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Review

LncRNA: Shedding light on mechanisms and opportunities in fibrosis and aging

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ABSTRACT

Fibrosis is universally observed in multiple aging-related diseases and progressions and is characterized by excess accumulation of the extracellular matrix. Fibrosis occurs in various human organs and eventually results in organ failure. Noncoding RNAs (ncRNAs) have emerged as essential regulators of cellular signaling and relevant human diseases. In particular, the enigmatic class of long noncoding RNAs (lncRNAs) is a kind of noncoding RNA that is longer than 200 nucleotides and does not possess protein coding ability. LncRNAs have been identified to exert both promotive and inhibitory effects on the multifaceted processes of fibrosis. A growing body of studies has revealed that lncRNAs are involved in fibrosis in various organs, including the liver, heart, lung, and kidney. As lncRNAs have been increasingly identified, they have become promising targets for antifibrosis therapies. This review systematically highlights the recent advances regarding the roles of lncRNAs in fibrosis and sheds light on the use of lncRNAs as a potential treatment for fibrosis.

1. Introduction

Aging is a complicated progression involving attenuated cellular function and weakened stress resistance (Detienne et al., 2018) and it has been generally recognized as the starting point for several chronic diseases, including neurodegenerative disorders (Lv et al., 2018), cardiovascular diseases (Favero et al., 2017), cancer (Jackaman et al., 2017; Li et al., 2018a), and metabolism disorders (Salminen et al., 2017). Of note, fibrosis, a pathological process characterized by aberrant inflammatory injury and excessive fibrous connective tissue production (Birbrair et al., 2014), is accepted as the primary cause for the functional deterioration of various human organs such as the liver (Lemmer et al., 2018), lungs (Espindola et al., 2018), heart (Li et al., 2018b; Valiente-Alandi et al., 2018), and kidneys (Nastase et al., 2017) during the aging period. Under normal conditions, mild or transient fibrosis is important for organic structural integrity and wound healing (Cao et al., 2017). Nevertheless, excessive or progressive fibrosis is a pathological state that results in tissue architecture destruction and even organ failure (Herrera et al., 2018). Fibrotic changes share common pathogenic processes, regardless of the difference in organs or tissues, where the aberrantly sustained production of cytokines and angiogenic factors disrupts tissue homeostasis, causing interstitial hyperplasia and excessive accumulation of the extracellular matrix (ECM) (Rockey et al., 2015). Although recent investigations have revealed numerous molecules underlying the pathogenesis of fibrosis, the repression of fibroblast activity by targeting these mechanisms may not always be desirable, and the treatment options for fibrosis remain limited.

For a long time, the focus of the gene regulatory network has been mainly on protein coding genes, whereas genomic analyses have determined that approximately 90% of the noncoding sequences of the human genome are transcribed into noncoding RNAs (ncRNAs), which play critical regulatory roles in multiple biological processes (Cech and Steitz, 2014). It is now recognized that ncRNAs are classified into two main subgroups: short ncRNAs (< 200 nucleotides) and long ncRNAs (lncRNAs) (> 200 nucleotides) (Kapranov et al., 2007). LncRNAs encompass the major proportion of the noncoding transcriptome and are receiving increasing interest. The position of lncRNA genes relative to

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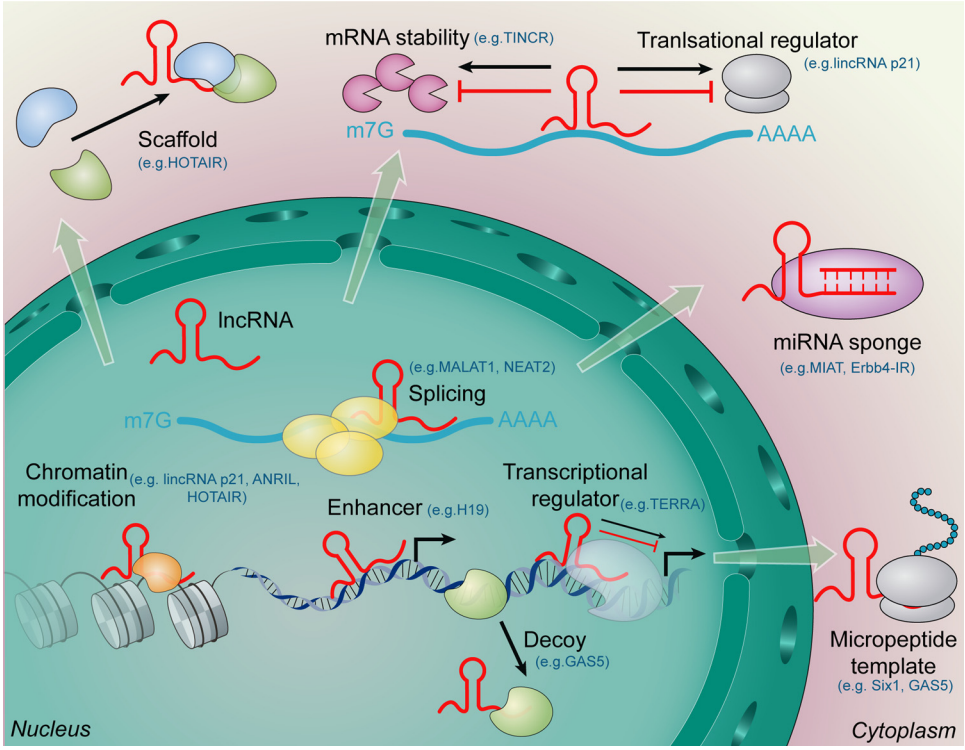

Fig. 1. General functions and mechanisms of lncRNAs. (1) In the nucleus, lncRNAs can guide chromatin modifiers and various transcriptional regulators to DNA in order to repress and/or activate gene expression. LncRNAs can function as enhancers of target gene activation. They can also act as molecular decoys to move proteins away from a specific DNA location. (2) In the cytoplasm, lncRNAs may act as scaffolds to bring two or more proteins into a complex. In addition, they act as sponges for other transcripts or proteins, serve as protein templates, or regulate mRNA degradation and translation.

their adjacent protein coding genes is often used as an elementary way to classify their transcripts into six major categories: sense lncRNAs, antisense lncRNAs, intronic lncRNAs, bidirectional lncRNAs, long intergenic noncoding RNAs (lincRNA), and enhancer RNAs. LncRNAs can be further distinguished by their abilities to act at genomic loci *in cis* or *in trans* (Kopp and Mendell, 2018; Mukherjee et al., 2017). LncRNAs exert their functions by directly binding to DNA, RNA, and proteins. These interactions can significantly classify lncRNAs as guides, enhancers, decoys, or scaffolds that participate in the posttranscriptional and posttranslational regulation of gene expression (Rinn and Chang, 2012) (Fig. 1). For instance, numerous lncRNAs have been demonstrated to mediate transcriptional inhibition by guiding chromatin modifiers, such as the polycomb repressor complex 2 (PRC2), to genomic targets (Kotake et al., 2011). In contrast, decoying lncRNAs have the capacity to impound regulatory factors in the cytoplasm or nucleus. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), for example, can trap splicing factors in nuclear speckles to control pre-mRNA alternative splicing (Tripathi et al., 2010), whereas cytoplasmic lncRNAs can bind to miRNAs to abolish their suppression of mRNA translation (Cesana et al., 2011). LncRNAs can also act as scaffolds that collect RNA binding proteins in spatial proximity to each other or that collect DNA (Puvvula et al., 2014). Moreover, lncRNAs can function as coactivators or enhancers of target gene activation (Redfern et al., 2013; Trimarchi et al., 2014). Several annotated lncRNAs encode short peptides, enhancing the complexity of lncRNAs. Often, a single lncRNA may have more than one function, which varies based on cell type, stimuli, and cellular localization. More recent investigations have demonstrated that lncRNAs serve as master mediators of a wide range of biological behaviors and diseases, such as aging (Neppl et al., 2017), cancer (Wang et al., 2018c), and neurological diseases (Briggs et al., 2015). The growing body of investigations suggests that lncRNAs also participate in the pathologic process of fibrosis, but the relationship between these processes remains unclear. Therefore, the emerging associations between lncRNAs and fibrosis or aging have opened up a new field of therapeutic and diagnostic opportunities.

