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Invited Review Article

Systemic sclerosis: Is the epithelium a missing piece of the pathogenic puzzle?

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ABSTRACT

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by three cardinal pathological features, such as autoimmunity/inflammation, vasculopathy and extensive organ fibrosis. Therefore, numerous interests have been put on the roles of immune cells, vascular cells (endothelial cells and pericytes/vascular smooth muscle cells) and interstitial fibroblasts as well as their precursors in the field of SSc research. However, recent studies with clinical samples and animal models have drawn much attention to the potential role of epithelial cells as a member of critical drivers and/or modifiers in the pathogenesis of SSc. Indeed, phenotypically altered epithelial cells possibly explain the selective organ fibrosis in the skin, esophagus and lung, the origin of autoimmunity and Köbner phenomenon-associated localized scleroderma-like lesions, the mechanisms of which had remained unknown in the canonical idea of SSc pathogenesis. This article overviews the recent progress in understanding the contribution of epithelial cells to the pathogenesis of SSc. Although further studies are required to confirm the potential role of epithelial cells in SSc development, this notion may provide us with a missing piece of the puzzle to solve the unanswered questions in the pathogenesis of SSc.

1. Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and fibrosis of the skin and various internal organs with unknown etiology [1]. In the field of SSc research, much attention has been paid to immune cells, vascular cells (endothelial cells [ECs] and pericytes/vascular smooth muscle cells [PCs/vSMCs]) and interstitial fibroblasts, corresponding to the three cardinal pathological features of this disease, namely, autoimmunity/inflammation, vasculopathy and organ fibrosis. During recent decades, however, epithelial cells have received much interest as a part of critical drivers and/or modifiers in SSc development. This article overviews recent progress in understanding the role of epithelial cells in SSc pathogenesis and discusses the potential therapies against SSc targeting those cells.

2. The canonical idea of SSc pathogenesis

Although SSc pathogenesis still remains enigmatic, it is generally accepted that this disease is caused by a complex interplay between genetic factors and environmental influences. This idea is supported by the following epidemiological and genetic data; (i) the biggest risk factor for SSc is family history [2], (ii) concordance for SSc is around 5% in the twins and similar in monozygotic and dizygotic twins, whereas anti-nuclear antibodies are more frequently detected in the healthy monozygotic twin sibling than in the healthy dizygotic twin sibling of an SSc patient [3], (iii) most of SSc susceptibility genes are HLA haplotypes and non-HLA immune-related genes which are shared by other collagen diseases [4]. Thus, genetic factors seem to be associated with autoimmunity increasing the susceptibility to autoimmune diseases including SSc, but additional environmental factors are required to induce clinically definite SSc in genetically predisposed individuals.

A part of initial triggers of SSc-specific disease process is believed to be vascular injury due to autoimmunity and/or environmental influences. At least, anti-EC antibody and abnormally activated γδT cells are involved in the immunological aspect of this initial process [5,6]. After that, the phenotypically altered ECs and PCs/vSMCs undergo impaired vascular remodeling,

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namely, abnormally activated angiogenesis and deteriorated vasculogenesis, eventually resulting in the development of SSc-specific vascular structural abnormalities (arteriolar stenosis, capillary loss and capillary dilation) [7]. Vascular injury also induces a variable degree of luminal thrombosis, contributing to disturbed peripheral circulation and the activation of ECs, PCs/vSMCs and fibroblasts. Furthermore, abnormally activated ECs and PCs/vSMCs produce cytokines, growth factors and chemokines, promoting the infiltration of a variety of immune cells, including B cells, T cells, macrophages, mast cells and plasmacytoid dendritic cells, into the involved organs [8,9]. These vascular and inflammatory reactions eventually facilitate the transition of interstitial fibroblasts originating from multiple sources, such as resident fibroblasts, bone marrow-derived progenitors [10], and epithelial-, endothelial- and adipocyte-to-mesenchymal transition [11–13], to myofibroblasts producing excessive amount of extracellular matrix (ECM) proteins, which is a final consequence of the sequential pathological events of SSc.

