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Review

Regulatory mechanisms of atrial fibrotic remodeling in atrial fibrillation

C.-S. Lin* **and C.-H. Pan**

Department of Biological Science and Technology, National Chiao Tung University, No. 75 Po-Ai Street, Hsinchu 30068 (Taiwan), Fax: +886 3 5729288, e-mail: lincs@mail.nctu.edu.tw

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Abstract. Electrical, contractile and structural remodeling have been characterized in atrial fibrillation (AF), and the latter is considered to be the major contributor to AF persistence. Recent data show that interstitial fibrosis can predispose to atrial conduction impairment and AF induction. The interplay between cardiac matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of MMPs (TIMPs), is thought to be critical in atrial extracellular matrix (ECM) metabolism. At the molecular level, angiotensin II, transforming growth factor-β1, inflammation and oxidative stress are particularly important for ECM dysregulation and atrial fibrotic remodeling in AF. Therefore, we review recent advances in the understanding of the atrial fibrotic process, the major downstream components in this remodeling process, and the expression and regulation of MMPs and TIMPs. We also describe the activation of bioactive molecules in both clinical studies and animal models to modulate MMPs and TIMPs and their effects on atrial fibrosis in AF.

Keywords. Angiotensin II, atrial fibrillation, atrial remodeling, inflammation, matrix metalloproteinases, oxidative stress, tissue inhibitors of matrix metalloproteinases, transforming growth factor-β1.

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia and is associated with cardiovascular morbidity and excessive mortality [1, 2]. AF can occur in patients without evident heart disease (so-called lone AF), but organic heart diseases such as congestive heart failure (HF), mitral valve disease, cardiomyopathy and coronary artery disease are major co-existing conditions that contribute to the occurrence and persistence of AF [3, 4]. AF causes changes in the electrophysiological properties of the atria, reducing the refractory period and enabling the presence of more re-entry wavelets at the same time. Hence, AF becomes more inducible and spontaneous sinus rhythm more difficult to recoever. These findings have led to the theory known as AF begets AF [5]. Although the details are poorly understood, the persistence of AF is thought to result from atrial remodeling. Atrial remodeling includes electrical, structural and contractile remodeling, which are the central contributors to the development and maintenance of AF [6–8]. Electrical remodeling in AF is defined as shortening in atrial refractoriness and loss of the normal rate of adaptation of the refractory period, which were thought to be due to alterations in the expression of ion channels [5, 9]. Contractile remodeling of the atria contributes to AF-induced atrial hypocontractility, and loss of atrial contractility is the primary cause of atrial dilatation during the early

* Corresponding author.

stages of AF [10, 11]. Histologically, structural remodeling in AF has revealed the presence of increasing cell size associated with myolysis and perinuclear accumulation of glycogen, alteration in connexin expression and mitochondrial shape, induction of cellular apoptosis [12, 13], and changes in the quantity and localization of structural cellular proteins. Structural remodeling may be an adaptive process (dedifferentiation of cardiomyocytes) aimed at protecting the atrial myocytes, or a maladaptive process (degeneration of cells with fibrotic replacement) [14].

It is controversial whether AF itself directly promotes atrial fibrosis. In the goat model, studies have shown that the increase in AF stability is not a result of atrial fibrosis [11, 15, 16]. In contrast to goat AF model of lone AF without fibrosis, the studies of AF in the setting of heart failure and cardiomyopathy show intra-atrial conduction disturbances as a substrate for AF with atrial fibrosis [17–19]. It was proposed that homogeneous conduction of atrial activity not only relies on cardiomyocyte integration but also can be affected by ECM (extracellular matrix) among the atrial myocytes. Atrial fibrosis – abnormal deposition of ECM proteins in the atrium – may be part of the substrate of AF by increasing the heterogeneity of atrial conduction and playing an important role in the maintenance of AF [18, 19]. Because atrial fibrotic remodeling could result in increased AF vulnerability and is hard to reverse [20], atrial fibrosis has also been considered as a second factor in the progression from paroxysmal to persistent and permanent AF. Interstitial fibrosis may facilitate local intra-atrial conduction block and increase atrial susceptibility to AF [20, 21], as well as formation of stable local sources for atrial microre-entry as well as AF induction [19, 22–25]. Atrial interstitial fibrosis also increases AF vulnerability in animal models of CHF [26, 27] and in a transgenic mouse model of selective atrial fibrosis [28]. Several reviews and original papers report many dominant factors in atrial fibrosis, such as angiotensin peptides, transforming growth factor-beta1 (TGF-β1), inflammatory cytokines and reactive oxygen species (ROS) [28–31]. In addition, regulation of matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of MMPs (TIMPs), have recently been regarded as potential etiologic agents in atrial fibrotic remodeling [32–34]. However, the mechanisms of atrial fibrosis in AF are still under debate and not well understood. This article reviews recent contributions to our understanding of the regulatory mechanisms of atrial fibrosis and ECM metabolism in AF. We also review the bioactive molecules that modulate MMP and TIMP expression in atrial fibrotic remodeling during AF.

Molecular mechanisms of atrial fibrosis

Classical mechanisms describe how AF is initiated or triggered by single or multiple rapidly firing atrial ectopic foci, leading to fibrillation, a single rotor (i.e., mother wave) with fibrillatory conduction, or multiple circuit re-entry [35]. The later mechanism may help to explain how AF is maintained after initiation by the propagation of multiple re-entrant circuits [36]. However, it has been recently stated that a substantial increase in fibrous tissue content, e.g., atrial fibrosis, can interfere with electrical conduction and cause AF that seems to be due to single-circuit re-entry [24, 25]. Many aspects of AF-induced structural changes, including abnormal ECM accumulation or atrial fibrosis at the level of cardiomyocytes and atrial tissue, have been extensively studied in human [23, 37] and animal AF models [22, 26, 38]. Yet the precise mechanisms and signaling pathways involved in the development of atrial fibrosis remain to be clarified. Four predominant interrelated pathways appear to be involved: the renin-angiotensin system (RAS), TGF-β1, inflammation and oxidative stress pathways. Figures 1 and 2 show the major signal transductions concerning these four interrelated pathways.

RAS

RAS is a hormone system that helps regulate blood pressure and extracellular volume in the body. Activation of RAS plays a central role in the development of cardiovascular diseases [39, 40]. Studies have shown that RAS is involved in cardiac structural remodeling and the development of myocardial fibrosis in several disease states, including CHF [41, 42], myocardial infarction (MI) [43, 44], cardiomyopathy [45] and AF [29, 46]. In the RAS system, angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II (Ang-II), which acts via the counter-regulatory Ang-II receptors, type I (AT-1) and type II (AT-2) receptors, that induce opposing responses [42, 47]. The AT-1 receptor is responsible for vasoconstriction, sodium and water retention, cardiac hypertrophy and fibroblast stimulation with increased cardiac fibrosis [48–50]. In contrast to the effects of AT-1, the AT-2 receptor is able to inhibit proliferation of cardiac myocytes and fibroblasts, and induces a decrease in the cellular matrix [51, 52]. Blockade of the RAS signaling pathway by either ACE inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) could improve endothelial function and reduce both morbidity and mortality of cardiovascular disease [39, 40, 53]. A detailed treatise explaining the role of RAS, particularly involving ACE and Ang-II, in structural remodeling in AF has been presented elsewhere [29, 46, 54, 55]. Our present

