillin-1, Myd88), TGFβ/Smad signalling (TGFBR1, Smad3, Smad4, Smad7), transcript factors for cell cycle progression and apoptosis (C-fos, foxO3) and stress signalling (p38MAPK).\textsuperscript{85}

In animal and clinical experiments, a series of miRNAs have been linked to ageing-related cardiac fibrosis. Compared with young mice, older mice possess higher miR-22 levels in cardiac tissue, contributing to increased senescence and activation of cardiac fibroblasts in the ageing heart.\textsuperscript{87} The anti-fibrotic factor, miR-17, acts as a negative modulator of cardiac cellular senescence by repression of proteinase-activated receptor-4 (PAR4). However, miR17 is downregulated in the elderly.\textsuperscript{88} Other miRNAs such as miR-34a show both protective effects by inhibiting age-related cardiomyocyte death and remodelling and anti-protective effects when overexpressed, by promoting pro-inflammatory factor secretion in SMC and inducing inflammation.\textsuperscript{89,90}

In the context of heart disease, the role of miRNAs have been intensely studied, whereas the role of lncRNAs remains largely unexplored. To date, only a few lncRNAs have been characterised for their function. MHC-associated RNA transcript, (Mhrt) and CHRF (AK048451), have been implicated in cardiac hypertrophy. Mhrt can bind to the BRM/SWI2-related gene helicase domain and prevent it from recognising genomic DNA targets, which has been shown to be reactivated in cardiac stress and promote pathological gene expression.\textsuperscript{91} CHRF is significantly upregulated in heart failure patients, and it has been found to induce cardiomyocyte hypertrophy and apoptosis in vitro,\textsuperscript{92} as well as being upregulated in cardiac fibrosis models.\textsuperscript{93} The complex roles of noncoding RNAs, including miRNAs and IncRNAs, in ageing-related cardiac fibrosis are yet to be fully explored.

#### 4.4 | Autophagy

Autophagy is the natural, destructive mechanism by which cytoplasmic constituents, including organelles and intracellular pathogens, are sequestered in a double-membrane-bound auto-phagosome and delivered to the lysosome for degradation, and involves regulation of autophagy-related genes. In the ageing heart, damaging of proteins, DNA and cellular organelles, promotes stress in cardiac myocytes and further induces cellular apoptosis and death. Sufficient evidence suggests that autophagy flux is downregulated in the heart during ageing. Persistent inflammation, cellular senescence and depression of up-regulators, such as Sirt, may be the cause of this.\textsuperscript{94,95} Failure of cardiac cells to undergo autophagy is thought to be one of the main reasons for promoting cardiac damage in ageing.\textsuperscript{96} Ageing is also characterised by the loss of stress-induced adaptations capacity, which may result partly from the suppression of autophagy, and lack of autophagy during stress appears to promote cell death and morbidity.\textsuperscript{97,98} Stress factors, such as ROS, regulate the activity of the protein kinases, mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK).\textsuperscript{99} In ageing animal models, several targets including CREG1,\textsuperscript{100} Atrogin-1,\textsuperscript{100} Calstabin2 and Akt\textsuperscript{101,102} are downregulated and have been identified for the amelioration of myocardial fibrosis by the activation of autophagy. Furthermore, obesity and/or metabolic syndromes in older persons may also induce progressive changes in myocardial inflammation, apoptosis and fibrosis which involves the activation of mTOR signalling and depression of autophagy.\textsuperscript{103} Calorie restriction may exert a cardiac protective effect by attenuation of mitochondrial ROS production, activate autophagy and inhibit inflammatory signalling pathways.\textsuperscript{104} Restoring autophagy in the ageing heart may be a potential strategy for treating ageing-related cardiac fibrosis in the future.

### 5 | CONCLUSION

The process of cardiac fibrosis involves increased collagen expression and deposition due to fibrogenic growth factors, cellular transdifferentiation by inflammation, oxidative stress, senescence and apoptosis. The mechanisms of ageing related to cardiac fibrosis may be explained by a series of fibrogenic pathways, such as activation of MAPK and TGFβ/Smad pathways, and depression of autophagy. Many of the factors and mechanisms involved in ageing-related cardiac fibrosis are operative in disease or pathological conditions in the younger heart. However, there are significant characteristic difference particularly the imbalance of pro- and anti-fibrotic factors in ageing. Further investigation is likely to develop novel strategies that may potentially reduce cardiac fibrosis in the elderly. Furthermore, novel therapeutic targets have been identified which could lead to the development of new treatments for the management of ageing-related cardiac fibrosis.

The data was derived from the control and old heart animal model of the GEO public database (GSE8146, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE8146), and Figures were created with the ReactomePA package in R/Bioconductor. The GEO is a public repository that archives and freely distributes microarray, next-generation
sequencing, and other forms of high-throughput functional genomic data submitted by the scientific community. The data from GEO can be re-analyzed and published freely (https://www.ncbi.nlm.nih.gov/home/about/policies.shtml). We have re-analyzed the raw data from the database and the results are include it in our manuscript. Some of the matrix data from cDNA microarray (cDNA chip) have been published before by others who also analyzed the same database from a different prospective (Reiter E, Mol Aspects Med 2007, 28:668–91).

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