Thus, little attention had been paid to the role of epithelial cells in the canonical idea of SSc pathogenesis (Fig. 1).

3. The phenotypical alterations of SSc keratinocytes

Over three decades, several studies have demonstrated the elevated expression of disease-associated molecules in the epidermis of SSc involved skin, such as endothelin-1 [14], transforming growth factor (TGF)-β [15], CCL2 [16], vascular endothelial growth factor [17] and IL-21 receptor [18]. In 2008, Aden et al. [19] published the first study demonstrating a broad range of phenotypical alterations in SSc epidermis. Through proteomic analysis with 4 mm excision biopsies obtained from the forearm involved skin of 12 diffuse cutaneous SSc and 12 healthy subjects, the authors demonstrated some expected results, such as altered abundance of proteins involved in extracellular matrix production, myofibroblast contractility, energy metabolism and response to oxidative stress, but also identified an activated, wound healing phenotype of SSc epidermis. It includes abnormal persistence of basal cell marker keratin 14, delayed expression of maturation markers keratin 1/10 and the induction of keratins 6 and 16, normally absent from interfollicular skin and induced following epidermal injury. Consistent with these findings, SSc epidermis is thickened, and has an expanded nucleated cell layer. Furthermore, they and others demonstrated the up-regulated expression of IL-1α and CCN2 in SSc epidermis [20,21]. Considering the pro-fibrotic effect of IL-1α and CCN2, SSc keratinocytes likely contribute to fibroblast activation *in vivo*. Taken together, these previous studies revealed a potential contribution of the epidermis to the development of SSc.

4. Potential roles of epithelail cells in SSc pathogenesis -a breakthrough idea obtained from epithelail cell-specific *Fli1* knockout mice-

Friend leukemia virus integration 1 (Fli1) is a member of the Ets family transcription factor, the deficiency of which is a potential predisposing factor of SSc [22]. Fli1 expression is suppressed in dermal fibroblasts, ECs, keratinocytes and perivascular inflammatory cells in involved and non-involved skin of SSc patients [23]. Although the detailed mechanism explaining Fli1 downregulation in SSc still remains unknown, an epigenetic mechanism is reported at least in dermal fibroblasts [24]. According to a series of studies on *Fli1*-mutated mice and *FLI1* siRNA-treated cultured cells, Fli1 deficiency induces SSc-like phenotypes in dermal fibroblasts, dermal microvascular ECs and macrophages [8,25–27]. Most importantly, mice with simultaneous haploinsufficiency of the *Fli1* and *Klf5* genes, both of which are epigenetically suppressed in SSc dermal fibroblasts, spontaneously develop the three cardinal pathological features of SSc [28]. These animal models are useful to obtain a clue to understand the role of certain cell types and to elucidate the mechanism of disease modifying drugs in SSc [29–31].

In keratinocytes Fli1 deficiency also induces SSc-like phenotype. For instance, *FLI1* siRNA-treated normal human keratinocytes

