



Review

Regional Diversities in Fibrogenesis Weighed as a Key Determinant for Atrial Arrhythmogenesis

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Abstract: Atrial fibrosis plays a key role in atrial myopathy, resulting in the genesis of atrial fibrillation (AF). The abnormal distribution of fibrotic tissue, electrical coupling, paracrine interactions, and biomechanical–electrical interactions have all been suggested as causes of fibrosis-related arrhythmogenesis. Moreover, the regional difference in fibrogenesis, specifically the left atrium (LA) exhibiting a higher arrhythmogenesis and level of fibrosis than the right atrium (RA) in AF, is a key contributor to atrial arrhythmogenesis. LA fibroblasts have greater profibrotic cellular activities than RA fibroblasts, but knowledge about the regional diversity of atrial regional fibrogenesis remains limited. This article provides a comprehensive review of research findings on the association between fibrogenesis and arrhythmogenesis from laboratory to clinical evidence and updates the current understanding of the potential mechanism underlying the difference in fibrogenesis between the LA and RA.

Keywords: fibroblasts; fibrosis; atrial fibrillation; heart failure; left atrium; right atrium; Ca²⁺; transforming growth factor; oxidative stress; nitric oxide

1. Introduction

Atrial fibrosis is a distinctive pathological finding of atrial myopathy and contributes to the genesis of various cardiovascular diseases. A higher level of left atrium (LA) fibrosis is associated with a greater recurrence of atrial fibrillation (AF) after surgical management or catheter ablation [1,2]. Patients with heart failure (HF) exhibited a higher prevalence of atrial fibrosis [3], and mineralocorticoid receptor antagonist treatment decreases the incidence of new-onset AF in patients with HF [4]. AF also increases the area of fibrosis in patients with HF [5], and the crosstalk between fibrogenesis and arrhythmogenesis thus plays a pivotal role in AF. For decades, numerous studies about antiatrial remodeling therapy, also called “upstream therapy”, for AF management have focused on this crucial process. The LA exhibits greater levels of fibrosis compared with the right atrium (RA) in

patients with AF, according to the results of fibrotic tissue staining [6–8]. In addition, the LA exhibits higher gene expression of collagen I and collagen III compared to the RA [8]. Moreover, LA biopsies exhibit greater expression of pro-fibrotic transforming growth factor (TGF)- β and angiotensin (Ang) II, compared with RA biopsies [8]. By contrast, immunohistological staining reveals higher collagen I and III expression in RA tissue than in LA tissue [9]. Studies of LA and RA regional biopsies have reported heterogeneous conclusions about the atrial regional fibrotic diversity, which may be because of the differences between studies in the area being sampled. Studies have also demonstrated that late-gadolinium enhancement magnetic resonance imaging (LGE-MRI) can detect the fibrosis of the whole LA or RA [10]. Notably, in patients with AF, the majority of the LGE in the RA is located in the intra-atrial septal region with lower enhancement in the remainder of the RA. The levels of LGE are considerably lower in the whole RA than in the LA, indicating that the RA has a lower level of fibrosis than the LA [11]. In a study using a sheep model, the activation frequencies in certain areas of the LA were always faster than those in the RA [12,13]. Further, results from the noncontact mapping of biatrial activation in canines with HF have demonstrated that the LA has a higher frequency of focal discharge and greater effective refractory period dispersion than the RA [14]. Four possible interactions between fibroblasts and cardiomyocytes may result in atrial arrhythmogenesis: (1) abnormal distribution of fibrotic tissue, (2) modulations in electrical coupling, (3) paracrine interactions, and (4) biomechanical–electrical interactions [15,16]. Moreover, the LA and RA exhibit diverse characteristics in cytokine production [17], gene expression [18,19], and epigenetic modification [20], which may contribute to their different fibrogenesis. This review clarifies the crosstalk mechanisms of fibrogenesis and arrhythmogenesis and the regional differences associated with the diversity of fibrogenesis between the LA and RA. This review also provides an update on the existing body of laboratory and clinical evidence, for fibrosis-related electrophysiological diversity between the LA and RA.