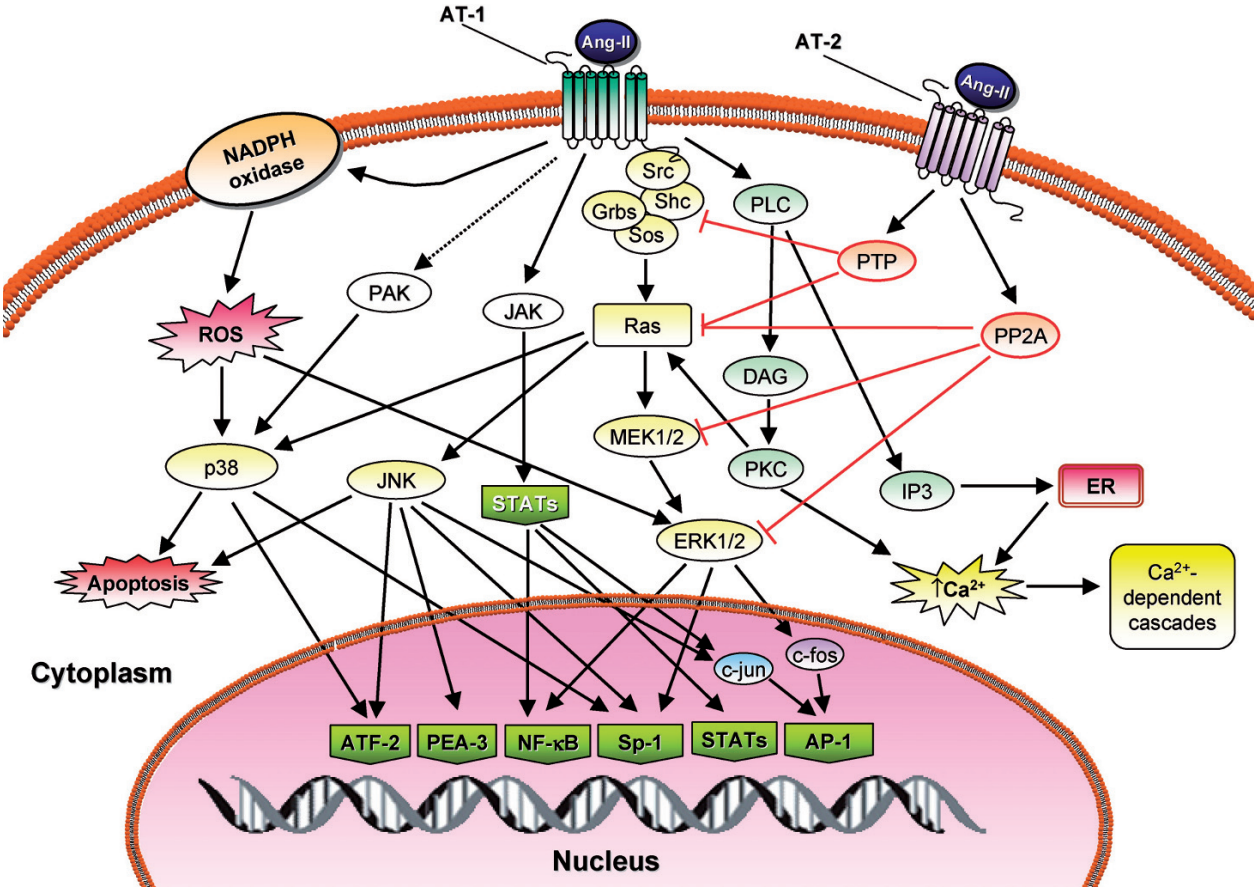

Figure 1. Overview of important components of Ang-II signaling pathways involved in atrial fibrotic remodeling during AF. Ang-II, angiotensin II; AP-1, activator protein-1; AT-1, angiotensin type I receptor; AT-2, angiotensin type II receptor; ATF-2, activated transcription factor-2; DAG, diacylglycerol; ER, endoplasmic reticulum; ERK 1/2, extracellular signal-regulated kinase 1/2; Grbs, growth factor receptor-binding proteins; IP3, inositol 1,4,5-trisphosphate; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MEK 1/2, mitogen-activated/ERK kinase 1/2; PAK, p21-activated kinase; PEA-3, polyoma enhancer A-binding protein-3; PKC, protein kinase C; PLC, phospholipase C; PP2A, protein serine/threonine phosphatase 2A; PTP, phosphotyrosine phosphatase; ROS, reactive oxygen species; Shc, src homologous and collagen protein; Sp1, specific protein-1; STATs, signal transducers and activators of transcriptions.

review focuses on the regulatory mechanisms linking the angiotensin peptides, including Ang-II and angiotensin 1-7 [Ang-(1-7)], to atrial fibrotic remodeling in AF.

Signaling pathways induced by Ang-II. Current knowledge of the signaling pathways induced by Ang-II underlying atrial fibrosis has been gleaned from studying HF and hypertrophic cardiomyopathy. However, Goette et al. [56] explicitly proposed a role for signal transduction pathways and their regulation in fibrillating atria. In brief, AT-1 receptors activated by Ang-II binding induce a phosphorylation cascade that activates mitogen-activated protein kinases (MAPKs), which stimulate proliferation of fibroblasts, cellular hypertrophy and apoptosis [57–59]. Signaling pathways mediated by AT-1 receptors are linked predominantly to G proteins [60]. Binding of Ang-II to AT-1 receptors activates kinases of the Src family (c-Src) via G proteins [61]. Thereafter, a Shc/Grb2/SOS complex is formed that leads to activation of the small GTPase, Ras. Ras-GTP interacts with Raf-1 (MAPK kinase kinase), which then phosphorylates ERK-activating kinase-1 and -2 (MEK-1 and MEK-2). Finally, extracellular signal-regulated kinases-1 and -2 (ERK-1 and ERK-2) are activated by phosphorylation in this signaling cascade [58]. ERKs activate transcription factors such as Elk-1 and c-fos, which are responsible for the cellular effects.

Activation of the AT-1 receptor also stimulates phospholipase C, leading to diacylglycerol-mediated activation of protein kinase C (PKC) and to inositol 1,4,5-trisphosphate-mediated release of calcium from intracellular stores [62]. The sustained elevation of cytosolic calcium that occurs in early-stage AF could activate the calcineurin-nuclear factor of activated T-cell signaling pathway to regulate cardiac genes [63]. In addition to ERKs, activation of other members of the MAPK family, such as p38 MAPK and c-Jun N-terminal kinase (JNK), may induce apoptotic cell

