Review

Matrix gene expression and decompensated heart failure: The aged SHR model

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Abstract

Impaired functional performance despite hypertrophic enlargement, and an excessive accumulation of extracellular matrix, are hallmarks of the decompensated failing heart. Age is the leading risk factor for heart failure, and there is evidence suggesting that a number of age-associated changes in the cardiac phenotype predispose the heart to failure. The spontaneously hypertensive rat (SHR) exhibits compensated cardiac hypertrophy followed by a transition to heart failure in the last quartile of the lifespan, and thus provides a useful model of the transition from stable compensated hypertrophy to decompensated heart failure in the context of aging. The transition to failure in the SHR is accompanied by marked changes in the expression of an array of genes in the heart, including increased expression of a number of genes associated with the extracellular matrix. Drug treatments that prevent or reverse matrix gene expression in the SHR heart improve myocardial function and survival. The aged SHR model of decompensated heart failure has provided insight into the role of the extracellular matrix in the transition to failure, and can be useful to further investigate the mechanistic bases of heart failure, as well as to evaluate the potential efficacy of novel therapeutic approaches to the treatment of heart failure. © 2000 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Impaired functional performance despite hypertrophic enlargement characterizes the decompensated failing heart. Manifestations of decompensated function include ventricular dilatation, reduced fractional shortening, diminished ejection fraction, and decreased myocardial force production. Interstitial fibrosis is a hallmark of cardiac hypertrophy in heart failure [1–3] and other pathological conditions [4,5], as well as normal aging [6–8], but is absent from hearts in which the stimulus for hypertrophy is exercise training [9] or hyperthyroidism [10]. Fibrosis increases the stiffness of the myocardium leading to diastolic dysfunction and exacerbation of heart failure [11]. Fibrosis results, in part, from increased expression of genes encoding extracellular matrix proteins that make up the scaffolding that provides the framework in which myocytes function.

Heart failure is relatively rare in younger individuals, but the incidence increases exponentially with advancing age [12]. Thus, age-associated changes in the myocardium likely contribute to the progression from stable hypertrophy to dysfunction and heart failure. The spontaneously hypertensive rat (SHR) exhibits compensated cardiac hypertrophy for more than 50% of its lifespan, ultimately becoming susceptible to cardiac dysfunction and congestive heart failure at a mean age of 21 months [13,14]. Thus it provides a useful model of the transition from stable compensated hypertrophy to decompensated heart failure in the context of aging. This review will focus on the expression of extracellular matrix genes in the aged SHR model of decompensated heart failure.

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2. The spontaneously hypertensive rat (SHR) model of heart failure

Systolic blood pressure becomes markedly elevated in early adulthood in the SHR, and remains elevated for the remainder of the lifespan (Fig. 1). Most of the SHR adulthood is associated with compensated left ventricular hypertrophy, progressive increases in LV volume, and fibrosis [13,15]. At approximately 18 months of age, SHR begin to develop signs of heart failure, and by 24 months of age, more than 50% have evidence of heart failure [14]. Salient features of heart failure in the SHR include cardiac hypertrophy, depressed myocardial function, extensive interstitial fibrosis, and apoptotic myocyte loss [14,16,17]. The virtues of the SHR model of heart failure include its numerous similarities to human heart failure, with a spontaneous transition to failure in the context of aging, and a relatively short lifespan compared to other mammals that allows for study in a timely manner. Another strength of the SHR model is that the primary stimulus for hypertrophy and failure is hypertension, second only to myocardial infarction as a common precursor of heart failure in humans. Finally, the SHR model of failure has been studied extensively and a large literature has accumulated describing its important features. One major limitation of the SHR model is that the genetic factors that cause hypertension remain unidentified, and thus must be considered as an unlikely, but possible, direct cause of the transition to failure.