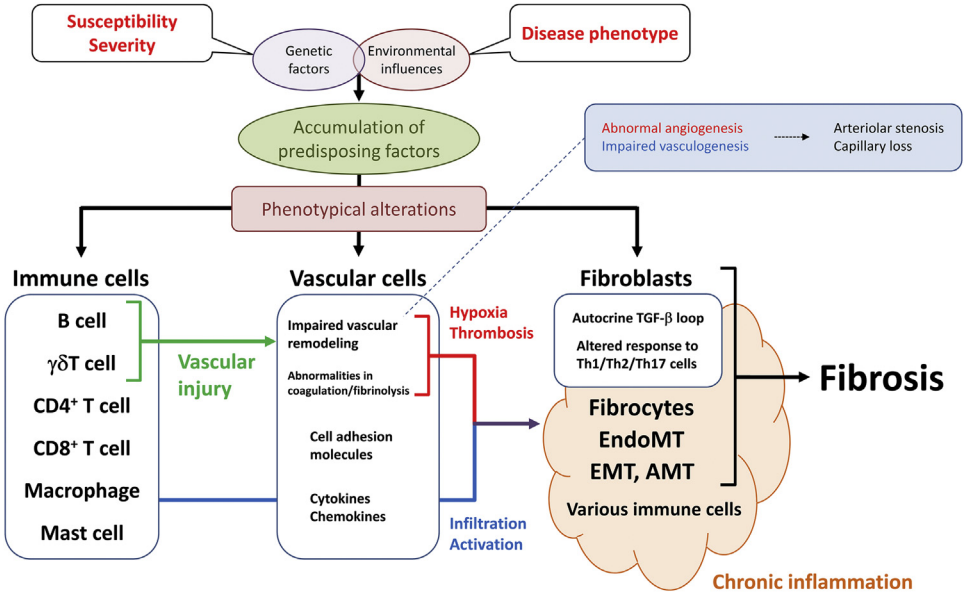

Fig. 1. The canonical idea of SSc pathogenesis.
The accumulation of predisposing factors through the interaction of genetic factors and environmental influences induces the phenotypical alterations of immune cells, vascular cells and interstitial fibroblasts. Vascular injury due to autoimmunity and environmental influecnes triggers an SSc-specific disease cascade, starting with vascular activation and vascular structural abnormalities and subsequently resulting in the development of tissue fibrosis through the extensive activation of interstitial fibroblasts and its precusors. TGF-β, transforming growth factor-β; Th, T helper; EndoMT, endothelial-to-mesenchymal transition; EMT, epithelial-to-mesenchymal transition; AMT, adipocyte-to-myofibroblast transdifferentiation.

(NHKs) exhibit the up-regulated expression of K6 and K16, representative wound healing-associated cytokeratins, as well as IL-1α and CCN2 [23]. Furthermore, the up-regulation of Snai1 and no change of E-cadherin expression are evident in *FLI1* siRNA-treated NHKs, which is identical to the phenotype of SSc keratinocytes showing partially evoked epithelial-mesenchymal transition [11]. Importantly, the phenotypical alteration of Fli1-deficient keratinocytes is reproduced in epithelial cell-specific *Fli1* knockout mice (*Fli1*$^{flox/flox}$; *K14*-Cre mice) *in vivo*, suggesting that Fli1 deficiency serves as a critical predisposing factor to induce SSc-like phenotypes in keratinocytes.

A couple of novel findings have been obtained from *Fli1*$^{flox/flox}$; *K14*-Cre mice. First, this animal model spontaneously develops dermal fibrosis along with aging. The number of α-smooth muscle actin-positive cells is increased, and the infiltrations of T cells, macrophages and mast cells are also enhanced in the dermis. Its cytokine expression profile is also reminiscent of that of SSc lesional skin, such as the elevation of IL-1β, IL-6, IL-13, IL-17 A, CCL2, TGF-β1 and CCN2. Second, this animal model exhibits esophageal fibrosis which is characterized by the thickened lamina propria and the atrophic circular muscle. Molecularly, the increased expression of IL-1β, IL-6, IL-8 and TGF-β1 is evident in the bulk esophagus tissue, and esophageal squamous epithelia highly express IL-1β. Third, this animal model manifests interstitial lung disease with lymphoid aggregates and increased expression of IL-1β, IL-6, IL-13, IL-17 A and CCL2. Importantly, Fli1 is downregulated in medullary thymic epithelial cells (mTECs) which express keratin 14, leading to the suppression of autoimmune regulatory (Aire) in those cells. Generally, Aire is indispensable for the deletion of autoreactive T cells and the development of regulatory T cells in the thymus, and the adaptive transfer of NK1.1^{-}CD3^{+} T cells from *Fli1*$^{flox/flox}$; *K14*-Cre mice to *Rag1*$^{-/-}$ mice recapitulates interstitial lung disease in recipient mice, but not dermal and esophageal fibrosis. On the other hand, *Fli1*$^{flox/flox}$; *K14*-Cre mice lacking mature T cells and B cells (*Rag1*$^{-/-}$; *Fli1*$^{flox/flox}$; *K14*-Cre mice) suffer from dermal and esophageal fibrosis, but not interstitial lung disease. Taken together, dermal and esophageal fibrosis occurs through the activation of squamous stratified epithelia and interstitial lung disease develops due to impaired immune tolerance in *Fli1*$^{flox/flox}$; *K14*-Cre mice (Fig. 2).