1.1. Abnormal Distribution of Fibrotic Tissue in Atrial Electrical Coupling and Arrhythmogenesis

Atrial fibrotic tissue induces a unidirectional block, leading to the development of reentry [21]. Impulse conduction is forced to travel through the tortuous electrically insulating conduit formed by the fibrotic tissue, thereby inducing slow, discontinuous, or fractionated electrical wave propagation, inducing reentry [22,23]. Propagation waves perpendicular to the collagen fiber exhibit slower conduction velocity [23]; hence, the organization of fibrotic tissue may be highly correlated with reentry stability. Atrial fibrosis can be classified as patchy and diffuse type, according to its architecture [24]. Patchy fibrosis contributes to wavebreak, slower conduction, and a higher incidence of reentry multiplication rather than diffuse fibrosis [24]. In normal myocardium, connexins are located primarily at the end of intercalated disks, which contribute to the impulse conduction of myocyte–myocyte coupling. AF with atrial fibrosis exhibits the heterogeneous redistribution of Cx43 in the atrial myocardium [25]. The lateralization of gap junctions induces lower conduction velocity in AF with atrial fibrosis [26]. Besides, atrial myofibroblasts isolated from the surgical specimens of the patients with AF exhibit high Cx43 expression [27]. This finding indicates that fibrogenesis may induce the remodeling of the gap junction and activate arrhythmogenesis.

Studies have revealed that atrial myofibroblasts maintain their resting membrane potential of approximately -30 mV, which is considerably less negative than that of myocytes [27]. Myocytes, when coupled with an increased number of myofibroblasts, exhibit greater depolarized resting membrane potential, thereby inactivating sodium channels, decreasing conduction velocity, and increasing the complexity of wave propagation [28]. Accordingly, the distribution and density of atrial myofibroblasts–cardiomyocytes heterocellular coupling may be a key element of atrial arrhythmogenesis.

1.2. Fibrosis-Related Impairment of Biomechanical–Electrical Properties

The resting membrane potential of atrial fibroblasts can be modulated by cardiac contraction stretch through mechanosensitive channels, thereby depolarizing the coupled cardiomyocytes and slowing down conduction velocities [29]. A simulation study revealed that atrial fibroblasts–myocytes coupling through the stretch-activated ion channel prolonged repolarization, action potential duration, and depolarized the resting potential of human atrial myocyte, thereby slowing down wave propagation and decreasing strain in fibrotic tissue [30]. Patients with AF exhibited higher levels of atrial stiffness compared with patients with sinus rhythm because of atrial fibrosis [31], suggesting that the higher levels of atrial fibrosis contribute to increased heterogeneous impulse wave transmission and conduction block.

1.3. Enhancement of Atrial Arrhythmogenesis by Paracrine Signaling from Fibrosis

Paracrine mediators contribute to the indirect communication between cardiomyocytes and myofibroblasts. Atrial myofibroblast-secreted platelet-derived growth factor induces calcium channel remodeling and shortening of action potential duration of coupled atrial myocytes [32]. TGF- β 1 increases ion-channel remodeling of atrial myocytes [33]. Besides, transgenic mice with TGF- β 1 overexpression exhibit atrial heterogeneous conduction and prolonged intracellular calcium transient with selective atrial fibrosis, leading to high AF vulnerability [34,35]. Our previous study verified that LA fibroblasts secreted greater TGF- β 1 than RA fibroblasts [36]; hence, the paracrine interaction of TGF- β 1 may explain the diversity in arrhythmogenesis between the LA and RA. MicroRNA (Mir) is a small noncoding RNA of approximately 22 nucleotides that can negatively modulate gene expression [37] through mRNA degradation, translation inhibition, or transcriptional inhibition [38,39]. Atrial myofibroblasts-derived exosomes decrease the Cav1.2 gene expression of cardiomyocytes through Mir-21-3p, thereby decreasing the L-type Ca^{2+} current and increasing AF vulnerability [40,41]. Oxidative stress is a central mediator of AF and atrial fibrosis [42,43]. Notably, in our previous study, we observed that LA fibroblasts produce higher oxidative stress than RA fibroblasts [36]. Moreover, oxidative stress increases intracellular Ca^{2+} overloading, thereby inducing delayed afterdepolarization of atrial myocytes [44]. Therefore, oxidative stress may not only contribute to the dissimilarities of atrial fibrogenesis but also augment the diversity of atrial arrhythmogenesis through fibrogenesis. Consequently, the myofibroblast may not only play a passive role as an impulse conduction conduit but also be an active modulator of arrhythmogenesis through paracrine interaction. Moreover, cultured atrial myocytes after rapid pacing (10 Hz) can also increase collagen and TGF- β 1 production of atrial fibroblasts through the secretion of Ang II [45]. Besides, atrial myocytes were found to produce calcitonin, acting as a paracrine signal that inhibits migration, proliferation, and collagen production of neighboring atrial fibroblasts [46]. These findings suggest that paracrine factors from the atrial myocytes may also affect the development of fibrosis.