The focus of the current review is to evaluate the latest research progress regarding the emerging roles of lncRNAs in fibrosis. First, we introduce the basic overview of the processes of fibrosis as well as the important regulatory roles of lncRNAs in different phases of fibrotic pathogenesis. Subsequently, we discuss the functions of lncRNAs in fibrosis in different organs and tissues, including the liver, lung, heart, and kidney. Furthermore, the relationship between lncRNAs and fibrosis in aging is evaluated. Finally, we discuss several features and challenges of lncRNAs in aging-related fibrosis and provide potential therapeutic strategies for targeting lncRNAs. Collectively, our aim is to compile a comprehensive repository of information related to lncRNAs in fibrosis, aid in the design of future experimental research, and present the therapeutic potential of lncRNAs in fibrosis.

2. Roles of lncRNAs during the fibrotic pathogenic process

Fibrosis is caused by deregulated wound healing in response to chronic tissue injury or chronic inflammation (Jiang et al., 2017). Fibrogenesis is now increasingly regarded as the result of a multistage process that occurs in various organs, and it incorporates three major complex pathophysiologic processes: (i) primary inflammatory responses induced by tissue damage; (ii) effector cell activation and myofibroblast differentiation mediated by increased cytokines; and (iii) consequently excessive ECM secretion followed by ECM remodeling (Rockey et al., 2015) (Fig. 2). Once initiated, fibrosis can escalate through these feed-forward amplification loops, which cause destruction to normal parenchymal and epithelial cells, eventually leading to end-stage organ failure. By analyzing existing studies, we found that lncRNAs have clear stimulatory effects on inflammatory injury, while they have different effects on fibrogenic effector cell activation and ECM production.

2.1. Roles of lncRNAs at the beginning of fibrosis

During the initial phase of fibrosis, impaired epithelial cells or parenchymal cells trigger a fibrotic response, subsequently leading to the recruitment and activation of immunocytes, which can secrete cytokines and facilitate fibrotic processes. Transforming growth factor-β (TGF-β) has been well recognized as a pro-fibrogenic cytokine in almost

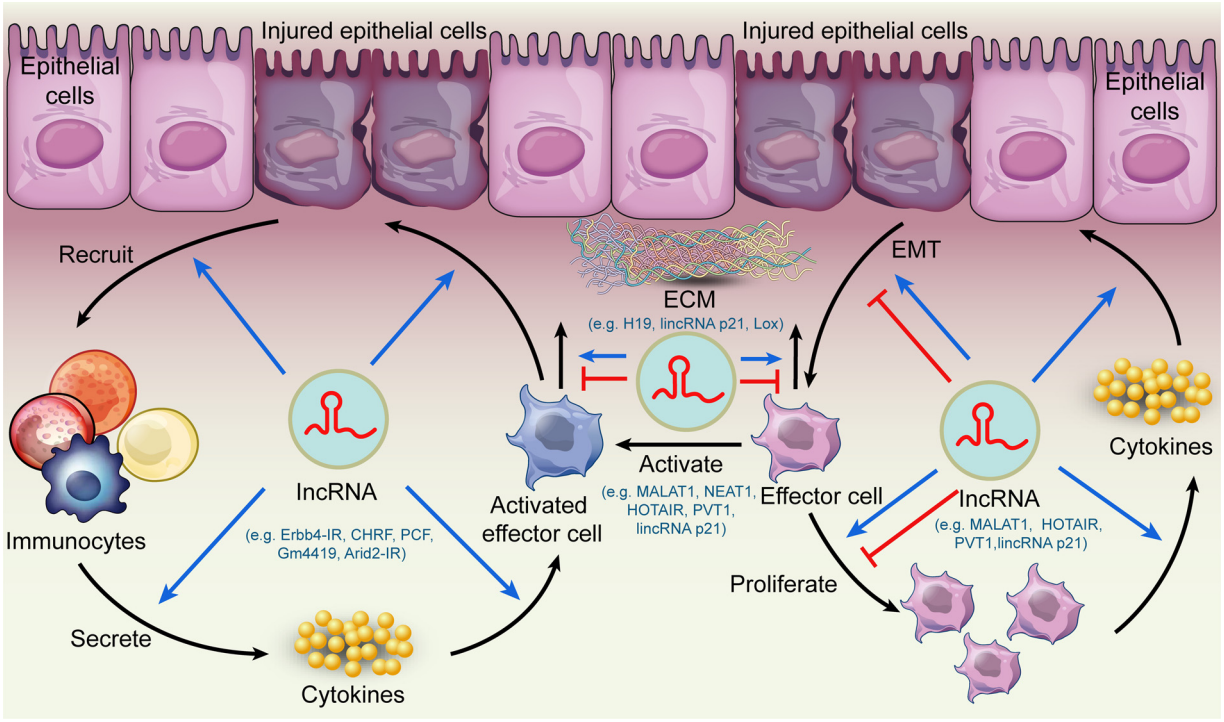

Fig. 2. Schematic representation of lncRNAs in fibrogenesis. The injured endothelial cells and parenchymal cells recruit immunocytes, which release cytokines such as TGF-β and NF-κB, thus triggering the fibrosis process. Effector cells (*e.g.*, HSCs, myofibroblasts and mesenchymal cells) also proliferate and transdifferentiate into activated effector cells, which may enhance ECM deposition and reversely destroy the normal nutrient supplement of epithelial cells. LncRNAs can exert clear promotive roles in the initial process of fibrosis. However, they may play diverse roles in the proliferation and activation of fibrogenic effector cells and the accumulation of the ECM.

all types of fibrosis (Meng et al., 2016). TGF-β/Smad3 signaling plays a crucial role in inflammation and fibrosis by interacting with multiple lncRNAs (Zhou et al., 2014). LncRNA Erbb4-IR is highly upregulated *via* a TGF-β1/Smad3-dependent mechanism in the fibrotic kidneys of unilateral ureteral obstructive (UUO) nephropathy mice, which represent a well-established renal fibrotic model (Feng et al., 2018). Erbb4-IR silencing inhibits the TGF-β1-induced expression of alpha-smooth muscle actin (α-SMA) and collagen I as well as effectively suppresses renal fibrosis in the kidneys of UUO nephropathy mice (Feng et al., 2018). In addition, TGF-β1/Smad3 signaling can also induce the upregulation of the lncRNAs TCONS_00088786 and TCONS_01496394 to promote renal fibrosis in the UUO nephropathy mouse model (Sun et al., 2017). Various lncRNAs have been identified to function as competing endogenous RNAs (ceRNAs) that compete for shared miRNAs and subsequently activate their target RNA transcripts, promoting the TGF-β1-mediated epithelial–mesenchymal transition (EMT) and exacerbating pulmonary fibrosis (Liu et al., 2017b). Among these various lncRNAs, the lncRNA PCF, which demonstrates increased expression *via* TGF-β1 activation, can promote the proliferation of activated epithelial cells by competitively binding to miR-344a-5p-targeted map3k11 and augmenting map3k11 expression in pulmonary fibrosis (Liu et al., 2017a). Moreover, lncRNA cardiac hypertrophy-related factor (CHRF) reverses the suppressive effect of miR-489 on Smad3 and myeloid differentiation primary response gene 88 (Myd88), an essential upstream regulator of IL-1β, and consequently provokes the inflammation and fibrotic signaling pathways in silica-induced pulmonary fibrosis (Wu et al., 2016). These findings reveal that the interaction between lncRNAs and the TGFβ1/Smad3 pathway provides a positive feedback loop to increase the TGFβ-induced inflammation response and fibrosis.

The nuclear factor kappa light-chain enhancer of activated B cells (NF-κB), a pivotal cytokine in inflammation pathways, has also been implicated in fibrosis by interacting with lncRNAs. Long intergenic noncoding RNA (LincRNA)-Gm4419 knockdown ameliorates NF-κB/NACHT, LRR and PYD domain-containing protein 3 (NLRP3) inflammasome-mediated inflammation as well as inhibits the expression of fibrosis biomarkers in diabetes-induced renal fibrosis (Yi et al., 2017). In the kidney of UUO nephropathy wild-type mice, knockdown of lncRNA Arid2-IR, whose expression is upregulated by TGFβ/Smad3 activation, in tubular epithelial cells can suppress the interleukin-1β (IL-1β)/NF-κB-dependent inflammatory response and decrease inflammatory cytokine expression (Zhou et al., 2015). Together, the obvious pro-inflammatory effects of lncRNAs through TGFβ- and NF-κB-mediated pathways provide a promotive mechanism for fibrogenesis in different organs.

2.2. Roles of lncRNAs in the proliferation and activation of fibrogenic effector cells

Under normal conditions, fibrogenic effector cells, including myofibroblasts, hepatic stellate cells (HSCs), and mesenchymal cells, are important for sustaining tissue homeostasis. However, the aberrant activation and excessive proliferation of these effector cells result in progressive fibrotic diseases (Gourdie et al., 2016). Much effort has been made to dissect the underlying mechanisms of both the activation and apoptosis of various fibrogenic effector cells by lncRNAs.