This animal model provides us a novel clue to answer the fundamental questions of SSc; 'why does tissue fibrosis selectively occur in the skin, esophagus and lung?' and 'What is the origin of autoimmunity?'. Although further studies are required, epithelial cells may be a key piece of the puzzle to disclose unidentified mechanisms underpinning the pathogenesis of SSc.

5. The imbalance of nuclear factor (NF)-κB and peroxisome proliferator-activated receptor (PPAR)-γ pathways in SSc keratinocytes

An excellent study by McCoy et al. [32] further reinforces the critical contribution of keratinocytes to SSc development. Normal dermal fibroblasts exposed to SSc keratinocyte-conditioned media produce excessive amount of α-smooth muscle actin and type I collagen even in the presence of neutralizing anti-TGF-β antibody in cell culture. Of interest, the activation of NF-κB and the repression of PPAR-γ are common changes in keratinocytes isolated from limited cutaneous SSc and diffuse cutaneous SSc, and the list of genes commonly differentially regulated in both disease subtypes are enriched in genes having potential binding sites in their promoters for NF-κB and PPAR-γ. According to upstream regulator analysis, oxidative stress seems to be involved in NF-κB up-regulation in SSc keratinocytes. Consistent with NF-κB activation and/or PPAR-γ inhibition, IL-6, TNF-α and CCL5 are up-regulated in SSc keratinocytes, and the expression levels of NF-κB and these cytokines/chemokines correlate with skin score. Thus, SSc keratinocytes possess disease-specific phenotype contributing to the development of this disease.

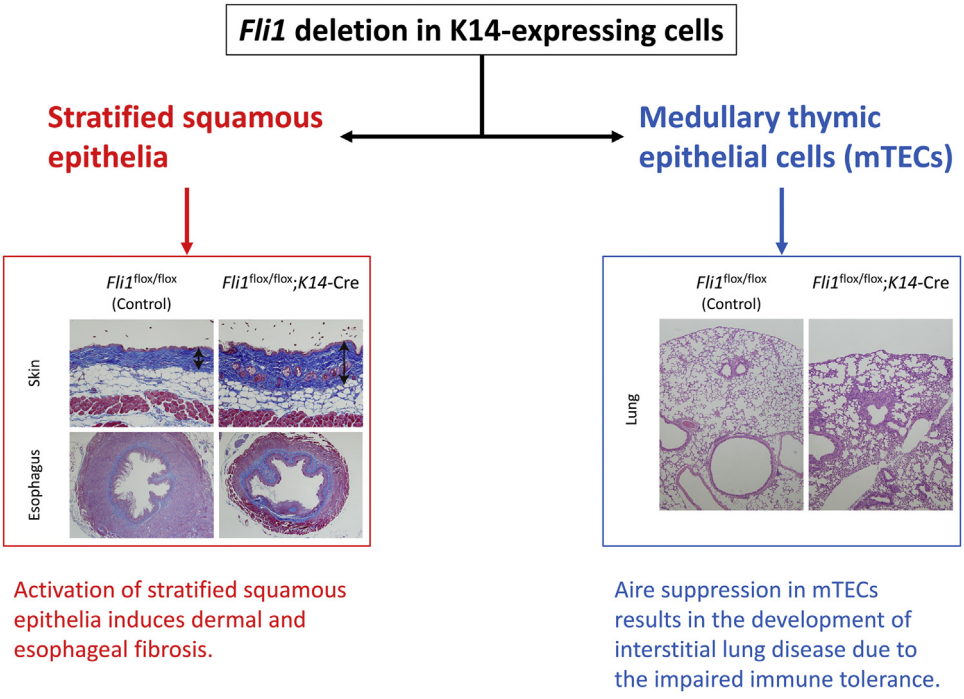

Fig. 2. The role of Fli1-deficient epithelial cells in the induction of SSc-like organ involvement.
Conditional *Fli1* deletion in K14-expressing cells results in the induction of dermal and esophageal fibrosis through the activation of stratified squamous epithelia, as well as the development of autoimmune interstitial lung disease due to the downregulation of autoimmune regulatory (Aire) in medullary thymic epithelial cells (mTECs).