3. Matrix gene expression during the transition to failure in the aged SHR

The transition to failure in the SHR is accompanied by marked changes in the expression of an array of genes in the heart (Fig. 2). Among the most prominent changes are increases in the levels of mRNAs encoding fibronectin, collagen Type I, collagen Type III, and osteopontin; all components of the extracellular matrix [18,19]. In situ hybridization suggested interstitial as well as perivascular localization of collagen mRNA in failing hearts [20]. Since increases in fibrillar collagen in the interstitium contribute to tissue stiffness, increases in fibronectin and collagen gene expression likely contribute to impaired function. The strong relationship between fibrosis and stiffness is best demonstrated by studies in which the angiotensin converting enzyme (ACE) inhibitor lisinopril was used to treat young adult SHR with doses that allowed dissociation of hypertrophy and fibrosis [21]. The experiments demonstrated that fibrosis was associated with LV stiffness independent of LV hypertrophy. Moreover, it was shown that lisinopril could regress fibrosis and normalize LV stiffness in aged SHR, thereby preventing LV dysfunction.
Although it is difficult to separate cause and effect in the failing heart without manipulating individual cardiac matrix components, a degenerative feedback interaction between function and stiffness appears implicated. Identification of upstream instigators of extracellular matrix proliferation could provide targets for therapies aimed at preventing the deterioration of function associated with heart failure. There is considerable evidence from studies of extracardiac tissues that transforming growth factor β1 (TGFβ1) plays a key role in regulating many aspect of the remodeling process including the upregulation of ECM genes. In the failing hearts of SHRs that exhibited markedly increased levels of fibronectin and collagen gene expression, a small but significant increase in TGF-β1 mRNA levels is also observed in both ventricles [18]. The upregulation of TGF-β1 gene expression observed in the failing heart suggests that it may direct accumulation of extracellular matrix, as it does in wound repair [23]. Selective inhibition of the TGFβ family of cytokines using a soluble type II receptor reduced fibrosis and collagen formation in the adventitial layer of balloon-injured rat carotid arteries [24]. Another feature that resembles wound repair is the preferential expression of alternatively spliced fibronectin transcripts containing EIIIA and EIIIB segments [18]. Why and how a process resembling wound repair is initiated in the failing heart is not well understood, but there are several lines of evidence suggesting that myocyte loss is one trigger stimulating interstitial fibrosis. Myocytes may be lost by two well-described mechanisms, necrotic cell death and apoptotic cell death [25,26]. Necrosis is defined as cell death originating from an external insult that results in damage to the cell membrane and release of cellular contents that in turn triggers a classic inflammatory response, including the recruitment of immune cells. Apoptosis, on the other hand, is typically characterized by involution of the cell without triggering an inflammatory response. In the case of necrosis, interstitial fibrosis would appear to be the expected response to inflammatory signals. In the case of apoptosis, however, the fate of the space vacated by the apoptotic myocyte is not so clear. Although the myocyte is not believed to initiate an inflammatory response, it may still trigger events leading to interstitial fibrosis. Cardiac fibroblasts, which make the matrix components leading to interstitial fibrosis, are normally regulated tightly by their surroundings (i.e. myocytes and matrix). When space is available, however, as is the case in cell culture, fibroblasts rapidly initiate mitosis and proliferate while producing matrix components until confluent. Whether or not cardiac fibroblasts are similarly “released” from mitotic inhibition after myocyte apoptosis in vivo is not known. The findings that both necrotic and apoptotic cell death are markedly more prevalent in the failing heart [17,25] suggests that myocyte loss [16] whether it be by necrosis, apoptosis, or both processes, stimulates salient features of the wound repair process that result in interstitial fibrosis. It should be noted that current techniques used to identify necrosis and apoptosis have limitations [27], and in the failing heart the...
two methods of cellular death may represent ends of a continuum rather than a true dichotomy. It will be an imposing challenge to determine the precise sequence of events and signals that trigger the accumulation of interstitial fibrosis in the failing heart.