Upregulation of the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) accounts for the transdifferentiation of HSCs to an active form and the promotion of nonalcoholic steatohepatitis (NASH)-related fibrosis by increasing inflammatory chemokines such as C-X-C motif chemokine ligand 5 (CXCL5) (Leti et al., 2017). In addition, MALAT1 may increase myofibroblast markers and HSC activation by suppressing silent information regulator 1 (SIRT1) expression in liver fibrogenesis (Wu et al., 2015). Moreover, lncRNA Alu-mediated p21 transcriptional regulator (APTR) accelerates HSC activation and negatively regulates cell cycle inhibitor p21 expression, leading to increased HSC proliferation in mouse models of liver fibrosis (Yu et al.,

2015b).

Moreover, the mechanism of lncRNAs competitively binding to miRNAs is significantly involved in the activation of fibrogenic effector cells. LncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) increases HSC activation by competitively binding to miR-122; then, it facilitates the expression of Kruppel-like factor 6 (KLF6), a pro-fibrotic gene in liver fibrosis (Yu et al., 2017c). In CCl_4-induced liver fibrosis mouse models, the overexpression of lncRNA HOX transcript antisense RNA (HOTAIR) promotes the proliferation and activation of HSC LX-2 cells by acting as an endogenous sponge of miR-148b (Yu et al., 2017a). Similarly, lncRNA plasmacytoma variant translocation 1 (PVT1) demonstrates negative effects on miR-152 to enhance protein patched homolog 1 (PTCH1), a repressor of the Hh pathway, levels, which further promotes HSC proliferation (Zheng et al., 2016). Interestingly, recent studies identified the repressive effects of lncRNA on HSC activation. For example, enhanced levels of lincRNA-p21 reduced HSC proliferation and activation by upregulating p21 and phosphatase and tensin homolog deleted on chromosome ten (PTEN) (Yu et al., 2016; Zheng et al., 2015). However, if other lncRNAs exist that provide protection for inhibiting fibrogenesis, further investigations are required.

In addition, lnc-PCF could stimulate the proliferation of myofibroblasts derived from epithelial–mesenchymal transition by facilitating cell cycle progression (Liu et al., 2017a). Moreover, high expression of lncRNA H19 decreases dual-specificity phosphatase 5 (Dusp5) levels, the overexpression of which can inhibit the proliferation of cardiac fibroblasts (CFs) and can increase the proliferation of cardiac fibroblasts, whereas H19 silencing causes the opposite effects (Tao et al., 2016). Taken together, these results demonstrate that most known lncRNAs have the explicit ability to facilitate the activation and proliferation of these fibrogenic effector cells. Nevertheless, there also exist a minority of lncRNAs that regulate effector cells in opposite directions. Thus, further studies should focus on how to increase protective lncRNAs and decrease unfavorable lncRNAs so that effector cells can be transformed from activation toward apoptosis in fibrogenesis.

2.3. Roles of lncRNAs in the dynamic regulation of ECM

In general, ECM is the result of the accumulation of extracellular molecules that provide structural and biochemical support for the surrounding cells as well as segregate tissues from one another and regulate intercellular communication (Gaggar and Weathington, 2016). Excessive deposition of ECM, resulting from activated fibrogenic effector cells, proteoglycan, collagen, and adhesive glycoproteins, leads to significant progressive fibrotic alterations (Vogel, 2018).

As discussed above, the diverse effects of lncRNAs on fibrogenic effector cell activation may suggest their complicated roles in ECM production. Moreover, coexpression network analysis revealed that numerous lncRNAs in HSCs form networks with ECM proteins, including collagen, matrix metalloproteinases (MMP), and lysyl oxidase (Lox)-like protein, and that they contribute to ECM collection and liver fibrosis (Zhou et al., 2016a). For example, positively correlated coexpression of the lncRNAs NONRATT013819.2 and Lox, which cannot be detected in normal HSCs but in activated HSCs following CCl_4 injury, may promote the transformation and proliferation of HSCs and may significantly upregulate collagen levels, leading to ECM remodeling during hepatic fibrogenesis (Guo et al., 2017; Liu et al., 2016).

In summary, at the initial stage, these well-known lncRNAs have clear stimulatory effects on inflammatory responses. However, these different lncRNAs may exert either beneficial or detrimental effects on effector cell activation and ECM accumulation. Because the majority of lncRNAs have not been functionally characterized yet, further research and advanced biological techniques will be helpful for understanding the accurate functions of each specific lncRNA and even their interactions in fibrogenesis.

3. Roles of lncRNAs in hepatic fibrosis

Hepatic fibrosis is typically triggered by the injury of hepatocytes or biliary cells, followed by inflammatory responses that activate HSCs and facilitate ECM accumulation (Ramirez et al., 2017). HSCs are the master regulators in fibrotic pathogenesis and can be activated by multiple cellular signal-transduction pathways and cytokines (Marrone et al., 2018). Numerous factors have been identified to induce hepatic injury and subsequent fibrosis, including a high-fat diet, hepatitis viruses, toxicants and biliary obstruction. LncRNA changes have been implicated in primary hepatocyte injury and subsequent HSC activation during the development of fibrosis. Importantly, different lncRNAs may control fibrosis in opposite directions.

3.1. lncRNA as a promoter of hepatic fibrosis

As mentioned above, the lncRNA MALAT1 can expedite the fibrotic process by regulating SIRT1 and several inflammatory chemokines (Leti et al., 2017; Wu et al., 2015). In addition, MALAT1 can also decrease miR-101b levels and increase RAS-related C3 botulinum substrate 1 (Rac1) by directly binding to miR-101b, giving rise to augmented proliferation and activation of HSCs (Yu et al., 2015a). The lncRNA PVT1 demonstrates negative effects on miR-152/PTCH1 signaling, accounting for excessive HSC proliferation and collagen accumulation in CCl_4-induced fibrotic livers (Zheng et al., 2016). In addition, NEAT1 accelerates the development of liver fibrosis *via* the regulation of the miR-122-KLF6 axis (Yu et al., 2017c).

Additionally, lnc-LFAR1 knockdown represses HSC activation, attenuates TGFβ-induced hepatocyte apoptosis *in vitro* and attenuates both CCl_4- and bile duct ligation (BDL)-induced liver fibrosis by activating TGFβ1/Smad2/3 and Notch pathways in mice (Zhang et al., 2017b). Additionally, APTR silencing results in attenuated HSC activation and alleviated α-SMA and collagen collection *in vivo*, indicating the promoting role of APTR in liver fibrosis (Yu et al., 2015b).

Hepatitis C virus (HCV) infection in the liver has been identified to modulate the expression of lncRNAs. In HCV-infected cells, the lncRNA ATB shares the common miRNA-recognition element (MRE) of miR-425-5p with TGF-β type II receptor (TGF-βRII) and Smad2, which can increase the levels of TGF-βRII and Smad2, thus facilitating HSC activation and collagen I production (Fu et al., 2016). In addition, Fu et al. indicated that ATB can increase β-catenin expression by decreasing miR-200a and provoking the activation of LX-2 cells in liver tissues of patients with HCV-related hepatic fibrosis (Fu et al., 2017). Increased cyclooxygenase-2 (COX-2) levels have also been reported to be involved in the progression of liver cirrhosis (Jeong et al., 2010). Notably, COX-2 mRNA expression was significantly positively correlated with lncRNA COX-2 expression, both of which were increased in the progression of liver fibrosis in cirrhotic mice induced by CCl_4, suggesting the promoting role of the lncRNA COX-2 (Tang et al., 2017).

Moreover, DNA methylation has been implicated in liver fibrosis. The loss of HOTAIR obviously prevented CCl_4-induced HSC activation and fibrotic progression by epigenetically regulating and decreasing PTEN expression (Yu et al., 2017a). The high expression of HOTAIR in CCl_4 mice downregulates miR-29b and attenuates its control on DNA methyltransferase 3b (DNMT3b), leading to the restoration of DNMT3b and enhancement of PTEN methylation. Additionally, HOTAIR enhancement has also been revealed to regulate the DNMT1/MEG3/p53 epigenetic pathways through sponging miR-148b in TGF-β1-activated HSCs, leading to facilitated fibrotic development (Bian et al., 2017).

