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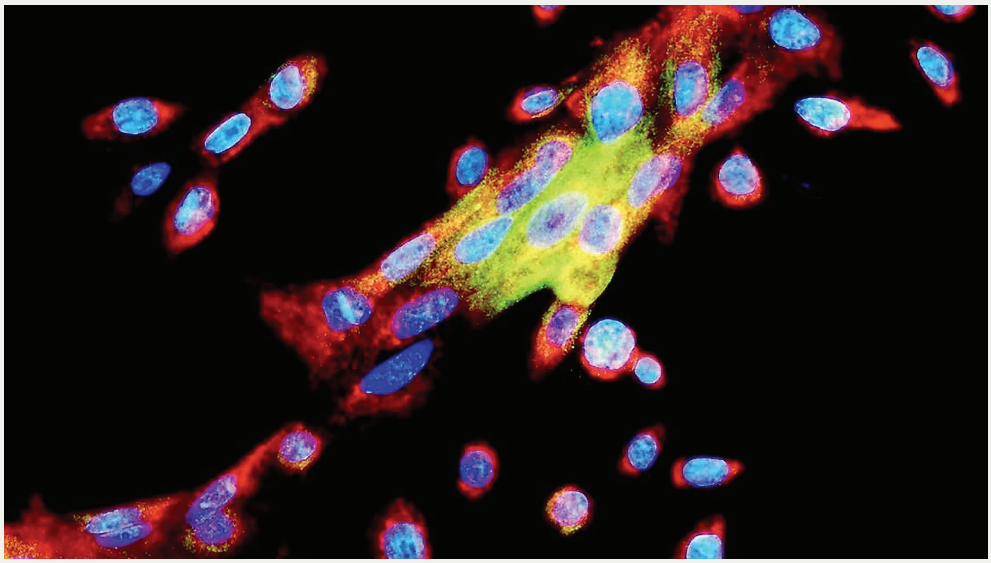
MicroRNAs in cutaneous lupus erythematosus: Role in pathogenesis and clinical applicability

Cristina Solé Marcé

Premi IEC de la Secció de Ciències Biològiques
August Pi i Sunyer de Ciències de la Salut 2023



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Cover image: Immunofluorescence of primary keratinocytes isolated from a discoid lupus lesion, used to study its pathogenesis. The cell nuclei are stained blue (DAPI), the phosphorylated protein NF-κB green, and interleukin-1 alpha red. Photograph by Cristina Solé Marcé, senior-junior principal investigator, Lupus Unit, Vall d'Hebron Research Institute (VHIR).

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At the proposal of the committee formed by Messrs. and Mmes. Anicet Ramon Blanch i Gisbert, Jordi Camí Morell, Josefina Castro Fornieles, Marta Estrada i Miyares, and Jaume Reventós Puigjaner, members of the Secció de Ciències Biològiques, the Institut d'Estudis Catalans, at its plenary session held on 22 March, 2023, resolved to award the Premi IEC de la Secció de Ciències Biològiques August Pi i Sunyer de Ciències de la Salut to Cristina Solé Marcé for her project *Gene therapy with interference miRNAs as a new treatment alternative in discoid lupus erythematosus (DLE)*.

Morever, in compliance with the terms and conditions of this award, the Secció de Ciències Biològiques publishes the review study on the subject of the winning research under the title *MicroRNAs in cutaneous lupus erythematosus: Role in pathogenesis and clinical applicability*.

Table of contents

Abstract

Cutaneous lupus erythematosus (CLE) is a chronic autoimmune dermatological disease that often appears in young women (20-40 years old). It is classified into different subtypes based on clinical and histological characteristics, duration of lesions, and clinical progression. The most important subtypes include acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). Current treatment involves topical corticosteroids, antimalarial drugs, and sun exposure prevention. However, this conventional treatment is not sufficient, and over 30% of patients are refractory. Non-treated or non-responsive lesions can lead to serious sequelae such as alopecia or facial scars.

The pathogenesis of CLE is not fully understood; nevertheless, it is defined as a multifactorial disease involving environmental factors, dysregulation of the immune response, and potential genetic predisposition. While no specific genes causing CLE lesions have been identified, small single-stranded RNAs (miRNAs) have been involved in activating the pathological molecular pathways of the skin. These miRNAs have been extensively studied in autoimmune skin diseases like psoriasis and atopic dermatitis, and their role in CLE lesion formation has recently been discovered. Several specific miRNAs have been identified for each CLE subtype, with some being common across different subtypes. For instance, miR-31 and miR-485-3p are specific to discoid lupus erythematosus (DLE), and miR-885-5p is described as common among DLE and SCLE subtypes.

Similar to what happens with other dermatological diseases like psoriasis and atopic dermatitis, miRNAs in CLE can be applied in clinical practice as diagnostic,

activity, or treatment monitoring biomarkers. Their applicability in gene therapy is also under investigation. This therapy involves inhibiting or overexpressing miRNA gene expression to reduce local inflammation and prevent fibrosis formation in lesions. In dermatological diseases, topical therapy direct to the affected skin region could minimize potential adverse effects and enhance therapeutic efficacy. It is worth mentioning that only preliminary results have been obtained in the use of miRNAs as psoriasis treatment; for CLE, this would be a pioneering therapy still in very early research stages. This research could open the possibility of finding a therapeutic alternative for chronic and refractory patients.

1. Definition and subtypes of cutaneous lupus erythematosus

Cutaneous lupus erythematosus (CLE) is a chronic inflammatory autoimmune disease with a broad spectrum of clinical manifestations and a variable course. It can manifest as a dermatological disease without any other alterations or as a clinical manifestation of systemic lupus erythematosus (SLE) [1].

SLE is also a chronic autoimmune disease characterized by circulating autoantibodies in the blood, primarily antibodies against the nucleus or cellular DNA, known as *antinuclear antibodies* (ANAs), *anti-dsDNA antibodies*, *anti-Sm*, *anti-Ro*, *anti-La*, or *anti-RNP* [2]. The patient's immune system in SLE identifies the genetic material of their own cells as antigens and, for this reason, produces autoantibodies as an immune protective response. It is believed that these autoantibodies deposit on organs, causing inflammation and the variety of clinical manifestations associated with SLE. Cutaneous manifestation is one of the most prevalent, with 70-80% of SLE patients presenting it [3], and it is the initial manifestation in 20-25% of patients [3]. Malar rash, widely known as *butterfly rash*, is the most characteristic cutaneous lesion. It consists of erythematous macules and papules, confluent at times with edema, distributed bilaterally and symmetrically on the cheeks and the dorsum of the nose. Due to its butterfly wing-like appearance, one of the most representative symbols of SLE is a butterfly (Figure 1).

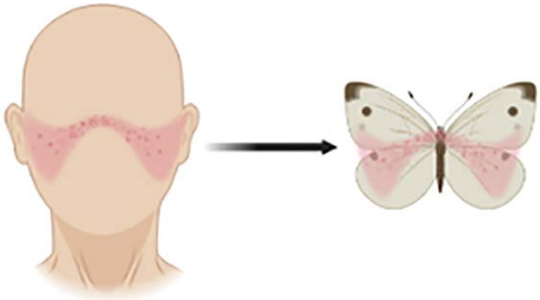

Figure 1. The most typical cutaneous lesion of SLE is malar rash. It is a lesion of acute cutaneous lupus erythematosus characterized by an erythematous macule and papule distributed bilaterally and symmetrically on the cheeks and the dorsum of the nose. Because its distribution resembles butterfly wings and is one of the most characteristic lesions of SLE, the butterfly has become the symbol of the disease.
Source: Author.

When CLE is not associated with SLE, its clinical manifestations are typically limited to dermatological involvement [4]. However, it should be noted that a patient with CLE can develop SLE at any time. The risk of this occurrence and the

reason behind it are still completely unknown. The only known fact is that patients with only CLE do not have circulating autoantibodies such as anti-dsDNA, anti-Sm, or anti-RNP; instead, their most characteristic autoantibodies are usually anti-Ro/SSA or anti-La/SSB [5].

According to recent studies, the age- and sex-adjusted prevalence of CLE was 108.9 per 100,000 people in the United States [4]. They also report that the overall incidence rate between 1976 and 2018 was 3.9 per 100,000 people (95% CI, 3.4 to 4.5), remaining stable concerning age and sex variables [4]. Like systemic lupus erythematosus (SLE), CLE is slightly more common in women (3:1), although this prevalence is not as high. There is no difference between different racial groups [4]. The clinical expression of CLE is highly heterogeneous and typically follows a chronic and recurrent course. By performing histological analysis of skin biopsies, Dr. Gilliam and Dr. Sontheimer [5] classified CLE into two major subtypes: lupus erythematosus (LE)-specific and LE-nonspecific cutaneous lesions. Non-specific cutaneous lesions can be associated with lupus but are not specific to it and can also be associated with other diseases; the most common include vasculitis, livedo reticularis, alopecia, and Raynaud's syndrome, among others. In contrast, specific lesions are rarely found in other diseases and are characteristic of lupus. These can be further subdivided based on clinical characteristics, duration of lesions, and histopathological findings into [6]: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE), among others (Table 1).

Table 1. Characteristics of cutaneous lupus erythematosus (CLE) subtypes.

LE specific lesions				**LE non-specific lesions**
Acute CLE (ACLE)	**Subacute CLE (SCLE)**	**Chronic CLE (CCLE)**	**Other**	• Vasculitis • Livedo reticular • Alopecia • Raynaud's syndrome
• Associated with SLE • Facial • Malar rash	• Annular • Photosensitive • Large size	• Discoid lupus erythematosus (DLE) • Tumid lupus erythematosus (TLE) • Lupus profundus • Chilblain lupus	• Bullous CLE • Rowell's syndrome	

Source: Author.

