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# The role of inflammatory and fibrogenic pathways in heart failure associated with aging

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## Abstract

Heart failure is strongly associated with aging. Elderly patients with heart failure often have preserved systolic function exhibiting left ventricular hypertrophy accompanied by a decline in diastolic function. Experimental studies have demonstrated that age-related cardiac fibrosis plays an important role in the pathogenesis of diastolic heart failure in senescent hearts. Reactive oxygen species and angiotensin II are critically involved in fibrotic remodeling of the aging ventricle; their fibrogenic actions may be mediated, at least in part, through transforming growth factor (TGF)-$\beta$. The increased prevalence of heart failure in the elderly is also due to impaired responses of the senescent heart to cardiac injury. Aging is associated with suppressed inflammation, delayed phagocytosis of dead cardiomyocytes, and markedly diminished collagen deposition following myocardial infarction, due to a blunted response of fibroblasts to fibrogenic growth factors. Thus, in addition to a baseline activation of fibrogenic pathways, senescent hearts exhibit an impaired reparative reserve due to decreased responses of mesenchymal cells to stimulatory signals. Impaired scar formation in senescent hearts is associated with accentuated dilative remodeling and worse systolic dysfunction. Understanding the pathogenesis of interstitial fibrosis in the aging heart and dissecting the mechanisms responsible for age-associated healing defects following cardiac injury are critical in order to design new strategies for prevention of adverse remodeling and heart failure in elderly patients.

### Keywords

Aging; Fibroblast; Inflammation; Remodeling; Infarction; Heart failure

## Introduction: heart failure in the elderly

Heart failure is strongly associated with advanced age [1,2] and represents the most common cause of hospitalization for patients older than 65 years [3]. As the number of people over the age of 65 in North America is expected to double over the next 25 years, more elderly patients will develop heart failure. The increased incidence of heart failure in the elderly is due to the convergence of several distinct factors. First, aging is associated with a progressive increase in the prevalence of coronary disease, hypertension, and diabetes, resulting in the development of ischemic, hypertensive or diabetic cardiomyopathy. Second, cardiac aging is linked with the development of left ventricular hypertrophy and fibrosis, leading to diastolic dysfunction and heart failure with preserved systolic function [4,5]. Third, aging-associated changes in other organ systems may affect cardiac pathophysiology

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contributing to the pathogenesis of heart failure. Fourth, the senescent heart exhibits defective responses to cardiac injury, leading to accentuated adverse remodeling and increased dysfunction.

Evolving evidence suggests that aging-associated alterations in inflammatory and fibrogenic pathways may be critically involved in the pathogenesis of heart failure in elderly subjects. Our review deals with the role of cardiac inflammation and fibrosis in the development of structural and functional alterations in the senescent heart. In addition, we will discuss the significance of age-related defects in inflammatory and reparative pathways in the development of adverse remodeling and heart failure following cardiac injury.

## The effects of aging on cardiovascular pathology and function

Physiologic aging is associated with gradual loss of function in many organ systems. Both clinical and experimental studies suggested that aging is associated with significant alterations in cardiac structure and function. Epidemiological data from the Framingham Heart Study [6] and the Baltimore Longitudinal Study on Aging [7] demonstrated that in healthy populations, there is an age-dependent increase in the prevalence of left ventricular hypertrophy accompanied by a decline in diastolic function. Systolic function at rest is relatively preserved; however, exercise capacity is reduced. Diastolic dysfunction plays a dominant role in the pathogenesis of heart failure and impaired exercise tolerance in elderly individuals. Changes in cardiovascular anatomy and physiology that occur with aging appear to be responsible for the functional and hemodynamic alterations observed in senescent subjects.

Age-associated remodeling of the vascular wall results in luminal dilation, vascular stiffening, intimal, and medial thickening. Loss of aortic elasticity plays an important role in the hemodynamic alterations noted in elderly individuals. As the aorta becomes less compliant, an increased pulse pressure and a lower diastolic pressure are noted. In addition, age-related arterial stiffening may increase vascular load, contributing to the development of cardiomyocyte hypertrophy. Vascular aging is also associated with increased expression of endothelial adhesion molecules [8,9] and enhanced adherence of mononuclear cells to the endothelial surface [10], promoting an inflammatory microvascular environment.