3.2. lncRNA as an inhibitor of hepatic fibrosis

In some cases, alterations of several lncRNAs can significantly provide protective mechanisms for fibrosis development. Downregulation of lincRNA-p21 can be observed in mouse models of CCl_4-induced liver fibrosis and the liver tissues of cirrhotic patients

(Zheng et al., 2015). However, overexpression of lincRNA-p21 in HSCs reduced α-SMA and Col1A1 levels and attenuated HSC proliferation *via* increased p21 (Zheng et al., 2015). The inhibitory effects of lincRNA-p21 can also be identified in patients with liver cirrhosis. In addition, lincRNA-p21 enhanced PTEN expression by competitively binding miR-181b, therefore inhibiting HSC activation (Yu et al., 2016). In addition, lincRNA-p21 was shown to suppress HSC activation and the Wnt/β-catenin pathway by binding to miR-17-5p, whereas the knockdown of lincRNA-p21 by small interfering RNA (siRNA) reversed these effects in Salvianolic acid B-treated cells (Yu et al., 2017b). In addition, lncRNA maternally expressed gene 3 (MEG3) overexpression has the capacity to reduce TGF-β1-induced cell proliferation and increase cell apoptosis by enhancing the levels of p53, the Bax/Bcl-2 ratio and cytoplasmic cytochrome c in LX-2 cells (He et al., 2014). In addition, HIF1A-AS1 also exerts suppressive effects on the proliferation of LX-2 cells (Zhang et al., 2014). Moreover, growth arrest-specific transcript 5 (GAS5) is significantly decreased in fibrosis models induced by CCl_4 and BDL and acts as a ceRNA for miR-222 in order to increase p27 levels, thereby repressing the activation and proliferation of HSCs (Yu et al., 2015c).

Interestingly, H19 may play a paradoxical role in liver fibrosis. In a BDL-induced fibrosis mouse model, H19 upregulated the expression of epithelial cell adhesion molecule (EpCAM) to promote cholestatic liver fibrosis by downregulating the expression of hepatic zinc finger E-box-binding homeobox 1 (Zeb1) (Song et al., 2017). In contrast, H19 expression was decreased in rat liver tissues in a CCl_4-induced liver fibrosis model and in TGF-β1-activated HSCs, with an increase in methyl-CpG-binding protein 2 (MeCP2), insulin-like growth factor 1 receptor (IGF1R), a-SMA and Col1A1. MeCP2 is recognized as a transcription repressor that can repress H19 levels in cultured HSCs (Yang et al., 2016b). Further, decreased H19 contributed to increased HSC proliferation by enhancing the expression levels of IGF1R, indicating the repressive effects of H19 in fibrogenesis (Yang et al., 2016b). Notably, recent studies have revealed that epigenetic events could regulate H19 in HSC activation. The increased expression of DNMT1 could be found in fibrotic rat liver tissue, where DNMT1 methylated H19 and attenuated HSCs activation through inhibiting H19-extracellular regulated protein kinases (ERK) signal pathway. Thus, inhibiting epigenetic alteration of H19 might be a novel target for suppressing liver fibrosis (Yang et al., 2018).

4. Roles of lncRNAs in cardiac fibrosis

The aging heart is characterized by a progressive increase in cardiac fibrosis (Gu et al., 2018; Lv et al., 2019; Wang et al., 2018b). Excessive ECM deposition leads to stiffening of the heart, which is found in nearly all forms of cardiac diseases (Travers et al., 2016).

4.1. lncRNA as a promoter of cardiac fibrosis

LncRNAs participate in regulating the expression of ECM genes and cardiac fibrosis during the development of ischemic cardiomyopathy (Huang et al., 2016). The upregulation of CHRF was observed in mice after angiotensin II treatment and transverse aortic constriction (TAC) surgery (Wang et al., 2014). CHRF decreases miR-489 levels, thus increasing Myd88 levels in order to trigger hypertrophic responses. Notably, the knockdown of CHRF elevated miR-489 and antagonized cardiac fibrosis, suggesting that CHRF may contribute to cardiac fibrosis by miR-489 (Wang et al., 2014). Interleukin 17 (IL-17) is confirmed to accelerate the pathogenesis of cardiac interstitial fibrosis. The level of lncRNA AK081284 was elevated in CFs treated with high levels of glucose or IL-17 (Zhang et al., 2018a). AK081284 overexpression in CFs enhanced the levels of TGFβ1 and collagen, and this result was reversed by the deletion of IL-17, suggesting the critical role of IL-17/AK081284 in facilitating cardiac fibrosis (Zhang et al., 2018a).

Elevated H19 has been significantly implicated in cardiac fibrogenesis. As discussed previously, H19 increased the proliferation of CFs by reducing Dusp5 expression (Tao et al., 2016). In addition, H19 deletion can increase the anti-fibrotic role of miR-455 and decrease miR-455 targeted connective tissue growth factor (CTGF) expression, leading to attenuated fibrosis-associated protein synthesis, such as collagen I and α-SMA (Huang et al., 2017). These results importantly demonstrate the mechanism of H19 in promoting cardiac fibrosis.

Wisp2 super-enhancer-associated RNA (Wisper), a CF-enriched lncRNA, is significantly associated with cardiac fibrosis both in murine myocardial infarction (MI) models and in heart tissues from human patients suffering from aortic stenosis (Micheletti et al., 2017). Wisper regulates the expression of several CF-related genes that are crucial for cell survival and ECM deposition. For example, Wisper overexpression attenuates the expression of the proapoptotic gene Dusp6 and caspase3 while enhancing the antiapoptotic gene Bcl2 to augment cell proliferation (Micheletti et al., 2017). The antisense oligonucleotide (ASO)-mediated silencing of Wisper *in vivo* repressed MI-induced fibrosis and cardiac dysfunction (Micheletti et al., 2017). Another CF-enriched lncRNA, maternally expressed gene 3 (MEG3), increases the production of MMP-2 in a p53-dependent manner in order to increase ECM remodeling, thus promoting fibrosis in a murine model after TAC (Piccoli et al., 2017). Moreover, myocardial infarction-associated transcript (MIAT) is confirmed as a pro-fibrotic lncRNA in cardiac fibrosis. In a mouse model of MI, increased MIAT was accompanied by attenuated miR-24 and elevated Furin and TGF-β1 levels, giving rise to cardiac interstitial fibrosis (Qu et al., 2017).

4.2. lncRNA as an inhibitor of cardiac fibrosis

LncRNA GAS5 is reported to exert inhibitory effects in cardiac fibrosis. Downregulation of GAS5 can be observed in cardiac fibrosis tissues treated with isoproterenol (ISO) and in TGF-β1-treated CFs (Tao et al., 2017). GAS5 overexpression suppresses CF proliferation and reduces TGF-β1-induced α-SMA and Col1A1 levels in CFs by inhibiting miR-21 expression in order to decrease MMP-2 levels, leading to repressed fibrosis (Tao et al., 2017). Moreover, Mhrt acts as a cardioprotective lncRNA in the pathogenesis of cardiac fibrosis. It was reported that the development of fibrosis was virtually inhibited 6 weeks after TAC in Mhrt transgenic mice (Han et al., 2014).

5. Roles of lncRNAs in renal fibrosis

Renal fibrosis, characterized by the aberrant accumulation of ECM in the renal interstitium, is a deteriorative process in multiple end-stage renal diseases (Duffield, 2014).

5.1. lncRNA as a promoter of renal fibrosis

Altered lncRNA expression could contribute to renal fibrosis *via* Smad3-dependent mechanisms in the UUO nephropathy kidney and in kidneys with glomerulonephritis (Zhou et al., 2014). Arid2-IR was upregulated by TGFβ/Smad3 signaling, and then it enhanced NF-κB-induced inflammation in the UUO kidney (Zhou et al., 2015). In addition, in the fibrotic kidney of the UUO nephropathy mouse model, Erbb4-IR overexpression induced by activated TGF-β/Smad3 signaling expedited fibrosis development (Feng et al., 2018). Additionally, increased lncRNA TCONS_00088786 and miR-132 have been revealed in UUO nephropathy kidneys and have been shown to activate NRK52E cells. LncRNA TCONS_00088786 silencing attenuates miR-132 as well as collagen I and III, resulting in an inhibited fibrotic response in the UUO nephropathy kidney (Zhou et al., 2018). Furthermore, in UUO nephropathy-induced renal fibrosis and TGF-β2-mediated proximal tubular epithelial (HK-2) cell fibrosis, the knockdown of H19 by short hairpin RNA (shRNA) importantly repressed renal fibrosis (Xie et al., 2016). Fibronectin, an adhesive glycoprotein and a major ECM constituent, plays a critical role in fibrogenesis (Muro et al., 2008). H19 sponges miR-17 to increase the expression levels of fibronectin in renal

interstitium fibrosis (Xie et al., 2016). In addition, lncRNA HCHD4P4 overexpression suppresses HK-2 cell proliferation and accelerates EMT in kidney injury and fibrosis caused by calcium oxalate crystallization and deposition (Zhang et al., 2017a).