Acute cutaneous lupus erythematosus (ACLE) is the manifestation most associated with SLE and it may be localized or generalized. The characteristic localized form is the malar rash, an erythema symmetrically affecting the bridge of the nose and the cheeks, sparing the nasolabial folds, and usually leaving no sequelae as there is no depigmentation. Malar rash is present in 52% of patients with SLE at the time of diagnosis. The generalized form of ACLE is less common and often occurs concomitantly with systemic disease activity. It is an erythematous maculopapular rash that manifests on the upper body, neck, back, or extremities, especially in areas exposed to ultraviolet radiation. It is strongly associated with SLE, 95% of patients are positive for antinuclear antibodies (ANAs), anti-dsDNA, and anti-Sm. Histologically, lesions show liquefaction degeneration of the basal layer, a scattered interface, edema of the upper dermis, and a mild perivascular and periadnexal lymphocytic infiltrate [7]. Immunofluorescence analysis reveals granular deposits at the dermal-epidermal junction and perivascular deposits in the upper dermis, typically IgM immunoglobulin deposits.

Subacute cutaneous lupus erythematosus (SCLE) presents as photosensitive lesions localized in sun-exposed areas of the body, such as the neck, chest, upper back, arms, and hands, but rarely on the face or scalp. The lesions are erythematous macules evolving into extended annular polycyclic plaques, papulosquamous psoriasis-like lesions, or a combination of both [7]. Despite their large size, these lesions do not cause hypopigmentation or leave any sequelae. Around 70% of SCLE patients have circulating anti-Ro/SSA antibodies, but in 5% of cases, they are also positive for anti-dsDNA [8]. An estimated 50% of SCLE patients have associated systemic lupus disease. The annual incidence of this type of cutaneous lupus is 0.7 per 100,000 inhabitants in Sweden [9] and 0.63 per 100,000 inhabitants in Minnesota [10]. Histologically, SCLE lesions show hydropic degeneration of basal keratinocytes, dermal edema, hyperkeratosis, follicular plugging, and a sparse superficial and deep inflammatory infiltrate, predominantly lymphocytic [11]. Unlike other types of cutaneous lupus, the density and depth of the inflammatory infiltrate are lower and less restricted to periadnexal and perivascular areas. SCLE also exhibits less hyperkeratosis and the most specific feature is IgG immunoglobulin deposits in a dust-like particles distribution pattern detected by immunofluorescence [12].

Chronic cutaneous lupus erythematosus (CCLE) is the most severe subtype, which leaves more sequelae in patients. Among various subtypes such as tumid lupus, discoid lupus erythematosus (DLE), lupus profundus, and chilblain lupus (lupus erythematosus pernio), DLE is the most common, occurring in 50-98% of cases [5]. DLE lesions are characterized by variable-sized maculopapular lesions with scaling and poorly defined borders [5]. As a repetitive and persistent inflammatory process with relapses, it leaves scars with hyperpigmentation, leading to significant cutaneous deformity and, in some

cases, mutilation (Figure 2). Patients with DLE have low levels of ANAs, anti-dsDNA, anti-Sm, or anti-Ro/SSA antibodies, and only 5-18% progress to SLE [13]. Microscopic characteristics include hyperkeratosis with follicular plugging, thinning and flattening of the epithelium, and hydropic degeneration of the basal layer (liquefaction degeneration). Additionally, apoptotic keratinocytes (Civatte bodies) are present at the basal layer or epithelium. In more chronic lesions, thickening of the basement membrane becomes evident with periodic acid-Schiff (PAS) staining. The dermis exhibits an irregular lichenoid or lymphocytic infiltrate, mainly located in pilosebaceous follicles. There are interstitial mucin deposits and edema, usually without eosinophils or neutrophils. Direct immunofluorescence is an important test in this subtype, detecting the presence of immunoglobulins, both IgG and IgM, in the lesion in 50-90% of cases. The observed incidence varies by study origin, with reports of 3.56 per 100,000 inhabitants in Minnesota, 27.24 in New Zealand, 6.57 in Europe, and 3.56 in French Guiana [14, 15].

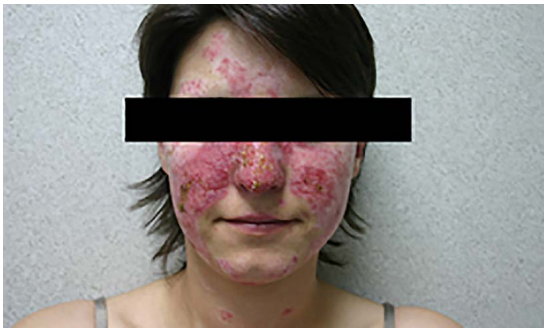

FIGURE 2. A thirty-four-year-old patient with chronic cutaneous lupus erythematosus (CCLE) lesions is experiencing challenges despite treatment. The lesions are scarring, and their recurrence is frequent, significantly impacting the patient's professional and social life.
SOURCE: Photo by the author.

2. DIAGNOSIS AND TREATMENT OF CUTANEOUS LUPUS ERYTHEMATOSUS

To diagnose cutaneous lupus erythematosus (CLE), a comprehensive patient medical history, an in-depth physical examination, and blood analysis to assess circulating autoantibodies and determine serology are essential. However, the most critical step is to perform a skin biopsy of the lesion to be analyzed by immunohistochemistry and immunofluorescence techniques, which are crucial for diagnosis and identifying the subtype of CLE [16].

Usually, the skin biopsy is performed using a sterile punch with a diameter of 4 or 6 millimeters. It is advisable to biopsy the lesion in the active phase, with a

minimum of about three months of age, to ensure proper characterization of the immunologic system and immunoglobulin deposits [16]. The biopsy should be taken above the subcutaneous fat layer; however, in the case of the lupus panniculitis subtype, a deeper incision biopsy is necessary. The biopsy specimen is prepared in paraffin and examined using the hematoxylin and eosin immunohistochemistry technique for histological characterization. A crucial aspect for the diagnosis of CLE is the identification of vacuolar or hydropic changes in the skin, as well as the presence of lymphocytic infiltrates [16].

However, the most important technique for diagnosis is direct immunofluorescence [17]. Through this technique, a band known as the *lupus band* can be observed, characterized by the presence of accumulation of immunoglobulins and complement at the dermo-epidermal junction. These accumulations usually have a granular appearance and contain complement 3 (C3), immunoglobulins of the G type (IgG) and M type (IgM), and in some cases, A type (IgA) [17]. The three essential characteristics of the lupus band are: 1) the detection of deposition of IgG or IgM, either alone or combined with other immunoglobulins, in the area of the epidermal basal membrane or appendix; 2) the band can be homogeneous or granular, although it can also be formed by fibrils, threads, or scattered points; 3) the band must show intense brightness, i.e., be highly positive in immunofluorescence (Figure 3).

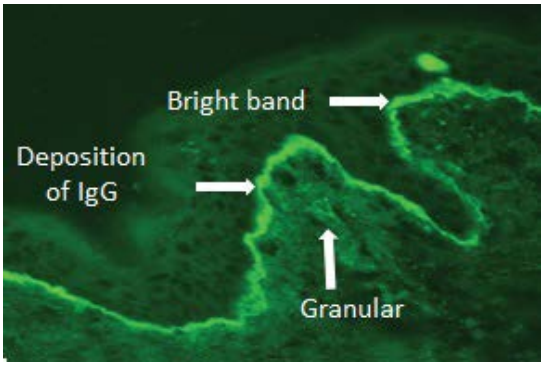

FIGURE 3. Immunofluorescence determining the lupus band in a skin biopsy for diagnosing CLE. It encompasses the three main characteristics: IgG deposits, granular or homogeneous appearance, and a bright band.
SOURCE: Picture modified from Reich et al. [17].

This band, known as the *lupus band*, is specific to CLE, but not exclusive; in some histological samples, it may not be present. Therefore, the diagnosis must be based on a comprehensive evaluation that includes clinical, serological, and histological data. Serology is particularly important in determining whether there is

an association with systemic lupus or if the disease is limited to CLE. However, in many cases, patients with CLE without systemic lupus disease may, at some point, develop systemic manifestations and evolve towards SLE. The reasons for this evolution are not yet entirely clear, and there are no prognostic biomarkers that can predict or control this progression. The only known fact is that there is an 18.1% probability of this happening in the first three years after the diagnosis of CLE, and elevated levels of autoantibodies such as ANAs, anti-dsDNA, anti-Ro, or anti-La are risk factors [18].

Overall, the management of CLE is simple compared to SLE, mainly because the manifestation is only cutaneous. However, the impact of this disease on society is significant, ranking as the third most common cause of disability in the context of dermatological diseases, with 45% of lupus patients reporting some aesthetic limitation in their professional and social life [19]. For this reason, it is crucial to allocate resources to improve treatment, especially for the CCLE subtype, with the aim of preventing disfiguring scars, atrophy, and depigmentation.