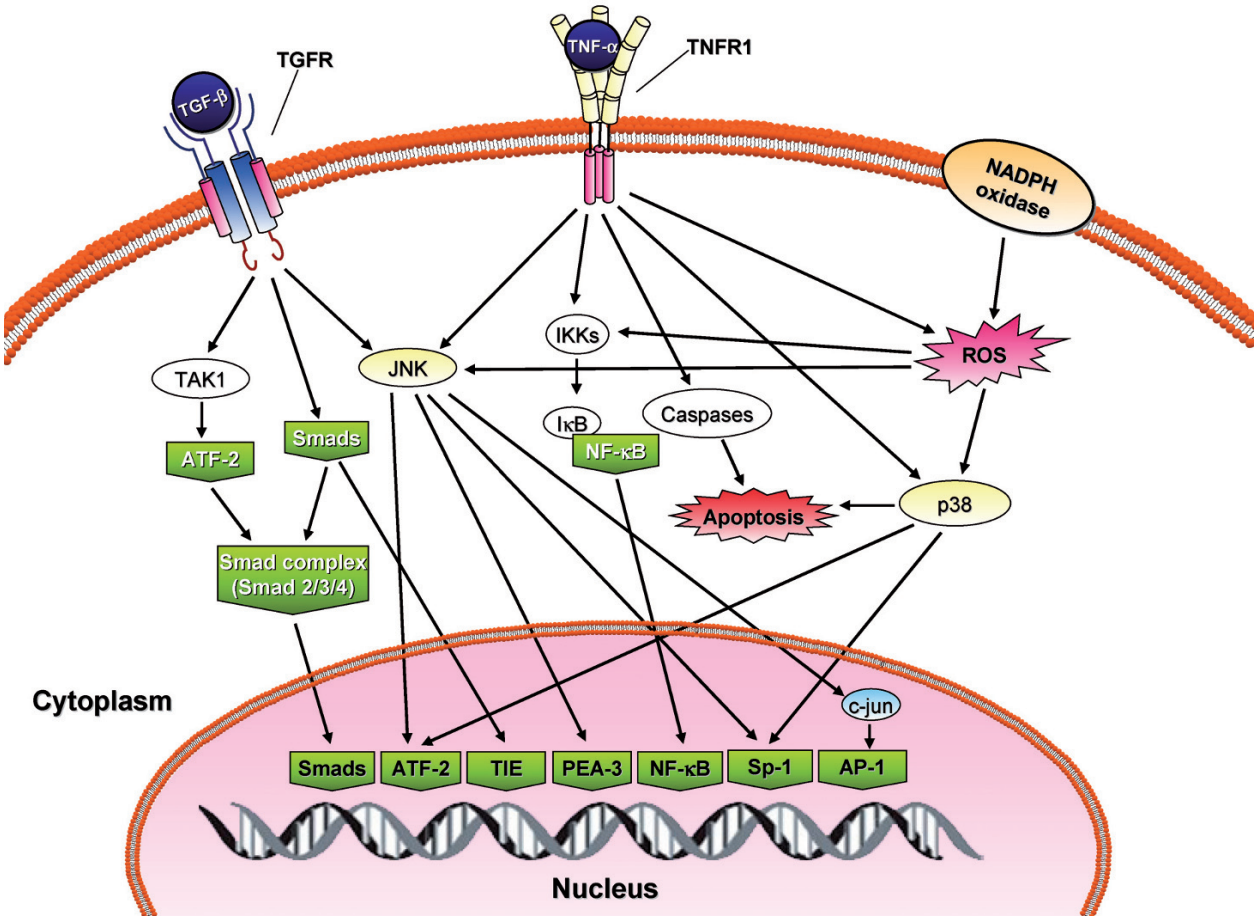

Figure 2. Overview of important components, TGF-β1, ROS and TNF-α, of major signaling pathways involved in atrial fibrotic remodeling during AF. IKKs, IκB kinases; NF-κB, nuclear factor-kappa B; Smads, sma-and-mad related proteins; TAK1, TGF-β1-activated kinase 1; TGF-β, transforming growth factor-beta; TGFR, transforming growth factor-beta receptor; TIE, TGF-β inhibitory element; TNF-α, tumor necrosis factor-alpha; TNFR1, tumor necrosis factor-alpha receptor I.

death [59]. Activation of p38 MAPK by Ang-II is also mediated by H_2O_2 and JNK, which involves activation of the p21-activated kinase (PAK)-mediated signaling cascade. Ang-II signal transduction also has been demonstrated to activate the JAK/STAT pathways (i.e., Janus kinase/signal transducers and activators of transcription) [57]. JAK2 initiates activation of transcription factors STAT-1 and STAT-3 [64]. STAT-1 can translocate into the nucleus and bind promoters of early growth response genes such as *c-fos* and *c-jun.* Transcription factors activated by this pathway include activating protein-1 (AP-1), STATs and nuclear factor-kappa B (NF-κB).

In contrast, activation of the AT-2 receptor can inhibit MAPK via activation of different phosphatases. Thus, activation of the AT-2 receptor has antiproliferative effects and supports cell survival [65]. Binding of Ang-II to the AT-2 receptor leads to uncoupling of the G_I-protein, which then activates protein serine/threonine phosphatase 2A and phosphotyrosine phosphatase, which inhibit protein-serine/threonine phosphorylation and protein-tyrosine phosphorylation, respectively [66, 67]. Through these pathways, it is proposed that activation of the AT-2 receptor suppresses MAPK activation stimulated by the activated AT-1 receptor and therefore inhibits AT-1 receptor-mediated signaling pathways [42, 47].

The function of cardiac Ang-(1-7). Angiotensin-converting enzyme II (ACE2) is a newly discovered enzyme in the RAS pathway. ACE2 cleaves Ang-II to produce a vasodilatory/antihypertrophic peptide Ang-(1-7) [68, 69]. ACE2 provides a counter-regulatory system to Ang-II, thereby contributing to the beneficial effects of the RAS blockade in AF. The potential role of Ang-(1-7) as a cardioprotective peptide having vasodilator, antigrowth and antiproliferative actions has been recognized [70, 71]. In addition, Ang-(1-7) is proposed to downregulate both transcription and translation of the AT-1 receptor [71]. Ang-(1-7) also augments nitric oxide release, which has a key role in the regulation of cardiac

fibrosis in response to MI (myocardial infarction), in part by antagonizing the action of Ang-II [72].

Normal cardiac function in *ace/ace2* double-knockout mice suggests that a catalytic product of ACE triggers contractile impairment in the absence of ACE2, supporting the hypothesis that ACE2 is indeed a critical negative regulator of the cardiac effects of RAS [73]. Huentelman et al. showed that systemic lentiviral delivery of ACE2 to Sprague–Dawley rats results in significant attenuation of the increased heart weight/body weight ratio and myocardial fibrosis induced by Ang-II infusion [74]. These observations demonstrate that ACE2 overexpression is protective for Ang-II-induced cardiac hypertrophy and fibrosis. Recently, Pan et al. demonstrated that ACE2 expression is significantly downregulated in porcine atria with sustained AF, and the MEK/ERK-MAPK cascade is activated by the Ang-II-signaling pathway [75]. They suggested that atrial interstitial fibrosis might be due to an imbalance of RAS caused by markedly reduced expression of ACE2 during AF development. Ishiyama et al. provided evidence that AT-1 receptor blockers increase angiotensin peptide concentrations, return AT-1 receptor expression to normal and increase ACE2 expression in hearts suffering from MI [76]. These results argue that AT-1 receptor blockade may upregulate ACE2 expression. Thus, decreasing ACE2 expression during AF may affect the Ang-II-dependent signaling pathway.

Based on the above findings, there are at least three potential mechanisms by which ACE2 may be cardioprotective via the prevention of cardiac fibrotic processes during AF: first, Ang-II is cleaved to Ang-(1-7) by ACE2, thereby attenuating Ang-II-induced cardiac fibrosis; second, Ang-(1-7) may reduce the effects of Ang-II by downregulating expression of the AT-1 receptor; and third, production of nitric oxide is potently induced by Ang 1-7, which might protect against cardiac remodeling and oxidative stress by Ang-II overproduction during AF with MI [72, 77].

Studies of RAS roles in atrial remodeling and atrial fibrosis. Many studies have supported the role of RAS activation in AF [55, 56, 78–80]. Several studies have shown that the use of ACEIs or ARBs can reduce atrial fibrosis, the occurrence of AF and AF vulnerability in patients with CHF or in rapid atrial or ventricular pacing AF models [55, 81]. In Table 1 [82–99], we present recent reports that focus on the roles of RAS in atrial remodeling and atrial fibrosis in clinical AF and pacing-induced AF animal models.

The use of an ACEI, such as enalapril or cilazapril, inhibits the induction of Ang-II, attenuates atrial fibrosis and decreases AF duration in canines with either HF or pacing-induced AF [78, 94, 97, 99]. Similarly, administration of an AT-1 receptor blocker, candesartan, prevents atrial structural remodeling and atrial fibrosis in dog and rat models [95, 98]. Moreover, increased local production of Ang-II causes atrial fibrosis and cardiac arrhythmia in a mouse model overexpressing cardiac-specific ACE [96].

In clinical studies, Goette et al. [56] reported elevated Ang-II concentrations and increased ERK activation in patients with atrial fibrosis and AF development. One study has shown that ACEIs reduce fibrosis in patients with lone AF [93]. Several retrospective clinical studies also support the role of RAS by demonstrating a decrease in the incidence of AF in patients treated with ACEIs or ARBs, mostly in the setting of depressed left ventricular (LV) function [82, 85–87, 89–93]. ACEI administration also prevents the progression of paroxysmal AF to chronic AF [54], and increases the efficacy of electrical cardioversion of AF [89, 91]. Multiple planned or prospective clinical trials clarified the role of RAS inhibition in the treatment of specific AF patient populations [80]. In a retrospective study using the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) database, treatment with ACEIs reduced AF recurrence in patients with CHF or LV dysfunction [87]. Recently, several meta-analyses have suggested that RAS inhibition may prevent AF [40, 53]. In the largest study, Healey and co-workers [40] analyzed 11 trials, which included 56,308 patients, and found that treatment with ACEIs or ARBs reduced the relative risk of developing AF. However, the authors found that the evidence for ACEIs and ARBs in the AF was only convincing in contexts associated with structural remodeling, like CHF and LV hypertrophy/hypertension. The clinical data suggest that the use of ACEIs and/or ARBs may be useful for delaying progression of atrial fibrosis and AF. Furthermore, there is now evidence linking polymorphisms in RAS-related genes, such as those encoding ACE and ACE2, with an increased risk of subsequent AF development, further supporting the role of RAS in AF development [83, 84, 88].

