



# Novel role of long non-coding RNAs in autoimmune cutaneous disease

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## Abstract

Systemic autoimmune rheumatic diseases (SARDs) are a heterogeneous group of chronic multisystem inflammatory disorders that are thought to have a complex pathophysiology, which is not yet fully understood. Recently, the role of non-coding RNAs, including long non-coding RNA (lncRNA), has been of particular interest in the pathogenesis of SARDs. We aimed to summarize the potential roles of lncRNA in SARDs affecting the skin including, systemic sclerosis (SSc), dermatomyositis (DM) and cutaneous lupus erythematosus (CLE). We conducted a narrative review summarizing original articles published until July 19, 2021, regarding lncRNA associated with SSc, DM, and CLE. Several lncRNAs were hypothesized to play an important role in disease pathogenesis of SSc, DM and CLE. In SSc, *Negative Regulator of IFN Response (NRIR)* was thought to modulate Interferon (IFN) response in monocytes, *anti-sense gene to X-inactivation specific transcript (TSIX)* to regulate increased collagen stability, *HOX transcript antisense RNA (HOTAIR)* to increase numbers of myofibroblasts, *OTUD6B-Anti-Sense RNA 1* to decrease fibroblast apoptosis, *ncRNA00201* to regulate pathways in SSc pathogenesis and carcinogenesis, *H19X* potentiating TGF- $\beta$ -driven extracellular matrix production, and finally *PSMB8-AS1* potentiates IFN response. In DM, *linc-DGCR6-1* expression was hypothesized to target the USP18 protein, a type 1 IFN-inducible protein that is considered a key regulator of IFN signaling. Additionally, AL136018.1 is suggested to regulate the expression Cathepsin G, which increases the permeability of vascular endothelial cells and the chemotaxis of inflammatory cells in peripheral blood and muscle tissue in DM. Lastly, *linc-MIPOL1-6* and *linc-DDX47-3* in discoid CLE were thought to be associated with the expression of chemokines, which are significant in Th1 mediated disease. In this review, we summarize the key lncRNAs that may drive pathogenesis of these connective tissue diseases and could potentially serve as therapeutic targets in the future.

**Keywords** lncRNA · Systemic sclerosis · Cutaneous lupus erythematosus · Dermatomyositis

## Background

Only 1.2% of RNA encodes messenger RNA (mRNA) that is further translated into proteins (Jarroux et al. 2017). Remaining RNA belongs to a class of non-coding RNA (ncRNA) and includes regulatory RNAs such as

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microRNAs (miRNAs), small interfering RNAs (siRNAs) and long (> 200 nucleotides) non-coding RNA (lncRNA) (Jarroux et al. 2017; Mariotti et al. 2019; Le et al. 2020; Zhang et al. 2019). There are ~ 30,000 lncRNAs detected in the human genome. They are further classified according to their location into intergenic, intronic, bidirectional, enhancer, sense, and antisense (AS) (Devaux et al. 2015). They exert important biologic effects including remodeling chromatin and regulating gene expression at transcriptional and post-transcriptional levels. Previous studies suggested that the transcription process of the lncRNA appears to regulate the corresponding coding DNA expression (Salviano-Silva et al. 2018). Antisense-lncRNAs (AS-lncRNAs) are transcribed from the opposite strand to protein-coding genes and overlap in one or several exons and introns with the sense strand. High-throughput RNA sequencing analysis showed that for most AS-lncRNAs, their expression was ~ tenfold lower than their corresponding coding genes (Derrien et al. 2012; Oszolak et al. 2010). Interestingly, the expression of AS-lncRNAs was found to be more tissue specific than those of protein coding genes. AS-lncRNAs can also regulate the expression of transcription sites on the same (*cis*) or other chromosomes (*trans*) (Kornienko et al. 2013).

To date, lncRNAs have been implicated in carcinogenesis and autoimmune disease pathways. Particularly, the function of lncRNAs in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have been well-documented (Gao et al. 2018; Chen et al. 2019; Wang et al. 2020). However, the role of lncRNA in Cutaneous Lupus Erythematosus (CLE) and other Systemic Autoimmune Rheumatic Diseases (SARDs) affecting the skin such as systemic sclerosis (SSc) and dermatomyositis (DM) remains poorly understood. In this manuscript, we comprehensively review published literature regarding the role of lncRNAs in the pathogenesis of SSc, DM, and CLE and present the key lncRNAs, discovered over the last 40 years, that are thought to be involved with the pathogenesis of these conditions (Nor Muhammad 2019; Jarroux et al. 2017).

## Methods

We searched PubMed, Medline and EMBASE up to July 19th, 2021 and included original studies. Review papers were excluded. Studies must have reported one or more lncRNA as was identified through their experiments. Studies on SLE were excluded given there are recent review papers summarizing the key roles of ncRNAs including lncRNA in disease pathogenesis (Cai et al. 2021; Tsai et al. 2020; Taheri et al. 2020).

## Systemic sclerosis

SSc is a rare, autoimmune disease resulting in fibrosis of the skin and multiple internal organs (Denton and Khanna 2017; Gabrielli et al. 2009), which leads to increased morbidity and mortality (Ouchene et al. 2020). Diagnosis is usually confirmed according to the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria (except one study which used Subcommittee for scleroderma criteria 1980 (Messe-maker et al. 2018)) and patients are classified into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (van den Hoogen et al. 2013; LeRoy et al. 1988). Subtypes include overlap SSc and SSc sine scleroderma (ssSc) (also known as non-cutaneous SSc) (Diab et al. 2014). Similar to other autoimmune diseases, SSc is thought to be environmentally triggered in individuals with genetic susceptibility (Kassamali et al. 2021). In this respect ncRNAs may be central to the pathogenesis of this disease since they often modulate this gene-environment interaction (Bergmann and Distler 2017; Aslani et al. 2018).

The SSc pathogenesis and signaling pathways have been described in detail elsewhere (Pattanaik et al. 2015; Katsunoto et al. 2011; Sierra-Sepúlveda et al. 2019; Boletto et al. 2018). Briefly, immune dysregulation, endothelial dysfunction, and subsequent fibrosis are the key features (Fig. 1). The initial damage to the small/medium vessel walls in the skin and internal organs triggers subsequent inflammation (Matucci-Cerinic et al. 2013). Interferon (IFN) signaling pathway has been initially described based on observations of patients receiving IFN- $\alpha$  injections leading to new onset and/or worsening of SSc-related features (Solans et al. 2004; Black et al. 1999). Increased expression of type I IFN-regulated genes, is a hallmark of SSc, which is present both in the fibrotic skin, peripheral blood cells (Eloranta et al. 2010; Tan et al. 2006), and in monocytes of SSc patients from the earliest phases of the disease, even prior to the evident skin fibrosis (Brkic et al. 2016). The role for adaptive immunity involving autoantibodies as well as Th2 and Th17 pathways has been demonstrated (Ihn et al. 1995; Badea et al. 2009) with the Th2 pathway gaining more importance in the late fibrotic stages (Saracino et al. 2017). IL-4 and IL-13 are thought to stimulate fibrosis through their ability to activate type 2 macrophages and fibroblasts and via upregulation of the critical profibrotic cytokines such as the transforming growth factor beta (TGF- $\beta$ ) (Saracino et al. 2017; Huang et al. 2015; Kawakami et al. 1998; Varga and Pasche 2009; Zehender et al. 2018) and platelet-derived growth factor (PDGF) (Iwayama and Olson 2013; Liakouli et al. 2018; Klareskog et al. 1990). While vasculopathy and immune dysregulation play a crucial role in SSc pathogenesis, fibroblasts, that are capable of excess matrix production and

deposition, are thought to be the effectors cells and hallmark of this disease. Once removed from affected tissues, SSc fibroblasts maintain their profibrotic phenotype in vitro, with elevated production of collagen and extracellular matrix proteins (ECM) (mainly type 1 collagen which consists of  $\alpha 1(I)$  and  $\alpha 2(I)$  collagen) and higher frequency of  $\alpha$ -smooth muscle actin (SMA) with subsequent differentiation into myofibroblasts (Garrett et al. 2017; Hinz et al. 2012; Kähäri et al. 1988). Activation of fibroblasts, differentiation into apoptosis resistant myofibroblasts, and subsequent sustained production of ECM components leading to tissue fibrosis is thought to occur through TGF- $\beta$  signaling (Pachera et al. 2020). Therefore, its deletion by genetic modification in animal models was found to decrease fibrosis and scar formation (Hoyles et al. 2011).