Aging also directly influences cardiac structure by affecting cardiomyocyte survival [11], growth, and function. Increased cardiomyocyte necrosis and apoptosis are noted in senescent rat hearts [11,12], while remaining cardiomyocytes undergo hypertrophy. Age-associated alterations in expression and function of sarcoplasmic reticulum $Ca^{2+}$ pump (SERCA2) and phospholamban [13] result in reduced rate of calcium sequestration in the sarcoplasmic reticulum, and prolonged cytosolic calcium transient after excitation, leading to prolongation of contraction and relaxation times [14]. Because of the delayed relaxation and the increased ventricular stiffness, the force of atrial contraction increases and its contribution to left ventricular end-diastolic volume becomes more important.

Beyond its effects on cardiomyocytes, aging also affects the phenotype and function of cardiac interstitial cells, including endothelial cells and fibroblasts. Fibrotic remodeling of the aging ventricle plays an important role in the pathogenesis of diastolic heart failure. In addition, fibrosis of the conduction system contributes to the development of bradyarrhythmias and conduction abnormalities.

## Fibrosis of the senescent heart

Extensive evidence, derived from both clinical and experimental studies, suggests that aging is associated with fibrotic cardiac remodeling. Hearts from senescent individuals exhibited

increased collagen deposition and thicker endomysial and perimysial collagen fibers [15,16]. Eghbali and coworkers [17] demonstrated that collagen content in the left ventricle increased from 5.5% of total protein in young Fischer 344 rats to approximately 12% in senescent animals. In addition, collagen content was significantly increased in old normocholesterolemic rabbits [18] and in senescent mice [19]. Collagen cross-linking is also enhanced in senescent hearts and may contribute to the increased stiffness [20].

Fibrosis in senescent hearts is primarily associated with a stiffer ventricle and diastolic dysfunction. However, active fibrotic remodeling of the cardiac interstitium often results in activation of matrix-degrading pathways, leading to the development of ventricular dilation and systolic failure [21]. Although systolic hypocontractility is not observed in healthy aging hearts, aging-associated fibrotic remodeling of the ventricle may contribute to the pathogenesis of systolic dysfunction in the presence of other conditions, such as hypertensive or diabetic cardiomyopathy. Disturbance of the collagen network in the fibrotic heart may cause systolic dysfunction through several distinct mechanisms. First, fibrosis may result in impairment of systolic function through disruption of the coordination of myocardial excitation–contraction coupling [22]. Second, loss of fibrillar collagen may impair transduction of cardiomyocyte contraction into myocardial force development, resulting in uncoordinated contraction of cardiomyocyte bundles [23]. Third, interactions between endomysial components (such as laminin and collagen) and their receptors may play an important role in cardiomyocyte homeostasis [24]. Finally, fibrotic remodeling of the cardiac interstitium is often associated with matrix metalloproteinase (MMP) activation and enhanced matrix degradation, resulting in sliding displacement (slippage) of cardiomyocytes and leading to a decrease in the number of muscular layers in the ventricular wall and subsequent left ventricular dilation [25]. Beyond its profound effects on cardiac function, fibrotic ventricular remodeling also promotes arrhythmogenesis through impaired anisotropic conduction and subsequent generation of reentry circuits [26].

## The mechanistic basis of aging-related cardiac fibrosis

Although fibrosis is a hallmark of cardiac aging, the mechanisms responsible for fibroblast growth and expansion of the collagen network in senescent subjects remain poorly understood. Evolving evidence suggests that the renin–angiotensin system and generation of reactive oxygen species (ROS) may be involved in age-associated cardiac fibrosis (Fig. 1).

Several lines of evidence suggest that the renin–angiotensin system is critically involved in fibrotic cardiac remodeling of senescent hearts. First, cardiac angiotensin II concentrations increase significantly with aging [27]. Second, long-term angiotensin II inhibition, or angiotensin II receptor type 1 (AT1) blockade, protected aging rats from the development of cardiac fibrosis and diastolic dysfunction [28]. Third, AT1A null mice exhibited prolonged survival and had significantly reduced cardiac fibrosis when compared to wild-type littermates [29]. In contrast, knock-in mice with a gain-of-function mutation of AT1A developed progressive cardiac fibrosis with increased expression of collagen [30].