TGF-β1

In the heart, fibrosis is thought to be partially mediated by TGF-β1, a potent stimulator of collagen-producing cardiomyofibroblasts [100, 101]. Pathogenic effects of TGF-β1 have now been suggested to play a major role in several heart diseases, including MI [102], dilated and hypertrophic cardiomyopathies [102–104], valve disease [104, 105] and arrhythmia [104, 106]. Learning more about the physiological roles of TGF-β1 will help to develop

Table 1. Studies of RAS roles in atrial remodeling and atrial fibrosis in human studies and animal models

Authors	Year	Experimental model and study design	Key findings
Human studies			
Pedersen et al. [82]	1999	* 1577 post-MI patients with sinus rhythm * trandolapril (n=790) *vs.* placebo (n=787)	Trandolapril treatment reduces the incidence of AF in patients with LV (left ventricular) dysfunction after acute MI.
Goette et al. [56]	2000	* 43 patients undergoing open heart surgery * chronic AF (n=17), paroxysmal AF (n=8) and no history of AF (n=18)	An ACE-dependent increase in the amounts of activated ERK1/ERK2 in atrial interstitial cells may contribute as a molecular mechanism for the development of atrial fibrosis in patients with AF.
Ogimoto et al. [83]	2002	*138 patients with hypertrophic cardiomyopathy * sinus rhythm (n=112) *vs.* AF (n=26)	Genotype (polymorphism) of ACE2 gene is a significant risk factor for AF in patients with hypertrophic cardiomyopathy.
Gensini et al. [84]	2003	* control (n=210) *vs.* persistent AF (n=148)	DD genotype of ACE is a predisposing factor for AF and ACE inhibition might reduce the incidence of AF in patients with LV dysfunction.
Vermes et al. [85]	2003	* enalapril (n=186) *vs.* placebo (n=188)	Treatment with ACEI markedly reduces the risk of development of AF in patients with LV dysfunction.
L'Allier et al. [86]	2004	* retrospective, longitudinal cohort study * eight million people in the United States. Patients age $\geq$18 years with hypertension * ACEIs *vs.* CCBs (long-acting calcium- channel blockade)	ACE inhibition was associated with a reduced incidence of AF for patients with hypertension in a usual care setting.
Murray et al. [87]	2004	* retrospective, longitudinal cohort study using the AFFIRM database * ACEIs (n=421) *vs.* placebo (n=732)	ACEI use may be beneficial in some patient subgroups with AF and underscores the need for randomized clinical trials defining more fully the role of Ang-II inhibition in treating AF.
Tsai et al. [88]	2004	* AF (n=250) vs. control (n=250)	ACE gene polymorphisms are associated with nonfamilial structural AF.
Zaman et al. [89]	2004	* 47 patients with persistent AF undergoing electrical cardioversion * ACEIs (enalapril, n=11; lisinopril, n=8; captopril, n=5) *vs.* other medications (n=23)	The use of long-term ACEI therapy facilitated electrical defibrillation in patients with persistent AF. ACEI therapy also reduced signal-averaged P-wave duration, suggesting amelioration of the arrhythmogenic substrate.
Healey et al. [40]	2005	* retrospective, longitudinal cohort study * 56308 patients with hypertension, HF, MI or cardioversion for AF * treated with ACEIs or ARBs	Both ACEIs and ARBs appear to be effective in the prevention of AF. This benefit appears to be limited to patients with systolic LV dysfunction or LV hypertrophy.
Hirayama et al. [54]	2005	* 95 patients with paroxysmal AF * ACEIs (n=42) *vs.* treated with non-ACEI or ARB drugs (n=53)	ACEI can prevent progression from paroxysmal AF to chronic AF.
Maggioni et al. [90]	2005	* patients with HF * valsartan (n=113) *vs.* placebo (n=174)	Adding ARBs to prescribe therapy for HF can significantly reduce the incidence of AF.
Van Noord et al. [91]	2005	* 107 patients with persistent AF underwent electrical cardioversion * pretreated ACEIs (n=28) *vs.* not pretreated ACEI group (n=79)	Pretreatment with ACEIs may improve acute success of electrical cardioversion but does not prevent AF recurrence.
Wachtell et al. [92]	2005	* hypertensive patients with electrocardiogram-documented LV hypertrophy * losartan (n=4298) *vs.* atenolol (a β-blocker, n=4182)	New-onset AF and associated stroke were significantly reduced by losartan-based compared to atenolol-based antihypertensive treatment with similar blood pressure reduction.
Boldt et al. [93]	2006	* 59 patients with chronic AF (n=32) or sinus rhythm (n=27) * groups were divided into AF and sinus rhythm both with or without ACEIs (benalapril, captopril, cilazapril, enalapril, iisinopril, or ramipril)	For AF patients undergoing ACEI therapy, the increase of atrial collagen deposition was attenuated and the atrial microcapillary density was not diminished compared to patients in sinus rhythm.

Table 1 *(Continued)*

Authors	Year	Experimental model and study design	Key findings
Animal models			
Li et al. [78]	2001	* rapid ventricular tachypacing canine CHF model * enalapril (n = 10) *vs.* placebo (n = 10)	CHF-induced increases in Ang-II content and MAPK activation contribute to arrhythmogenic atrial structural remodeling. ACE inhibition interferes with signal transduction, leading to the AF substrate in CHF.
Shi et al. [42]	2002	* rapid ventricular pacing canine CHF model * enalapril (n = 10) *vs.* placebo (n = 10)	Experimental HF causes structural and functional abnormalities in both atria, which are correlated with AF duration. ACE inhibition attenuates HF-induced atrial fibrosis and remodeling and reduces associated AF promotion.
Cardin et al. [94]	2003	* rapid ventricular tachypacing canine CHF model * enalapril (n = 10) *vs.* placebo (n = 10)	AF-promoting atrial structural remodeling in experimental HF involves Ang-II-dependent and -independent pathways. ACE inhibition can partially prevent atrial structural remodeling and apoptosis.
Kumagai et al. [95]	2003	* rapid-pacing canine AF model * candesartan (n = 10) *vs.* placebo (n = 10)	The ARB can prevent AF promotion by suppressing the development of structural remodeling in atria.
Xiao et al. [96]	2004	* cardiac-specific expression of ACE in a transgenic mice model	Increased local production of Ang-II in the heart is not sufficient to induce ventricular hypertrophy or fibrosis. Instead, it leads to atrial morphological changes, cardiac arrhythmia and sudden death.
Sakabe et al. [97]	2004	* rapid-pacing canine AF model * enalapril (n = 10) *vs.* placebo (n = 14)	ACEIs can suppress atrial pacing-induced AF by suppressing interstitial fibrosis, connexin43 overexpression and conduction delay.
Okazaki et al. [98]	2006	* hypertensive rat model * control (n = 11), L-NAME (a NOS inhibitor, n = 11), L-NAME + candesartan (n = 11), and L-NAME + hydralazine (a vasodilator) (n = 11)	ARBs can prevent atrial structural remodeling, a possible contributing factor of the development of AF, in hearts with hypertension induced by long-term inhibition of nitric oxide synthesis.
Li et al. [99]	2007	* rapid atrial pacing canine model * sham-operated (n = 6), placebo (n = 7), and cilazapril group (n = 7)	The ACEI can suppress structural and functional remodeling of atria and prevent the induction and promotion of AF induced by chronic rapid atrial pacing.
Pan et al. [75]	2007	* rapid atrial pacing AF model of pig * AF (n = 9) *vs.* sinus rhythms (n = 6)	Decreasing ACE2 expression during AF may affect the Ang-II dependent signaling pathway and atrial fibrosis in AF. The result may be regulated by antagonistic function between ACE and ACE2.