In total there were 11 studies (Table 1) which identified 14 important lncRNAs that were differentially expressed in SSc patients and had a plausible role in disease pathogenesis (Table 2). Since fibrosis, the last step in proposed SSc pathogenesis, clinically leads to complications and poor outcomes, the majority of studies focused on evaluating lncRNAs role in tissue fibrosis. This includes *Negative Regulator of IFN Response (NRIR)* modulating IFN response in monocytes, the *anti-sense gene to X-inactivation specific transcript (TSIX)* regulating increased collagen stability, *HOX transcript antisense RNA (HOTAIR)* leading to increased numbers of myofibroblasts, *OTUD6B-Anti-Sense RNA 1 (OTUD6B-AS1)* leading to decreased fibroblast apoptosis, *ncRNA00201* which regulates pathways of all three parts of SSc pathogenesis and is also involved in carcinogenesis, *H19X* potentiating TGF- $\beta$ -driven ECM production, and finally *PSMB8-AS1* is implicated in cell activation, response to viral and external stimuli, and pro-fibrotic cytokine production.

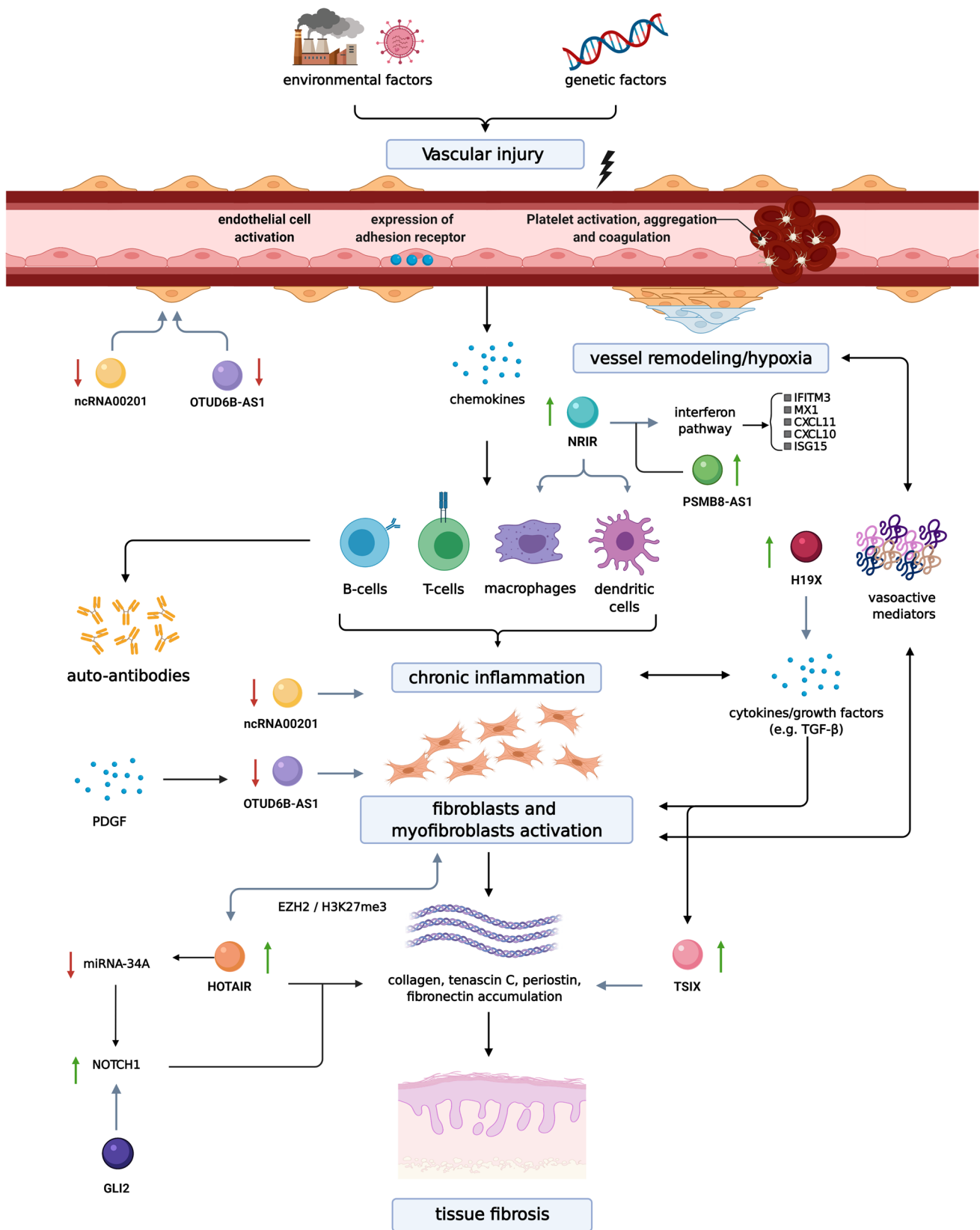
## NRIR

NRIR is currently thought to be an important regulator of IFN response, a mechanism implicated in SSc. Activation of type 1 IFN pathway, described above, may occur by the action of Toll-like receptor 4 (TLR4). Initially, TLR4 was thought to bind to lipopolysaccharides (LPS), but overtime, endogenous ligand binding has also been described such as the damage-associated molecular patterns (DAMPs), released upon cell damage or stress (Farrugia and Baron 2017; Bhattacharyya and Varga 2015). In SSc increased levels of DAMPs have been reported and their binding to TLR4 contributes to fibrosis (O'Reilly and van Laar 2018) through type 1 IFN pathway and downstream TGF- $\beta$  production (Bhattacharyya et al. 2013; Bhattacharyya and Varga

2015; Ciechomska et al. 2013; Lafyatis and Farina 2012; Ivashkiv and Donlin 2014).

The study by Mariotti et al. (2019) evaluated the role and function of lncRNAs in regulating the type 1 IFN pathway in peripheral blood monocytes. Their study revealed that *NRIR* was highly expressed and was implicated in biological processes related to immune response and the IFN/antiviral response. It also demonstrated that this IFN-dependent lncRNA was a positive regulator of the LPS-induced IFN response in human monocytes and suggested that abnormal expression of *NRIR* can be involved in the dysregulation of immune system seen in SSc. Monocytes from lcSSc and ssSSc patients showed *NRIR* overexpression which correlated with the IFN signature, thus, confirming the implication of *NRIR* in the IFN response. The highest levels of *NRIR* were consistently seen in ssSSc alongside the strongest IFN-signature (Brkic et al. 2016).