Diabetic nephropathy (DN) is an important cause of the incidence of end-stage renal disease, and it exacerbates fibrotic changes in lesioned renal tissues. Reactive oxygen species (ROS)-induced mesangial matrix expansion and an incrassated glomerular basement membrane are major features of DN. ASncmtRNA-2 is upregulated by ROS and facilitates glomerular fibrosis in DN by enhancing the expression levels of pro-fibrotic factors, including TGFβ1 and fibronectin (Gao et al., 2017a). Moreover, Sun et al. (2018) found that Erbb4-IR silencing protected the kidney against the development of DN, including progressive renal fibrosis, in db/db mouse models. Erbb4-IR promotes renal fibrosis in DN by repressing miR-29b expression. Furthermore, lincRNA Gm4419 is upregulated in mesangial cells (MCs) under high glucose conditions (Yi et al., 2017). Enhanced Gm4419 increases the production of proinflammatory cytokines and fibrosis biomarkers as well as promotes cell proliferation in MCs, and this result can be ameliorated by Gm4419 knockdown (Yi et al., 2017).

5.2. lncRNA as an inhibitor of renal fibrosis

Recent studies have revealed the protective mechanisms of several lncRNAs in renal fibrosis. Downregulation of CYP4B1-PS1-001 was found during early DN both *in vitro* and *in vivo*, whereas CYP4B1-PS1-001 overexpression significantly suppressed the proliferation and fibrosis of mesangial cells (Wang et al., 2016a). This study provides a protective mechanism of CYP4B1-PS1-001 underlying renal fibrosis. Besides, overexpression of lncRNA ENSMUST00000147869 can protect MCs from aberrant proliferation and fibrosis in the kidneys of db/db and db/m mice (Wang et al., 2016b). In addition, TGF-β/Smad3-interacting lncRNA (lnc-TSI) inhibited the phosphorylation of TGF-β-induced Smad3 and attenuated fibrosis in the kidneys of UUO mice. Moreover, lnc-TSI upregulation was also observed in a cohort of 58 patients with immunoglobulin A nephropathy, which correlated negatively with renal fibrosis process (Wang et al., 2018a).

6. Roles of lncRNAs in pulmonary fibrosis

Pulmonary fibrosis is recognized as a serious interstitial lung disease in which extreme fibroblast proliferation and ECM accumulation occur in the lesioned lung tissues. The pathogenesis of pulmonary fibrosis can be attributed to various factors and diseases, including exposure to CCl_4, silica or bleomycin; idiopathic pulmonary fibrosis (IPF); and acute respiratory distress syndrome (ARDS) (Sundarakrishnan et al., 2017).

Cao et al. first demonstrated that the expression of numerous lncRNAs was significantly altered in fibrotic lung tissue induced by bleomycin (Cao et al., 2013). Among these lncRNAs, lncRNAs AJ005396 and S69206 were observed to be upregulated in the cytoplasm of interstitial lung cells, indicating that these two lncRNAs might be significantly involved in lung fibrogenesis (Cao et al., 2013). In some cases, lncRNAs have been recognized as ceRNAs for regulating other RNA transcripts in lung fibrogenesis. For example, in a bleomycin-treated mouse model, the two significantly increased lncRNAs, namely, MRAK088388 and MRAK081523, were identified to have high sequence similarity to two increased protein-coding genes, N4bp2 and Plxna4, which have the ability to promote lung myofibroblast growth and angiogenesis (Song et al., 2014). The miRNA-target prediction revealed that MRAK088388 and N4bp2 possess the same MRE for miR-29, while MRAK081523 and Plxna4 have the same MRE for let-7 (Song et al., 2014). MRAK088388 and MRAK081523 sponge miR-29 and let-7, leading to a decrease in the expression levels of miR-29 and let-7 and an increase in N4bp2 and Plxna4 levels, which contribute to enhanced myofibroblast growth and collagen deposition in lung interstitial tissues (Song et al., 2014). Furthermore, overexpression of lnc-PCF can promote the proliferation of TGF-β1-activated epithelial cells and then accelerate pulmonary fibrogenesis in a bleomycin-induced animal model competitively targeting miR-344a-5p in order to regulate map3k11, which is a positive regulator of cell proliferation (Liu et al., 2017a). Moreover, H19 significantly decreases miR-29b expression by directly binding to the 3' UTR, and then it promotes the fibroblast proliferation and EMT of alveolar epithelial cells in a bleomycin-induced mouse model of idiopathic pulmonary fibrosis (Tang et al., 2016).

Additionally, in a mouse model of paraquat-induced pulmonary fibrosis, overexpression of lncRNA uc.77 and 05Rik was demonstrated to facilitate EMT by increasing mesenchymal markers, including vimentin and α-SMA, and reducing epithelial markers, such as E-cadherin (Sun et al., 2016). Zinc finger E-box-binding homeobox 2 (Zeb2) is well known for its critical promotive role in EMT, and the homeobox protein Hox-A3 (Hoxa3) has been identified to coordinate alterations in epithelial cell gene expression (Das et al., 2009; Mace et al., 2005). Upregulated uc.77 increased Zeb2 expression, while the overexpression of 05Rik inhibited Hoxa3 expression in paraquat-induced pulmonary fibrosis, suggesting that increased uc.77 and 05Rik contribute to pulmonary fibrosis by promoting EMT *via* the regulation of Zeb2 and Hoxa3 (Sun et al., 2016).

In addition, obviously increased lncRNA cardiac hypertrophy-related factor (CHRF) can abolish the inhibitory effect of miR-489 on its target genes, MyD88 and Smad3, and can subsequently facilitate inflammation and fibrotic processes in a mouse model of silica-induced pulmonary fibrosis (Wu et al., 2016). In addition, lncRNA MALAT1 can directly bind to miR-503, leading to downregulated miR-503 levels and thus triggering the activation of the PI3K/Akt/mTOR/Snail pathway in order to promote the EMT process in a silica-induced mouse model of pulmonary fibrosis(Yan et al., 2017). Additionally, silica-stimulated macrophages secreted TGF-β1 to increase lncRNA ATB in epithelial cells, thus promoting EMT by directly binding with miR-200c and activating Zeb1 as well as leading to the development of pulmonary fibrosis (Liu et al., 2018).

Of note, IPF is a type of chronic and progressive interstitial pneumonia of an undetermined cause featured by aberrant fibrotic pathological changes (Evans et al., 2016). The decreased levels of lncRNA CD99 molecule pseudogene 1 (CD99P1) and n341773 were identified in IPF (Huang et al., 2015). Interestingly, the knockdown of CD99P1 reduced the levels of α-SMA in lung fibroblasts and inhibited fibroblast proliferation, whereas silencing lncRNA n341773 enhanced collagen expression in lung fibroblasts. LncRNA n341773 was demonstrated to function as a ceRNA of miR-199 in lung fibroblasts (Huang et al., 2015). Therefore, CD99P1 and n341773 may regulate lung fibrosis in opposite directions, in which CD99P1 acts as a promoter, and n341773 acts as a suppressor. However, the mechanism underlying the decrease in both CD99P1 and n341773 levels in the fibrotic lung still requires further investigation. More importantly, aging is an essential risk factor for IPF. LncRNA telomeric repeat-containing RNA (TERRA) expression levels were augmented in the peripheral blood mononuclear cells of IPF patients. In the epithelial injury model of IPF, silencing of TERRA by RNA interference (RNAi) could significantly improve the structure and functions of telomeres and mitochondria in order to hinder aging-related IPF pathogenesis (Gao et al., 2017b). LncRNA-ITPF, a novel upregulated lncRNA in IPF model, has been revealed to promote pulmonary fibrosis by targeting heterogeneous nuclear ribonucleoprotein L (hnRNP-L) depending on regulating H3 and H4 histone acetylation in its host gene integrin b-like 1 (ITGBL1) promoter (Song et al., 2019).

Moreover, upregulated lincRNA-p21 could lead to pulmonary fibrosis in a mouse model of ARDS *via* epigenetic inhibition of the expression of thymocyte differentiation antigen-1 (Thy-1), a glycosylphosphatidylinositol-linked cell surface glycoprotein that is proposed as a "fibrosis suppressor" (Hagood et al., 2005; Zhou et al., 2016b). LincRNA-p21 overexpression increases the lipopolysaccharide (LPS)-induced fibroblast proliferation and collagen accumulation in a model

of ARDS (Zhou et al., 2016b).