Experimental studies have demonstrated increased generation of ROS in the aging heart. A significant increase in superoxide radical production was seen in mitochondria prepared from aging rat hearts [31]. In senescent mice, overexpression of catalase targeted to mitochondria reduced cardiomyocyte hypertrophy, diminished cardiac fibrosis, and attenuated diastolic dysfunction [27], suggesting an important role for ROS in the pathogenesis of aging-associated fibrotic cardiac remodeling. Which pathways are responsible for ROS-induced fibrosis in aging hearts? ROS may exert fibrogenic actions both through direct effects on cardiac fibroblasts and through modulation of cytokine signaling. Oxidative stress regulates the quantity and quality of extracellular matrix by

modulating both collagen synthesis and metabolism [32]. In addition, ROS mediate cytokine and angiotensin II-induced effects on fibroblasts [33]. On the other hand, ROS are capable of inducing expression of inflammatory and fibrogenic mediators that may play an essential role in aging-associated fibrosis. ROS-mediated upregulation of CC chemokines (such as monocyte chemoattractant protein (MCP)-1/CCL2), accompanied by induction of adhesion molecules in the microvascular endothelium [18], may promote recruitment of mononuclear cells and fibroblast progenitors in the aging myocardium creating a fibrogenic milieu [34,35]. Although both animal and human studies have suggested a significant role for MCP-1/CCL2 in ischemic cardiac fibrosis [36,37], its involvement in aging-associated fibrotic cardiac remodeling has not been investigated.

TGF-$\beta$ may also play an essential role in cardiac aging by inducing myofibroblast transdifferentiation [38] and by enhancing matrix protein synthesis by cardiac fibroblasts [39]. Loss of one TGF-$\beta$1 allele in TGF-$\beta$1 heterozygous mice appears to ameliorate age-associated myocardial fibrosis and improve left ventricular compliance [40]. Both ROS and angiotensin II may activate TGF-$\beta$ signaling pathways in the senescent heart. ROS activate TGF-$\beta$ and upregulate its downstream fibrogenic effector [41], connective tissue growth factor (CTGF) [42]. In addition, angiotensin II markedly upregulates TGF-$\beta$1 synthesis by cardiac fibroblasts and myofibroblasts [43,44]. Angiotensin II-induced TGF-$\beta$ upregulation is followed by the development of cardiac fibrosis [45]; however, the dependence of the pro-fibrotic actions of angiotensin II on TGF-$\beta$ has not been established [46].

Although cross-linking of the extracellular matrix has been proposed as a major mechanism in the development of increased stiffness in the aging heart, direct evidence suggesting the role of specific matrix cross-linking pathways is lacking. Protein cross-linking through advanced glycation end products (AGEs) may be important in the pathogenesis of diastolic dysfunction in the aging heart. However, experimental studies examining this concept have produced contradictory results. Treatment with the AGE breaker ALT-711 attenuated age-related left ventricular stiffness [47] in normal aged dogs, suggesting a significant role for accumulation of AGE cross-links in promoting the decreased cardiovascular compliance of aging. In contrast, a more recent study showed no effects of the same AGE breaker on diastolic ventricular function in elderly hypertensive canines and suggested that AGE accumulation and AGE cross-link breaker effects were confined to the vasculature without evidence of myocardial accumulation [48].

## Aging-related defects in the inflammatory and reparative response following cardiac injury—implications for cardiac remodeling

Mortality due to coronary artery disease is known to increase progressively with age. Older age was associated with a higher risk of in-hospital and post-discharge mortality in the GISSI-2 trial [49] and was a predictor of death and left ventricular dilatation in patients with acute myocardial infarction enrolled in the SAVE trial [50]. The exponential age-related increase in infarction-related mortality rates was not explained by larger infarcts [49]. Thus, distinct responses of the senescent heart to cardiac injury may play a role in aging-associated heart failure.

Post-infarction remodeling is closely intertwined with an inflammatory reaction that ultimately results in formation of a scar [51]. Inflammatory signals regulate key reparative pathways in the infarcted heart, modulating deposition, and metabolism of extracellular matrix proteins in the wound [52,53]. These actions have profound effects on the mechanical properties of the heart and ultimately determine the geometric characteristics of the infarcted ventricle by affecting the tensile strength of the scar [54–57]. Using a mouse model of reperfused infarction, we compared the inflammatory and fibrotic response between young

and old animals [58]. We found that aging was associated with an attenuated post-infarction inflammatory response and delayed phagocytosis of dead cardiomyocytes in the infarcted heart. Decreased phagocytotic activity [59] and diminished oxidative response to activating signals [60] displayed by senescent macrophages and neutrophils may explain the impaired clearance of dead cardiomyocytes in the infarcted myocardium.