ACEIs: Trandolapril, enalapril, lisinopril, captopril, benalapril, cilazapril, iisinopril and ramipril.
ARBs: Valsartan, losartan and candesartan.
L-NAME, NG-nitro-L-arginine methyl ester; NOS, nitric oxide synthase.

approaches for TGF-β1-targeting therapy in a variety of cardiovascular diseases.

TGF-β1-Smad signaling pathway. TGF-β1 can induce a signaling cascade through binding to serine/threonine kinase receptors and then trigger the TGF-β1 signaling pathway, which is mediated through phosphorylation of the Smad family [107, 108]. The Smad proteins are a family of intracellular signal transducers that act downstream of receptors for TGF family members [109]. Once Smad2 has been phosphorylated, Smad forms a complex (Smad2/Smad3/Smad4) and then translocates to the nucleus and binds to Smad-binding sequences in the regulatory regions of specific genes, resulting in the alteration of gene expression levels [110]. The TGF-β1-Smad signaling pathway appears to be involved in the activation of collagen gene promoter sites, primarily enhancing the expression of collagen type I. Evidence from a transfected mesangial cell line indicates that the gene encoding collagen type I is a primary site for Smad binding [111]. Verrecchia et al. found that the TGF-β1-Smad pathway in dermal fibroblasts induces the expression of genes encoding several types of collagens, including collagen type I, type III and type VI [112]. TGF-β1 also initiates JNK signaling pathways, and then translocates to the nucleus where it phosphorylates several transcription factors including c-Jun, activated transcription factor-2 (ATF-2) and Elk-1, leading to specific transcriptional responses [113, 114].

An alternative pathway for TGF-β1-induced fibrosis involving TGF-β1-activated kinase 1 (TAK1) has been suggested. TAK1, a member of the MAPK kinase kinase family, is thought to be a significant downstream modulator for the TGF-β1 superfamily [115]. Transgenic overexpression of constitutively active TAK1 causes cardiac hypertrophy, fibrosis and severe myocardial dysfunction [116]. Hanafusa et al. reported that TAK1, once activated by TGF-β1, can phosphorylate ATF-2, which then combines with Smad2, Smad3 and Smad4 to form a transcription complex [117]. Therefore, overexpression of non-phosphorylated ATF-2 results in inhibition of TGF-β1 transcriptional activity.

TGF-β1-mediated atrial fibrosis. Pathogenic effects of TGF-β1 have now been suggested to play a major role in AF [104, 118]. Recent studies using microarray analysis have demonstrated that expression of TGF-β1 is upregulated in human AF patients, indicating that activation of TGF-β1 signaling is involved in atrial fibrosis development in AF [119]. Hanna et al. [120] have reported a potential role for TGF-β1 in CHF-related atrial remodeling. In addition, a transgenic mouse model overexpressing constitutively active TGF-β1 revealed selective atrial interstitial fibrosis, whereas ventricular histology was normal [28]. This study demonstrated that atrial fibrosis alone is a sufficient substrate for AF and that TGF-β1 may play an important role in the genesis of atrial fibrosis. Interestingly, this mouse model also suggests that the atrium is more susceptible than the ventricle to the development of fibrosis in response to high TGF-β1. In porcine fibrillating atria induced by rapid atrial pacing, upregulation of *TGF-β1* was detected and the atria showed significantly accumulated ECM [121]. Accordingly, TGF-β1 may be an interesting therapeutic target as more is learned about the precise pathways involved in the development of atrial fibrosis.

The role of TGF-β1 in tissue fibrosis is not fully understood. Many transcriptional elements related to TGF-β1 signaling pathways may be involved in the process of tissue fibrosis. For example, P311, a protein that can block TGF-β1 autoinduction and downregulate the expression of genes encoding ECM proteins in cardiomyofibroblasts, causes anti-fibrotic effects by inhibiting TGF-β1 signaling [122]. The gene encoding another protein, *TSC-22* (TGF-β1 stimulated clone-22), which has an effect opposite to P311, is markedly upregulated in the same AF samples. *TSC-22* is a TGF-β1-inducible gene and represents a transcriptional regulator that enhances the activity of TGF-β1 signaling by binding to the transcriptional activity of Smad3 and Smad4 [123]. These results suggest that the dramatic P311 downregulation or TSC-22 upregulation may contribute to the development of fibrosis during AF when expression of TGF-β1 is also increased. Interestingly, Chen et al. recently found markedly downregulated *P311* and upregulated *TSC-22* in atrial tissues with AF in a pig model [121].

Inflammation

Accumulating evidence suggests a link between cardiac inflammatory states and AF pathogenesis [81, 124–126]. The signaling cascades triggered by inflammatory mediators can induce transcription factors, such as NF-κB and AP-1, through the pathways of ERKs, JNK, p38-MAPK, IκB kinases (IKK) or ROS, which might involve in the atrial fibrotic during AF (Fig. 2). The inflammatory cytokines are potent regulators of ECM protein metabolism which can mediate repair and remodeling through activating MMPs and collagen. The studies found that interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can directly decrease collagen synthesis and procollagen mRNA expression in cardiocytes, and increase the breakdown of collagen by increased MMP activity [127–129]. Patients with lone AF have inflammatory infiltrates, myocyte

necrosis and fibrosis in atrial biopsies [130]. Similar findings of atrial perimyocarditis with inflammatory infiltrates and fibrosis in dogs with pacing-induced sustained AF and atrial dilation have also been reported [131]. It was shown that prednisone suppresses AF susceptibility and C-reactive protein expression in canine sterile pericarditis and in a pacing-induced AF model [132, 133]. Treatment with anti-inflammatory agents such as glucocorticoids and statins seems to reduce recurrence of AF [53, 134, 135]. In a dog model, CHF-induced atrial structural remodeling and AF promotion could be attenuated by simvastatin, an antioxidant and anti-inflammatory agent [136, 137]. In the studies, the authors showed that simvastatin-induced inhibition of pro-fibrotic atrial fibroblast response and attenuation of LV dysfunction may contribute to preventing the CHF-induced fibrotic AF substrate.

The anti-inflammatory functions of statins are involved in reducing the expression and function of inflammatory mediators IL-6, TNF-α and cyclooxygenase 2, and in attenuating oxidant-induced mitochondrial dysfunction in cardiac myocytes [138].

Oxidative stress

Several studies have indicated that oxidative stress within the atrial tissue during AF suggests a potential role in structural remodeling of atrium [139–141]. Also, several pharmacologic approaches with antioxidant properties are effective for treating AF [79, 81, 142]. AF is often accompanied by oxidative changes, which include mitochondrial DNA damage and upregulation of NADPH oxidase, a major producer of ROSs [31, 143]. ROSs arising from oxidative stress include superoxide anion, hydroxyl radicals, hydrogen peroxide and peroxynitrite, which in turn modify myocardial cellular and extracellular protein structure and function [144].

The role of oxidative stress in atrial remodeling was established using a pacing-induced AF dog model [145]. This study suggested that reduced vitamin C levels in atrial tissue and increased oxidative stress due to calcium accumulation in the atria result in a cellular redox state that facilitates the formation and perpetuation of AF [146, 147]. Similarly to inflammatory cytokines, ROSs activate ERKs, JNK and p38-MAPK in both cardiac myocytes and fibroblasts (Figs. 1, 2). By these signaling pathways, the pro-fibrotic effects of ROS are well recognized, involving several processes such as an increase in fibroblast proliferation, the expression of pro-fibrotic genes and alterations in ECM metabolism as well as balance between MMP and TIMP activities [148, 149]. ROS production might be stimulated by Ang II, inflammatory cytokines or NADPH oxidase, etc. Inhibition of ROSs prevents atrial remodeling, suggesting that oxidative stress may play a critical role in the pathogenesis of AF [136, 150]. The direct addition of ROSs can decrease the expression of collagen at the transcriptional level in cardiac fibroblasts [151]. Furthermore, ROSs have been shown to cause direct activation of MMPs in conditioned media from cardiocytes [152–154]. MMPs are responsible for digesting ECM proteins between cells, and abnormal regulation of MMP activity results in ECM remodeling. These findings show that ROS can directly or indirectly regulate the metabolism of ECM proteins and might be involved in atrial fibrotic remodeling during AF.