2. Diversity in Atrial Fibrogenesis and Arrhythmogenesis: Clinical Evidence

Electroanatomic mapping results have demonstrated that the average conduction velocities are slower in the LA than in the RA in patients with AF [47], suggesting a key role for regional differences in fibrosis in the pathophysiology of AF. The average cycle length in LA is shorter than that in the RA in AF patients [48], indicating that the LA has greater reentrant activation than the RA. Sites that exhibited high-frequency activity compared with the surrounding atrial tissue are defined as dominant-frequency (DF) sites, which can also be identified as the atrial tissue sustaining rotational activity in fibrillation [49]. DF mapping is used to identify the localized sites of maximal DF during AF [50]. LA DFs are considerably greater than RA DFs in AF patients [7]. Interestingly, collagen I deposition in atrial tissue is highly positively correlated with the levels of DF in patients with AF [7], which provides strong evidence to support the crosstalk between atrial arrhythmogenesis and fibrogenesis. The rotor frequency identified by optical mapping was found to correlate

well with the DF, as determined by signal analysis [51]. Rotors, representing stable but meandering spiral waves, can anchor to areas of anatomic discontinuity such as fibrosis [52], and therefore, voltage mapping may reveal sites important to maintaining atrial rotational activity. In patients with AF, the AF rotors are primarily located in the heterogeneous LGE areas. Moreover, the combination of LGE-MRI and 3D phase-mapping makes it feasible to precisely identify the fibrogenic and arrhythmogenic substrates correlated with the AF rotor [53]. A previous study using a mapping strategy, which targeted the focal impulse and rotor modulation with a novel 64-electrode basket catheter in AF patients, revealed that the location of rotors is higher in the LA than in the RA, with a ratio of 4.54:1 [54]. This is highly correlated with the LGE-MRI fibrosis imaging, which demonstrates that the LA features greater enhancement relative to the RA [11]. Accordingly, these clinical images and novel diagnostic tools indicated the atrial regional diversities in electrical and structural remodeling, which may provide further information for planning electrical physiological ablation or drug discovery.

Laboratory Evidence of Diversity in Atrial Fibrogenesis and Arrhythmogenesis

Similar to the results of the human study [48], those of our previous study revealed that LA tissue exhibits higher atrial fibrosis than RA tissue in rats with HF with reduced ejection fraction assessed by echocardiography (Figure 1) [36]. Similarly, in dogs with atrial myopathy, the mean atrial fibrillatory cycle length is shorter in the LA than in the RA, suggesting that the LA has higher fibrogenesis [55]. In addition, a sheep AF model revealed the left-to-right decrease in DF [56], suggesting that LA may be the source of higher-frequency activation, which transmits fibrillatory conduction to RA, thereby inducing AF. Moreover, in mitral regurgitation pigs, which are highly vulnerable to AF, the area of fibrosis in the LA is larger than that in the RA, but the conduction velocity of the LA is lower than that of the RA [57]. This study also found that conduction velocity is negatively correlated with the area of fibrosis [57]. These pieces of laboratory evidence confirm the regional heterogeneity and the possible crosstalk between fibrogenesis and arrhythmogenesis.

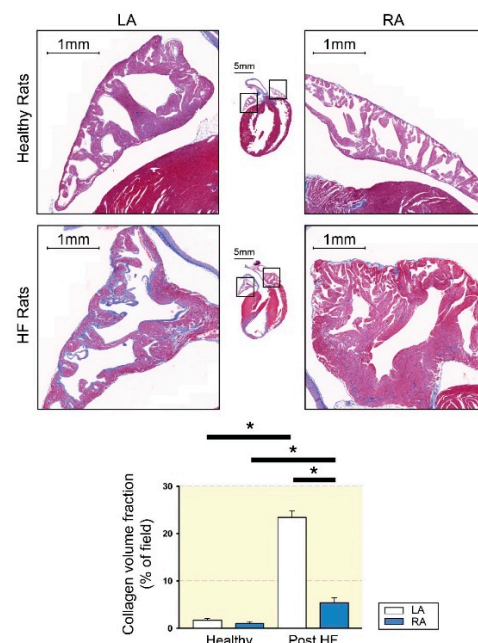


Figure 1. Atrial fibrosis of left atrium (LA) and right atrium (RA) tissues from healthy and heart failure with reduced ejection fraction (HF) rats. The upper photographs show representative photos with Masson's trichrome staining of healthy LA and healthy RA atrial fibrosis. The lower photographs show representative photos of HF LA and HF RA atrial fibrosis. Compared to HF RA, HF LA exhibited greater levels of atrial fibrosis. LA and RA from healthy rats revealed a similar extent of

atrial fibrosis. HF increased fibrosis to a greater severity in LA than in RA. * $p < 0.05$ (modified from [36] with permission of the publisher).