4. Prevention or reversal of changes in matrix gene expression by drug treatment of heart failure in the aged SHR

One of the few treatments available with established clinical efficacy for heart failure patients is inhibition of the angiotensin converting enzyme (ACEI) with pharmacological agents such as captopril. ACEI intercepts multiple effects of angiotensin II, including peripheral effects on blood vessels that reduce blood pressure, and direct effects on both myocytes and fibroblasts in the heart. To better understand the mechanisms by which ACEI exerts its effects in vivo, captopril was administered to SHR at 12, 18, and 21 months of age (prior to failure) and to SHR-F (after the onset of failure). Treatment of SHR rats with captopril from the age of 12 months completely prevented the development of heart failure [28] and markedly altered the pattern of gene expression (Fig. 3). Captopril-treated rats had higher levels of α-MHC mRNA, and lower levels of mRNA encoding ANF, collagen Type III, and TGFβ1 than age-matched SHR-F [29]. Similar results, although not quite as dramatic in every case, were obtained when captopril treatment was initiated at 18 or 21 months of age. Thus, ACEI initiated prior to the onset of heart failure prevented changes in the expression of genes encoding matrix and other proteins that typically occur with advancing age in the SHR. It should be noted that the dose of captopril used in these studies significantly reduced systolic blood pressure, making it impossible to separate direct and indirect effects of ACEI on the fibrotic process in the heart. Treatment of rats with captopril for 2–4 months after they are identified with failure (SHR-F) improves survival, but does not significantly improve papillary muscle function, nor does it significantly reverse myocardial fibrosis [28]. Reactive treatment with captopril does reverse some of the failure-associated changes in gene expression as it leads to a marked increase in α-MHC mRNA and a significant reduction in the levels of TGFβ1 mRNA compared to untreated SHR-F (Fig. 4). Inhibition of ACE with lisinopril does regress myocardial fibrosis in SHR of advanced age [22], if treatment is begun prior to the onset of signs of heart failure. In summary, preventive treatment of the SHR with ACEI is extremely successful, while the effects of reactive ACEI are ameliorative, but limited. Thus, there is a need to identify new therapeutic agents that can reverse established fibrosis and improve myocardial function after the onset of failure [30].

Identification of fibrosis as a contributor to the impaired function of the failing myocardium has led to attempts to reverse fibrosis by agents that retard collagen formation or disrupt collagen crosslinking. While colchicine is ineffec-
5. The role of aging in the development of heart failure in the SHR

Age is the leading risk factor for heart failure in human patients. The incidence of heart failure increases more than 5-fold during the 7th and 8th decades of life [12]. From 1980 to 1991 the incidence of heart failure among the oldest Americans more than doubled [39] such that for Americans over the age of 65, heart failure is currently the single most common hospital discharge diagnosis and the most expensive medicare item. Aging in healthy humans and experimental animals is associated with a constellation of changes in the myocardium that reduce the reserve capacity of the heart to respond to a challenge [40,7]. The best pharmaceutical therapies for heart failure remain ameliorative rather than reparative [41]. The heterogeneity and paucity of human heart tissue render it inadequate as a sole source of biological study material to solve the problems of heart failure in a timely manner. Taken together with the projected increase in population of aged individuals in the early decades of the 21st century, these facts provide a rationale for animal models of heart failure that feature aging to study the mechanisms that contribute to heart failure in the aging human population.

The transition from compensated hypertrophy to failure in the SHR seems to demonstrate quite well the consequences of an interaction between “normal aging” and disease. Although elevated blood pressure and marked cardiac hypertrophy are established during the first quartile of the lifespan, myocardial function remains well compensated through the second and third quartiles. During the last quartile of the SHR lifespan, heart failure is a common occurrence. While the accumulated effects of long term hypertension and the genetic nature of the model may play contributory roles, it seems appropriate to hypothesize that the effects of “normal aging” reduce the adaptive capacity of the SHR heart leading to heart failure. What changes occur in the hearts of normotensive rats with advancing age that might contribute to fibrosis and reduce the functional reserve capacity?