Currently, the first-line treatment includes sun protection through the use of UV radiation protective creams, as over 60% of patients are photosensitive. The use of UV-resistant clothing, type A and B, is also recommended [20]. The first drugs usually employed are topical corticosteroids or calcineurin inhibitors [20]. In this regard, topical corticosteroids can vary in the intensity of action. Soft corticosteroids (such as methylprednisolone) are commonly used on facial lesions, medium-strength ones (such as mometasone furoate, betamethasone valerate, or triamcinolone acetonide) for lesions localized on the back or arms, and stronger ones (such as clobetasol) for lesions on the hands or feet. Calcineurin inhibitors, such as tacrolimus or pimecrolimus, act to reduce the activity of T lymphocytes by inhibiting calcineurin, the enzyme responsible for phosphorylating the nuclear factor that activates T lymphocytes [21]. These agents are applied as topical treatment for the more chronic and aggressive subtypes of cutaneous lupus, with a 0.1% solution [22]. If topical treatment is unsuccessful, systemic treatments are added, starting with the inclusion of antimalarial agents such as chloroquine or hydroxychloroquine. It is important to note that these drugs have various side effects, with ocular toxicity being one of the most frequent and critical complications. The prevalence of ocular toxicity is 7.5% in the first five years and can increase to 20% after continuous treatment lasting twenty years [23]. Given that CLE is a chronic disease that requires continuous treatment, it is crucial to consider these data. Following the guidelines of the American Academy of Ophthalmology, the optimal dose to prevent retinal damage is 5 mg of hydroxychloroquine per kilogram of the patient's actual weight [24]. If the desired results are not achieved with this treatment, quinacrine, another antimalarial, can be added, although it has a higher risk of retinopathy [25]. Finally, as initial treatment, systemic corticosteroids can also be added, as studies conducted

by the European Society of Cutaneous Lupus Erythematosus (EUSCLE) have shown significant efficacy, with a 94.3% positive response rate [26]. It should be noted that systemic corticosteroids can have many side effects, particularly in women, and can lead to the premature onset of osteoporosis.

The second line of treatment for refractory CLE patients involves the use of immunosuppressive drugs such as methotrexate or mycophenolate [27, 28]. Oral retinoids or dapsone have also been investigated, but the most promising results have been obtained with the use of immunomodulators, such as thalidomide or lenalidomide [29].

Immunomodulators, despite being considered the third line of treatment, have shown a high rate of clinical remissions, approximately 80-90%. This effectiveness has led many specialists to choose to use them earlier, before resorting to other established treatment methods. This allows them to prevent chronic inflammation of cutaneous lesions and, therefore, the formation of fibrosis and permanent sequelae, especially in patients with DLE lesions [30, 31]. It is worth noting that a drawback of these drugs is that, when withdrawn, more than 80% of patients experience relapses, requiring continuous treatment. Similar to corticosteroids, immunomodulators can cause significant side effects. Among the most common are drowsiness, amenorrhea, and gastrointestinal problems. Additionally, it should be mentioned that they are teratogenic drugs, and neuropathy has been observed in 20-30% of patients [32]. For this reason, research is being conducted to better understand their mechanism of action and find therapeutic alternatives to minimize the mentioned side effects [33].

Regarding biological drugs, so far only belimumab, a monoclonal antibody that inhibits the activation factor of B cells, known as *B-lymphocyte stimulator* (BLyS), has been approved for the treatment of SLE. However, it is not indicated for the treatment of CLE in the absence of systemic manifestations [34]. Among other biological drugs that have been investigated as possible treatments for CLE, rituximab, a monoclonal antibody against CD20, has shown effectiveness in a small series of patients with lupus profundus and SCLE [35]. Another biological drug gaining acceptance in the treatment of SLE and showing a good response in cutaneous manifestations is anifrolumab. This monoclonal antibody inhibits the receptor of interferon subunit 1. In a small series of CLE patients, anifrolumab has demonstrated a clinical improvement of 41% in just eight weeks [36]. However, it should be emphasized that these results are still very preliminary, and further research is needed to draw definitive conclusions. In this context, the use of monoclonal antibodies targeting receptors on dendritic plasma cells, such as litifilimab (anti-BDCA2), is being studied. In a phase-2 clinical trial lasting sixteen weeks, a significant reduction in lesions with acceptable tolerability has been achieved. Nevertheless, larger trials with a greater number of patients and a longer duration are necessary [37].

It is essential to consider that the established treatment algorithm mentioned for CLE (Figure 4) primarily applies to local and simple lesions. In cases of patients with generalized and more aggressive lesions, treatment usually begins with a combination of topical and systemic treatment, including the use of antimalarial agents and/or corticosteroids. Additional options for second and third-line treatment are quickly added to avoid the formation of atrophy and permanent sequelae that could significantly affect the patient's quality of life.

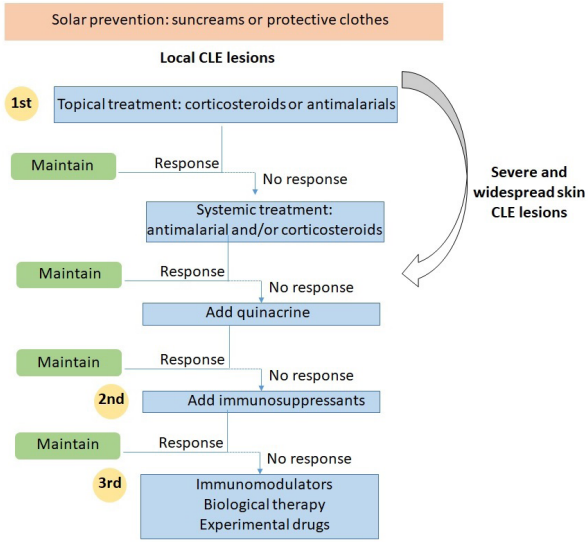

FIGURE 4. Treatment algorithm for local or generalized and complex lesions of CLE. The first line of treatment involves topical therapies followed by systemic treatment with antimalarials or corticosteroids. The second line consists of the use of immunosuppressants, and finally, the third line involves the use of immunomodulators, biological therapies, or experimental drugs. The maintenance of therapy depends on each patient and the type of CLE lesion, always with the aim of minimizing treatment-related adverse effects.
SOURCE: Image modified from Kuhn et al. [20].

However, no specific medication has been approved for the treatment of CLE, and various agents authorized for SLE and other autoimmune diseases are currently still being used. It should be noted that 30% of patients, especially those with DLE, are refractory, and lesion resolution is either not achieved or is very slow, often leaving lasting sequelae. Accordingly, there is neither a consensus nor an established treatment guideline for refractory cases of DLE since the response to immunosuppressants is highly variable [38]. There remains a crucial need to develop a specific treatment for refractory chronic lupus skin lesions.

3. PATHOGENESIS OF CUTANEOUS LUPUS ERYTHEMATOSUS

The pathogenesis of CLE is not yet fully understood. Nevertheless, research has revealed that it is a multifactorial disease in which environmental factors, dysregulation of the immune response, and genetic predisposition have determining roles.

Among environmental factors, it has been observed that various drugs can induce skin lesions in patients diagnosed with SLE (Figure 5). Typically, these drug-induced lesions are of the subacute subtype and rarely correspond to chronic cutaneous lupus erythematosus. The drugs most often associated with CLE lesions are antihypertensive, particularly hydrochlorothiazide and calcium channel blockers, as well as terbinafine. Other drugs that have been involved in these lesions, although less frequently, include chemotherapy agents, antihistamines, leflunomide, interferon, antiepileptics, statins, lansoprazole, and nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen and piroxicam [39]. The exact mechanism by which these drugs induce lesions is not yet fully understood, but it is suspected that they enhance the innate immune response by increasing the number of neutrophils. These neutrophils form structures known as *neutrophil extracellular traps* (NETs), which are composed of chromatin networks, granular proteins, and DNA, aiming to capture and eliminate pathogens. NETs could expose more autoantigens and, therefore, contribute to an increase in autoantibodies and autoimmunity [40]. Some tumor necrosis factor-alpha (TNF-α) inhibitors may cause CLE as a result of the immunogenicity of these drugs, although newer formulations have lower immunogenicity and they have also induced CLE lesions. The possibility of an "unmasking" component of a pre-existing CLE, which may be predisposed but inactive, is also considered [41].

Other environmental factors that have been described could include smoking or sedentary lifestyle, as they increase cytokine levels and promote inflammatory states [42]. Nevertheless, the environmental factor most associated with CLE seems to be exposure to ultraviolet (UV) radiation (Figure 5).

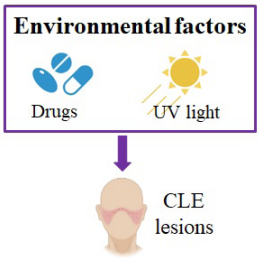

FIGURE 5. Environmental factors can induce CLE lesions. Antihypertensive drugs, NSAIDs, antihistamines, among others, and UV irradiation are the most significant factors.
SOURCE: Author.

Research suggests that exposure to UV rays can act as a triggering factor in CLE, promoting skin damage, increasing cytokine production by epithelial cells, and inducing apoptosis or necrosis of keratinocytes [43]. When keratinocytes die, they release inflammatory cytokines and chemokines that attract lymphocytes and plasma cells to the lesion. The cellular death of keratinocytes also results in the release of nuclear genetic material, and in combination with a deficient cellular clearance process, these genetic materials can stimulate antigen-presenting cells, thereby increasing autoantibody production [44]. Protection against ultraviolet radiation through the use of protective creams has been shown to significantly prevent cutaneous lesions in CLE, reinforcing the idea that UV exposure is a crucial factor in pathogenesis [45].

The dysregulation of the immune system is also considered crucial in understanding the pathogenesis of CLE. This dysregulation affects both innate and adaptive immunity, involving antigen-presenting cells, T cells, and B cells (Figure 6).