3. Mechanisms Contributing to the Regional Diversities of Atrial Fibrogenesis

Ali et al. used lineage tracing and histochemistry to study the origins of cardiac fibroblasts in transgenic mice and found that the majority of the neural crest-derived fibroblasts were localized in RA [58]. This finding suggests that part of the RA fibroblasts may come from different embryonic germ layers to those of LA fibroblasts. In addition, the dissimilar characteristics between LA and RA fibroblasts are correlated with the diversity in oxidative stress, nitric oxide (NO) signaling, TGF- β production, and Ca²⁺ signaling [36,59,60]. Table 1 summarizes the potential targets underlying different fibrogenesis between the RA and LA.

Table 1. List of targets that activate the atrial regional diversities in fibrogenesis.

Predominant Chamber	Molecules	Signaling That Induces Atrial Diversities	Effects of Molecules on the Signaling	References
RA	Nitric oxide	Nitric oxide signaling	+	[6,61]
	eNOS	Nitric oxide signaling	+	[61]
	sGC	Nitric oxide signaling	+	[61]
	Adrenomedullin	Nitric oxide signaling	+	[18]
		TGF- β signaling	–	[62]
		Oxidative stress signaling	–	[63]
	Estrogen receptor- α	Nitric oxide signaling	+	[64–66]
		Ca ²⁺ signaling	–	[67,68]
		Oxidative stress signaling	–	[69]
	ANP	Nitric oxide signaling	+	[17,64,70–74]
		Ca ²⁺ signaling	–	[75]
	Smad6	TGF- β signaling	–	[76,77]
	BMP-10	TGF- β signaling	–	[18,20,78]
	HSP-70	Oxidative stress signaling	–	[79,80]
	Hepcidin	Oxidative stress signaling	–	[20,81]
	Mir-135a	Ca ²⁺ signaling	–	[20,82]
	Mir-100	TGF- β signaling	–	[82]
Oxidative stress signaling		–	[83,84]	
LA	Chymase	Ca ²⁺ signaling	+	[85]
	CGRP	Ca ²⁺ signaling	+	[86]
	Wnt related gene	Ca ²⁺ signaling	+	[87,88]
		TGF- β signaling	+	[89]
	Iron	TGF- β signaling	+	[7,90]
	Mir-10b	TGF- β signaling	+	[20,91,92]
	Mir-208	Oxidative stress signaling	+	[93]
		TGF- β signaling	+	[94,95]

eNOS: endothelial nitric oxide synthase, sGC: soluble guanylyl cyclase, ANP: atrial natriuretic peptide, Smad6: SMA and MAD-related protein 6, BMP-10: bone morphogenetic protein-10, HSP-70: heat shock protein-70, Mir: micro RNA, CGRP: calcitonin gene-related peptide, ATF3: activating transcription factor 3.

3.1. NO and Ca²⁺ Signaling Modulation

NO plays a pivotal role in fibrogenesis and AF. NO is a highly reactive radical that is generated from L-arginine by NO synthase (NOS). Inhibition of NOS can enhance myocardial fibrosis [96]. The NO/soluble guanylyl cyclase (sGC)/cyclic GMP (cGMP) signal pathway can decrease Ang II-induced profibrotic mitogen-activated protein kinase activities or attenuate collagen production of fibroblasts by interfering with phosphorylated SMA and MAD-related protein (Smad) 2 expression [97,98]. Endothelial NOS (eNOS) gene expression negatively correlates with the risk of AF [99]. Compared with LA tissue,

RA tissue exhibits higher NO, eNOS, and sGC expression [6,61], indicating that the RA produces greater levels of NO, thereby decreasing the cellular activities of RA fibroblasts and attenuating RA fibrogenesis. Moreover, in different mouse strains and human atrial tissue experiments, the RA exhibited greater gene expression of adrenomedullin than the LA [18], indicating that this endothelial cell and vascular smooth muscle cell-secreted peptide can contribute to atrial regional diversity in fibrogenesis caused by the dissimilarity in NO/sGC signaling [100].