Upregulation of *NRIR* was seen in early SSc patients suggesting a potential role of *NRIR* in disease initiation and progression. *NRIR*-silencing reduced the LPS-induced expression of type 1 IFN target genes, such as *C-X-C motif chemokine ligand 10 (CXCL10)*, also known as *Interferon gamma-induced protein 10 (IP-10)*, *MX dynamin like GTPase 1 (MX1)*, *IFN Induced Transmembrane Protein 3 (IFITM3)*, *IFN Induced Protein 44 (IFI44)* and *Ubiquitin Like Modifier (ISG15)*. *CXCL10* and *CXCL11* are pro-inflammatory chemokines involved in multiple processes including chemotaxis, differentiation, and activation of peripheral immune cells, regulation of cell growth, apoptosis and modulation of angiogenesis. They were found to be upregulated and clinically are associated with more severe disease including lung and kidney involvement (Eloranta et al. 2010). These two chemokines have been proposed to act as biomarkers for identification of early and non-fibrotic subset of SSc (Cossu et al. 2017). Anifrolumab, an agent which inhibits IFN receptor signaling was found to lead to a reduction in *CXCL10* levels and in transcripts related to fibrosis (e.g., *CXCL10* and *CD40 Ligand (CD40LG)*) (Guo et al. 2015) and could be explored as a therapeutic target in the future. *IFI44* correlated with modified Rodnan skin score (Merkel et al. 2003) and *MX1* with ischemic skin ulcers and reduced forced vital capacity of the lungs, therefore predicting more severe disease. (Christmann et al. 2011; Mariotti et al. 2019). Thus, *NRIR* was found to control the expression of certain IFN stimulated genes, and overexpression of *NRIR* in SSc monocytes could explain the type 1 IFN signature in SSc. *NRIR* is thought to contribute to eventual development of fibrosis seen in SSc through regulation of the IFN pathway in monocytes (Fig. 1).



**Fig. 1** Pathogenesis of systemic sclerosis (SSc). The first step in the pathogenesis is thought to involve vascular injury leading to vessel remodeling and hypoxia on one hand and inflammation on the other. Chronic inflammation is important for subsequent activation of fibroblasts/myofibroblasts and tissue fibrosis, it also contributes to further vascular remodeling and hypoxia. The long non-coding RNAs (lncRNAs) at their proposed sites of action are shown. Upregulation of *Negative Regulator of IFN Response (NRIR)* modulates Interferon (IFN) response in monocytes, the overexpression of *anti-sense gene to X-inactivation specific transcript (TSIX)* regulates increased collagen stability, higher levels of *HOX transcript antisense RNA (HOTAIR)* leads to increased numbers of myofibroblasts, downregulation of *OTUD6B-Anti-Sense RNA 1 (OTUD6B-AS1)* leads to decreased fibroblast/endothelial smooth muscle cell apoptosis, decrease in *ncRNA00201* regulates pathways of all three parts of SSc pathogenesis and is also involved in carcinogenesis, *H19X* potentiating TGF- $\beta$ -driven extracellular matrix production, and finally *PSMB8-AS1* potentiating the IFN response. Created with Biorender.com

### TSIX

*TSIX* is the anti-sense gene to *XIST* (X-inactivation specific transcript, a key gene regulating X-chromosome inactivation in females) (Brooks and Renaudineau 2015) and may help explain the female predisposition in a number of autoimmune diseases. Both *TSIX* and *XIST* are expressed on the X-chromosome, which is marked for inactivation. There is a balance in their action, and overexpression of *TSIX* prevents increases in *XIST* expression and blocks inactivation of that X-chromosome. Numerous studies have shown that some genes on the inactive-X ( $X_c$ ) escape inactivation and become expressed. One study looking at mature naïve T and B cells, found dispersed patterns of *XIST/XIST* RNA, and they lacked the typical heterochromatic modifications of  $X_i$  (Wang, et al. 2016a, b). Of note, there was evidence of biallelic expression of immunity-related genes in SLE.

Increased expression of *TSIX* observed in SSc serum in vivo and in vitro fibroblasts from affected patients, which was thought to be due to intrinsic TGF- $\beta$  activation seen in disease pathogenesis (Wang, et al. 2016a, b). Increased *TSIX* expression correlated to mRNA expression of  $\alpha 1(I)$  and  $\alpha 2(I)$  collagen in dermal fibroblasts and was thought to have a direct regulatory effect on collagen production through regulating collagen mRNA stability (Wang, et al. 2016a, b). Increased collagen production may explain the fibrosis observed in SSc pathogenesis (Fig. 1). Elevated levels of *TSIX* in the serum of dcSSc patients appeared to correlate with the level of skin fibrosis, and hence were proposed as a novel disease biomarker (Wang, et al. 2016a, b). A trial of inhibition of *TSIX* in vivo led to subsequent decreased collagen production which could be a possible treatment target in SSc.

### HOTAIR

*HOTAIR* is an important factor in the epigenetic differentiation of skin and has previously been implicated in various cancers (Tang and Hann 2018). *HOTAIR* also appears to have a role in tissue fibrosis through priming of myofibroblasts (Wasson, et al. 2020a, b; Wasson, et al. 2020a, b). Myofibroblasts are defined by  $\alpha$ -SMA expression (Gilbane et al. 2013). In the study by Wasson et al. increased expression of *HOTAIR* was observed in SSc skin fibroblasts derived from cutaneous biopsies, and this overexpression resulted in myofibroblast activation through EZH2 activation and subsequent histone H3K27me3 methylation (Fig. 1) (Wasson, et al. 2020a, b). EZH2 is an enzymatic subunit of the polycomb repressor complex involved in silencing target genes. In fact, *HOTAIR* expression was sufficient to induce profibrotic activation of dermal fibroblasts in vitro. As a result of *HOTAIR* overexpression, there was reduced expression of miRNA-34 which leads to increased NOTCH signaling and increased downstream collagen, ECM secretion, and  $\alpha$ -SMA positive cells – all leading to the fibrosis phenotype. Importantly, the number of myofibroblasts was previously found in vivo to correlate with disease severity (Farina et al. 2009). Thus, when the fibroblasts were treated with a *HOTAIR* inhibitor, reductions in type 1 collagen and  $\alpha$ -SMA protein levels were noted. Therefore, it was hypothesized that a population of cells can be epigenetically ‘primed’ to differentiate into myofibroblasts. *HOTAIR* was identified as one such epigenetic factor. Interestingly, the expression of *HOTAIR* is higher in dermal fibroblasts in the hands and feet which may explain why those are typically the first areas of disease manifestation (Rinn et al. 2007; Wasson, et al. 2020a, b).

A subsequent study revealed that *HOTAIR*-resultant Notch pathway activation stimulated expression of the Hedgehog pathway transcription factor GLI2 (Wasson, et al. 2020a, b). This observation was further strengthened by inhibiting H3K27 methylation and Notch signaling which led to decreased expression of GLI2 in *HOTAIR* expressing fibroblasts and SSc fibroblasts. Additionally, the inhibition of GLI2 reduced the pro-fibrotic phenotype induced by *HOTAIR*. Thus, GLI2 expression is upregulated in SSc myofibroblasts through *HOTAIR* expression and GLI2 mediates the expression of pro-fibrotic markers downstream of Notch and may serve as a more specific therapeutic target in the future.

### H19X

H19 X-linked co-expressed lncRNA (*H19X*), also referred to as MIR503HG, is an intergenic lncRNA with its gene located on chromosome X. The study by Pachara et al. identified it as a direct potent mediator of prolonged myofibroblast



survival, potentiating TGF- $\beta$ -driven ECM production and progressive tissue fibrosis where upregulation of *H19X* was dose dependent across biologically relevant TGF- $\beta$  concentrations (Pachera et al. 2020). Other pro-fibrotic cytokines such as IL-1 $\beta$ , IL-4, IL-13, and IL-17a did not induce *H19X* expression. *H19X* was found to be upregulated in the skin of patients with SSc and lung tissues in patients with severe SSc related interstitial lung disease undergoing lung transplantation compared to controls. When tested in other fibrotic diseases including idiopathic pulmonary fibrosis, fibrotic ileum in Crohn's disease, liver tissue in primary sclerosing cholangitis, and dermal wounds compared to normal tissue, expression was also significantly elevated. Specifically, of all the cell types explored, fibroblasts of different origins and fibroblast-like cells showed the strongest induction of *H19X* by TGF- $\beta$ .