7. Roles of lncRNAs in other organs/tissues

As discussed above, lncRNAs participate in fibrotic processes in the liver, lung, heart, and kidney, and they appear to play important roles in other organs/tissues. Similar to HSCs, pancreatic stellate cells (PSCs) can be activated and can transform into myofibroblasts under fibrogenic stimuli, ultimately leading to pancreatic fibrosis (Apte et al., 2012). Further exploration indicated that lncRNA syntaxin-12 (STX12) functions as a miRNA sponge to decrease miR-148a levels, consequently relieving Smad5 to increase the secretion of a-SMA and accelerate the transformation of PSCs into myofibroblasts (Wang et al., 2017). Oral submucous fibrosis (OSF) is characterized by the gradual deposition of dense fibrous connective tissue (Phatak, 1993). Downregulation of lncRNA GAS5-AS1 was found in fibrotic buccal mucosal fibroblasts (fBMFs) and OSF tissues (Lin et al., 2017). The ectopic expression of GAS5-AS1 significantly reduced the abilities of collagen gel contraction and migration in fBMFs. GAS5-AS1 inhibited myofibroblast activities by decreasing the expression of p-Smad and α-SMA (Lin et al., 2017). Moreover, differentially expressed lncRNAs have been identified in a mouse model of peritoneal dialysis fluid-induced peritoneal fibrosis (Liu et al., 2015) and cystic fibrosis (McKiernan et al., 2014). Nevertheless, further investigations may provide a clear understanding of whether these lncRNAs exert beneficial and unfavorable effects in peritoneal and cystic fibrosis.

8. Relationship between lncRNAs and fibrosis in aging

A growing body of studies has revealed that lncRNAs are involved in aging. To date, transcription analysis has revealed the roles of lncRNAs in various aging organs such as brain, skin, muscle, and vessels (Table 3). For example, in the brain cortex, the expression of lnc-RBE and lnc-RSAS showed a significant decrease in old rats compared to adult rats, which is significantly correlated with neuronal degradation (Kour and Rath, 2015, 2017). Yo and Runger (2018) have found that lncRNA FLJ46906 was upregulated consistently with aging in skin fibroblasts, which led to the activation of NF-κB and AP-1 and further promoted skin aging. Of note, lncRNA H19 is also implicated in skeletal muscle development from birth to old age. It encodes miR-675-3p and miR-675-5p and downregulates the anti-differentiation Smad transcription factors (Dey et al., 2014). Another muscle-specific RNA, muscle anabolic regulator 1 (MAR1), could also bind with miR-487b as a decoy to limit its impact on the repression of Wnt5a protein and thereby promote muscle differentiation and regeneration during muscle aging (Zhang et al., 2018b). Moreover, lncRNA antisense non-coding RNA in the INK4 locus (ANRIL) could promote cell viability and inhibit the senescence of vascular smooth muscle cells (VSMCs) possibly by regulating miR-181a/SIRT1. ANRIL could also alleviate cell cycle arrest by inhibiting p53/p21 pathway in vascular aging development (Tan et al., 2019). In addition, White et al. (2015) reported a series of networks in the aging liver mediated by differentially expressed lncRNAs (MEG3, RIAN, and MIRG), which leads to various pro-aging processes, including proliferative homeostasis, inflammation, and metabolism. Interestingly, the networks correlate lncRNAs with certain genes, such as p53 and NF-κB, which have been related to mammalian aging and aging-related inflammation (Chien et al., 2011; Hewitt et al., 2012).

Notably, lncRNAs have been implicated in the regulation of telomeres, the shortening of which is correlated with the etiology of degenerative diseases, including IPF and cryptogenic liver cirrhosis (Armanios, 2013). As previously discussed, knockdown of lncRNA TERRA by siRNA can improve telomerase reverse transcriptase (TERT) expression, leading to elongated telomeres and delayed aging (Gao et al., 2017b). Moreover, essential senescence-regulatory genes, such as p53, were activated in IPF, and RNAi on TERRA could reverse this condition and ameliorate aging-related IPF (Gao et al., 2017b). Moreover, lncRNA AP003419.16 was found to be increased in patients with IPF compared with that in healthy controls (Hao et al., 2017). AP003419.16 expression may be utilized to predict a high risk of aging-associated IPF. In addition, we have previously reviewed the beneficial effects of forkhead box proteins O (FoxO) on aging-related fibrosis (Jiang et al., 2018a,b; Xin et al., 2018), and recent studies have revealed lncRNAs to be crucial negative regulators of the expression of several aging-related pathways, especially FoxO signaling, in *Drosophila melanogaster* models during dietary restriction, suggesting the important role of lncRNA in aging and aging-related fibrosis (Yang et al., 2016a).

9. Conclusion and future perspectives

Fibrotic pathogenesis is characterized by fibrotic replacement in functional parenchymal organ tissues, which significantly causes aging-related organic deterioration. Over the past two decades, lncRNAs have become a popular research topic of aging and human diseases. This review is devoted to describing the important effects of lncRNAs during the diverse processes of fibrogenesis. Various lncRNAs function as either promoter or suppressors in the fibrosis of different organs, which is summarized in Tables 1 and 2, respectively. However, the same lncRNA may as well take on this paradoxical phenomenon in the same tissue. For example, H19 has been revealed to be involved in pneumonic, hepatic, renal and cardiac fibrosis with different mechanisms, indicating that H19 probably serves as a common therapeutic target for fibrosis. Interestingly, H19 may exert both inhibitory and promotive effects for liver fibrosis, because several lncRNAs may be protective during the early phases of the fibrotic process before fibroblasts face unmanageable activation and proliferation. Additionally, several studies used very aggressive models of organ fibrosis (*e.g.*, overexpression of highly toxic proteins in cellular models). Obviously, lncRNA will trigger excessive inflammation in such a cellular context. Therefore, the selection for fibrotic models still require unified standards. Furthermore, as the mysteries of increasing numbers of lncRNAs continue to be unraveled, several aspects of lncRNA biology underlying aging and fibrosis make lncRNAs highly attractive as therapeutic targets.

Organic injury causes inflammation, which is to some extent necessary for proper and precise wound healing. Chronic inflammation promotes the development of fibrosis by inducing fibroblast differentiation. However, the activation of fibroblasts induced by moderate inflammation is also essential for proper wound healing (Haertel et al., 2014; Xin et al., 2018). As previously described, well-known lncRNAs exert clearly stimulative effects on inflammation by increasing fibroblast proliferation and differentiation in fibrogenesis. In addition, an increasing number of lncRNAs such as ATB have been implicated in promoting wound healing, whereas the relationship of lncRNAs in this process remains largely unexplored (Zhu et al., 2016). Herein, the application of inhibiting these lncRNAs might be the potential disruption of wound healing through modulation of fibroblast activation. The balance between inhibiting fibrotic process and maintaining wound healing should be more attractive for future investigations. Therefore, we propose that further approaches targeting lncRNA should take full advantage of their pro-fibrosis effect and avoid their potential influence on wound healing.

Circulating lncRNAs show useful characteristics that may help them serve as important biomarkers for cancer (Lin and Yang, 2018), kidney injury (Lorenzen and Thum, 2016), and heart failure (Uchida and Dimmeler, 2015). Thus far, it has been reported that lncRNAs packed in plasma exosomes regulate the inflammatory response (Gezer et al., 2014). Therefore, it is possible to monitor endogenous lncRNAs involved in fibrosis in noninvasive ways. It will be appealing to find out whether plasma lncRNAs regulate organ fibrosis with aging and whether the combination of well-known biomarkers with novel lncRNAs will be more helpful in predicting fibrogenesis in human organs. In addition, the investigations regarding the tissue specific lncRNAs may

Table 1
Overview of different lncRNAs as promoters in diverse organ/tissue fibrosis.