6. A possible contribution of phenotypically altered keratinocytes to delayed wound healing in SSc

Refractory skin ulcers, including digital and non-digital ulcers, severely affect the morbidity of SSc patients. Generally, the impairment of peripheral circulation and vascular remodeling is thought to be a major cause of delayed wound healing in SSc, leading to the development of refractory digital ulcers. Another critical factor relevant to delayed wound healing is the dysregulated re-epithelialization due to the altered phenotype of SSc epidermis. A possible molecular mechanism underlying impaired re-epithelialization is the downregulation of galectin-7 in SSc epidermis, as demonstrated by proteomics analysis and immunohistochemistry [19]. Galectin-7 is abundantly expressed by keratinized and non-keratinized stratified epithelia in healthy individuals, and plays a critical role during wound healing by functioning as a regulator of keratinocyte proliferation and migration, as well as restoring epidermal homeostasis. Indeed, *Lgals7*$^{-/-}$ mice manifest delayed wound healing due to impaired re-epithelialization, which is primarily attributable to reduced migratory ability of galectin-7-deficient keratinocytes [33]. Importantly, galectin-7 expression is mediated by endothelin-1 stimulation in keratinocytes, and bosentan, a dual endothelin receptor antagonist, reverses galectin-7 expression in SSc keratinocytes [34], suggesting that the migratory ability of SSc keratinocytes may be improved by bosentan administration. Considering that bosentan prevents the development of new digital ulcers in SSc patients, and that SSc digital ulcers are caused by multiple mechanisms including impaired re-epithelization after microtrauma, the reversal expression of galectin-7 in the epidermis by bosentan may promote the re-epithelization of mildly injured skin, leading to the prevention of new digital ulcers in SSc patients. Thus, the epidermis seems to be a critical factor involved in the development of refractory skin ulcers in SSc.

7. Köbner phenomenon-induced localized scleroderma (LSc)-like lesions in SSc

LSc or morphea is an autoimmune inflammatory disorder of the skin and underlying tissues, such as subcutaneous fat, fascia, muscles and bone, eventually resulting in extensive fibrosis and irreversible deformity [35]. LSc differs from SSc in that it is not accompanied by Raynaud's phenomenon, acrosclerosis and internal organ involvement. Although LSc is a different entity from SSc, coexistence of SSc with LSc or LSc-like skin lesions has been reported. Apart from typical LSc, LSc-like lesions are generally characterized by multiple hyperpigmented plaques with mild skin sclerosis. Tissue fibrosis of typical LSc possibly spreads to subcutaneous tissues with variable degrees of severity, while tissue fibrosis is generally mild and restricted to the dermis in LSc-like lesions. Importantly, LSc-like plaques are mostly seen on the upper arms, lateral forearms, knees, waist, lumbar area and back with a symmetric distribution. Although a potential contribution of Köbner phenomenon to the development of LSc-like lesions is proposed based on the characteristic distribution of plaques [36], it still remains unknown why such LSc-like lesions are complicated in a certain subset of SSc patients.

The histopathological analysis of LSc-like skin lesion demonstrated the following findings; (i) spongiosis, vacuolar changes or liquefaction degeneration, and satellite cell necrosis are exclusively seen in LSc-like lesions, and the former 2 features are much more frequently detected in LSc-like lesions than in SSc forearm skin lesions (typical SSc involved skin), (ii) melanin incontinence and perivascular infiltrate are significantly greater in LSc-like lesions than in SSc forearm skin lesions, while the degrees of epidermal atrophy, basal pigmentation, periappendageal infiltrate and dermal fibrosis are comparable between the two biopsy sites [36]. Importantly, these histological features of LSc-like lesions are similar to those of typical LSc plaques [37], though the degree of each feature was uniformly milder in LSc-like lesions. These data suggest that SSc patients with LSc-like lesions possess some specific developmental process which is different from that of typical SSc patients.