Interstitial fibrosis is a hallmark of cardiac hypertrophy in heart failure [1–3] and other pathological conditions [4,5], as well as normal aging [42,6–8], but is absent from hearts in which the stimulus for hypertrophy is exercise training [9] or hyperthyroidism [10]. Fibrosis increases the stiffness of the myocardium leading to diastolic dysfunction and exacerbation of heart failure [11].

Fibronectin is an integral protein of the extracellular matrix that acts to bind together various components of the heart. The levels of fibronectin mRNA decrease somewhat between development and adulthood [43], and are markedly increased in the senescent LV and atria [7]. Increased expression of fibronectin in the senescent heart is likely part of an overall increase in the proportion of extracellular matrix as evidenced by the increase in collagen content [44,45]. The expression of collagen genes undergoes a
dramatic decrease from development to adulthood, and then increases only slightly in the senescent heart [6,43]. While the relatively high level of collagen mRNA in the hearts of young rats does not result in accumulation of collagen, the barely detectable increase in collagen mRNA observed in senescence is associated with a two-fold increase in hydroxyproline content compared to levels in adult hearts [6]. These finding suggest that collagen in the aged heart degrades at a slower rate. The increased levels of fibronectin in the aged heart may contribute to the reduced turnover of collagen by protecting collagen fibers from degradation. The net effect is an accumulation of extracellular matrix with advancing age that conspires with hypertension in the SHR to cause and/or exacerbate the decline in myocardial function leading to failure.

Age-associated changes in expression of non-matrix genes undoubtedly limit functional reserve of the aged myocardium as well [7]. The content of the α-MHC isoform (often referred to as the V1 isoform), which has a high ATPase activity, decreases progressively with age [46]. This decrease appears to be a major factor that underlies the decreased myosin ATPase activity [47,48]. The mRNA coding for α-MHC also declines with age [47,49–51], and the diminished expression of this gene with aging accounts, in large part, for the reduction in the α-MHC content with aging. Conversely, the mRNA coding for the β-MHC isoform (also referred to as the V2 isoform), which has a lower ATPase activity than the V1 isoform, exhibits a several fold increase [47,49] with aging and this is the mechanism for the increase in βMHC protein that occurs with aging. Phenotypic changes that occur with aging of the heart are, to some extent, due to changes in gene expression. The age-associated changes in MHC isoform expression are likely regulated transcriptionally, since corresponding changes are observed in α- and β-MHC mRNA levels. In addition to the isoform switch there may be a reduction in the total MHC mRNA levels with age [52]. MHC gene expression is regulated by thyroxine via binding of thyroid hormone receptors (THRs) to thyroid response elements (TREs) in the 5′ flanking regions of the genes. Binding of THRs to the TRE of α-MHC upregulates its expression, while binding to the β-MHC TRE inhibits [53–57]. Although levels of circulating thyroid hormone may be slightly depressed with advancing age [58], the magnitude of the MHC shift suggests other mechanisms may play a more important role in the age-associated changes observed. THRs are members of a superfamily of receptors which include retinoic acid receptors (RARs), Vitamin D receptors, and retinoid X receptors (RXRs). Three RXR genes have been cloned (α,β, γ) and it has been shown that RXRs form heterodimers with other members of the superfamily [53,59,60]. The RXRα isoform plays a critical role in heart development as demonstrated by the lethal effects of RXRα gene knockout [61]. In many cases, the RXR-THR heterodimers bind with much higher affinity than do THR homodimers to TREs. It might be postulated, therefore, that a reduction in the number of THRs or RXRs might contribute to the downregulation of α-MHC with age. In fact, a significant reduction (approximately 50%) between 6 and 24 months has been observed in the levels of THRβ and RXRγ proteins in hearts of senescent rats [62]. Levels of mRNA encoding these receptor subtypes are similarly depressed in hearts of older rats, suggesting that the age-associated decreases in THRβ and RXRγ are regulated transcriptionally.