Ca²⁺ homeostasis plays a key role in the pathophysiology of cardiac fibrosis. Ca²⁺ signaling augments the profibrotic cellular activities of fibroblasts [101–104]. Extracellular Ca²⁺ entry and endoplasmic reticulum (ER) Ca²⁺ release contribute to the increase in intracellular Ca²⁺. In our previous study, we found that, compared with RA fibroblasts, LA fibroblasts exhibited higher Ca²⁺ entry, thereby inducing greater collagen production (Figure 2) [59]. In addition, compared with RA tissue, LA tissue exhibited greater chymase production, which is a profibrotic protease that can induce Ca²⁺ influx [85,105,106]. The cardiovascular neurotransmitter calcitonin gene-related peptide, highly expressed in LA tissues but not in RA tissue, can increase the amount of intracellular Ca²⁺ through Ca²⁺ entry [86,107]. Moreover, compared to LA tissue, RA tissue exhibits higher estrogen receptor- α expression, which is constitutively expressed on cardiac fibroblasts and may inhibit the profibrotic cellular activities of cardiac fibroblasts through the modulation of Ca²⁺ homeostasis [64,67,68,108–110]. In our previous study, we identified the diverse protein expression in transient receptor potential (TRP) channels, phosphorylated phospholipase C (PLC), and the stromal interaction molecule (STIM)1 between LA and RA fibroblasts [59]. Phospholipase C (PLC), the second messenger of multiple profibrotic cytokines [111,112], hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂), thereby producing diacylglycerol (DAG) and inositol trisphosphate (IP₃). TRP channels are one of the gateways for extracellular Ca²⁺ entry [113]. TRP channels, which can be activated by DAG [114,115], are upregulated in patients with AF and contribute to atrial fibrosis [116]. The blocking of TRP channels attenuates Ca²⁺ entry-induced collagen production and myofibroblast differentiation in atrial fibroblasts [117]. IP₃ signaling activates Ca²⁺ release from the ER [118,119]. The emptying of Ca²⁺ from the ER can be sensed by STIM1, a single-pass membrane protein in the ER membrane, leading to the activation of the store-operated Ca²⁺ entry [120]. In ovariectomized rats, 17 β -estradiol-induced atrial natriuretic peptide (ANP) production is higher in the RA than in the LA [64]. This finding of higher estrogen-induced ANP is consistent with findings from other studies, which have revealed that the RA expresses higher ANP protein and gene levels than the LA in various species [17,70–74]. ANP/cGMP signaling can attenuate Ca²⁺ influx by downregulating the phosphorylation of the TRP channels, thereby decreasing profibrotic signaling [75,121]. Interestingly, estrogen receptor- α signaling can also activate cGMP and eNOS and protect against cardiac remodeling [65,66]; hence, this chamber-specific protein diversity in estrogen receptor- α /ANP/cGMP promotes the differences in atria fibrogenesis through NO and Ca²⁺ signaling crosstalk.

In patients with AF, gene expression involved in the Wnt signaling pathway is greater in LA tissue than in RA tissue [87]. The noncanonical Wnt signaling phosphorylates PLC and increases IP₃ production, leading to the induction of Ca²⁺ homeostasis [88]. In addition, cGMP attenuates Wnt stimulator-activated Ca²⁺ mobilization [122]. Accordingly, the LA constitutively expresses a higher amount of the Ca²⁺ activator, whereas RA expresses greater levels of the Ca²⁺ signal inhibitor, leading to the regional diversity in atrial fibrogenesis.