An important finding to speculate the developmental mechanism of LSc-like lesions came from epithelial cell-specific *Fli1* knockout mice lacking mature B cells and T cells (*Rag1*$^{-/-}$; *Fli1*$^{flox/flox}$; *K14*-Cre mice). These mice develop dermal and esophageal fibrosis accompanied by the infiltration of mast cells [36], indicating that the activation of stratified squamous epithelia induces tissue fibrosis through the activation of innate immunity including mast cells. This phenomenon seems to be partly mediated by IL-1 overproduction in stratified squamous epithelia [23]. This theory may be applicable to SSc because IL-1α is upregulated in SSc keratinocytes and stimulates type I collagen production in cultured dermal fibroblasts [20]. Also, IL-1α promotes the secretion of IL-6, a key driver of SSc development, from mast cells without degranulation [38]. Given that IL-1α is basically pooled in squamous epithelia and secreted from those cells in response to various stimuli, this cytokine may be involved in the development of Köbner phenomenon-related sclerotic plaques in SSc. Supporting this idea, IL-1α expression is elevated to a greater extent in both the forearms (typical SSc skin lesion) and LSc-like lesions of SSc patients with LSc-like lesions than in the forearms of SSc patients without LSc-like lesions. In each of individual SSc patients with LSc-like lesions, furthermore, the increased infiltration and degranulation of mast cells are much more evident in the dermis of LSc-like lesions than in the dermis of forearms (typical SSc skin lesion). Therefore, LSc-like lesions occur in SSc patients at least partly by highly activated keratinocytes and mast cells. Given that LSc-like lesions are preferentially distributed over areas mechanically compressed by underclothes, it is postulated that LSc-like lesions associated with SSc are induced by some specific mechanism associated with the activation of the epidermis.

Thus, the epidermis of SSc patients with LSc-like lesions possesses an inflammatory phenotype, leading to the development of LSc-like lesions through the activation of mast cells in the dermis of mechanically stressed skin. This may be a potential mechanism by which Köbner phenomenon may be involved in the induction of LSc-like lesions in a certain subset of SSc (Fig. 3).

8. A potential contribution of antimicrobial peptides/proteins (AMPs) to cutaneous manifestations of SSc

Generally, epithelial cells locate on the surface of the skin and respiratory and gastrointestinal tracts, and are thus continuously exposed to large numbers of microorganisms. To cope with the substantial microbial exposure, epithelial cells produce and secrete a variety of AMPs, also known as host defense peptides/proteins, which are an evolutionarily conserved component of innate immune response against bacterial, fungal, and viral invasion. In addition to antimicrobial properties, AMPs also play critical roles in a broad range of biological activities, such as inflammation, angiogenesis and tissue remodeling. Therefore, clinical studies on AMPs, especially those expressed in the epithelium, provide us with a useful clue to better understand the role of epithelial cells in SSc pathogenesis.

Psoriasin, also known as S100A7, is involved in keratinocyte differentiation and epidermal remodeling, as well as inflammation and angiogenesis [39]. Psoriasin is highly expressed in the epidermis of SSc lesional skin, and the elevation of serum psoriasin levels correlates with diffuse cutaneous involvement and higher

prevalence of telangiectasia and pitting scars. Psoriasin up-regulates the expression of wound healing-associated cytokeratins, K6 and K16, in NHKs [40], suggesting that psoriasin contributes to the maintenance of SSc epidermal phenotype in autocrine and paracrine manners. Also, psoriasin promotes the secretion of IL-6 from NHKs [40], contributing to the up-regulated expression of IL-6 and the increased phosphorylation of STAT3 in SSc keratinocytes [41,42]. Given that IL-6 is a potential target for the treatment of dermal and pulmonary fibrosis associated with SSc [43], the elevation of psoriasin in the early stage of SSc may reflect its contribution to tissue fibrosis at least partially through the induction of IL-6. Telangiectasia is histologically characterized by dilated post-capillary venules in upper horizontal plexus due to the proliferation of ECs [44], suggesting that psoriasin secreted from the epidermis distributes around upper horizontal plexus at a high concentration, and serves as a potent pro-angiogenic factor in SSc lesional skin. Indeed, psoriasin promotes the proliferation and tubulogenesis of ECs to a comparable extent to vascular endothelial growth factor [45]. Pitting scars are characterized by digital hyperkeratotic lesions pathologically associated with the impaired wound healing following repetitive microtrauma [46]. Since the association of psoriasin with hyperkeratosis is reported in psoriasis and atopic dermatitis [47], altered epidermal phenotype including the up-regulated expression of psoriasin may be associated with hyperkeratotic epidermal changes in SSc.