LncRNA categories	Organ/ tissue	Models	Downstream targets	Effects	Reference
MALAT1	Liver	CCl_4-induced mouse liver fibrosis model BDL-induced mouse liver fibrosis model Activated HSCs	MALAT1-SIRT1 MALAT1-miR-101b-Rac1	MALAT1 expedites the fibrotic process, increases proliferation, and activates primary HSC through SIRT1-induced inflammation.	Leti et al. (2017), Wu et al. (2015) Yu et al. (2015a)
PVT1	Liver	CCl_4-induced mouse liver fibrosis model	PVT1-miR-152-PTCH1	PVT1 aggravates HSC proliferation and collagen accumulation.	Zheng et al. (2016)
NEAT1	Liver	CCl_4-induced mouse liver fibrosis model Activated HSCs	NEAT1-miR-122-KLF6	NEAT1 promotes HSC activation.	Yu et al. 2017c
LFAR1	Liver	CCl_4-induced mouse liver fibrosis model BDL-induced mouse liver fibrosis model	LFAR1-TGFβ1/Smad2/3 LFAR1-Notch	lnc-LFAR1 knockdown represses HSCs activation and attenuates TGFβ-induced hepatocytes apoptosis.	Zhang et al. (2017b)
APTR	Liver	Fibrotic liver samples Activated HSCs	APTR-p21	APTR silencing attenuates HSC activation and alleviates the collection of α-SMA and collagen.	Yang et al. (2015)
ATB	Liver	Fibrotic liver tissues Activated LX-2 cells	ATB-miR-200a-β-catenin ATB-miR-425-5p-TGF-βRII/Smad2	ATB provokes the activation of LX-2 cells in liver tissues from patients with HCV-related hepatic fibrosis. ATB facilitates HSCs activation and collagen I production.	Fu et al. (2016) Fu et al. (2017)
HOTAIR	Liver	Human fibrotic tissues and cirrhotic tissues CCl_4-induced mouse liver fibrosis model Activated HSCs	HOTAIR-miR-29b-DNMT3b-PTEN HOTAIR-miR-148b-NMT1/MEG3/p53	Loss of HOTAIR prevents HSCs activation and fibrotic progression.	Yu et al. (2017a) Bian et al. (2017)
COX-2	Liver	CCl_4-induced cirrhotic mouse model	LncRNA COX-2	COX-2 promotes the progression of liver fibrosis.	Tang et al. (2017)
H19	Liver	BDL-induced mouse liver fibrosis model	H19-EpCAM-Zeb1	H19 promotes cholestatic liver fibrosis.	Song et al. (2017)
CHRF	Heart	Ang II-treated myocytes TAC mouse model Human heart failure sample	CHRF-miR-489-Myd88	CHRF triggers hypertrophic responses and cardiac fibrosis.	Wang et al. (2014)
AK081284	Heart	High glucose or IL-17-treated CFs	AK081284-TGFβ1	AK081284 facilitates cardiac fibrosis.	Zhang et al. (2018)
H19	Heart	Cardiac fibroblast Fibrotic heart tissues	H19-DUSP5 H19-miR-455-CTGF	H19 promotes the synthesis of fibrosis-associated protein such as collagen I and α-SMA.	Huang et al. (2017)
Wisp2	Heart	MI murine models Heart tissues from aortic stenosis patients	Wispe-Dusp6	Wisp2 augments cell proliferation and promotes MI-induced fibrosis and cardiac dysfunction.	Micheletti et al. (2017)
MEG3	Heart	Murine model after TAC	MEG3-MMP-2	MEG3 aggravates ECM remodeling.	Piccoli et al. (2017)
MIAT	Heart	MI mouse model	MIAT-miR-24-Furin	MIAT facilitates cardiac fibrosis.	Qu et al. (2017)
Arid2-IR	Kidney	UUO kidney of WT mice	TGFβ/Smad3-Arid2-IR-NF-κB	Arid2-IR-enhances inflammation.	Zhou et al. (2015)
Erbb4-IR	Kidney	UUO mouse model Diabetic kidneys of db/db mice	Erbb4-IR-miR-29b	Erbb4-IR expedites fibrosis development.	Feng et al. (2018) Sun et al. (2018)
TCONS_00088786	Kidney	UUO mouse model Activated NRK52E cells	TCONS_00088786-miR-132	TCONS_00088786 increases fibrotic response.	Zhou et al. (2018)
H19	Kidney	TGF-β2-treated HK-2 cell UUO mouse model	H19-miR-17-fibronectin	H19 decreases adhesive glycoprotein.	Xie et al. (2016)
HCHD4P4	Kidney	Calcium oxalate-induced kidney damage mouse model	–	HCHD4P4 suppresses HK-2 cell proliferation and accelerates EMT.	Zhang et al. (2017a)
ASncmtRNA-2	Kidney	Diabetic kidneys of db/db mice High glucose-treated mesangial cells	ROS-ASncmtRNA-2-TGFβ1	ASncmtRNA-2 facilitates glomerular fibrosis in DN.	Gao et al. (2017a)

(*continued on next page*)

Table 1 (*continued*)

LncRNA categories	Organ/ tissue	Models	Downstream targets	Effects	Reference
Gm4419	Kidney	High glucose-treated MCs	Gm4419-NF-κB/NLRP3	Gm4419 increases the production of proinflammatory cytokines and fibrosis biomarkers and promotes the proliferation of MCs.	Yi et al. (2017)
AJ005396 S69206	Lung	Bleomycin-induced fibrotic lung tissue	–	Both AJ005396 and S69206 increase lung fibrosis.	Cao et al. (2013)
MRAK088388 MRAK081523	Lung	Bleomycin-treated mouse lung fibrosis model	MRAK088388-miR-29b-3p-N4bp2 MRAK081523-let7-Plxna4	Both enhance myofibroblast growth and collagen deposition in lung interstitial tissues.	Song et al. (2014)
Lnc-PCF	Lung	Bleomycin-treated mouse lung fibrosis model	miR-344a-5p-map3k11	miR-344a-5p promotes the proliferation of TGF-β1-activated epithelial cells and then accelerates pulmonary fibrogenesis.	Liu et al. (2017a)
H19	Lung	Bleomycin-treated mouse lung fibrosis model	H19-miR-29b	H19 promotes fibroblast proliferation and the EMT of alveolar epithelial cells.	Tang et al. (2016)
uc.77 05Rik	Lung	Paraquat-induced mouse lung fibrosis model	uc.77-Zeb2-EMT 05Rik-Hoxa3-EMT	uc.77 and 05Rik facilitate EMT by increasing mesenchymal markers.	Sun et al. (2016)
CHRF	Lung	Silica-induced mouse lung fibrosis model	CHRF-miR-489-MyD88/Smad3	CHRF facilitates inflammation and fibrotic process.	Wu et al. (2016)
MALAT1	Lung	Silica-induced mouse lung fibrosis model	MALAT1-miR-503-PI3K/Akt/ mTOR/Snail	MALAT1 promotes EMT process.	Yan et al. (2017)
ITPF	Lung	Bleomycin-treated mouse lung fibrosis model	ITPF-ITGBL1-hnRNP-L	ITPF facilitates inflammation and fibrotic process.	Song et al. (2019)
ATB	Lung	Silica-induced mouse lung fibrosis model	ATB-miR-200c-Zeb1-EMT	ATB promotes EMT.	Liu et al. (2018)
CD99P1	Lung	Lung tissues of IPF patients LL29 cells from IPF patient.	–	CD99P1 increases the levels of α-SMA in lung fibroblasts and promotes fibroblast proliferation.	Huang et al. (2015)
TERRA	Lung	Human pulmonary fibrosis sample Epithelial injury model of IPF	TERRA-TERT	TERRA augments mononuclear cells in the peripheral blood of IPF patients and destroys the structure and function of telomeres and mitochondria to promote aging-related IPF pathogenesis.	Gao et al. (2017b)
lincRNA-p21	Lung	ARDS mouse model	lincRNA-p21-Thy-1-LPS	LincRNA-p21 increases the LPS-induced fibroblast proliferation and collagen accumulation	Hagood et al. (2005) and Zhou et al. (2016b)

BDL, bile duct ligation; SIRT1, silent information regulator 1; HSC, hepatic stellate cell; PTCH1, protein patched homolog 1; KLF6, Kruppel-like factor 6; PTEN, phosphatase and tensin homolog deleted on chromosome ten; COX-2, cyclooxygenase-2; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; LPS, lipopolysaccharide.

Table 2
Summary of the lncRNAs involved in inhibiting organ fibrosis.