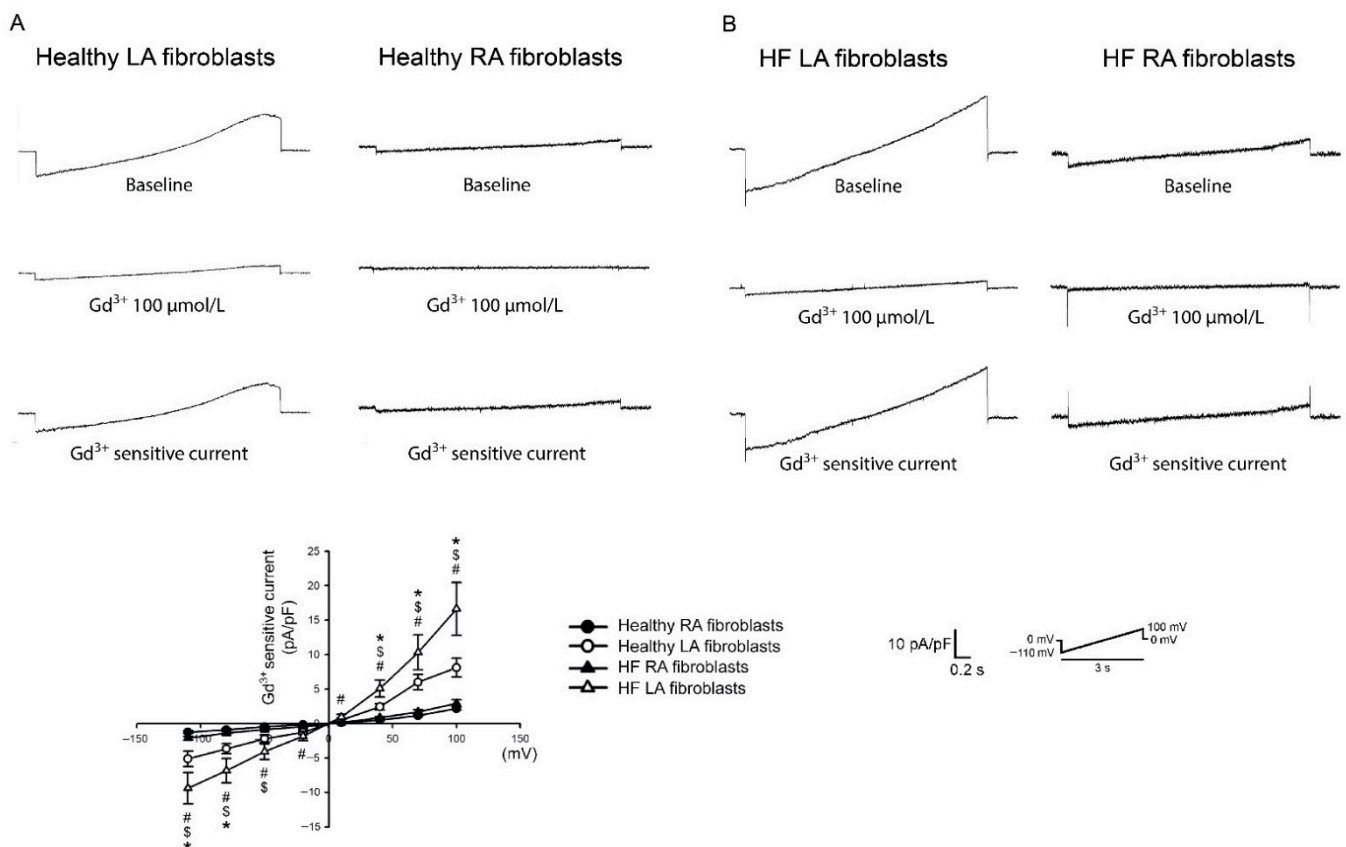


Figure 2. Membrane gadolinium (Gd^{3+})-sensitive Ca^{2+} currents of the left atrium (LA) and right atrium (RA) fibroblasts in healthy and heart failure with reduced ejection fraction (HF) rats. (A). Left and right panels, respectively, reveal tracings of the Gd^{3+} ($100 \mu\text{mol/L}$)-sensitive nonselective cation current of LA and RA fibroblasts isolated from healthy rats. Healthy LA fibroblasts exhibited greater Gd^{3+} -sensitive Ca^{2+} currents compared with healthy RA fibroblasts. (B). Left and right panels, respectively, reveal tracings of the Gd^{3+} ($100 \mu\text{mol/L}$)-sensitive nonselective cation current of LA and RA fibroblasts isolated from HF rats. The statistical results revealed that healthy LA fibroblasts exhibited greater Gd^{3+} -sensitive Ca^{2+} currents compared with healthy RA fibroblasts. HF LA fibroblasts exhibited greater Gd^{3+} -sensitive Ca^{2+} currents compared with HF RA fibroblasts. LA fibroblasts from HF rats showed higher Gd^{3+} -sensitive currents compared with LA fibroblasts from healthy rats. The insets in the current traces showed the various clamp protocols. * Healthy LA versus healthy RA fibroblasts; \$ HF LA versus healthy LA fibroblasts; # HF LA versus HF RA fibroblasts (adapted from the published article by Chung et al. [59]).

3.2. TGF- β Paracrine Effect

TGF- β is the key driving force of atrial fibrosis [123] and has higher levels in patients with AF and atrial remodeling or fibrosis than in patients with sinus rhythm [124,125]. TGF- β 1 induces profibrotic cellular activities of atrial fibroblasts through downstream Smad2/3 signaling [126]. Smad6 can be considered as an inhibitory Smad that interferes with the phosphorylation of Smad2/3 [76]. The overexpression of Smad6 decreases the collagen expression of fibroblasts [127], and compared with LA tissue, RA tissue exhibits greater Smad6 gene expression [77]. Bone morphogenetic protein (BMP) is part of the TGF- β signaling superfamily. BMP plays an essential role in the cardiac development and pathogenesis of various cardiovascular diseases [78]. BMP-10, a gene that is 282-fold greater expressed in RA than in LA, reduces the collagen-production capability of cardiac fibroblasts [18,20,128]. Moreover, BMP-10 transgenic mice or mice treated with BMP-10 exhibit lower levels of cardiac fibrosis. Consequently, the RA expresses a greater amount of TGF- β inhibitory factor and induced lower levels of fibrogenesis than the LA. However, the LA exhibits greater activating transcription factor 3, which can induce an increased amount of TGF- β 1 and greater collagen type I production in fibroblasts [89,129]. The LA exhibits greater iron deposition [7], and the inhibition of iron deposition suppresses TGF- β