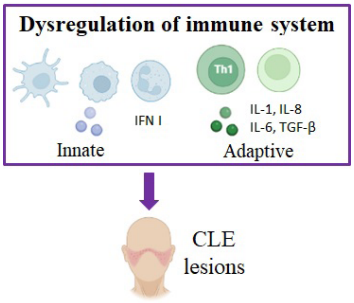

FIGURE 6. Immunological dysregulation is also another determining factor in the formation of CLE lesions. Innate immunity is essentially dysregulated at the level of dendritic cells, neutrophils, and macrophages, producing high levels of type I interferon (IFN I). In adaptive immunity, lymphocytes, especially Th1 cells, are responsible for producing inflammatory cytokines such as interleukins (IL) type 1, type 8, type 6, or transforming growth factor-beta (TGF-β).
SOURCE: Author.

As mentioned earlier, the death of keratinocytes, whether due to UV exposure or other reasons, produces cellular debris that antigen-presenting cells, such as plasmacytoid dendritic cells (pDCs), identify, causing them to activate the T-cell response. It has been discovered that there are many pDCs present in discoid lupus lesions, and these increase further after overexposure to UV radiation [46]. pDCs are the primary producers of type I interferon, which is one of the key cytokines described in CLE lesions. Interferon-alpha induces the production of chemokines involved in recruiting lymphocytes, such as CXC chemokine ligand 9 (CXCL9) or ligand 10 (CXCL10), further promoting the inflammatory state [47].

Large quantities of neutrophils have also been observed in discoid lupus, acute lupus, subacute lupus, and panniculitis lesions [48]. Neutrophils form neutrophil extracellular traps (NETs) that further promote immune activation. Macrophages have also been prominently observed, especially in discoid lupus lesions. They modulate the differentiation of T cells toward T-helper 1 (Th1) differentiation, promoting local inflammation [49].

It has been found that CLE lesions share extensive lymphocytic infiltrates with a predominance of $CD4^+$ T lymphocytes with an imbalance toward Th1, cytotoxic $CD8^+$ T lymphocytes, as well as a type I interferon signature and proinflammatory cytokines, including IL-1α, IL-1, IL-8, TNF-α, IL-6 [50]. In CLE lesions, fewer Th17 lymphocytes have been observed compared to psoriasis lesions or systemic lupus erythematosus (SLE) [51], but some studies have noted elevated gene expression of IL-17 [52]. The role of Th17 lymphocytes in CLE lesions is not entirely clear. However, there is evidence of a reduced number of $FoxP3^+$ regulatory T cells (Tregs) in CLE lesions, explaining the lack of efficient inflammation suppression [53]. Regulatory T cells are involved in inhibiting inflammation by secreting inhibitory cytokines such as IL-10 and TGF-β, as well as through direct contact with helper T cells [54]. The role of B lymphocytes is not entirely clear in CLE lesions. Some patients do not exhibit autoantibodies, while others have high levels. The concept is that autoantibodies bind to autoantigens present in the skin releasing cytokines and consequently causing local inflammation. However, the exact involvement in the pathogenesis is not fully understood. Moreover, when monoclonal therapies against B cells have been applied, significant improvement in lesions has not been observed, suggesting that this cell type may not play a crucial role in lesion pathogenesis.

Genetic studies, including those of families, affected individuals, and populations in genome-wide association studies (GWASs), have identified genetic polymorphisms, mutations, and risk alleles in CLE populations. However, no single gene has been identified as the direct cause of the lesion [55] (Figure 7). The pathways most affected or altered by these polymorphisms are related to the function of innate and adaptive immune responses, predisposing to the immune dysregulation described earlier. The most important pathways include apoptosis and/or cell death, DNA processing, the type I interferon pathway, leukocyte migration, the complement cascade and clearance of cellular debris, immune checkpoint control of T cells, antigen presentation, and antibody production [56]. Although several risk alleles have been found in CLE, only one monogenic cause has been identified [57]. Mutations in the three-prime repair exonuclease 1 (TREX1) represent the only monogenic cause of cutaneous lupus identified so far, resulting in the rare familial manifestation of chilblain lupus [58]. These patients develop red-purple lesions induced by cold on the distal part of the extremities, which can

ulcerate or blister. TREX1 is a cytoplasmic DNA exonuclease that plays an essential role in the homeostatic degradation of single-stranded DNA, and TREX1 deficiency leads to intracellular accumulation of this DNA. The recognition of these accumulated nucleic acids by innate immune receptors results in chronic hyperactivation of the type I interferon pathway [59].

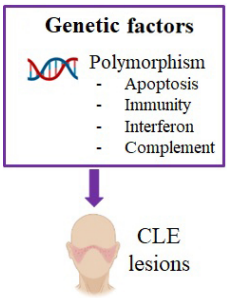

FIGURE 7. Genetic factors predispose individuals to CLE lesions. There is no single gene but polymorphisms related to cellular apoptosis, innate or adaptive immunity, interferon pathway, or the complement pathway, among others, have been observed.
SOURCE: Author.

Recent research on sexual dimorphism in human skin identified the transcription co-factor vestigial-like family member 3 (VGLL3) as an essential regulator of genes biased in the female gender that may contribute to an autoimmune phenotype in women [60]. VGLL3 influences type I interferon responses and promotes the expression of genes encoding inflammatory molecules, many of which are genetic risk variants previously identified in autoimmune diseases, including SLE. In normal skin, VGLL3 is expressed more highly in tissues derived from females. Additionally, the overexpression of the *VGLL3* gene in the skin of mice used in scientific experiments induced a disease similar to CLE. When analyzing the expression of *VGLL3* and other genes related to it, such as B-cell activating factor (BAFF) or integrin alpha M (ITGAM), in the lesions of patients with CLE, no gender differences were observed. This suggests that blocking VGLL3 could be a good therapy for CLE, as it is present in both men and women in active lesions, and that the regulation of the *VGLL3* gene and the mechanisms involved in the initial activation of autoimmunity in women need to be studied in more detail.

Gene expression studies using DNA chips with tissue samples from lesional and non-lesional skin of patients with CLE and discoid lupus erythematosus (DLE) in recent years have revealed differences in gene profiles, confirming the importance of the type I interferon pathway, pathways related to dendritic cells,

Toll-like receptor (TLR) pathways, and T-cell pathways, with a higher prevalence of type 1 helper T-cell populations compared to type 2 populations [61, 51]. A notable difference has been the persistence of regulatory T-cells in DLE lesions that produce high levels of TGF-β, an anti-inflammatory protein that also contributes to fibrosis [62]. Elevated levels of TGF-β have been associated with fibrosis formation in primary fibroblasts from patients with DLE, resulting in more pronounced scars and marked atrophy [63].

The study of the changes in gene expression that activate or deactivate biological pathways without altering the underlying genetic code is known as *epigenetics*. These changes can be regulated by factors such as age, external environmental factors, and internal factors [64]. DNA methylation, involving the addition of methyl tags to the gene, is an example of this epigenetic regulation. When a gene is methylated, its expression is silenced. In patients with DLE lesions, methylated regions have been observed in the DNA of naive $CD4^+$ T cells, affecting their cellular proliferation, apoptosis, and antigen presentation [65]. On the other hand, in CLE lesions, demethylated genes related to the formation of perforin and CD70, co-stimulatory molecules for B cells, have been detected. This demethylation results in an overexpression of these proteins, inducing the production of more autoantibodies by B cells [66, 67].

In recent years, there has been an emphasis on the research of microRNAs or miRNAs as another epigenetic mechanism to control gene expression in diseases such as CLE. Studying the impact of miRNAs on CLE can provide a better understanding of the underlying pathogenic mechanisms and may identify new therapies to restore normal epigenetic patterns.

4. Definition and biogenesis of microRNAs

MicroRNAs, also known as *miRs* or *miRNAs*, are small, highly-conserved non-coding RNA sequences ranging from 19 to 25 nucleotides [68]. Although they are currently recognized as indispensable in the regulation of many biological pathways and a key mechanism in epigenetics, they were not discovered until 1993. The discovery occurred when researchers were sequencing the nematode *Caenorhabditis elegans* (*C. elegans*) genome to investigate heterochronic genes involved in the synchronized development of *C. elegans*. During this research, they noticed that the *lin-4* gene had a 700-base pair (bp) fragment that did not contain conventional start and stop codons [69]. Interestingly, this mutation did not seem to affect the function of the *lin-4* gene. They also discovered that the *lin-4* gene had two transcripts: one of 61 nucleotides and another of 22 nucleotides. Independently, another group of researchers was studying the *lin-14* gene and found that a mutation in this gene could reverse the phenotype associated

with the *lin-4* gene. This led researchers to consider that *lin-4* transcripts could be complementary to a 3′ untranslated region of the *lin-14* gene messenger RNA, and therefore, they could regulate the translation of the *lin-14* gene through a 3′-4′ interaction of antisense RNA. For the first time, a new regulatory mechanism was described and the first miRNA was discovered, *lin-4* [70]. Subsequently, another miRNA, let-7, was identified in the same organism, with a length of 21 nucleotides, and it was related to *lin-14*, *lin-28*, *lin-41*, *lin-42* and *daf-12* genes. When let-7 miRNA was mutated, alterations in these genes' functions occurred, as observed during the development of *C. elegans* [71].

In recent years, thousands of miRNAs have been discovered using new advances in molecular biology and bioinformatics, gaining relevance in translational research. miRNAs can modulate gene expression in the same cell where they are synthesized, or they can be secreted, packaged in extracellular vesicles, transported from a parent cell to neighboring cells, and regulate important biological functions in recipient cells [72]. Moreover, a single miRNA can have multiple target genes, and a single gene can be targeted by multiple miRNAs [73], making them a potent system for modulating and fine-tuning gene expression. They regulate approximately 60% of all protein-coding genes [74].