There is evidence that Ang-II increases NADPH oxidase-mediated superoxide production through the activation of the AT-1 receptor, whereas inhibition of Ang-II production ameliorates oxidative stress in the vasculature [155, 156]. The NADPH oxidase-mediated signaling pathway is associated with p38-MAPK [157]. On the other hand, elevated levels of ACE and increased expression of Ang-II receptors have been found in the atrial tissue of AF patients [56, 158]. It is therefore reasonable to assume that angiotensin-induced oxidative stress contributes to the atrial remodeling process. Interstitial fibrosis triggered by ROS may be mediated via Ang-II activation and alternations in MMP/TIMP activity through several divergent signaling pathways in fibrillating atrium [155–157]. Fibrosis may also be directly generated by substantial oxidative damage, for example dysfunction of myofibrillar energy controllers or depletion of antioxidants [139, 159].

At the gene regulation level, Kim et al. examined gene transcriptional profiles in human atrial tissue from patients with permanent AF who underwent the Maze surgical procedure [160]. Changes in the expression of 1152 known genes were examined by DNA microarrays. Among those genes, five genes associated with the production of ROSs (flavin containing monooxygenase-1, monoamine oxidase B, ubiquitin-specific protease 8, tyrosinase-related protein 1 and tyrosine 3-monooxygenase) were upregulated [160]. The alteration of redox status toward oxidative-related gene expression has significant implications for atrial damage, promoting atrial remodeling.

MMPs and atrial remodeling in AF

Cardiologists have commonly conceived of the ECM as a central structural support and dynamic signaling system for cells to assemble into functional heart tissue. The composition of the cardiovascular ECM, which predominately includes collagen types I and III, fibril, fibronectin and laminin, is under strict control.

Cardiac ECM remodeling is the maladaptive response to changes in cardiac structure and function during the progression of heart disease [18, 161, 162]. Metabolism of ECM is a process tightly and dynamically regulated by the delicate balance between MMPs and TIMPs.

MMPs are a family of zinc-dependent endopeptidases that are responsible for degradation of all the matrix components between cells. Thus, an abnormal increase in MMP activity caused by disruption of the balance between MMPs and TIMPs may result in degradation of matrix proteins and ECM remodeling [163–165]. MMPs play a critical role in ECM turnover and are involved in the physiopathogenesis of a variety of cardiovascular disorders [166–168]. To date, at least 26 human MMPs are known; all MMPs are extracellular, most are pericellular and only a few are membrane-bound, such as membrane type I MMP (MT1-MMP) [169–171]. There are four known members of the TIMP family, TIMP-1, -2, -3 and -4, which are differentially regulated in the heart, but their specific role(s) during heart disease remains unclear [171–173]. TIMPs can directly inhibit the proteolytic activity of activated MMPs by forming tight-binding noncovalent 1:1 stoichiometric complexes with them [174], constituting a key system that regulates ECM composition and remodeling [172]. In the heart, proper balance between synthesis and degradation of ECM molecules is of utmost importance for maintaining normal function [165, 175]. Most clinical studies and animal models over the past decade have focused on the role of MMPs and TIMPs in ventricular remodeling of CHF and cardiomyopathies [162, 176, 177]. Here, we review recent work related to the effect of atrial remodeling and atrial fibrosis on the metabolism of ECM and the regulation of MMPs/TIMPs during AF.

Prolonged production of cytokines induced by the wound repair process, lasting shear stress and static pressure, or ROS challenge can lead to excessive ECM accumulation and chronic fibrosis, often resulting in organ failure such as HF [178] as well as atrial diseases such as AF [18, 23, 37, 179]. Collagen, the major heart matrix protein, shows marked accumulation in fibrillating atria of humans [18, 23, 37], and ECM accumulation is considered to be a secondary effects influenced by cytokines or physical stress-induced cellular signaling pathways [180]. Besides collagen, change in other ECM proteins such as fibrillin or fibronectin has also been found to be associated with the development of AF in a porcine model [181].

Atrial fibrosis or ECM accumulation is frequently associated with AF arising from multiple causes, including age [182], HF [18, 26] and cardiomyopathy [18, 183]. Such structural and pathological changes are also observed in atrial biopsies from patients diagnosed with lone AF [23, 130] and in the fibrillating atria of rapid atrial pacing animal models, which are generally considered to mimic lone AF [179, 181]. However, little is known about the mechanisms of ECM metabolism and turnover in the development of AF [33].

Expression and regulation of MMPs and TIMPs

Most MMPs are generally expressed at low levels in normal adult tissue but are upregulated during certain physiological and pathological remodeling processes [184]. MMPs and TIMPs are mediated by a variety of bioactive molecules, such as neurohumoral peptides, growth factors, inflammatory cytokines and ROS [111, 184, 185]. At the level of transcription, MMPs and TIMPs are regulated through binding of transcription factors, enhancers and/or repressors to each gene promoter region [170]. In Figure 3 [185–194], we present the predictive binding sites of certain transcriptional factors within the promoter region of MMPs and TIMPs. The transcriptional factors identified include NF-κB, AP-1, polyoma enhancer A binding protein-3 (PEA-3), Fos, Jun, ETS transcription factors (Ets), TGF-β inhibitory elements (TIEs) and specific protein 1 (Sp1).

Several MMP and TIMP genes contain AP-1 and NF-κB binding sites in their promoter regions, and Ang-II can influence MMP transcription via AP-1 and NF-κB [185]. Stimulation of rat cardiomyofibroblasts with Ang-II induces both NF-κB and AP-1 production, which is associated with an increase in collagen type I production as well as a decrease in *MMP-1* expression [195, 196]. Likewise, Ang-II stimulation of neonatal rat ventricular myocytes triggers the nuclear translocation of cytoplasmic NF-κB, which in turn increases *MMP-9* transcription [197]. Ang-II upregulation of *MMP-2* and *MMP-14* expression is mediated by the JAK/STAT1 pathway [198]. In addition, increased abundance of membrane-bound extracellular MMP inducer (EMMPRIN), a cell-surface protein that can trigger MMP expression, has been identified in human myocardia with cardiomyopathies [199]. The p38-MAPK signaling pathway is proposed to mediate EMMPRIN regulation of MMP expression; therefore, a p38 inhibitor, SB203580, could potentially block EMMPRIN-mediated upregulation of MMPs [200].