production and reduces the extent of myocardial fibrosis [90]. Iron-reduction therapy can decrease the occurrence of paroxysmal AF in patients with chronic iron overload [130]. Patients with iron overload exhibited increased LA stiffness, which is a strong independent predictor of AF [131,132], suggesting that the LA has a higher propensity for TGF- β production and has greater potential for activating greater fibrosis as a result of iron overload.

Adrenomedullin can also decrease collagen production capability by decreasing TGF- β 1 production in fibroblasts [62]. ANP/cGMP decreases the profibrotic cellular activities of fibroblasts by interfering with Smad3 signaling [133], suggesting that cross-talk between NO and the anti-TGF- β pathway contributes to the lower fibrosis in the RA. The LA expresses a higher level of Mir-10b and Mir-208 than the RA [20,94]. The upregulation of circulating Mir-10b can predict myocardial fibrosis in patients with hypertrophic cardiomyopathy [134]. The inhibition of Mir-10b can decrease TGF- β 1 production and myofibroblast differentiation [91,92], and in patients with dilated cardiomyopathy, Mir-208 is positively correlated with the severity of cardiac fibrosis [135]. The overexpression of Mir-208 increases the expression of endoglin, a coreceptor of TGF- β , and augments the collagen expression of myofibroblasts [95]. By contrast, Mir-135a, which is more highly expressed in the RA than in the LA, can inhibit TGF- β 1 production and currents through TRP channels, thereby decreasing the collagen production and myofibroblast differentiation of cardiac fibroblasts [20,82]. These epigenetic diversities in TGF- β modulation may also contribute to atrial regional fibrogenic diversity.

3.3. Oxidative Stress Signaling

Oxidative stress plays an essential role in the pathogenesis of AF [136]. Reactive oxygen species (ROS) derived from nicotinamide adenine dinucleotide phosphate oxidase (Nox)-4 potentiates the TGF- β -induced collagen type I transcriptional activity of atrial fibroblasts [137]. ROS can also upregulate the production of TGF- β in cardiac fibroblasts [138]. Furthermore, oxidative stress increases the gene expression of the Ang type I receptor, thereby increasing the responsiveness of cardiac fibroblasts to Ang II [139]. Moreover, oxidative stress mediates the atrial fibrosis and AF vulnerability of diabetic animals [140]; hence, increased production of oxidative stress may enhance atrial fibrogenesis. Knocking out estrogen receptor- α increases Ang II-induced oxidative stress production [69]. Our previous study showed that LA tissue exhibited greater levels of oxidative stress and atrial fibrosis compared to RA in reduced ejection fraction HF rats measured by echocardiography [36]. The RA has a greater expression of heat shock protein 70, which may result in a cytoprotective effect against oxidative stress and, consequently, lower levels of fibrogenesis [79,80]. Hepcidin is an antimicrobial protein that controls iron metabolism in mammals [141]. Hepcidin also decreases oxidative stress in rats with myocardial infarction [81]. The RA expresses greater gene expression of hepcidin than the LA [20]. Adrenomedullin also attenuates oxidative stress production, leading to lower levels of cardiac fibrosis in hypertensive rats [63]. Moreover, Mir-100, which is more highly expressed in the RA than in the LA, decreases ROS production by targeting Nox 4 [83,84]. By contrast, the inhibition of the LA-enriched Mir-10b can decrease oxidative stress production [93]. In summary, these modulators protect RA against oxidative injury, thereby decreasing levels of atrial fibrogenesis.

4. Conclusions

In conclusion, as summarized in Figure 3, various factors with heterogeneous distribution between the LA and RA may activate diverse atrial regional fibrogenesis through NO, Ca²⁺, TGF- β , and oxidative stress signaling pathways, thereby inducing different atrial electrical remodeling.