The suppressed inflammatory reaction was followed by decreased myofibroblast infiltration and markedly attenuated collagen and matricellular protein deposition in senescent mouse infarcts, resulting in formation of a scar containing loose connective tissue. The impaired reparative response in old mice was not due to reduced TGF-$\beta$ isoform transcription in the infarcted heart. Because of the critical role of the Smad2/3 pathway in mediating fibrogenic TGF-$\beta$ responses [61,62], we hypothesized that defective fibrous tissue deposition in senescent infarcted hearts may be due to impaired responses of aged mouse fibroblasts to growth factor stimulation. Young mouse cardiac fibroblasts exhibited a robust increase in Smad2 phosphorylation after stimulation with TGF-$\beta$1. In contrast, fibroblasts isolated from senescent hearts showed a blunted response to TGF-$\beta$ stimulation [58], suggesting that aging results in impaired fibroblast responses to growth factors. The blunted response of senescent fibroblasts to fibrogenic mediators is not limited to TGF-$\beta$ stimulation. The stimulatory effect of angiotensin II on matrix synthesis is reduced in rat fibroblasts isolated from senescent hearts in comparison with fibroblasts harvested from young hearts [63].

The age-related reduction in scar collagen content was associated with markedly enhanced systolic dysfunction and increased dilative remodeling following infarction. Enhanced remodeling in senescent hearts was not due to an increase in the size of the infarct, but may be due, at least in part, to alterations in the qualitative characteristics of the scar. The marked decrease in collagen deposition in senescent mouse infarcts may reduce the tensile strength of the wound, resulting in increased dilation and dysfunction. Thus, the enhanced baseline activation of fibrogenic pathways and increased collagen deposition in senescent hearts may be associated with an impaired reparative reserve, due to blunted responses of mesenchymal cells to stimulatory signals. Defective scar formation may play an essential role in the pathogenesis of adverse remodeling and heart failure in senescent subjects (Fig. 2).

## Therapeutic targets to attenuate dysfunction and remodeling in senescent hearts

On a theoretical basis, targeting cardiac fibrosis in the elderly may be effective in reducing the consequences of heart failure by attenuating diastolic dysfunction. However, development of effective new strategies is hampered by poor understanding of the mechanistic basis of cardiac fibrosis and by concerns regarding potential deleterious consequences of anti-fibrotic approaches. Several key questions need to be answered. First, whether cardiac fibrosis can be reversed remains controversial. It has been suggested that established fibrotic changes may no longer be reversible due to the absence of cellular mediators that could produce the key proteases (MMPs) to degrade the collagen-rich tissue [64]. In addition, formation of crosslinked collagen in advanced fibrotic lesions of senescent hearts may prevent matrix remodeling. Thus, effective inhibition of age-associated cardiac fibrosis may require early and prolonged treatment, exposing patients to the consequences of therapeutic regimens interfering with tissue repair. Second, blockade of fibrogenic pathways may also inhibit adaptive processes with protective actions on the aging heart. For example, chronic MCP-1 inhibition may not only exert anti-fibrotic actions but also reduce collateral vessel formation, interfering with an essential protective pathway. Third, the clinical significance of age-associated cardiac fibrosis in patients without concomitant conditions (such as diabetes, hypertension, or coronary atherosclerotic disease) is unclear. Attenuation of the modest fibrosis noted in healthy elderly individuals may not confer clinically

significant benefits. Thus, it may be more reasonable to focus on specific subpopulations of senescent patients who are at a high risk for development of fibrotic remodeling and diastolic dysfunction due to the presence of hypertensive, diabetic, or ischemic heart disease. Beyond, the established beneficial effects of ACE inhibitors in patients with hypertension that may be due, at least in part, to attenuation of cardiac fibrosis, other anti-fibrotic strategies (such as AGE breakers, anti-MCP-1 strategies, or TGF-$\beta$ inhibitors) may exert beneficial actions in high-risk elderly patients with diastolic heart failure.