Functional experiments following *H19X* silencing revealed that *H19X* regulates *DDIT4L* gene expression, specifically interacting with a region upstream of the *DDIT4L* gene and changing the chromatin accessibility of a *DDIT4L* enhancer. *DDIT4L* is possibly implicated in mediating the profibrotic effects of TGF- $\beta$ -induced *H19X*. The resulting transcriptional repression of *DDIT4L* leads to increased collagen expression and fibrosis. Hence, *H19X* is an obligatory factor for TGF- $\beta$ -induced ECM synthesis, differentiation and survival of ECM-producing myofibroblasts. Silencing of *H19X* and therefore inducing apoptosis of myofibroblasts could be a therapeutic strategy which will allow selective removal of ECM-overproducing cells from fibrotic tissues (Lagares et al. 2017).

### OTUD6B-AS1

*OTUD6B-AS1* has a role in regulating apoptosis resistance in fibroblasts and vascular smooth muscle cells (Fig. 1) (Takata et al. 2019). Regulation of proliferation and apoptosis is thought to be mediated by a cell cycle regulator, cyclin D1, in a sense gene (*OTUD6B*) independent manner.

Significantly reduced expression of *OTUD6B-AS1* and its sense gene expression was observed in skin biopsies of SSc patients compared to healthy controls and non-affected skin biopsies in SSc individuals. This expression could be regulated by PDGF, as stimulation with PDGF in this study led to time-dependent down regulation of *OTUD6B-AS1* and *OTUD6B* in fibroblasts of healthy controls. *OTUD6B-AS1* did not appear to have an impact on expression of fibrotic genes such as type 1 collagen, fibronectin-1 (FN1), and  $\alpha$ -SMA. Inhibition of *OTUD6B-AS1*, using antisense oligonucleotide (ASO)-mediated transcripts, showed suppression of apoptosis in dermal fibroblasts and human pulmonary artery smooth muscle cells (HPASMC) (Takata et al. 2019). Although, inhibition of proliferation was observed, this was thought to be a compensatory mechanism and further larger

experiments are required to characterize this effect further. Expression of Cyclin D1 was significantly increased at both mRNA level and protein levels in both cell types which provides evidence for involvement of this lncRNA in proliferation and apoptosis. The study by Messemaker et al. also found this lncRNA to be dysregulated in patients with SSc, although no hypothesis as to function was presented (Messemaker et al. 2018).

Although most studies focus on expression in fibroblasts, the study by Takata et al. also studied HPASMC to further elucidate the pathogenesis of SSc in the lungs. Proliferation, and resistance to apoptosis of HPASMC in SSc is thought to be important in the development of microvascular lesions, which leads to proliferation of vascular smooth muscle cells and consequent vessel wall thickening and an occlusion of small arteries, which clinically translates to pulmonary arterial hypertension (Allanore et al. 2015; Distler et al. 2017). Thus, the regulation of Cyclin D1 by downregulation of *OTUD6B-AS1* is a possible novel mechanism to explain apoptosis resistance observed in SSc.

**ncRNA00201** The *ncRNA00201* was found to control many pathways related to the 3 steps of SSc pathogenesis (Fig. 1), as well as tumor development (Dolcino et al. 2019). This could serve as the link between SSc and increased rates of cancer observed in these patients. Transcriptional profiles of SSc patients compared to controls, including more than 50,000 lncRNAs, found only one lncRNA (*HNRNPU-AS1*, also referred to as *ncRNA00201*) to be significantly decreased (Dolcino et al. 2019). There were 56 known miRNA and 31 gene targets of *ncRNA00201* identified, many of which were involved in known SSc pathways. One of these is hnRNPC, which encodes a known autoantigen in SSc, the ribonucleoprotein complex (RNP) (Stanek et al. 1997). *lncRNA00201* was found to also be an important player in disease pathways of immune and inflammatory response, vasculitis, and fibrosis, which are seen in SSc as well as cancer proliferation (Sutaria et al. 2017; Dolcino et al. 2018). This provides insight into disease pathogenesis and opens avenues for the design of novel therapeutic strategies.

### PSMB8-AS1

Proteasome 20S Subunit Beta 8 Anti-Sense 1 (*PSMB8-AS1*) was identified as a top-ranking hub gene in co-expression modules implicated in cell activation and response to viral and external stimuli (Servaas et al. 2021). In the study by Servaas et al., transcriptomic data from two independent SSc patient cohorts revealed 886 lncRNAs with differential expression in monocytes. Then, the identified lncRNAs were associated with neighboring protein coding genes that are involved in regulating of IFN responses and apoptosis in monocytes. Further characterization of function of increased

**Table 1** Summary of the studies identified for SSc, DM and DLE

Study	Patient number	Patients additional characteristics	Controls type and number	Specimen source
<i>Mariotti et al NRIR</i> (Mariotti et al. 2019)	<i>Definite SSc cohort</i> ncSSc (7) lcSSc (11) dcSSc (7) <i>Non-fibrotic SSc cohort:</i> eaSSc (11) ncSSc (10) <i>SSc cohort 3:</i> eaSSc (15) ncSSc (27) lcSSc (23) dcSSc (19)	<i>Age (range); female %</i> <i>Definite SSc cohort</i> ncSSc 45 (26–63); 86% lcSSc 59 (45–70); 73% dcSSc 58 (34–72); 43% <i>Non-fibrotic SSc cohort</i> eaSSc 57 (40–77); 100% ncSSc 52 (25–70); 100% <i>SSc cohort 3</i> eaSSc 62 (25–81); 100% ncSSc 59 (29–80); 100% lcSSc 60 (41–80); 96% dcSSc 52 (27–80); 79%	All sex and age-matched <i>Definite SSc cohort</i> HCs (9) <i>Non-fibrotic SSc cohort</i> HCs (9) <i>SSc cohort 3</i> (21)	Blood
<i>Takata et al. OTUDB-ASI</i> (Takata et al. 2019)	dcSSc (4) lcSSc (5)	dcSSc average disease duration 5.34 years NA for lcSSc	HCs (14)	Skin biopsy dcSSc: 1/3 had fibrosis at biopsy site lcSSc: 0/5 had fibrosis at biopsy site
<i>Dolcino et al. ncRNA00201</i> (Dolcino et al. 2019)	dcSSc (10) lcSSc (10)	Mean age $\pm$ standard deviation; female/male number dcSSc: 55 $\pm$ 10; 9/1 lcSSc: 57 $\pm$ 13; 8/2 HCs: 55 $\pm$ 11; 17/3	Sex and age matched HCs (20)	Blood
<i>Wang et al TSIX</i> (Wang, et al. 2016a, b)	dcSSc (13) lcSSc (23)	Females/males number: 28/8 Mean age SSc: 60.9 years	Sex and age matched SLE (8) SSD (10) HCs (12)	Blood Skin biopsy of lesional skin
<i>Messemaker et al CTBP1-AS2, OTUD6B-ASI, AGAP2-ASI</i> (Messemaker et al. 2018)	dcSSc (10) lcSSc (4)	Mean disease duration of 1.5 years 43% received systemic drug (methotrexate $\pm$ prednisone)	Sex and age matched HCs (6)	Skin biopsy from proximal part of the lower arm, distal from the elbow. In 10 patients from affected area and 4 from unaffected area
<i>1) Wasson et al</i> <i>2) Wasson et al HOTAIR</i> (Wasson, et al. 2020a, b) (Wasson, et al. 2020a, b) (Pachera et al. 2020) <i>H19X</i>	(1) SSc (12) (2) SSc (3)  SSc: cohort 1: 5 cohort 2: 48 cohort 3: 14 cohort 4: 6 SSc – ILD: 11 patients (lung tissue in patients for lung transplant)	(1) Early onset SSc (2) Recent onset SSc (< 18 months from clinical skin induration)	(1) HCs fibroblasts (2) NA	1,2) Skin biopsy forearm of affected skin
(Servaas et al. 2021) <i>PSMB8-ASI</i>	<i>Definite Cohort</i> ncSSc (7) lcSSc (11) dcSSc (7)	Female/male number; mean age 6/1; 45 8/3; 59 3/4; 58	HC (9) Females (5) Males (4) Mean age: 52	Blood
<i>MGC12916</i>	SSc (15)	African American patients only included	HC (age-matched within 5 years) (15)	
(Abd-Elmawla et al. 2020) <i>ANCR</i> <i>TINCR</i> <i>HOTTIP</i> <i>SPRY4-IT1</i>	dcSSc (20) lcSSc (43)	Female/male number; age mean (range) SSc—47/16; 34.5 (20–60 years old) HC—24/11; 36.1 (19–55 years old)	Age and sex matched HC (35)	Blood