The biogenesis of miRNAs has been extensively investigated to understand how it can be regulated at the cellular level [75]. miRNA sequences found in DNA genes are transcribed in the cell nucleus by RNA polymerase II or III (Pol II or III). Once transcribed, the microprocessor complex cleaves the primary miRNA (pri-miRNA) to obtain a 70-nucleotide sequence called *pre-miRNA*. The microprocessor complex is composed of Drosha, a member of the RNase III family, and DGCR8, DiGeorge critical region 8. The pre-miRNA is transported from the cell nucleus to the cytoplasm through exportin-5, a protein responsible for nuclear transport. In the cytoplasm, the DICER RNase, together with the TRBP complex, removes the terminal loop, resulting in a miRNA duplex. The duplex binds to the Argonaute protein family (AGO2). The directionality of the miRNA determines its nomenclature in the mature form. The 5p and 3p strands can be loaded onto AGO2 proteins; however, the selection of 5p or 3p is based on thermodynamic stability at the 5′ ends of the miRNA duplex. Usually, strands with lower 5′ stability or 5′ uracil stability are preferentially loaded onto AGO2 and are called *guide strands*. The remaining strand is called the *passenger strand* and is degraded. The guide strand incorporates into the RNA-induced silencing complex (RISC), forming the minimal miRNA-induced silencing complex (miRISC), and then the mature form of the miRNA is able to recognize and pair with complementary mRNA sequences (Figure 8).

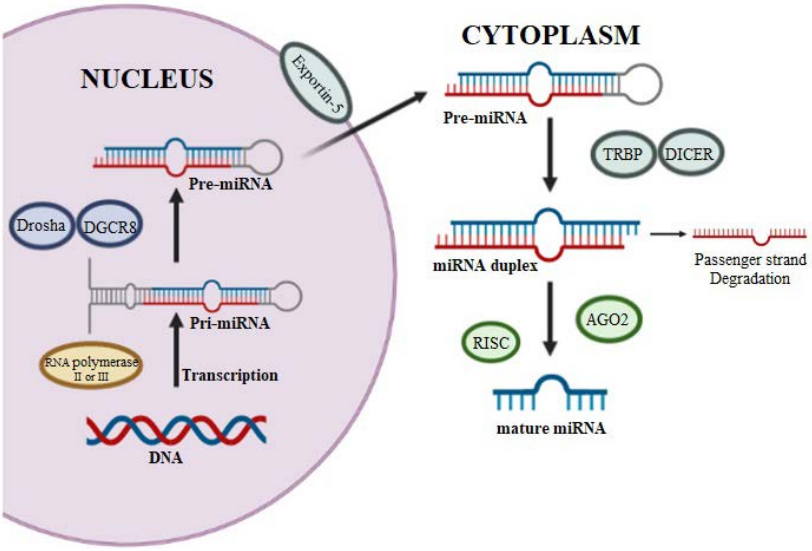

FIGURE 8. Mechanism of miRNA biogenesis. The process begins inside the cell nucleus, where the pre-miRNA is obtained. A transporting protein then carries the pre-miRNA to the cell cytoplasm, where the final mature functional form develops.
SOURCE: Author.

miRNAs are involved in almost all cellular processes [76]. Under normal physiological conditions, miRNAs regulate cellular functions. However, in diseases, miRNAs can change, inducing altered gene expression leading to an aberrant phenotype [77]. When they are dysregulated, they can disrupt relevant cellular processes, promoting pathological conditions. On the other hand, they can also play a protective role in attempting to restore cellular homeostasis. A balance of miRNAs is crucial for correct cellular and tissue physiology.

5. MICRORNAS IN CUTANEOUS AUTOIMMUNE DISEASES

MicroRNAs are involved in development, organogenesis, proliferation, apoptosis, and various other cellular processes. In skin physiology, several miRNAs have recently been identified, playing roles in epidermal and dermal proliferation, pigmentation, aging, wound healing, skin microbiome, and skin immunity [78]. miR-24 has been reported to regulate epidermal differentiation [78], and miR-21 controls epithelial proliferation, differentiation, and transition [78]. Under normal physiological conditions, miRNAs properly regulate cellular functions. However, in disease miRNAs can change, inducing altered gene expression

leading to an aberrant phenotype. When dysregulated, they can disrupt relevant cellular processes, promoting pathogenic conditions [79].

Among dermatological diseases, we can include those caused by infections (bacterial, viral, or fungal), allergies, parasites, cancer, or even genetic and/or unknown causes. However, focusing on cutaneous autoimmune diseases, we find that these are characterized by immune system dysregulation resulting in the formation of autoantibodies against skin autoantigens. Although the cause of this immune dysregulation is not fully known, triggers can include genetic, biochemical, environmental factors, among others. In recent years, there has been an increase in the prevalence of cutaneous autoimmune diseases [80]. Among the most well-known are psoriasis, vitiligo, scleroderma, pemphigus, cutaneous lupus erythematosus (CLE), and dermatomyositis. Globally, the most prevalent are psoriasis (2-3%) [81], vitiligo (0.5%) [82], scleroderma (7-48.9 per million) [83], and pemphigus (5-30 per million) [82]. Atopic dermatitis is also highly prevalent, affecting 1-3% of the global population. Initially more associated with allergic comorbidities such as asthma, allergic rhinitis, and food allergy; in recent years an important connection with autoimmunity has been established [84].

Both psoriasis and atopic dermatitis exhibit clinical similarities with CLE lesions, presenting with erythema and scaling. There are also similarities in inflammatory cytokines and biological pathways. Psoriasis is characterized by hyperproliferation and altered differentiation of epidermal keratinocytes and infiltration of leukocytes, mainly neutrophils, myeloid cells, and T cells, leading to the secretion of inflammatory mediators such as TNF-α, interferon-gamma (IFN-γ), and interleukin IL-1, IL-22, and IL-18. The IL-23/IL-17 signalling pathway has been identified as the primary one, causing molecular and cellular changes characteristic of psoriatic lesions [85]. Atopic dermatitis is characterized by the disruption of the epidermal barrier, activation of a type 2 helper T-cell (Th2) response, and disruption of the skin microbiota [86]. An increase in immunoglobulins E (IgE) and eosinophils in the lesion is observed, increasing inflammation and skin damage through the production of reactive oxygen species, inflammatory cytokines, and the release of toxic granule proteins [87]. Similarly, CLE presents with leukocytic infiltration in the lesion [47, 50], and it is also characterized by high levels of cytokines such as TNF-α, interferon-gamma (IFN-γ), and interleukin 1 (IL-1) [50]. In CLE lesions, T-helper cell type 1 or 2 (Th1 or Th2) profiles predominate rather than type 17 (Th17), although some authors have emphasized IL-17 [52]. We will now focus on the importance of miRNAs in psoriasis and atopic dermatitis to establish a set of miRNAs and common biological pathways between these two clinically similar autoimmune skin diseases and CLE.

The role of miRNAs in psoriasis has been extensively investigated, identifying over 30 miRNAs relevant to lesion development. We will focus on the most

prominent ones, starting with miR-203. It was the first miRNA identified in psoriasis lesions and it is primarily expressed in keratinocytes. It is directly related to inflammation production targeting *SOCS3* gene. Studies have confirmed that the main role of miR-203 is to regulate psoriasis-related cytokines production, such as TNF-α, IL-24, and IL-8, in keratinocytes [88-90]. In vitro experiments have demonstrated that inhibiting miR-203 reverses the effects induced by interleukin-17 stimulation in HaCaT cells, an immortalized human keratinocyte cell line. Inhibiting miR-203 reduces vascular endothelial growth factor secretion in these cells by inhibiting the JAK2/STAT3 signalling pathway involved in pathological angiogenesis [88]. Recent findings indicate that miR-203 promotes keratinocyte proliferation by targeting *NR1H3* and *PPARG* genes [90]. Thus, miR-203 plays a significant role in psoriasis, contributing to epidermal hyperplasia, inflammation, and angiogenesis (Figure 9).

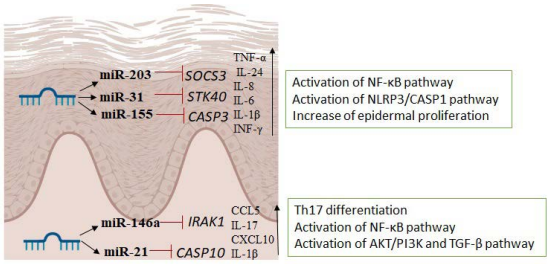

FIGURE 9. Role of the most relevant miRNAs involved in psoriasis lesions.
SOURCE: Author.