LncRNA categories	Organ/tissue	Models	Downstream targets	Effects	Reference
lincRNA p21	Liver	CCl_4-induced mouse liver fibrosis model Liver tissues of cirrhotic patients TGF-β1-treated LX-2 cells Sal B-treated HSCs	lincRNA p21-p21-α-SMA/Col1A1 lincRNA-p21-miR-181b-PTEN lincRNA-p21-miR-17-5p-Wnt/β-Catenin	lincRNA p21 reduces HSC proliferation and activation.	Zheng et al. (2015) Yu et al. (2016) Yu et al. (2017b)
MEG3	Liver	CCl4-induced mouse liver fibrosis model Human liver fibrotic tissues TGF-β1-treated LX-2 cells	MEG3-TGF-β1 MEG3-p53	MEG3 reduces TGF-β1-induced cell proliferation and increases cell apoptosis.	He et al. (2014)
HIF1A-AS1	Liver	TET3 siRNA-treated LX-2 cells	HIF1A-AS1-TET3	HIF1A-AS1 suppresses HSC proliferation and activation.	Zhang et al. (2014)
GAS5	Liver	CCl_4-induced mouse liver fibrosis model BDL-induced mouse liver fibrosis model Human fibrotic liver samples Activated primary HSCs	GAS5-miR-222-p27	GAS5 represses the activation and proliferation of HSCs.	Yu et al. (2015b)
H19	Liver	TGF-β1-treated HSCs Rat model of CCl_4-induced liver fibrosis	H19-IGF1R DNMT1-H19-ERK	Decreased H19 contributes to increased HSC proliferation.	Liang et al. (2016) Yang et al. (2018)
GAS5	Heart	ISO-treated cardiac fibrosis tissues TGF-β1-treated CFs	GAS5-miR-21-PTEN/MMP-2 GAS5-TGF-β1-α-SMA	GAS5 suppresses CF proliferation and reduces TGF-β1-induced α-SMA and Col1A1 levels.	Tao et al. (2017)
Mhrt	Heart	Pressure-overloaded hearts by transaortic constriction	Mhrt-Brg1	Mhrt prevents chromatin remodeling.	Han et al. (2014)
CYP4B1-PS1-001	Kidney	Early diabetic nephropathy *in vitro* and *in vivo*	–	CYP4B1-PS1-001 overexpression suppresses proliferation and fibrosis of mesangial cells.	Wang et al. (2016a)
ENSMUST00000147869	Kidney	Kidney of db/db and db/m mice	–	ENSMUST00000147869 protects MCs from aberrant proliferation and fibrosis.	Wang et al. (2016b)
TSI	Kidney	UUO kidneys of WT mice Human immunoglobulin A nephropathy samples	TSI-TGF-β-Smad	TSI attenuates renal fibrosis.	Wang et al. (2018a)
n341773	Lung	Lung tissues of IPF patients LL29 cells from the lungs adult IPF patient.	n341773-miR-199	n341773 decreases collagen expression in lung fibroblasts.	Huang et al. (2015)

HSC, hepatic stellate cell; BDL, bile duct ligation; CF, cardiac fibroblast; IPF, idiopathic pulmonary fibrosis; MC, mesangial cell.

Table 3
A list of different lncRNAs involved in organ aging.

LncRNA categories	Organ/tissue	Models	Alteration of expression	Effect during aging	Reference
Lnc-RBE Lnc-RSAS	Brain	Rat brain (immature with 4 weeks, adult with 16 weeks and old with 70 weeks)	Significantly increased from immature to adult and a decrease from adult to old age	Associated with the specific neuro-anatomical regions, cell types and sub-cellular compartments of the rat brain in an age-related manner Regulating neuron growth and development-specific transcriptional factors	Kour and Rath (2015, 2017)
MALAT1	Brain	Human individuals aged 21–81	Significantly increased during aging	Involved in neuronal function and proliferation	Tajiri et al. (2014)
NEAT1	Brain	Human neuronal degradation samples	Significantly increased during aging	Implicated in paraspeckle formation and alternative splicing in Huntington's disease	Johnson (2012)
lncRNA FLJ46906	Skin	Primary adult human dermal fibroblasts from abdominal skin of donors aged 18–70 Fibroblasts from neonatal foreskin irradiated with longwave ultraviolet light	Significantly increased during aging	Directly binding to NF-κB and AP-1 in the aging process.	Yo and Runger (2018)
H19	Muscle	Human satellite cells H19-deficient myoblast cells	Decreased rapidly on days 1 and 3 during the phase of muscle degeneration, and then increased through days 5–7 during muscle regeneration	Encoding miR-675-3p and miR-675-5p to downregulate the anti-differentiation Smad transcription factors	Dey et al. (2014)
MAR1	Muscle	C57BL/6J mice (2,6,12 and 24-month-old) C2C12 mouse myoblast cell line	Highly expressed in mice skeletal muscle	Binding to miR-487b as a decoy to limit its impact on the repression of Wnt5a protein and thereby promoting muscle differentiation and regeneration	Zhang et al. (2018)
ANRIL	Vascular	VSMCs isolated from the thoracic aorta of Sprague-Dawley rats	Significantly downregulated during aging	Promoting cell viability and inhibiting senescence of VSMCs possibly by regulating miR-181a/SIRT1, and alleviating cell cycle arrest by inhibiting p53/p21 pathway	Tan et al. (2019)
H19	Vascular	Endothelium of aged mice	Significantly downregulated during aging	Loss of H19 led to an upregulation of p16 and p21, reduced proliferation and increased senescence.	Hofmann et al. (2019)
lncRNA-ES3	Vascular	Human aorta VSMCs induced by high glucose	Significantly increased during aging	Inhibiting miR-34c-5p expression by direct interaction and its knockdown suppressed the calcification/senescence of HA-VSMCs.	Lin et al. (2019)

NF-κB, nuclear factor kappa light-chain enhancer of activated B cells; VSMC, vascular smooth muscle cell.

be more attractive for their application as biomarkers for aging-related fibrosis.

The biological relevance of lncRNAs has attracted major interest in the therapeutic applications of lncRNA-modifying drugs in fibrosis. However, due to the special expression pattern of lncRNAs, their mediation *in vivo* is challenging (Djebali et al., 2012). First, one major limitation of lncRNA therapeutics is that lncRNA is located in the nucleus and may therefore be less available to target. Second, another challenge of studying lncRNAs is their poor sequence conservation, which makes it difficult for translational research and medicine investigations, in particular, the identification of human homology of the therapeutic potential lncRNAs obtained from preclinical animal models. Notably, the development of novel experimental and bioinformatic technologies such as RNA antisense purification (RAP) and chromatin isolation by RNA purification (ChiRP) will help explore mechanistic details in lncRNA biology. These novel techniques can be used to predict the structure of lncRNAs and evaluate the discrepancy between animal lncRNAs and their human homology. In addition, because of the functional complexity of lncRNAs in regulating gene expression, including genomic imprinting, chromatin remodeling, miRNA control, and protein organization, there is more difficulty in evaluating the effects of therapeutic modulation of lncRNA by pinpointing an accurate regulatory process mediated by lncRNAs. Therefore, novel strategies for overcoming these challenges in lncRNA investigations, particularly the transformation of the effects and outcomes from experimental models into patients regarding aging and fibrogenesis, would be highly appreciated.

To date, both antisense oligonucleotides (ASO) and siRNAs have been promising tools to bind and cleave target lncRNAs *in vivo* (Matsui and Corey, 2017). The feasibility of lncRNA targeting was identified by Micheletti et al., revealing that Wisper depletion by the injection of modified ASO, namely, GapmeRs, albeit at 5 mg/kg, 2 days after MI injury in adult mice, provided a therapeutic benefit for preventing cardiac fibrosis (Micheletti et al., 2017). However, there are two major limitations to the application of ASO in regulating lncRNAs: ineffective tissue-targeted delivery and lack of minimum off-target effects in other uninvolved organs. Therefore, improvements of therapeutic tools to target lncRNAs in tissue-specific manners will no doubt be helpful for the development of future lncRNA-based therapies for aging and fibrosis.

Furthermore, the majority of available evidence linking lncRNAs and fibrosis is *in vitro* data. However, the lack of effective methods to conduct loss- or gain-of-function assays is still the primary hurdle for *in vivo* studies. To date, multiple tools have been identified to suppress lncRNA expression *in vivo*, including traditional RNAi, knockout, and clustered regularly interspaced short palindromic repeat (CRISPR/Cas9) gene-editing tools, which also have similar limitations as ASO in studies. Moreover, the use of adenovirus or lentiviral overexpressing a lncRNA to study the function of a lncRNA in fibrosis may confront some of these problems. Random integration into the genome may disrupt important genes that participate in fibrogenesis. In addition, random integration may significantly alter the genomic position of lncRNAs, which may be essential for influencing adjacent genes. Fortunately, Bassett et al. (2014) provided a useful guide regarding considerations before performing *in vivo* investigations of lncRNA functions, whereas a detailed introduction is beyond the scope of this manuscript.

In conclusion, lncRNA studies of aging and fibrosis are still at very early stages, and much effort is still required to understand the molecular mechanisms underlying lncRNA, aging and fibrosis. To date, there is still a large discrepancy between the number of lncRNAs being discovered and the number of lncRNAs being functionally described in detail. If we are able to overcome some of the challenges associated with modulating these lncRNAs, the patients suffering from fibrosis might benefit tremendously.

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