**Table 1** (continued)

Study	Patient number	Patients additional characteristics	Controls type and number	Specimen source
Peng et al. linc-DGCR6-1 (Peng et al. 2016)	DM (15)	Not reported	HCs (5)	Muscle biopsy
Liang et al. AL136018.1 (Liang et al. 2021)	DM (6)	Not reported	Paracancerous muscle tissue (3)	Muscle biopsy
Xuan et al. lnc-MIPOL1-6 lnc-DDX47-3 (Xuan et al. 2019)	DLE (3)	Not reported	None	Skin biopsy

The value in brackets indicated the number of patients. The treatment regimen the patients were using is described when reported

HC healthy controls, ncSSc non-cutaneous SSc defined as patients satisfying the classification criteria without skin fibrosis, eaSSc-early SSc defined as presence of Raynaud's and SSc autoantibodies and/or typical nailfold videocapillaroscopy abnormalities (LeRoy and Medsger 2001), SSD scleroderma spectrum disorder, lcSSc localized cutaneous SSc, dcSSc diffuse cutaneous SSc, SLE systemic lupus erythematosus, NA not available, ILD interstitial lung disease, DM dermatomyositis, DLE discoid lupus erythematosus

*PSMB8-AS1* expression in monocytes demonstrated that this lncRNA is involved in the secretion of IL-6 and TNF $\alpha$  both of which are important cytokines in SSc pathogenesis and associated with fibrosis (De Lauretis et al. 2013; Schmidt et al. 2009). Thus, *PSMB8-AS1* lncRNA is linked to monocyte dysregulation in SSc patients and may contribute to the pathogenesis.

### MGC12916

DNA methylation levels in dermal fibroblasts from African American patients with SSc revealed hypermethylation of Uncharacterized Protein MGC12916 (*MGC12916*) lncRNA which was associated with its downregulation (Baker Frost et al. 2021). In general, dermal fibroblasts from African American patients showed widespread reduced DNA methylation. Differential methylation was identified in 17 genes and 11 promoters, mostly in ncRNA genes and pseudogenes. Gene set enrichment analysis and gene ontology analyses showed enhancement of pathways related to IFN signaling and mesenchymal differentiation. This is the first report of this lncRNAs of differential gene methylation in African American patients.

### CTBP1-AS2, AGAP2-AS1

One study (Messemaker et al. 2018), evaluating 15,941 known annotated, lncRNAs found that 676 were dysregulated (122 decreased and 554 increased) in tissues of SSc patients compared to healthy controls. The top 3 deregulated anti-sense lncRNAs were *CTBP1-AS2*, *AGAP2-AS1*, and this study also identified *OTUD6B-AS1*. These were found to have a strong correlation with their paired sense genes. *CTBP1* and *CTBP1-AS2* levels had a positive correlation

across cell types studied, especially immune cells. Interestingly, *AGAP2* was only expressed in immune cells, while *AGAP2-AS1* was only expressed in dermal cell types, which in keeping with other studies that showed this discordance. Thus, several AS-lncRNAs were found to be differentially expressed in SSc and levels were found to be altered in a disease-specific manner. However, specific functions of these were not elucidated in this study.

### ANCR, TINCR, HOTTIP, SPRY4-IT1

The expression of these four lncRNAs, which have a role in skin biology, were explored in the plasma of SSc patients and correlated with presence of autoantibodies and subtype (Abd-Elmawla et al. 2020). Anti-differentiation ncRNA (*ANCR*) is a prototypical epidermal lncRNA which is expressed on undifferentiated keratinocytes and helps to maintain them in the basal layer (Kretz et al. 2012). Terminal differentiation-induced ncRNA (*TINCR*) is elevated in keratinocytes undergoing differentiation and contributes to regulation of gene expression involved with differentiation (Kretz et al. 2013). *SPRY4* intronic transcript 1 (*SPRY4-IT1*) which arises from the intron region of *Sprouty4* (*SPRY4*) gene, is found to be expressed in melanocytes, keratinocytes, and has been found to block apoptosis and promote viability and motility of melanoma cells (Khaitan et al. 2011). Finally, the *HOXA* transcript at the distal tip (*HOTTIP*) controls cellular growth, proliferation, and apoptosis (Wang et al. 2011).

Plasma levels of *TINCR*, *HOTTIP*, and *SPRY4-IT1* in SSc patients were found to be elevated and *ANCR*-downregulated compared to controls (Abd-Elmawla et al. 2020). *SPRY4-IT1* was found to be a strong diagnostic indicator and was higher in patients with dcSSc compared to lcSSc. Both *SPRY4-IT1* and *HOTTIP* correlated positively with the