Another important miRNA in psoriasis is miR-31, involved in normal skin physiology by regulating keratinocyte growth and hair differentiation [91]. Elevated levels of miR-31 have been detected in the blood and lesional psoriatic epidermis. Its pathogenic role is mainly based on disrupting the activated B cell nuclear factor kappa B (NF-κB) signalling [92, 93]. NF-κB is a crucial mediator in psoriasis pathogenesis, participating in inflammation, cell proliferation, differentiation, and apoptosis. Serine/threonine kinase 40 (STK40), a negative regulator of NF-κB signalling, has been identified as a direct target for miR-31 [94]. miR-31 activates the NF-κB pathway by blocking the *STK40* gene, and promotes the secretion of chemokines CXCL1, CXCL8, CXCL5, and interleukin-1β, activating vascular endothelial cells and attracting leukocytes to the lesion site. Primary keratinocytes stimulated with TGF-β1, a cytokine highly expressed in psoriasis lesions, significantly increased miR-31 gene expression [94]. This effect was also observed when keratinocytes were stimulated with other relevant cytokines in psoriasis lesions, such as IL-6, IL-22, interferon-gamma (IFN-γ), and TNF-α [94].

miR-31 is also involved in keratinocyte proliferation, as in vivo experiments have demonstrated that miR-31 promotes epidermal hyperplasia by blocking the *PPP6C* gene, a negative regulator of G1-S phase progression in the cell cycle [93]. Endothelin-1, a peptide involved in cell proliferation and leukocyte chemotaxis, has been positively associated with elevated miR-31 levels in the blood [92]. In summary, miR-31 plays a crucial role in psoriasis, favoring epidermal proliferation and local inflammation in the lesion (Figure 9).

miR-146a is overexpressed in skin lesions and peripheral blood mononuclear cells (PBMCs) of patients with psoriasis [95, 96]. Recognized for its protective role in epidermal inflammation, miR-146a inhibits the *NFKB1*, *IRAK1*, and *CARD10* genes, along with the production of the chemokine CCL5 [96-98]. Gene expression levels of miR-146a in both psoriatic skin and PBMC samples positively correlate with IL-17 levels found in the skin and serum of these patients [96]. However, the *IRAK1* target gene was only reduced in PBMC samples, not in lesional skin samples. In in vivo studies using murine models of psoriasis, inhibiting miR-146a was shown to promote the onset of psoriatic lesions, epidermal hyperproliferation, and inflammation formation through the accumulation of IL-17 and IL-8, enhancing neutrophil infiltration into lesion areas [98] (Figure 9).

miR-155 has been demonstrated to be regulated in the blood and lesional skin of psoriasis patients [99, 100]. Involved in the keratinocyte cell cycle, in vitro studies have shown that inhibiting miR-155 decreases keratinocyte proliferation and increases the expression of apoptotic genes *PTEN*, *PIP3*, *AKT*, *BAX*, and *BCL2* [100]. miR-155 is also involved in keratinocyte proliferation, apoptosis, and psoriasis inflammation. Overexpression of miR-155 hinders keratinocyte apoptosis, potentially by targeting the *CASP3* gene, a validated target gene of miR-155 [101]. Additionally, when keratinocytes are stimulated, miR-155 is overexpressed, leading to increased Toll-like receptor 4, NF-κB pathway-related proteins such as TNF-α, IL-18, IL-6, and IL-1β, and activation of the NLRP3/CASP1 inflammasome pathway [102] (Figure 9).

Finally, both epidermal cells and infiltrated T cells in psoriasis lesions exhibit increased expression of miR-21 [103]. Through in vitro experiments, this miRNA has been shown to regulate keratinocyte proliferation by blocking the *CASP8* gene [104]. It also promotes proliferation by regulating the AKT/PI3K and TGF-β signalling pathways [105, 106]. Concerning its role in inflammation, exposure of keratinocytes to UVB radiation increases miR-21 gene expression. This positive regulation promotes the production of proinflammatory cytokines such as IL-6 and IL-1β, as well as chemokines like CCL5 and CXCL10 in keratinocytes [106]. Gene expression of miR-21 increases in both differentiated type 1 and type 2 helper T cells after activation using anti-CD3 and anti-CD28 antibodies, indicating direct involvement in helper T-cell activation regardless of subtype [103] (Figure 9).

miRNA expression profiles in cutaneous lesions of patients with atopic dermatitis are characterized by elevated expression of miR-155, miR-146, let-7i, miR-24, miR-27a, miR-29a, miR-193a, miR-199a, and miR-222 [107]. Other authors have also found increased expression of miR-4270, miR-211, miR-4529-3p, and miR-29b [108], and decreased expression of miR-143, miR-184, miR-135a, and miR-4454 in skin biopsies of patients compared to healthy controls [109]. Among the extensively studied miRNAs in atopic dermatitis pathogenesis are miR-155-5p, miR-146a, and miR-143 (Figure 10).

miR-155 is predominantly expressed in the lesional skin of atopic dermatitis in infiltrated immune cells. This miRNA plays a role in regulating allergen-induced inflammation by targeting the *CTLA4* gene, a negative regulator of T-cell activation [110]. It affects T-cell proliferation and differentiation, shifting towards a Th17-type response [110]. Studies in mice have confirmed that increased miR-155 expression is associated with enhanced atopic dermatitis [111]. Additionally, gene expression levels of miR-155 increase in TNF-α-stimulated HaCaT cells, blocking its target gene *PKIA* and further promoting disruption of the epithelial tight junction, as well as increasing key factors that foster inflammation [112] (Figure 10).

miR-146a has been involved in the inflammatory response of atopic dermatitis, with increased expression in keratinocytes and chronic lesional skin of patients. Its role is anti-inflammatory, alleviating chronic skin inflammation in atopic dermatitis by suppressing innate immune responses in keratinocytes. It targets various proinflammatory factors, including *CCL5* and *CCL8* genes, and ubiquitin D (*UBD*), inducing interferon-γ production in primary human keratinocytes [113] (Figure 10).

Another dysregulated miRNA in the lesional skin of patients with atopic dermatitis is miR-143 [109]. It has a direct relationship with the IL-13 receptor alpha 1 (IL-13R) and modulates IL-13 activity involved in Th2 lymphocytic responses (Figure 10).

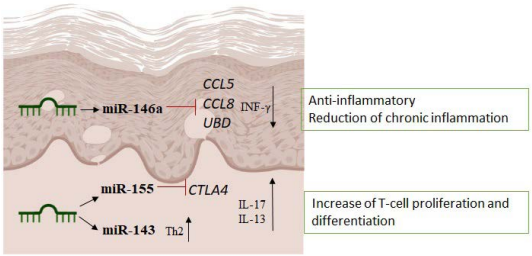

FIGURE 10. Role of the most relevant miRNAs involved in atopic dermatitis.
SOURCE: Author.

6. MicroRNAs in cutaneous lupus erythematosus: Similarities with cutaneous autoimmune diseases

The role of miRNAs in systemic lupus erythematosus (SLE) has been extensively explored, with studies investigating their detection in serum, plasma, urine, and peripheral blood mononuclear cells (PBMCs). Gene expression levels have also been linked to the different clinical manifestations of SLE; however, little research has been conducted focusing solely on CLE.

The initial study on miRNAs in CLE was published in 2018. It conducted a specific analysis of miRNAs to compare DLE lesions with SCLE lesions [114]. The results identified a distinct miRNA signature (miR-31 and miR-485-3p) in DLE lesions compared to non-lesional skin.

miR-31 was identified as a miRNA derived from keratinocytes located in the epidermis of DLE lesions. This miRNA plays a role in epidermal apoptosis by positively regulating apoptotic genes (*BIM*, *BAX*, *p53*, and *CASP3*). Additionally, it is involved in NF-κB activation, leading to increased secretion of inflammatory cytokines such as IL-1β, IL-12, and IL-8 in keratinocytes [114]. The interaction between keratinocytes and lymphocytes is crucial in cutaneous autoimmune diseases, and miR-31 was found to promote the recruitment of neutrophils and intermediate monocytes, thereby enhancing immune cell recruitment to the DLE lesion site and perpetuating inflammation [114].

miR-485-3p was found to be expressed in infiltrating lymphocytes and fibroblasts in DLE lesions. Its role focused on activating $CD4^+$ and $CD8^+$ T cells and promoting fibrosis by positively regulating fibrotic genes (*SMAD3*, *COL3A1*, and *TGFBR*) in primary fibroblasts [114]. The fibrosis mechanism controlled by miR-485-3p is based on the fact that its target gene is the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1A*), known for its protective role in the development of fibrosis. Therefore, when this miRNA blocks it, the protective function controlled by the *PPARGC1A* gene in fibrosis formation is eliminated (Figure 11).

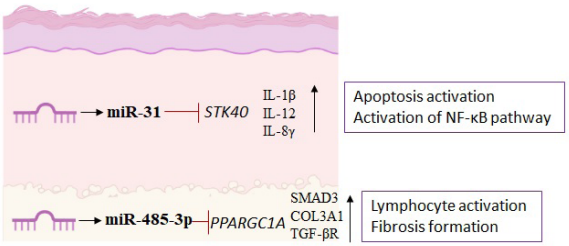

Figure 11. Role of miRNAs in the formation of DLE lesion.
Source: Author.

Subsequently, a study was conducted selecting a series of circulating miRNAs that could be related to the immune response, inflammation, or fibrosis formation in CLE lesions [115]. It was discovered that miR-150, miR-1246, miR-21, and miR-146 were all downregulated in PBMC samples from patients with both CLE subtypes, SCLE and DLE. These miRNAs were associated with specific cell types. $CD123^+/CD196^+/IDO^+$ cells positively correlated with miR-10 gene expression in DLE patient samples. In tissue analysis, $CD4^+/IL\text{-}4^+$ and $CD20^+/IL\text{-}10^+$ cells showed low regulation of miR-21 in SCLE patient samples. miR-21 regulates genes such as *SMAD3*, *SMAD7*, and *COL1A1*, directly related to fibrosis formation. Therefore, its role might be closely linked to lesion scarring, explaining why lesions in DLE patients leave scars while those in SCLE patients do not.