Cathelicidin family peptides are a class of AMPs found in many mammalian species and LL-37 is the only human cathelicidin known so far. LL-37 is expressed in many types of cells including myeloid cells, airway and gastrointestinal epithelial cells, macrophages, lymphocytes, neutrophils and ECs. Due to its numerous immunomodulatory properties, including interferon (IFN)-α induction from plasmacytoid dendritic cells through the conversion of self-DNA into a stimulatory ligand for Toll-like receptor 7 and 9, LL-37 has attracted particular interests in the research field of autoimmune and inflammatory diseases [48]. In SSc involved skin, LL-37 is up-regulated in dermal fibroblasts, dermal small vessels, perivascular inflammatory cells and keratinocytes, and there is a significant positive correlation between *LL37* and *IFNA1* mRNA expression. Given that serum LL-37 levels significantly correlate with skin score, LL-37 is likely involved in the activation of dermal fibroblasts via promoting the production of IFN-α from plasmacytoid dendritic cells. On the other hand, the elevation of serum LL-37 levels is associated with tissue fibrosis of the skin, esophagus and lung, all of which directly contact with external environment through the epithelium. Since LL-37 is remarkably up-regulated in SSc keratinocytes, phenotypically altered epithelial cells may be associated with the development of tissue fibrosis in SSc by producing various molecules, including LL-37 and other AMPs, in response to external environmental influences [49].

Taken together, these previous data on LL-37 and psoriasin support the idea that the phenotypical alteration of SSc epidermis may contribute to the development of various cutaneous symptoms and the selective organ fibrosis in SSc.

9. Future direction - how to target keratinocyte-dependent pathogenic process?

At this moment, immunosuppressants (cyclophosphamide, mycophenolate mofetil, etc.) and vasodilators (bosentan, calcium channel blockers, etc.) consist of the standard therapy against SSc, and biologics (tocilizumab, rituximab, etc.) and other new drugs (nintedanib, cannabinoid, etc.) are under the clinical trials. Basically, the pre-existing and up-and-coming therapies have been developed to target immune cells, vascular cells and/or fibroblasts, and most of them are systemically administered by oral intake, intravenous infusion or subcutaneous injection. Over the