In the TGF-β1 signaling pathway, the active Smad complex that translocates to the nucleus could bind to the TIE promoter region, in turn inducing transcriptional activation of specific target genes [108, 201]. Given that *MMP-1*, *-7* and *MT1-MMP* have TIE binding sites in their promoters, it is suggested that the

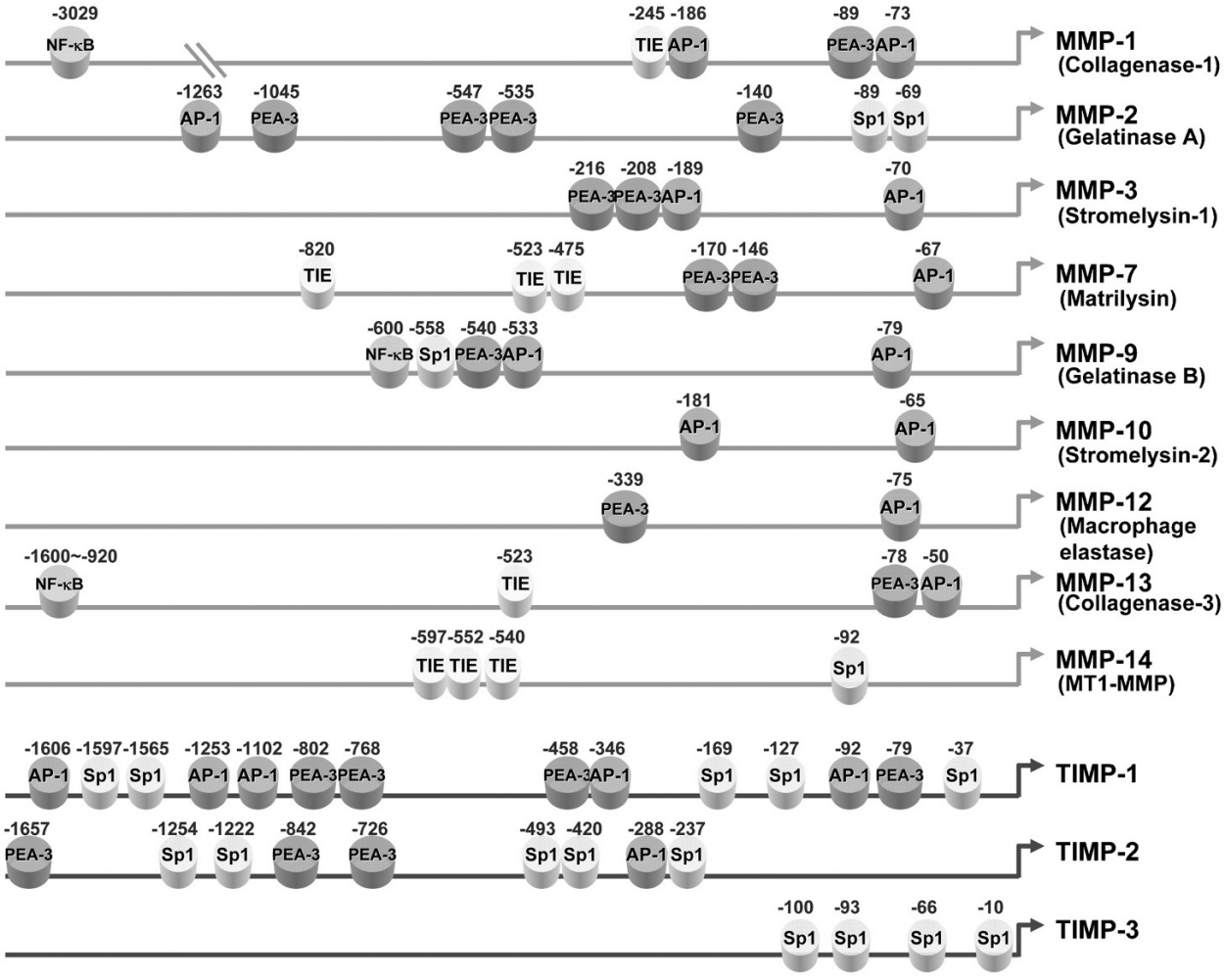

Figure 3. The predicted binding sites of transcription factors located within the proximal regulatory region of selected human MMPs and TIMPs gene. AP-1, activator protein-1; NF-κB, nuclear factor-kappa B; PEA-3, polyoma enhancer A binding protein-3; Sp1, specific protein-1; TIE, TGF-β inhibitory element. The figure was organized from [170] and [185–194].

expression of these MMPs might be altered with increased levels of TGF-β1 [202]. In addition, Smads can directly interact with members of the AP-1 family of transcription factors, thereby increasing the possible number of promoter interactions [203]. The proximal AP-1 site was reported by Hall et al. to be essential for both *TIMP-1* induction and *MMP-1* repression [204]. *MMP-1* repression could be mediated through TGF-β1-dependent Smad3 and Smad4 activation in dermal fibroblasts [205], and MT1-MMP and MMP-2 in cardiomyofibroblasts can be activated by TGF-β1 [206]. Taken together, these studies provide a mechanism for the fibrotic process associated with TGF-β1 stimulation through the gene regulation of MMPs and TIMPs.

The inflammatory cytokines are involved in MMP and TIMP regulation and control cardiomyofibroblast ECM metabolism and the resulting ECM deposition and cardiac remodeling in heart diseases, including HF [185, 207], hypertension [208] and AF [124]. TNF-α and IL-1β may contribute to ventricular dilation and myocardial failure by promoting interstitial collagen remodeling [127]. An *in vitro* study showed that TNF-α, IL-1β and IL-6 can directly decrease collagen synthesis and procollagen mRNA expression in cardiomyofibroblasts [127]. The increase in MMP activity in response to TNF-α and IL-1β in cultured neonatal cardiomyocytes and cardiomyofibroblasts also leads to a rapid decrease in ECM accumulation [129]. Cardiac-specific TNF-α overexpression in transgenic mice causes HF in association with ECM remodeling, with concomitant increases in MMP-2 and MMP-9 activity [209]. TNF-α and IL-1β coregulate the expression of collagenase and *c-jun*, and MMP activation may be due to prolonged activation of *c-jun* gene expression [210]. Both pre- and post-transcriptional mechanisms contribute to increases in MMP gene expression in response to inflammatory cytokines. An increase in

the stability of *MMP-1* transcripts and higher levels of steady-state mRNA in response to IL-1β has been reported [211].

ROS can directly activate MMPs and key transcription factors such as NF-κB, AP-1 and Ets [144, 149]. In rat ventricular cardiomyofibroblasts, periods of anoxia and reoxygenation increased the expression of transcription factor NF-κB but had no effect on AP-1 [212]. The changes in the levels of these molecules could therefore lead to selective modulation of MMP expression [170]. Moreover, increased hydrogen peroxide production resulted in an increase of *c-jun* and *c-fos* mRNA and the subsequent induction of MMP-1 mRNA in human skin fibroblasts [213]. In a clinical study, Kameda et al. demonstrated a positive correlation between a specific marker of oxidative stress, 8-iso-prostaglandin F2α, and the relative levels of MMP-2 and MMP-9 in patients with coronary artery disease [214]. In an *in vivo* mouse model of MI, delivery of hydrogen peroxide increased relative MMP-2 activity, whereas a ROS scavenger decreased relative MMP-2 activity [215]. The relationship between ROS exposure and MMP production has been confirmed in *in vitro* cell culture systems [151]. Siwik et al. demonstrated that a period of oxidative stress increased the relative activity of MMP-2 and MMP-9 in a cardiac fibroblast system [151]. Other studies have provided a mechanistic link between oxidative stress and the activation of MMPs in the myocardium [152, 153]. Therefore, the conditions of oxidative stress that commonly occur in cardiovascular disease states with subsequent ROS generation constitute a mechanism by which cardiac MMPs are dysregulated.

Studies of MMP/TIMP roles in atrial remodeling and atrial fibrosis

Cardiac MMP expression and activity reportedly increase in a number of pathological conditions, such as HF, hypertension and MI [44, 154, 199]. In AF, altered MMP and TIMP expression is also noted in the atrium; however, the number of studies is limited. In Table 2 [216–222] we present studies that report changes in MMP and TIMP expression and activity in atrial tissues isolated in both clinical and animal studies.

Boixel et al. [32] used a rat MI model to demonstrate atrial dilation and fibrosis 12 weeks after LV infarction, which is accompanied by increased expression and activity of MMP-2 and -7 but no change in the expression or activity of TIMP-1, -2 and -4. In an atrial pacing canine model with atrial failure, activity of MMP-9 was selectively and significantly increased by approximately 50%, and the level of TIMP-4 protein was decreased by half in the left atrium [221]. Increased expression of Ang-II in combination with diminished changes in atrial MMP-2 and increased *TIMP-2* expression were observed in a rapid pacing sheep model by Anné et al. [222]. The authors also demonstrated that inhibition of the angiotensin pathway can suppress atrial fibrosis and the development of persistent AF.