Recently, another article has been published on the role of miRNAs in the pathogenesis of CLE [116]. In this case, miR-885-5p was found to be downregulated in both SCLE and DLE lesions compared to healthy skin in the same patients. Its primary location is in the epidermis, indicating its regulation of biological processes related to keratinocytes. In in vitro experiments with primary keratinocytes, miR-885-5p gene expression decreased when cells were stimulated with interferon-α or exposed to UVB radiation, two triggers for CLE lesions. Two target genes of miR-885-5p were identified in the study: *PSMB5* and *TRAF1*. High levels of *PSMB5* led to the increase of inflammatory cytokines in the NF-κB pathway and of proliferation-related genes (*K16*, *BIRC5*, *TP63*, and *CDK4*). On the other hand, high expression of *TRAF1* resulted in enhanced leukocyte attraction to the lesion. Consequently, the study demonstrates that the role of miR-885-5p in CLE pathogenesis is to control epidermal inflammation and proliferation by inhibiting the *PSMB5* gene and to the regulate immune system recruitment by inhibiting the *TRAF1* gene [116]. The low levels of this miRNA in CLE lesions lead to abnormal inflammation and keratinocyte proliferation, along with continuous lymphocyte recruitment to the lesion site (Figure 12).

If we attempt to find similarities in miRNAs and/or biological pathways among CLE, psoriasis skin lesions, and atopic dermatitis lesions, we can conclude that there is no miRNA common to all three pathologies. However, miR-31 is shared by CLE and psoriasis, and miR-155 and miR-146 are common to psoriasis and atopic dermatitis. The fact that miR-31 is common to DLE and psoriasis means that both pathologies share the NF-κB inflammation pathway, a dysregulated keratinocyte apoptosis process, and epidermal hyperplasia. On the other hand, psoriasis and atopic dermatitis share miR-155 and miR-146a. This means that both pathologies share the regulation of Th17 helper T cells and the production of chemokines such as CXCL8, essential for these two dermatological diseases.

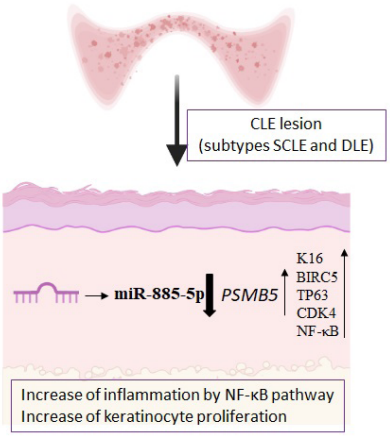

FIGURE 12. miR-885-5p is the only common miRNA in both subtypes of CLE. When found in low levels, it can lead perpetuation of inflammation, increased proliferation of keratinocytes, and enhanced lymphocytic attraction to the lesion area.
SOURCE: Author.

7. CLINICAL APPLICABILITY OF MICRORNAS AS BIOMARKERS OR GENE THERAPY IN CUTANEOUS AUTOIMMUNE DISEASES

Circulating miRNAs have been described as biomarkers as they can be found in various body fluids, such as serum, plasma, urine, saliva, tears, amniotic fluid, and cerebrospinal fluid. Some of their inherent properties make them very attractive as potential biomarkers. They are accessible, stable, resistant to degradation caused by ribonucleases, and can be easily detected in small sample volumes using reverse transcription quantitative polymerase chain reaction (RT-qPCR) [117]. However, their origin or function is still unclear. Nevertheless, changes in circulating miRNA profiles have been observed to correlate with many parameters and clinical manifestations, such as gastrointestinal diseases, cardiovascular diseases, and primary and metastatic cancers [118]. It is noteworthy that miRNAs with important immunomodulatory effects in pathogenesis are not necessarily the best biomarkers. For example, circulating miRNAs show limited or no correlation with miRNA expression in the skin, distinguishing them from other conditions. Additionally, it is unclear whether dysregulated miRNAs in the blood are specific to the disease or related to systemic inflammation. So far, despite the fact that various miRNAs have been studied, none of them are used as biomarkers in routine clinical practice.

Research demonstrates that, especially in the case of psoriasis, several miRNAs could be used as biomarkers in inflammatory skin diseases, either for diagnosis, assessing lesion activity, or monitoring treatment.

Diagnostic biomarkers

A good diagnostic biomarker should be able to easily differentiate affected skin areas from unaffected ones and be specific to the dermatological disease compared to other pathologies. In patients with psoriasis, elevated gene expression levels of miR-223 and miR-143 were observed in PBMC samples. Receiver operating characteristic (ROC) curve analysis demonstrated that both miR-223 and miR-143 had the potential to distinguish psoriasis patients from healthy controls [119], suggesting they could be possible diagnostic biomarkers. Similarly, elevated levels of miR-369-3p in serum and skin were also distinctive in psoriasis patients compared to healthy controls [120]. Using capillary tissue samples, it was demonstrated that miR-424 and miR-19a could be good diagnostic biomarkers for psoriasis lesions, as their levels were higher compared to atopic dermatitis lesions [121, 122]. ROC curve analysis revealed area under the curve (AUC) values of 0.77 and 0.87, respectively. In atopic dermatitis, elevated expression levels of miR-203 and miR-483-5p were found in patients' serum, with areas under the ROC curve (AUC) > 0.7. Surprisingly, differential expression of miR-203 was also observed in the urine of these patients, although in this case they had lower expression levels [123]. Elevated expression of miR-155 was also found in peripheral $CD4^+$ T cells of atopic dermatitis patients compared to healthy individuals, indicating it could also be a useful biomarker for disease diagnosis [107].

Several studies have analyzed miRNA profiles in patients with SLE, but there is less research in CLE. In SLE, miRNAs in serum, plasma, and urine have been examined, establishing a relationship between these and various lupus manifestations such as nephritis, oral ulcers, and lupus anticoagulant, among others [124]. Regarding cutaneous lupus, a study included patients with SCLE and DLE lesions, as well as healthy donors, to examine a selected panel of miRNAs related to inflammation and fibrosis in serum [115]. This study showed that miR-150, miR-1246, and miR-21 were downregulated in both SCLE and DLE cases compared to healthy controls. This suggests that these miRNAs could be useful as diagnostic biomarkers for CLE. As for differences between CLE subtypes, no specific miRNAs were identified for DLE; however, low levels of miR-23b and miR-146 could be characteristic of SCLE [115].

There is another study that determined miR-31 and miR-485-3p to have higher expression levels in DLE lesions compared to SCLE lesions [114]. These miRNAs have not yet been studied as diagnostic biomarkers to differentiate between the two subtypes of CLE, but such a study could be conducted using in situ hybridizations to aid in the diagnosis once a skin biopsy is obtained. Another similar study also described miR-885-5p as a characteristic miRNA for CLE lesions. However, it has also been considered as a possible diagnostic and selective biomarker [116].

Lesion activity biomarkers

Current data suggest that certain miRNAs could potentially serve as markers of activity in psoriasis. So far, the severity of psoriasis has been assessed through PASI and BSA scores [125]. However, serological markers reflecting disease activity have not been clinically used in psoriasis. As described earlier, gene expressions of miR-223 and miR-143 are elevated in PBMCs of psoriasis patients, positively correlating with PASI scores, and have an area under the ROC curve (AUC) > 0.8 [120]. The gene expression of miR-19a found in hair roots inversely correlates with disease duration and the first hospital visit [122]. Elevated levels of miR-1266 in serum [126], reduction of miR-126, and regulation of miR-200c in plasma [127, 128], as well as increased miR-146a and miR-155 in PBMCs, can also be indicators of psoriasis activity [99, 126]. On the other hand, miR-99a in PBMCs negatively correlates with disease severity [126]. Finally, miR-369-3p levels in serum and skin have been related to disease severity [129], with miR-369-3p levels in the skin showing a positive linear relationship with PASI scores [117, 129]. In contrast, low levels of miR-369-3p and miR-135b in the skin have been associated with disease improvement and lower severity [120, 130].

A study aimed to identify a prognostic miRNA signature in children with atopic dermatitis from serum and urine through a whole-genome miRNA profile analysis. It revealed that miR-203 levels were increased in the serum of children with atopic dermatitis compared to healthy controls and they were significantly associated with increased sTNFRI and sTNFRII. However, a notable decrease of miR-203 was observed in the urine of patients. This suggests that miR-203 could be a potential biomarker to assess the severity of inflammation in atopic dermatitis lesions in the pediatric population. It is not clear if the data can be extrapolated to adults, as children with atopic dermatitis may have different miRNA expression profiles compared to adults. Further research is needed to establish biomarkers in the adult population that can predict disease prognosis, quickly identify relapse phases, and monitor treatment response.

So far, disease activity in CLE has been assessed using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) [131]. Serum levels of miR-150 have been identified to show an inverse correlation with CLASI activity scores in patients with SCLE. As this miRNA has been associated with dermal and renal fibrotic processes, we can also infer that it may be involved in the activation of inflammatory and profibrotic pathways [132, 133]. Therefore, miR-150 could be a good candidate to assess disease severity in patients with SCLE. Future studies analyzing other miRNAs in plasma or other biological fluids could offer new and interesting insights to identify biomarkers for CLE.

Treatment monitoring biomarkers

Studies have been conducted to analyze changes in miRNA expression during and after treatment in psoriasis patients. Pathological T cells and dendritic cells can trigger abnormal keratinocyte proliferation in psoriasis progression through various cytokines, especially TNF-α, which is essential for psoriasis pathogenesis. For this reason, the anti-TNF-α biological drug, commercially known as *etanercept*, can significantly suppress the gene expression at serum levels of 38 miRNAs, including miR-106b, miR-26b, miR-142-3p, miR-223, and miR-126 [134]. On the other hand, it is described that adalimumab, another anti-TNF-α drug, increases the expression levels of miR-23b. These results indicate that changes in miRNA levels may reflect a previously unknown effect of anti-TNF-α therapy [135]. Interestingly, the levels of these miRNAs were not altered when patients were treated with methotrexate but only with the aforementioned drugs. Also, the gene expression of miR-146a-5p in PBMCs correlates with a good clinical response in psoriasis patients treated with adalimumab [136]. In contrast, patients responding to etanercept had elevated gene expression levels of miR-125a in plasma [137].