**Table 2** Summary of important lncRNAs in systemic autoimmune diseases affecting the skin

lncRNA	Expression level	Tissue or cell type	Target mRNA	Role
<i>Systemic sclerosis</i>				
<i>TSIX</i> (Wang, et al. 2016a, b)	↑ in fibroblasts in vivo and in vitro ↑ in serum	Skin tissue	mRNA expression of α1(I) and α2(I) collagen	High <i>TSIX</i> levels led to significantly elevated mRNA expression of α1(I) and α2(I) collagen, playing a role in tissue fibrosis
<i>OTUD6B-AS1</i> (Wang et al. 2019; Takata et al. 2019)	↓ Skin ↓ Human Pulmonary Artery ↓ Smooth Muscle Cells	Skin tissue Human pulmonary artery smooth muscle cells	Cyclin D1	Regulates proliferation and apoptosis of fibroblasts and vascular endothelial smooth muscle cells via cyclin D1 expression in a sense gene independent manner
<i>NR1R</i> (Mariotti et al. 2019)	↑	Monoocytes	CXCL10, CXCL11, MX1, IFTTM3, ISG15	Drives IFN-Response in monocytes Correlates strongly with the IFN score of SSc patients
<i>AGAP2-AS1</i> (Messemaeker et al. 2018)	↑	Skin	Not directly assessed	Not evaluated in this study. Previously shown to be involved in cell migration and can repress transcription by interacting with histone methyltransferase (EZH2) and LSD1 in cancer cells. (Messemaeker et al. 2018)
<i>CTBPI-AS2</i> (Messemaeker et al. 2018)	↑	Skin	Not directly assessed	Not evaluated in this study
<i>ncRNA00201</i> (HNRNPU-AS1)(Dolcino et al. 2019)	↓	Monoocytes	hnRNP (Heterogeneous nuclear ribonucleoproteins C) 56 miRNAs 31 genes	Regulates genes involved in the vasculopathy, immune dysregulation, and fibrosis seen in SSc and genes in tumor-associated pathways
<i>HOTAIR</i> (Wasson, et al. 2020a, b; Wasson, et al. 2020a, b)	↑	Skin	Direct the EZH2 to induce H3K27me3 in specific target genes Repression of miRNA-34A	Associated with increase in collagen and α-SMA expression in vitro Represses miRNA-34a activating NOTCH signaling This leads to expression of Hedgehog pathway transcription factor GLI2 which mediates expression of pro-fibrotic markers downstream
<i>H19X</i> (Fachera et al. 2020)	↑	Skin Lungs	DDIT4L gene expression, changing chromatin accessibility of DDIT4L enhancer upstream	Upregulated in the skin and lungs of patients with SSc. H19X is an obligatory factor for TGF-β-induced synthesis of extracellular matrix and differentiation and survival of myofibroblasts
<i>PSMB8-AS1</i> (Servaas et al. 2021)	↑	Monoocytes	IL-6 TNF-α	May be implicated in cell activation and response to viral and external stimuli IL-6 and TNF-α may be implicated in disease pathogenesis and fibrosis
<i>MGC12916</i> (Baker Frost et al. 2021)	↑ methylation ↓ expression	Skin	Not specified	Not specified

Table 2 (continued)

lncRNA	Expression level	Tissue or cell type	Target mRNA	Role
<i>ANCR</i>	↓	Plasma	Not specified	Serve as possible biomarkers for SSC and help distinguish subtypes
<i>TINCR</i>	↑			
<i>HOTTIP</i>	↑			
<i>SPRY4-IT1</i> (Abd-Elmawla et al. 2020)	↑			
<i>Dermatomyositis</i>				
<i>linc-DGCR6-1</i> (Peng et al. 2016)	↑	Muscle tissue	USP18	USP18 is a known gene encoding type 1 IFN-inducible protein, which is considered to be a key regulator of interferon signaling
AL136018.1 (Liang and Peng 2021)	↑	Muscle tissue	Cathepsin G (CTSG)	CTSG is thought to play an important role in muscle inflammatory cells infiltration by increasing the permeability of vascular endothelial cells
<i>Discoid lupus erythematosus</i>				
<i>linc-MIPOL1-6</i> (Xuan et al. 2019)	↑	Skin tissue	<i>IL19</i> , <i>CXCL1</i> , <i>CXCL11</i> , and <i>TNFSF15</i>	<i>IL19</i> , <i>CXCL11</i> and <i>TNFSF15</i> , have each been shown to be associated with Th1 dominant diseases (Azuma et al. 2011), promote Th1 cell recruitment (Kumar and Herbert 2017) and stimulate Th1 cytokine production (Zhang and Li 2012; Zhang and Zhang 2015)
<i>linc-DDX47-3</i> (Xuan et al. 2019)	↓	Skin tissue	<i>IL19</i> , <i>CXCL1</i> , <i>CXCL11</i> , and <i>TNFSF15</i>	<i>IL19</i> , <i>CXCL11</i> and <i>TNFSF15</i> , have each been shown to be associated with Th1 dominant diseases (Azuma et al. 2011), promote Th1 cell recruitment (Kumar and Herbert 2017) and stimulate Th1 cytokine production (Zhang and Li 2012; Zhang and Zhang 2015)

modified Rodnan skin score depicting the degree of fibrosis, and the latter also with antinuclear antibody profile. Both *SPRY4-IT1* and *ANCR* were positively associated with pulmonary hypertension. Hence, plasma *SPRY4-IT1*, *HOTTIP*, *ANCR* and *TINCR* may represent novel candidate biomarkers for SSc, where *SPRY4-IT1* could also help with subtype determination.

## Dermatomyositis

DM is an autoimmune disease primarily affecting skeletal muscle and skin (Waldman, DeWane, and Lu 2020). Clinically, DM is characterized by symmetrical skeletal muscle weakness and cutaneous manifestations including, heliotrope rash, Gottron papules, and Gottron sign (Lundberg et al. 2017; Sharma et al. 2017). A subset of DM may present as cutaneous stigmata of solid organ malignancy (Qiang et al. 2017; Yang et al. 2015), whereas all forms may be associated with systemic complications including interstitial lung disease (ILD), oesophageal dysmotility and cardiac disease (Kurasawa et al. 2018; Chen et al. 2013). While genetic associations and environmental factors, including infections, ultraviolet radiation, vitamin D deficiency and drugs, have been linked to DM, the overall molecular mechanism of DM remains largely unknown (Thompson et al. 2018). However, similar to other SARDs, the role innate immunity, humoral and cellular immune responses are of importance (Dalakas 2015). Studies have shown that the characteristic muscle pathology of DM demonstrates capillary abnormalities and small, abnormal appearing muscle fibers bordering the perimysial connective tissue, a lesion called perifascicular atrophy (PFA) (Salajegheh et al. 2010). Microarray data have pointed towards a mechanism of tissue injury in DM associated with the overexpression of type 1 IFN-inducible genes (Salajegheh et al. 2010). Compared to normal muscle and other inflammatory myopathies, over 85% of the highest expressed transcripts in muscle from DM are from genes known to be induced by type 1 IFNs (Greenberg et al. 2005a, b).

## *linc-DGCR6-1*

The role of lncRNA in DM was first studied by Peng et al. (2016) (Fig. 2). Of the differentially expressed lncRNAs, lncRNAs *ENST00000428205.1* and *ENST00000450016.1* displayed the most significant increase and decrease, respectively. Based on the results of correlation analyses of the differentially expressed lncRNAs and mRNAs, 12 mRNA-lncRNA co-expression networks were identified. This suggests the possibility that these lncRNAs are regulators of corresponding mRNA expression. Although the function of the target mRNA has not yet been elucidated in 11

lncRNA-mRNA pairs, *linc-DGCR6-1* was thought to target the USP18 protein, a type 1 IFN-inducible protein. This is in keeping with findings by Salajegheh et al., which showed marked USP18 transcript elevation (68-fold increase) in skeletal muscle biopsies from patients with DM compared to control subjects (Salajegheh et al. 2010). It is thought that USP18 plays a critical role in the enzymatic pathway for IFN-stimulated gene 15 (ISG15) conjugation to a target protein. ISG15 is known as a type 1 IFN-inducible protein and is the single most overexpressed gene in DM muscle compared to both normal muscle and muscle from patients with other inflammatory myopathies (Salajegheh et al. 2010; Greenberg, et al. 2005a, b). Specifically, USP18 deconjugates ISG15 from target proteins, although the role of ISG15 in the mediation of myofiber injury in DM/ PM remains to elucidated (Basters et al. 2018; Salajegheh et al. 2010). Besides being an active enzyme, USP18 has also been found to negatively regulate type 1 IFN signalling independent of its protease activity (Malakhova et al. 2006; Basters et al. 2018). Although, USP18 is currently hypothesized to play a critical role in the enzymatic pathway for ISG15 conjugation to a target protein, more studies are necessary to further elucidate the role of USP18 in the mediation of myofiber injury in DM/ PM.