It was reported that MMP-9 mRNA and protein levels increased in fibrillating atria of paroxysmal AF patients, whereas expression levels of *MMP-2* and *TIMP-1* were unchanged [217]. Increased MMP-2 activity and reduced *TIMP-2* expression were observed in AF atria with dilated cardiomyopathy or end-stage HF, which may contribute to atrial structural remodeling and atrial dilatation during AF [18]. Furthermore, a recent clinical study examined the myocardial collagen content and levels of MMP-1, -2, -8, -9, -13 and -14 and TIMP-1, -2, -3 and -4 in the four heart chambers, and concluded that cardiac remodeling occurs in a chamber-specific manner; however, collagen content was greater within the atrial myocardium but lower in the ventricular myocardium [34]. This study also showed that MMP-1 levels in the right atrium, MMP-9 in the left atrium and TIMP-3 in the ventricles as well as left atrium were greater with AF. The changes in the abundance of MMPs and TIMPs suggest that the presence of AF in patients with CHF may modulate MMP and TIMP levels and ECM composition in the atrial myocardium [34]. In addition, Arndt et al. provided evidence that points to a role of ADAM (a disintegrin and metalloproteinase) family members in atrial remodeling in human AF [216]. They reported that AF is associated with an increase in the expression of ADAM10 and ADAM15, suggesting that altered ADAM expression may contribute to structural remodeling of the atria during AF. Anné et al. [218] studied atrial structural remodeling and MMPs as well as TIMPs in patients with mitral valve disease with and without AF and showed concordant changes between MMP-1 and MMP-9 during mitral valve disease, suggesting the involvement of MMPs in structural atrial remodeling. However, AF itself did not contribute to altered fibrosis or MMP expression in the left atria. Plasminogen activator inhibitor, an inhibitor of a potent activator of many MMPs in the right atrial appendages, was significantly decreased with increasing duration of AF. In parallel, the levels of *TIMP-1* and *-2* transcripts also decreased significantly [219]. Recently, gene expression profiles in canine models of AF were reported by Cardin et al [223]. They concluded that increased levels of ECM-related transcripts in atria are consistent with fibrotic pathophysiology. However, similar to the result of atrial fibrosis in the canine AF model, ECM-related genes were strongly upregulated in a model of ventricular tachypacing, but not in a model of atrial tachypacing.

Table 2. Studies of MMP roles in atrial remodeling and atrial fibrosis in human studies and animal models.

Authors	Year	Experimental design	Key findings
Human studies			
Arndt et al. [216]	2002	* 30 patients undergoing cardiac surgery * persistent AF (n = 15) *vs.* no history of AF (n = 15)	AF is associated with an increase in the expression of ADAM10 and ADAM15.
Marín et al. [33]	2003	* chronic nonrheumatic AF (n = 48) *vs.* sinus rhythm (n = 32)	Patients with AF have evidence of impaired matrix degradation, which is dependently associated with the presence of AF. An independent relationship is found between the MMP/TIMP system and prothrombotic state in AF.
Nakano et al. [217]	2004	* 38 patients undergoing cardiac operation * AF (n = 13; paroxysmal AF, n = 6; chronic AF, n = 7) *vs.* sinus rhythm (n = 25)	MMP-9 expression is increased in fibrillating atrial tissue, which may contribute to atrial structural remodeling and atrial dilatation during AF.
Xu et al. [18]	2004	* 53 patients with dilated cardiomyopathy and end-stage HF who underwent heart transplantation * permanent AF (n = 19), persistent AF (n = 18) and no documented AF (n = 16)	Atrial ECM remodeling is manifested by the selective downregulation of TIMP-2 along with upregulation of MMP-2. Type I collagen volume fraction in the atrium is associated with the development of sustained AF in patients with cardiomyopathy and HF.
Anné et al. [218]	2005	* atrial appendages of patients undergoing coronary artery bypass grafting surgery (CABG) or mitral valve surgery (MVS) * MVS (n = 19; 9 with permanent AF, 10 in sinus rhythm) and CABG (n = 9; all sinus rhythm)	Concordant changes between atrial MMP expression and fibrosis in mitral valve disease with AF suggest involvement of MMPs in structural atrial remodeling. However, selective changes of fibrosis or MMP expression in the left and right atria of AF were found.
Mukherjee et al. [34]	2006	* 43 patients with end-stage CHF * AF (n = 23) *vs.* non-AF control (n = 20)	AF is associated with chamber-specific alterations in myocardial collagen content and MMP and TIMP levels. Differences in MMP and TIMP profiles may provide diagnostic and mechanistic insights into the pathogenesis of AF with CHF.
Gramley et al. [219]	2007	* right atrial appendages of 146 patients excised during heart surgery * AF group *vs.* sinus rhythm	A longer AF duration is associated with elevated atrial interstitial MMP activity, but decreased TIMP expression.
Kato et al. [220]	2007	* the genotypes for 40 polymorphisms of 32 candidate MMP genes * AF (n = 196) *vs.* control (n = 873)	The T allele of MMP2 polymorphism is a risk factor for the development of AF.
Animal models			
Hoit et al. [221]	2002	* dogs with rapid pacing-induced atrial failure * rapid atrial pacing (n = 8) *vs.* sham operation (n = 6)	Rapid pacing-induced atrial failure is associated with differential changes in MMP activity. The activity of MMP-9 was selectively increased by ~50%, and the level of TIMP-4 protein was decreased by ~50% in samples from dogs with atrial failure.
Boixel et al. [32]	2003	* rat model of MI * mild HF (n = 12) *vs.* severe HF (n = 15)	In MI and HF, MMP-7 appears to be involved in the early stage of hemodynamic overload in the atria.
Anné et al. [222]	2007	* rapid-pacing sheep model * The animals divided into his bundle ablation (HBA) group (n = 21) and non-HBA group (n = 14). Both groups were subdivided to receive medication: quinapril, losartan, or placebo.	Atrial fibrosis development in this model is the result of increased expression of Ang-II in combination with diminished changes in atrial MMP-2 and increased TIMP-2 expression. Inhibition of the angiotensin pathway by ACEIs or ARBs suppresses atrial fibrosis and the development of persistent AF.

Theoretically, an increase in MMP activity should result in a decrease in MMP substrates such as collagen; however, cardiac fibrosis has been associated not only with increased levels of collagens and alterations in ECM components but also with increased activity of MMPs, as seen in HF [32, 161]. This apparent discrepancy may be explained by temporal changes in the function of MMPs with concomitant heart disease, such as valve regurgitation and HF, which have a substantial effect on atrial MMP expression [218]. In addition, increased MMP activity has often been observed in profibrotic states, and long-term MMP inhibition has been shown to suppress fibrosis [224]. Moreover, a linear relationship exists between the extent of fibrosis in right atrial appendages at the time of open-heart surgery and the incidence of postoperative AF [180]. Accordingly, altered MMP levels may precede atrial ECM remodeling and fibrosis and eventually increase conduction heterogeneity in the atrium and AF vulnerability.

Conclusion

We have reviewed the literature that covers the effectors, signal transduction and physiopathogenesis concerning ECM dysregulation and atrial fibrosis in AF. Based on this body of research, we suggest that the Ang-II-MAPK and TGF-β1-Smad signaling pathways play a major and central role in directly or indirectly regulating atrial fibrotic remodeling in AF. Inflammation and oxidative stress are the important physiological stresses contributing to atrial ECM turnover and atrial fibrotic progression in fibrillating atria. Metabolism of the ECM is a process that is tightly and dynamically regulated in cardiac tissues by the balance of degradative enzymes, MMPs, and their endogenous inhibitors, TIMPs. Interplay of MMPs and TIMPs is regulated by bioactive molecules such as neurohumoral peptides, growth factors, inflammatory cytokines and ROS. However, so far, knowledge of the expression and regulation of MMPs and TIMPs in the atria with AF has had to be extrapolated from the studies of ventricular remodeling of CHF. A better understanding of the molecular mechanisms that mediate MMP/TIMP balance will help us find new approaches to treat atrial remodeling and to develop new medicines that prevent or reverse the physiopathogenesis of AF.

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