Targeting specific age-associated healing defects in senescent patients with cardiac injury may provide more practical therapeutic opportunities to prevent adverse remodeling and to protect from the development of heart failure [65,66]. In senescent mice, a suppressed post-infarction inflammatory response results in delayed replacement of dead cardiomyocytes with granulation tissue [58], while blunted responses of senescent fibroblasts to growth factors markedly decrease collagen deposition in the scar, resulting in reduced tensile strength and enhanced ventricular dilation. These findings suggest that age-associated adverse remodeling of the infarcted ventricle is not due to enhanced inflammatory injury or increased fibrosis, but rather results from a defective fibroblast response and impaired formation of the reparative matrix network, necessary to mechanically support the infarcted heart. Thus, caution is necessary when attempting to target the inflammatory cascade in patients with myocardial infarction. These observations may explain the failure of anti-inflammatory strategies in patients with acute coronary events. Although extensive experimental evidence supported the effectiveness of anti-inflammatory strategies in animal models [67,68], the clinical experience with selected interventions targeting the inflammatory response in patients with acute myocardial infarction has been disappointing [69]. Experimental studies are almost always performed in young adult animals, which exhibit a robust post-infarction inflammatory response and formation of dense collagenous scars in the infarcted heart. Although experiments in young animals provide valuable insight into the mechanisms involved in infarct healing, they may not accurately reflect the pathology of myocardial infarction in elderly human populations. The injurious potential of inflammatory mediators in patients with myocardial infarction may have been overstated due to extrapolation of findings from young animals to human patients. Evidence suggests that senescent hearts show impairment of important cytokine pathways providing cardioprotection to the ischemic heart involving TNF-$\alpha$ [70] and platelet-derived growth factor (PDGF)-AB [71] and have a decreased anti-apoptotic response to administration of granulocyte colony-stimulating factor (G-CSF) and stem cell factor (SCF) [72] in comparison with young animals. Thus, strategies aiming at enhancing reparative responses following cardiac injury through the cautious administration of growth factors along with injection of smart biomaterials [73] may represent new therapeutic opportunities for prevention of heart failure in elderly patients with acute myocardial infarction.

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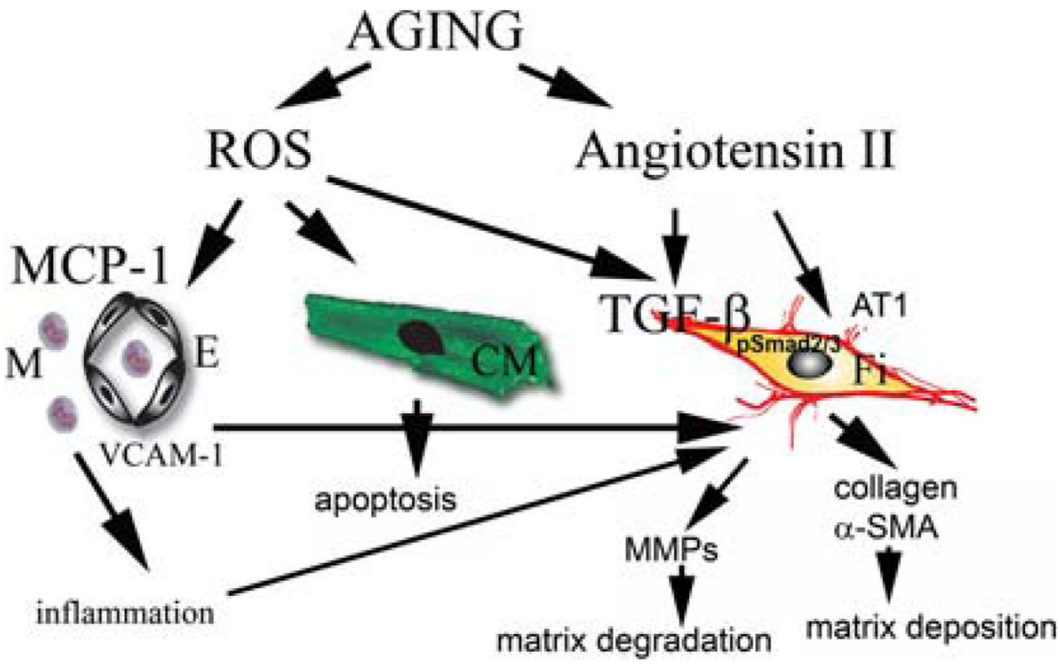


**Fig. 1.**

Pathways involved in the pathogenesis of cardiac fibrosis in the senescent heart. Reactive oxygen species (ROS) and angiotensin II signaling appear to play an important role in mediating fibrotic remodeling of the aging heart. Both ROS and angiotensin II activate transforming growth factor (TGF)-*β*/Smad2/3 signaling pathways, but also induce pro-inflammatory mediator expression. Inflammatory cytokines may induce and activate matrix metalloproteinases (MMPs) enhancing matrix degradation, whereas activation of TGF-*β*/Smad2/3 signaling may promote myofibroblast transdifferentiation and collagen deposition. Interstitial fibrosis in senescent hearts is associated with cardiomyocyte loss due to apoptosis and necrosis. *Symbols: M*, mononuclear cell; *E*, endothelial cell; *Fi*, fibroblast; *CM*, cardiomyocyte; *α*-SMA, *α*-smooth muscle actin; *VCAM-1*, vascular cell adhesion molecule-1; *MCP-1*, monocyte chemoattractant protein-1