There is an age-associated decrease in β-adrenergic receptor (β-AR) responsiveness in the heart that appears to be the result of age-related changes in multiple aspects of receptor-signal transduction coupling. Decreases in both the mRNA and protein levels of Gs [63,52], as well as in the mRNA levels of the β1-AR [51] have been observed in older rats. Whether these changes occur progressively over the lifespan or precipitously during development is not clear since only two ages were studied. In the case of Gsα the change appears to occur after 6 months of age in the male rat [63] and apparently does not occur in the female [64]. Since the β1-AR promoter is sensitive to thyroid hormone [65], decreased levels of THRs and RXRs may also contribute to the age-associated decrease in β1-AR gene expression.

The sarco/endoplasmic reticulum Ca2+ ATPase (SERCA) gene which is downregulated in several models of cardiac hypertrophy also exhibits lower levels of mRNA in the senescent heart. With advancing age, the decrease in SERCA mRNA levels in the rat ventricle occurs between 8 and 24 months of age [66]. This time course and the presence of a thyroid responsive element in the 5′ up-stream region of the [67,68] suggests that the THR/RXR hypothesis described above for regulation of myosin heavy chain may also apply to the SERCA gene.

In adult rat hearts, there is high-level expression of the atrial natriuretic peptide (ANP) gene in both the left and right atria. Among extra-atrial tissues studied, the ventricles of the heart express the most abundant level of ANP mRNA, approximately 1–2% of that in atria [69–71]. In the developing embryo, ventricular as well as atrial myocytes synthesize ANP [72,73], and before birth their respective levels are comparable [74,75]. One week after birth, granules containing ANP are widely distributed throughout both atria, but few granules are detectable in ventricular tissues [72,73]. The expression of ANP in adult ventricular tissues is reactivated when the heart encounters overload [76,77]. Aging from adulthood through senescence is accompanied by a striking increase in the expression of the ANP gene in the ventricles [78–80]. The concentration of ANP in hearts of older rats is closely related to the magnitude of the LV/body weight ratio [80]. Ventricular ANP expression is apparently upregulated in every model of cardiac hypertrophy in which it has been examined, suggesting that the elevated expression of ANP in the senescent heart may be a secondary consequence of
the age-associated myocyte hypertrophy. By virtue of their relatively large mass, the ventricles can contribute significantly to circulating plasma ANP and thereby have considerable impact on systemic fluid balance. Work in cultured neonatal cardiac myocytes suggests that ANP may inhibit hypertrophic growth [81]. The implications of this finding for adult and senescent hearts remain to be evaluated.

Thus, there are striking changes in the expression of non-matrix genes with advancing age that contribute to the aging phenotype as well as to the functional changes discussed previously. The second pattern to emerge from this analysis is the age-associated downregulation of at least three thyroid-sensitive genes, α-MHC, β1-AR and SERCA. As pointed out above, several aspects of thyroid hormone signaling may be altered with aging in the heart, including a reduction in the availability of THR/RXR heterodimers; these changes may thus contribute to the senescent phenotype.

One of the leading theories of aging is the notion that oxidative stress resulting from increased exposure to free radicals causes damage to cells [82,83]. Effects of oxygen radical species may include peroxidation of lipid membranes, enzymatic deactivation, and DNA damage. Aging into adulthood is associated with a reduced ability to defend against reactive oxygen [84]. In young adult SHR with established hypertension, altered levels of antioxidant enzymes are observed compared to normotensive WKY rats, such that decreased levels of superoxide dismutase and increased levels of glutathione peroxidase and catalase are evident [85,86]. Additionally, levels of xanthine oxidase activity, which may generate free radicals, are elevated in hearts of young adult SHR [86]. The interactive effects of age and hypertension on the cardiac tolerance to reactive oxygen species and the levels of antioxidant enzymes have not been evaluated, but may be another factor that predisposes aged SHR to heart failure. In culture, oxygen radicals may initiate apoptosis in cardiac myocytes while inducing proliferation and expression of TGFβ1 by cardiac fibroblasts [87]. If these cell types respond similarly to oxygen radicals in vivo, and if the antioxidant system of the heart is compromised by the interactive effects of age and hypertension, the potential contribution of oxygen radical damage to heart failure could be considerable.