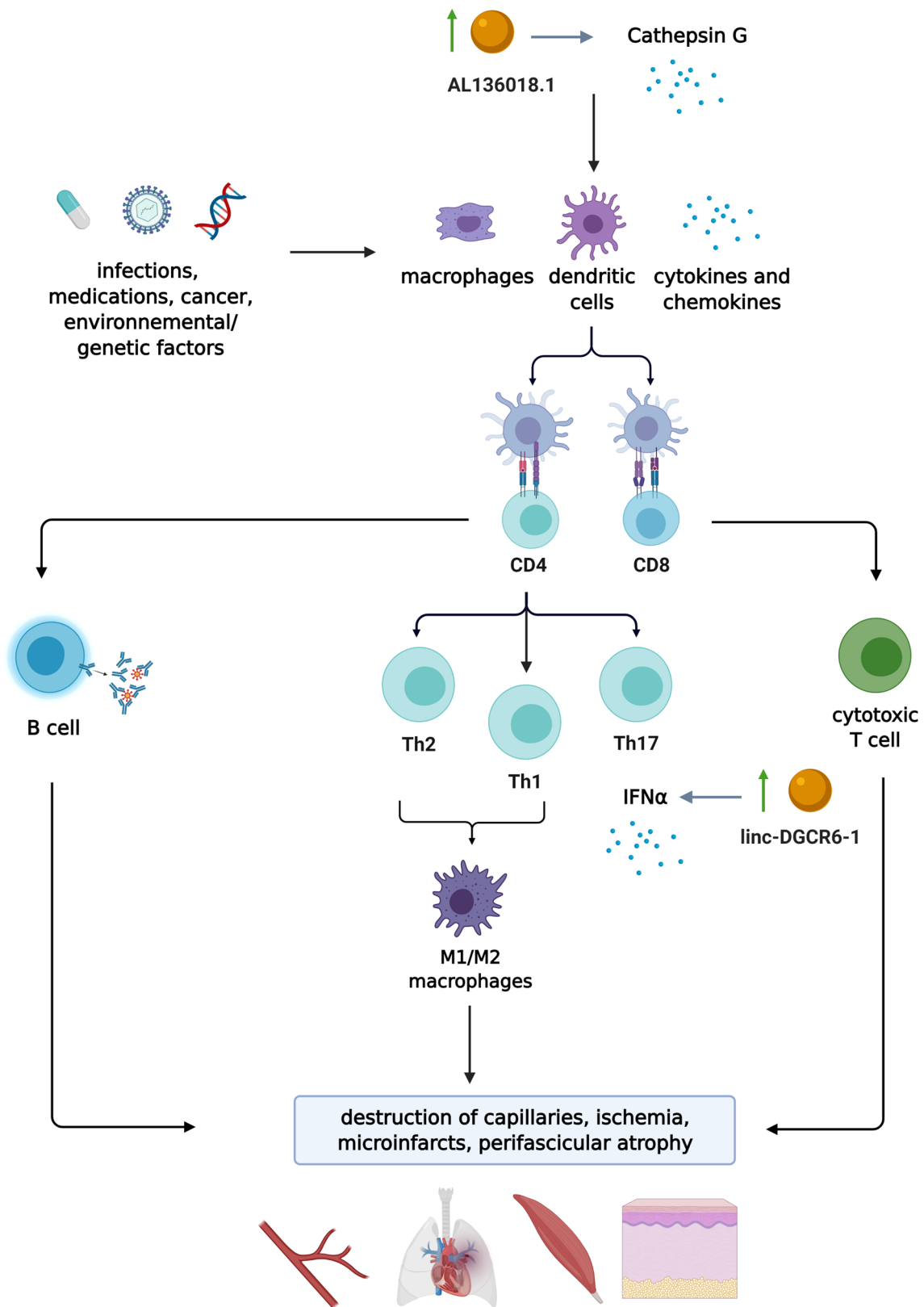
## AL136018.1

In a recent study by Liang and Peng (2021), the antisense lncRNA, *AL136018.1*, was discovered to be highly expressed in skeletal muscle tissues of patients with DM (Liang and Peng 2021). Interestingly, *AL136018.1* expression positively correlated with transcription level and DNA methylation of its contiguous *CTSG* gene, which encodes Cathepsin G. A member of the serine protease family, Cathepsin G plays an important role in increasing the permeability of vascular endothelial cells and the chemotaxis of inflammatory cells. Previous studies have demonstrated increased expression and activity of Cathepsin G in peripheral blood and muscle tissue in patients with DM (Gao et al. 2017). It is suggested that *CTSG* may play an important role in facilitating CD4+ T cell and B cell infiltration in perivascular and muscle tissue by increasing the permeability of vascular endothelial cells in DM (Gao et al. 2017).

Further studies investigating the function of *AL136018.1* transcripts may reveal their role in regulating *CTSG* expression and their overall importance in the pathogenesis of DM.

## Discoid CLE

CLE encompasses a wide range of dermatologic manifestations that may or may not be associated with the development of systemic disease (Okon and Werth 2013). In fact, the pathophysiology of CLE and SLE has been hypothesized



to be closely comparable where elevations in cytokine expression, such as IFN- $\alpha$ , have been identified in both

diseases (Lee and Sinha 2006). CLE is divided into three main subtypes: acute CLE (ACLE), subacute CLE (SCLE)

**Fig. 2** Pathogenesis of dermatomyositis (DM). While the pathogenesis of DM is poorly understood, it is believed to be triggered by an environmental factor, medication or cancer in a genetically susceptible host. Complex interplay of aberrant innate and adaptive immune response leads to downstream capillary damage/ischemia in end organs and characteristic muscle disease (i.e. perifascicular atrophy). While several lncRNAs have been found to be differentially expressed and several were co-expressed along with mRNA, *linc-DGCR6-1* and *AL136018.1* have a proposed role in DM's pathogenesis through targeting the USP18 protein involved in the type 1 IFN pathway, and regulating CTSG expression involved in increasing vasopermeability and chemotaxis of inflammatory cells, respectively. Created with Biorender.com

and chronic CLE (CCLE) (Okon and Werth 2013; Grönhaugen and Nyberg 2014). ACLE typically presents as a malar rash (Kuhn, Landmann, and Bonsmann 2016) while SCLE presents as with widespread, non-scarring, photosensitive erythematous annular or psoriasiform plaques (Walling and Sontheimer 2009). The most common form of CCLE is discoid CLE (DLE), which is characterized by indurated discoid (coin-shaped) plaques that commonly involve the head and neck, including the scalp and ears (Walling and Sontheimer 2009). Unless diagnosed and treated in a timely fashion, DLE can lead to disfiguring scarring (Ghuri et al. 2012; Kuhn et al. 2016). Detailed molecular mechanisms of the pathogenesis of DLE are not well understood and the role of lncRNA in CLE has not yet been extensively explored. Current pathogenic concept focuses on epidermal DNA/RNA damage revealing neo-antigens and eliciting complex innate and adaptive immune responses (Fig. 3) (Wenzel 2019).