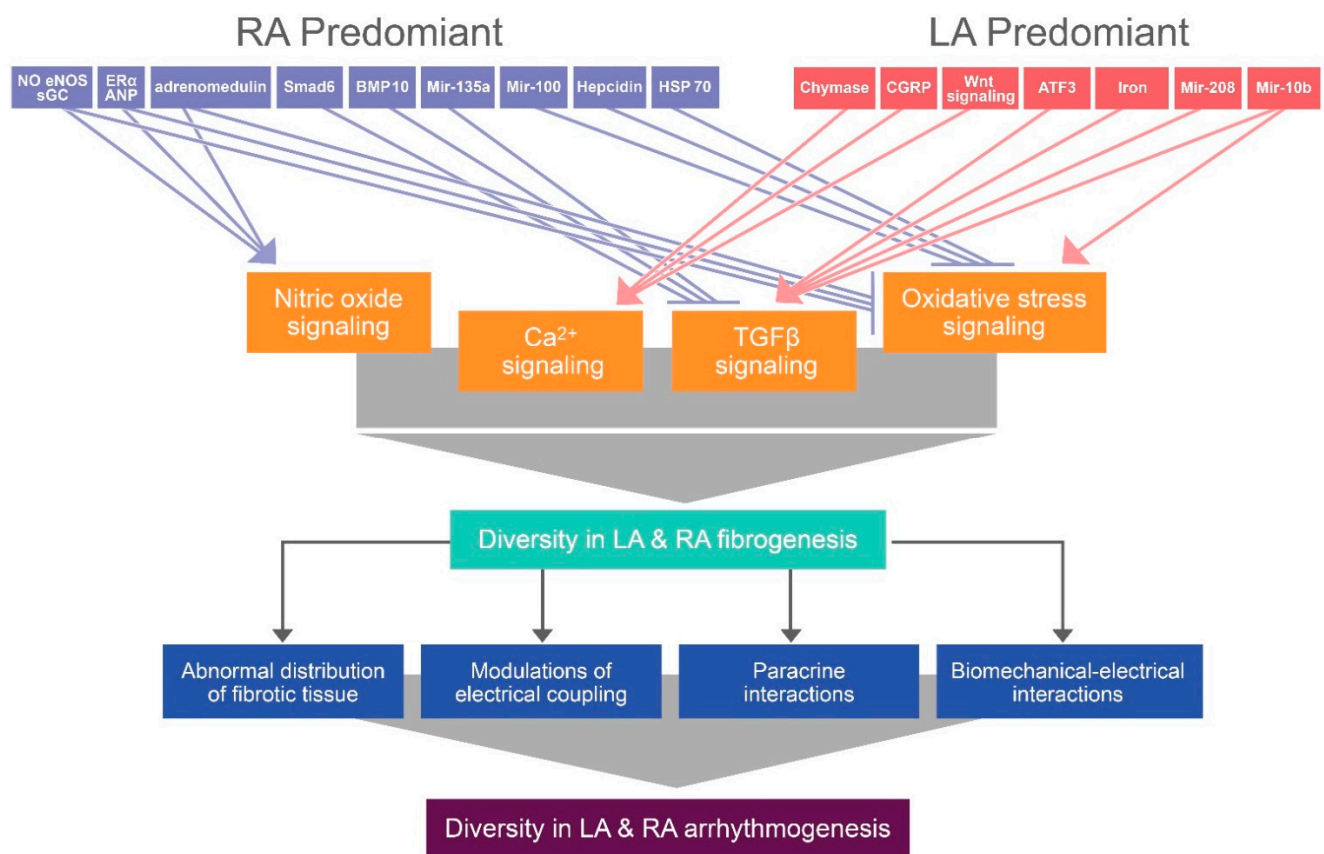


Figure 3. Illustration of the proposed mechanism that contributes to differential atrial fibrogenesis-induced arrhythmogenesis between the LA and RA. Diverse gene or protein expression induces differential atrial fibrogenesis by modifying nitric oxide, Ca^{2+} , transforming growth factor (TGF)- β , and oxidative stress signaling, thereby activating diversity in atrial arrhythmogenesis through the abnormal distribution of fibrotic tissue, modulations of electrical coupling, paracrine interactions, and biomechanical–electrical interactions. *ER α* : estrogen receptor- α , *eNOS*: endothelial nitric oxide synthase, *sGC*: soluble guanylyl cyclase, *ANP*: atrial natriuretic peptide, *Smad6*: SMA and MAD-related protein 6, *BMP-10*: bone morphogenetic protein-10, *HSP-70*: heat shock protein-70, *Mir*: micro RNA, *CGRP*: calcitonin gene-related peptide, *ATF3*: activating transcription factor 3.

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