So far, there have been no studies evaluating changes in miRNA levels in response to therapies for CLE or atopic dermatitis. In the clinical context, the use of miRNAs as treatment response biomarkers would be very useful as they could contribute to better monitoring disease, provide earlier indications of treatment effectiveness, and even help prevent the development of fibrotic scarring lesions that could significantly affect the quality of life of patients.

miRNA-based therapies are the most recent among RNA-based therapies that have emerged in the last 10 to 15 years [138]. The collected data suggest that miRNAs could be promising pharmacological targets for the treatment of various diseases [139]. One therapeutic approach involves inhibiting miRNAs using synthetic analogues with antisense inhibition capacity. Additionally, a therapy in which a miRNA analogue with a similar function, known as *miRNA mimics*, is administered can also be considered. However, when administered systemically, miRNAs can be susceptible to degradation by serum nucleases, eliminated by immune system cells, and excreted through the kidneys via renal filtration. On a cellular level, characteristics such as negative charge, hydrophilicity, and the relatively large size of miRNAs limit their ability to penetrate cell membranes.

For this reason, in dermatological diseases, topical administration of miRNAs could be a more attractive approach and could help avoid associated systemic problems [140]. Side effects, dilution, and toxicity often associated with systemic administration could be avoided when miRNAs are formulated and applied directly to the affected skin. The main limitation in transdermal administration of miRNAs

is the cutaneous barrier, as the inherent function of the skin is to protect the body from the undesired effects of the environment [141]. The stratum corneum, one of the layers of the skin, constitutes the main barrier for percutaneous absorption of compounds and, at the same time, prevents water loss, containing non-living keratinocyte scales stored in a lipid-rich matrix. This makes it impermeable and prevents the absorption of substances larger than 500 daltons, whether hydrophilic or lipophilic [141]. Furthermore, in the case of inflamed skin, penetration can be even more challenging [142].

Direct administration of miRNAs without the use of suitable vectors or vehicles, known as *"naked" miRNA administration*, will likely yield unsatisfactory results due to their rapid degradation and ineffective penetration through the skin. One option to counteract this problem is to incorporate miRNAs into nanocarriers that enhance their stability and administration, increasing their resistance to degradation by nucleases present in the skin [143].

Nanotechnology along with miRNA gene therapy forms a promising combination for the design of topical therapies in autoimmune dermatological diseases. Research in psoriasis has been a leader in this field. An example is the use of liposomal vesicles as a vehicle for miRNA administration in psoriasis treatment [145]. Liposomes are lipid-based nanocarriers that offer stability, high payload efficacy, and low cytotoxicity. The liposome formulation involves creating amphiphilic phospholipid bilayers that encapsulate an aqueous core. In this study, Lambert and colleagues combined DOTAP, DOPE, and cholesterol as stabilizers with 30% ethanol to create SECosomes, a variant of liposome with high penetration capacity. This system was used to deliver an RNA silencer in a humanized mouse model of psoriasis with the aim of silencing the expression of human beta-defensin 2 and an antimicrobial peptide that is overexpressed in psoriasis lesions [144]. By modifying the cholesterol composition and substituting sodium cholate with 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), they developed a modified type of SECosome called *DDC642*. This DDC642 was able to deliver pre-miR-145 or anti-miR-203 oligonucleotides to melanocytes and keratinocytes, respectively, in order to modulate the levels of their target genes. Moreover, DDC642 complexes proved to be selective, as they managed to repress target genes in the epidermis of the human psoriasis 3D skin model without affecting the dermis or accessing the circulatory system [144]. This study is proof of the concept that elastic liposomes could be used as a topical administration system for miRNA-based therapies in psoriasis (Figure 13).

Recently, gene therapy using a nanocarrier gel mimicking high-density lipoproteins (rHDL) as a vehicle to encapsulate anti-miR-210 has been developed. This therapy has been evaluated as a topical treatment in mice with imiquimod (IMQ)-induced psoriasis, a potent activator of the immune system through

TLR7/8 receptors. This substance is widely used in experimental models to induce psoriasis [145]. Gene therapy with the nano-carrier gel produced significant results in the treatment of psoriasis in these mice. This therapy reduced the expression of miR-210 in skin lesions and $CD4^+$ T cells in the spleen, improving various aspects of dermatitis, such as erythema, scales, acanthosis, and the infiltration of inflammatory cells in the skin. Moreover, a reduction in the proportion of Th1 and Th17 helper T cells in dermal and splenic cells of mice treated with this therapy was observed [145].

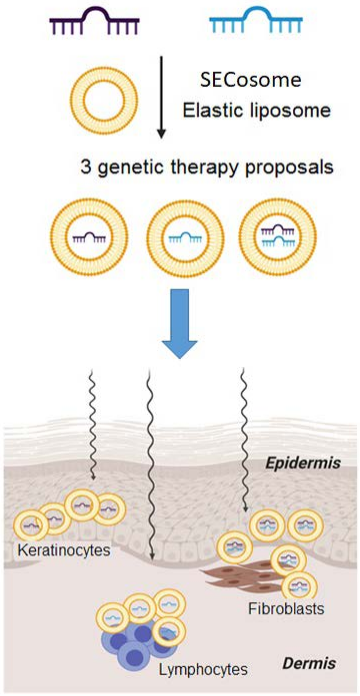

FIGURE 13. SECosome could be applied to protect miRNAs and design a novel genetic therapy for the treatment of autoimmune cutaneous lesions. The characteristics of the nanovehicles could be modified to lead the nanoparticle to the target cell.
SOURCE: Author.

8. FUTURE PERSPECTIVES

The world of miRNAs in CLE is still largely unexplored. Specific miRNAs for each type of lesion have been identified, and some are common to the most characteristic subtypes (SCLE and DLE). Studies have been conducted to understand

their role in the pathogenesis of CLE. However, it is yet to be determined whether they can be applied in clinical practice as biomarkers or gene therapies.

To advance in this field, research projects involving various research institutes and hospitals with multidisciplinary teams are necessary. These studies could explore the evolution of miR-885-5p expression in CLE lesions, how it varies with disease activity, and its relationship with activity indices such as CLASI. Additionally, it needs to be determined whether this expression normalizes when lesions disappear and if aberrant expressions of miR-885-5p still persist.

Similarly, comprehensive research should be conducted to understand how miR-31 and miR-485-3p expression changes in response to DLE treatment. This might involve studying differences between patients responding to first- or second-line treatments compared to those who do not respond. Variations in the expressions of these miRNAs related to drugs like immunomodulatory (IMIDs) or biological drugs could also be investigated to find biomarkers for treatment monitoring.

Another promising perspective could be focusing on the expression of CLE-specific miRNAs within extracellular vesicles (EVs). These vesicles have been observed to act as vehicles that transport and protect miRNA expressions [73]. In other manifestations of systemic lupus, such as renal involvement, various miRNAs encapsulated within EVs have been described, which can predict a positive response to treatment and could be applied in clinical practice [146].

The use of miRNAs as gene therapy for CLE lesions, using a topical treatment, is a highly innovative and pioneering research area. So far, no study has been conducted in this specific area. Although this idea may seem a bit bold, promising results have been obtained in psoriasis treatment through this approach [143, 145]. In the case of DLE, specific interference miRNAs (miRNAis), such as miR-31 and miR-485-3p, could be encapsulated using vehicles like elastic liposomes (SECosomes), which have reported good results for treating psoriasis skin lesions. In this way, the overexpression of these miRNAs in DLE lesions could be inhibited. Similarly, nanotherapy with a mimic of miR-885-5p could be used to restore normal expression of this miRNA in CLE lesions and thus restore optimal skin physiology.

To evaluate these new therapies in dermatological diseases, especially in the use of topical treatments, 3D skin models known as *organoids* are being used. The skin is a complex organ with multiple layers and structures, and creating these three-dimensional models in cell cultures represents a significant challenge in the field of biomedical bioengineering [147]. However, these models are useful for studying the interaction of dermal and epidermal cells, as they can simulate many of the processes that take place in skin lesions and therefore significantly reduce the need to use animals in research experiments. Nevertheless, the use of

animals is still necessary to study the safety, efficacy, and biodistribution of new experimental therapies. One of the most studied models of lupus-like skin disease is spontaneous cutaneous disease that develops in MRL/lpr inbred mice [148, 149]. These mice spontaneously develop skin lesions similar to those of cutaneous lupus as a result of T cell-mediated autoimmune processes and the production of tissue-specific antibodies. The use of these mice may be relevant for studying advances in the treatment of cutaneous lupus.

In summary, miRNA-based therapy has the potential to effectively address autoimmune dermatological diseases that do not adequately respond to current treatments, while avoiding associated side effects. Although many preclinical studies have been conducted to explore the role of miRNAs in the pathogenesis of dermatological diseases and their potential therapeutic applications, we are still in an early stage. To progress in this field, challenges related to miRNA degradation, potential off-target effects, and toxicity need to be addressed in order to develop safe, effective, and well-targeted miRNA-based therapies. It is also essential to standardize detection and normalization assays and improve statistical analysis of data to fully assess the applicability of miRNAs as biomarkers and innovative therapies for dermatological diseases related to CLE.

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