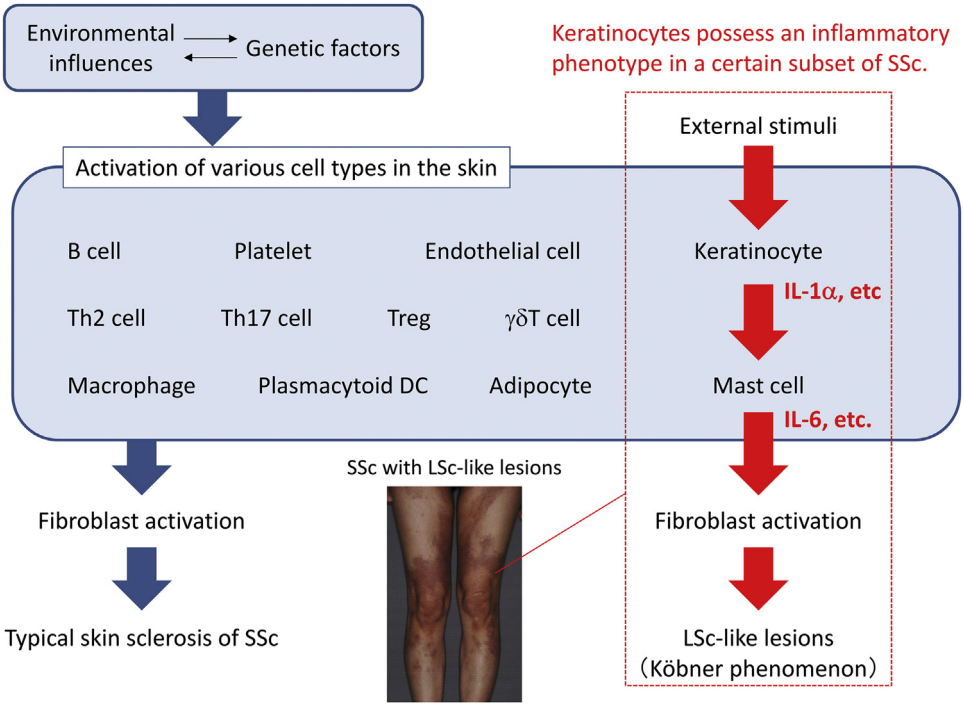

Fig. 3. A potential mechianism of Köbner phenomenon-induced LSc-like lesions in SSc.
As a result of the complex interplay among a variety of cell types in the skin, dermal fibroblasts are constitutively activated and produce an excessive amount of extracellular matrix in typical SSc involved skin. In a certain subset of SSc, keratinocytes with an inflammatory phenotype secrete pro-inflammatory cytokines, including IL-1α, in response to external stimuli. Then, such cytokines promote the infiltration and activation of mast cells, leading to the production of pro-fibrotic molecules, such as IL-6, from those cells. This pathway may contribute to the activation of dermal fibroblasts in mechanically compressed skin areas, resulting in the development of LSc-like lesions. LSc, localized scleroderma.

last decade, epithelial cells have attracted much attention as a potential therapeutic target of this disease. Indeed, the easy accessibility to the skin epithelium by topical therapies would be beneficial for SSc patients because the current standard SSc treatment can cause systemic adverse effects.

Clinical studies have demonstrated the efficacy of phototherapy, such as psoralen plus ultra violet A (PUVA) and UVA1, for skin sclerosis and/or joint mobility, or even Raynaud's phenomenon and digital ulcers in a certain subset of SSc [50]. Indeed, phototherapy alone is not enough to completely reverse skin sclerosis, but phototherapy as an adjunctive therapy together with other treatments may achieve much more improvement albeit the risk of skin cancer is a real concern when combined with immunosuppressive drugs. The clinical efficacy of phototherapy is possibly attributable to a broad range of its disease-modifying effects, including the modification of epithelial cell-dependent disease process as well as the direct and/or indirect effects on the canonical target cell types including dermal fibroblasts, immune cells and endothelial cells.

As described above, SSc keratinocytes produce a set of key molecules involved in the development of SSc, such as IL-1α, CCN2, IL-6, TNF-α and CCL5 [19–21,32]. Indeed, NF-κB activation, PPAR-γ inhibition and Fli1 deficiency seem to underlie the induction of SSc-like phenotype in keratinocytes [23,32]. Therefore, topical application of drugs acting on transcription factors, such as low-molecular-weight compounds and oligonucleotide therapeutics, would be a new therapeutic strategy targeting the keratinocyte-dependent SSc disease pathways. Especially, in the field of oligonucleotide therapeutics, recent advances in nucleic acid chemistry and delivery to improve stability, bioavailability, specificity and potency are now driving the rapid development.

Anyway, considering unsatisfactory results of pre-existing standard therapies against SSc, the new therapeutics focusing on epithelial cell-dependent disease process seems to have a potential to achieve much more favorable outcome through the combination with pre-existing therapies.

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Conflict of interests

Y Asano has received honoraria and research funding from Actelion pharmaceuticals Japan Ltd. The other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.04.007.

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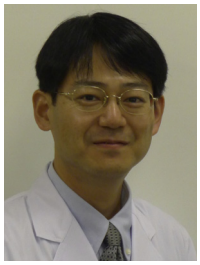

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