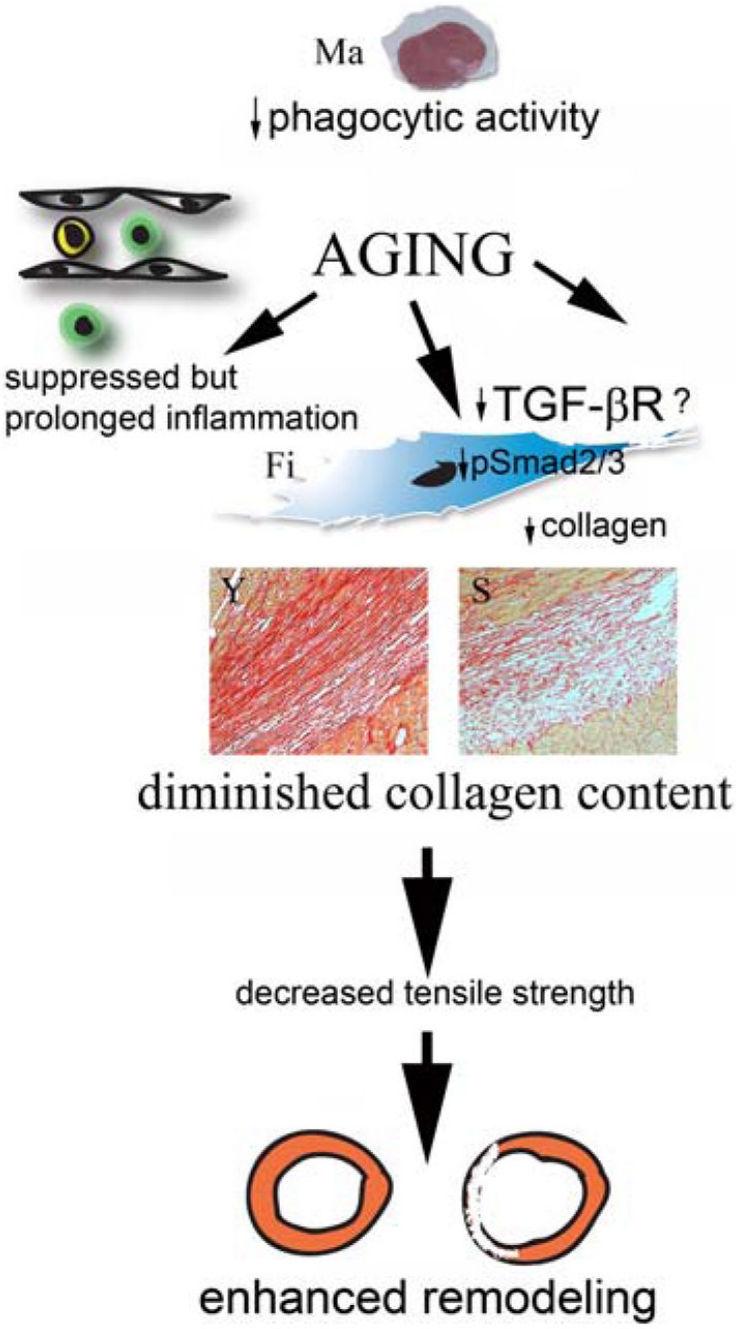


**Fig. 2.**

Age-related defects in the inflammatory and reparative response lead to enhanced adverse remodeling following myocardial infarction. Although aging is associated with enhanced baseline inflammation and fibrosis, acute infarction results in suppressed but prolonged inflammatory reaction, impaired cardiomyocyte phagocytosis, and markedly diminished collagen deposition in the scar. Evolving evidence suggests that the alterations in post-infarction cardiac repair may be due to impaired responsiveness of senescent fibroblasts to growth factors, such as TGF-*β*. Whether this is due to an aging-related reduction of TGF-*β* receptor (TGF-*β*R) expression by fibroblasts, or reflects impaired TGF-*β*/Smad2/3 signaling in senescent cells, remains unknown. Diminished collagen deposition may lead to a marked

reduction in tensile strength of the scar, resulting in accentuated dilation of the infarcted ventricle. *Symbols: Ma*, macrophage, *Fi*, fibroblast. Histopathological images show Sirius red–stained sections from young (Y) and senescent (S) mouse infarcts after 7 days of reperfusion identifying the collagen network