Cardiac hypertrophy is well-recognized to accompany aging in both rodents and humans [88,89]. The senescent rat heart exhibits moderate LV hypertrophy (25%) compared to hearts from young and middle-aged animals [90,91]. The majority of the increase in cardiac mass with aging is due to myocardial cell enlargement. In individual myocytes isolated from rats of 2, 6–9, and 24–26 months of age, the average myocyte length increases by 20% between 2 and 24–26 months of age, but the average slack sarcomere length does not change [92]. The average volume of individual cells approximately doubles over this age range. While this modest hypertrophic growth is compensatory, it may reduce the remaining “hypertrophic reserve”. Assuming an upper limit on myocyte size, this leaves less reserve to respond to the demands of hypertension or other cardiovascular stresses. Hypertrophic growth signals may be incompatible with other influences on cardiac myocytes and lead to necrosis or apoptosis. On this basis, inhibitors of cardiac hypertrophy might represent an untapped therapeutic treatment for heart failure. Recent advances in our understanding of signaling pathways that regulate cardiac hypertrophy present opportunities for such an approach. Two signaling pathways, one targeting transcriptional events in the nucleus, and one targeting translational events in the cytoplasm, may be inhibited by currently available immunosuppressant drugs, cyclosporin, and rapamycin (Fig. 5) [93–97].


Because it is extremely well characterized, and because it shares a large number of characteristics with human heart failure including age-associated events, the SHR model should provide an excellent opportunity to address a number of important issues. First, it offers an opportunity to further understand the mechanisms that contribute to the progression to failure. It is an ideal model to use for genomic/proteomic studies that have the potential to identify unknown genes or proteins involved in the progression to heart failure. Differential display of mRNA from SHR and WKY has led to the discovery of altered expression of endogenous retrovirus, and to the finding of markedly augmented osteopontin expression in heart failure [19,98]. It is also a good model in which to study possible contributing factors such as the role of mineralocorticoid receptors in heart failure. As discussed above, spironolactone reduces the mortality of heart failure patients by mechanisms that can only be speculated upon at present. To address this issue, specific changes in the cardiac renin-angiotensin-aldosterone system should be evaluated in the aged SHR. Second, the aged SHR is an excellent model in which to evaluate therapy of heart failure as exemplified by a number of published studies [28,29,31]. Future studies with the SHR could evaluate both preventive and reparative treatments with a wide range of therapeutic agents. This list should include agents that may inhibit fibrosis, such as spironolactone, agents that may inhibit myocardial hypertrophy such as cyclosporin and rapamycin (Fig. 5), specific angiotensin II receptor antagonists [99], β-adrenergic receptor antagonists [100], and agents that inhibit apoptosis [101]. Because exercise training induces cardiac hypertrophy without an increase in interstitial fibrosis [9], it should be studied in an animal model of heart failure to assess its efficacy as a preventive measure against fibrosis and as a supplement to pharmacological treatments aimed at revers-
Fig. 5. Signal transduction via the calcineurin and p70 S6 kinase pathways. Activation of each of these pathways has been linked to cardiac myocyte hypertrophy. Cardiac hypertrophy stimuli in the context of pathological stress may present the heart with incongruent signals that force the myocytes to “choose” between hypertrophy and apoptosis. Inhibition of either pathway represents a potential treatment of heart failure that might limit cardiac hypertrophy thereby reducing the incidence of apoptosis. CN, calcineurin; FRAP, FKBP-12-rapamycin associated protein; CAM, calmodulin; CsA, cyclosporin; NF/AT, nuclear factor of activated T-lymphocytes. See references [93–96].

ing established fibrosis. Study of these interventions in the SHR would afford a simultaneous assessment of their efficacy in the context of age-associated heart failure and of the mechanism(s) by which these agents exert their effects.

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