### ***lnc-MIPOL1-6* and *lnc-DDX47-3***

The role of lncRNAs in DLE pathogenesis was first investigated by Xuan et al., who discovered the dysregulation of two lncRNAs, *lnc-MIPOL1-6* and *lnc-DDX47-3* (Xuan et al. 2019) (Fig. 3). In total, 507 lncRNAs were found to be differentially expressed in lesional lip in comparison to non-lesional mucosa. Using 37 significantly expressed coding genes, authors constructed a coding-noncoding co-expression (CNC) network whereby a significant correlation was identified between lncRNA and their potential nearby genes. Up-regulation of *lnc-MIPOL1-6* was associated with increased IL-19, CXCL1, CXCL11, and TNFSF15 chemokine expression. On the other hand, downregulation of *lnc-DDX47* was also associated with the increased expression of the aforementioned chemokines (Fig. 3). Specifically, IL-19, has been shown to be associated with Th1 dominant diseases (Azuma et al. 2011; Wenzel 2019); CXCL11 has been found to promote Th1 cell recruitment (Kumar and Herbert 2017); and TNFSF15 has a role in stimulating Th1 cytokine production (Zhang and Li 2012; Zhang and Zhang 2015). A recent study by Jabbari et al. correspondingly

demonstrated a predominance of IFN- $\gamma$ -producing Th1 cells from the skin of DLE patients, suggesting the important role of Th1 cells in the pathogenesis of DLE (Jabbari et al. 2014). Results also showed that Transcription Factors (TF), STAT4, ETV6, and ZNF597, regulated most of the pathways that involved the differentially expressed lncRNAs, which suggested the importance of these TFs in the pathogenesis of this disease. STAT4 has been found to regulate the IL-12 response and is important in Th1 cell differentiation (Jordan et al. 2014). ETV6 has been linked to a number of hematologic neoplasms and was found to be an important TF for blood cell development (Lambert 2019). The role of ZNF597 has not been discovered (Schulze et al. 2019). Taken together, the role of Th1 pathway in DLE pathogenesis and the role of elicited lncRNAs warrants further investigation in larger studies.

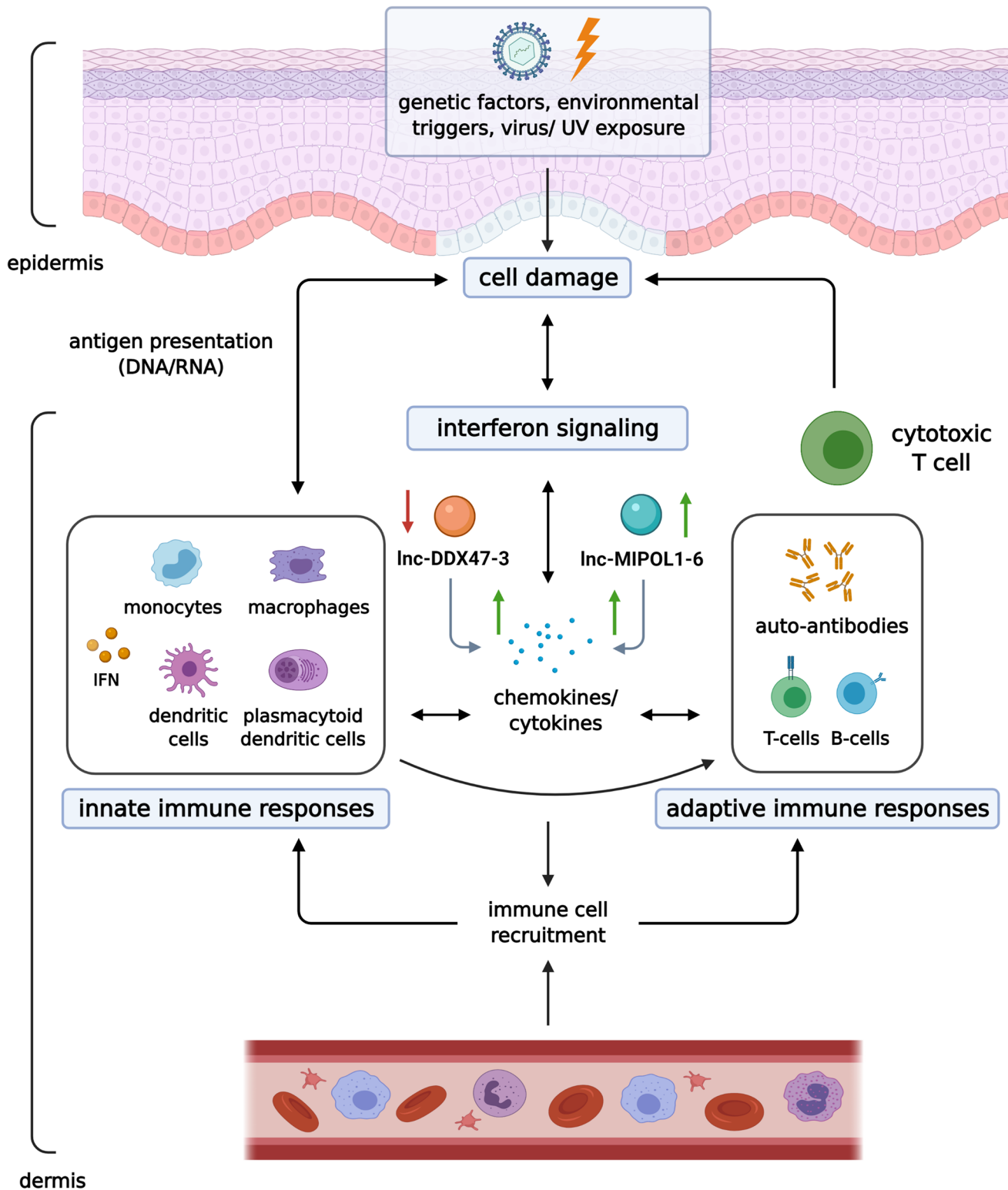
### **Limitations and call for future studies**

The main limitation for all studies included in this review was the small sample size. Thus, the interpreted results can only be applied to select individuals given that a diversity of participants is excluded. Additionally, a small sample size increases the risk of type II statistical error, and it is important to note that the predicted correlations of lncRNA-mRNA networks does not signify causation. Selection bias in choosing certain lncRNA and mRNA to create lncRNA-mRNA networks also limits the scope of studying the differential lncRNAs and their role in the studied diseases. Furthermore, in many instances, studies identifying significant lncRNAs are unique and have not been replicated or verified by external sources.

Future studies with a larger sample sizes designed to investigate the differential expression of lncRNA in patients with autoimmune and connective tissue diseases are warranted. With larger studies, the clinical application of these results could yield lncRNAs as biomarkers for disease development, targets for genetic testing, or for following the progression of the disease in patients with autoimmune skin conditions (Galeotti and Bayry 2020). Knockout lncRNA in vivo animal models or in vitro cell lines using CRISPR/Cas9 technologies for genomic engineering may be helpful in determining essential lncRNAs in disease development (Fu 2014). Further, these models may help in determining suitable lncRNAs as specific drug targets in autoimmune diseases. Given the strong family history among autoimmune diseases, it would also be of interest to investigate if lncRNA profiles suggest a familial inheritance pattern (Galeotti and Bayry 2020).

Overall, our understanding of the role of the differential expression of lncRNAs in connective tissue diseases is expanding, although there is still a large knowledge gap that must be addressed before making definitive conclusions





**Fig. 3** Pathogenesis of discoid lupus (DLE). It is believed that epidermal cell damage revealing nuclear DNA initiate the inflammatory process in DLE, featuring complex innate and adaptive immune responses. The role of Th1 response and interferon signaling has been demonstrated. In regards to lncRNAs, upregulation of *lnc-MIPOL1-6*

and downregulation of *lnc-DDX47-3* in lesional lip mucosa was associated with increased expression of Th1 cytokines and chemokines (IL19, CXCL1, CXCL11, and TNFSF15). Created with Biorender.com

regarding the significance of lncRNA in disease pathophysiology. Although lncRNAs have up to tenfold lower expression than mRNAs, these serve important regulatory functions including activation of IFN pathways in SSc, DM and DLE, increased collagen production and fibroblast survival in SSc, and Th1 shift in DLE, important in the pathogenesis of these cutaneous connective tissue conditions. The key lncRNAs that may drive pathogenesis of these connective tissue diseases could potentially serve as therapeutic targets in the future.

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**Availability of data and materials** Not applicable.

**Code availability** Not applicable.

## Declarations

**Conflict of interest** None.

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