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Brief Reviews

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Immune Cell–Stromal Circuitry in Lupus Photosensitivity

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Photosensitivity is a sensitivity to UV radiation (UVR) commonly found in systemic lupus erythematosus (SLE) patients who have cutaneous disease. Upon even ambient UVR exposure, patients can develop inflammatory skin lesions that can reduce the quality of life. Additionally, UVR-exposed skin lesions can be associated with systemic disease flares marked by rising autoantibody titers and worsening kidney disease. Why SLE patients are photosensitive and how skin sensitivity leads to systemic disease flares are not well understood, and treatment options are limited. In recent years, the importance of immune cell–stromal interactions in tissue function and maintenance is being increasingly recognized. In this review, we discuss SLE as an anatomic circuit and review recent findings in the pathogenesis of photosensitivity with a focus on immune cell–stromal circuitry in tissue health and disease. ***The Journal of Immunology*****, 2021, 206: 302–309.**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is strikingly associated with photosensitivity, a sensitivity to UV radiation (UVR) that results in the development of skin lesions. Notably, these lesions can be associated with triggering of systemic disease flares (Fig. 1). Marked by circulating autoantibodies and inflammatory damage of the kidneys, brain, and heart among other organs, SLE is strongly associated with cutaneous lupus erythematosus (CLE). CLE can occur with and without systemic disease and can be divided into acute, subacute, and chronic forms. Acute CLE is most often associated with SLE, although SLE patients can have any type of CLE (1–4). Defined by the American College of Rheumatology as "a skin rash as a result of an unusual reaction to sunlight" (5), photosensitivity is a common manifestation of SLE (1–4). Current treatment options for photosensitivity are limited, with first-line treatment involving topical steroids, calcineurin inhibitors, and systemic antimalarials such as hydroxychloroquine, which were fortuitously found to be effective during World War II (6). Reduced UVR exposure through sun avoidance, protective clothing, and sunscreen is effective and a mainstay in current therapy in the prevention of photosensitivity and its sequela (7–9). However, reduced UVR exposure can lead to reduced levels of UVR-dependent vitamin D synthesis seen in SLE patients (10), which is thought to contribute to poor bone health and osteoporosis (11). Furthermore, vitamin D is important in immune regulation; reduced vitamin D can potentially exacerbate SLE and its symptoms (12). Photosensitivity has been shown to have a large negative impact on quality of life (13–16). Understanding the mechanisms of photosensitivity will provide insights into pathogenesis and treatment of both CLE and SLE.

The histopathology of CLE lesions hints at some of the potential immune cell–stromal interactions. Although the lesions of acute, subacute, and chronic CLE have some distinct features, dermo-epidermal junction changes with basement membrane vacuolization and apoptotic keratinocytes are seen across the spectrum of changes (17, 18). There is often a perivascular- and periadnexal-mixed infiltrates composed of lymphocytes and dendritic cells (DCs) that can range from sparse to pronounced. Neutrophils can be found in early acute lesions and more densely in some of the rarer forms of CLE lesions (19). Monocytes, macrophages, DCs, and plasmacytoid DCs (pDCs) are also found in cutaneous lesions (20, 21). Langerhans cells (LCs) have been noted to be less dendritic in morphology and to be present in fewer numbers (22). Linear immune deposits and complement deposited at the dermal-epidermal junction form a "lupus band." Nonlesional skin, despite the absence of overt inflammation, also shows abnormalities, and positive lupus bands, endothelial activation, and fewer LCs can be seen (18, 23, 24). Epidermal and dermal stromal cells such as keratinocytes and endothelial cells are involved then, as are resident immune cells such as LCs and infiltrating cells such as monocytes, neutrophils, pDCs, and T cells.

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Abbreviations used in this article: ADAM17, a disintegrin and metalloproteinase 17; cGAS, cyclic GMP-AMP synthase; CLE, cutaneous lupus erythematosus; DC, dendritic cell; FRC, fibroblastic reticular cell; EGFR, epidermal growth factor receptor; IC, immune complex; ISG, IFN-stimulated gene; LC, Langerhans cell; pDC, plasmacytoid DC; SLE, systemic lupus erythematosus; STING, stimulator of IFN genes; T_{reg}, T regulatory cell; UVR, UV radiation.

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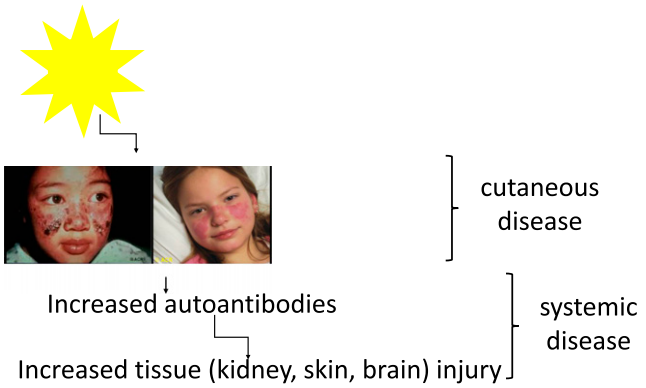

FIGURE 1. Photosensitivity in lupus. In patients with CLE or SLE, even ambient exposure to sunlight can trigger the development of skin lesions. In SLE patients, this photosensitivity can be associated with flares of systemic disease. Photos from American College of Rheumatology Image Library (c) 2020 American College of Rheumatology.

UVR is a form of electromagnetic radiation that is subdivided into the three categories of UVA (320–400 nm), UVB (290–320 nm), and UVC (200–290 nm) light. UVC emitted by the sun is filtered by the atmosphere and does not reach Earth's surface. The majority, some 90%, of UVB is similarly filtered. The shorter UVB waves that do reach the skin do not penetrate deeper than the epidermis, whereas the longer UVA waves penetrate into the dermis (3, 25, 26). UVA contributes to reactive oxygen species generation and photoaging, whereas UVB is more effective at generating DNA breaks. Both UVA and UVB are considered to contribute to the proapoptotic and consequent immune suppressive effects and to photosensitive lesion development. However, UVA1 (340–400 nm) in the longer range of UVA waves can have therapeutic effects, ameliorating systemic disease in a murine lupus model and in limited clinical studies. Its efficacy is attributed to the induction of apoptosis specifically of T and B cells, thus targeting the disease-causing cells. The relative contributions of the different UVR components remain to be fully elucidated.

Work over the past several decades has led to a model involving skin-intrinsic dysfunction combined with immune cell dysfunction. Work by Golan et al. and Furukawa et al. in the late 1990s showed that SLE keratinocytes were more sensitive to UVR-induced apoptosis (27, 28), a characteristic recently confirmed by Kahlenberg and colleagues (29), suggesting a keratinocyte-intrinsic contribution to the UVR-induced skin injury. These studies, combined with earlier findings, including those of Casciola-Rosen et al. that SLE autoantibodies bind Ags expressed by UVR-exposed keratinocytes (30, 31), contribute to the prevailing model that UVR causes greater keratinocyte apoptosis in SLE and subsequent higher autoantigen levels, opportunity for the selection of autoantibodies, and autoantibody-mediated damage. The autoantigen levels are further increased by reduced clearance of apoptotic cells in SLE (32, 33). More recent work has focused on the mediators of skin inflammation, whereby innate immune cell accumulation is followed by lymphocytic infiltration, leading to the clinical lupus cutaneous lesions (34), and the role and regulation of IFN-I (35). In addition to contributing to tissue injury, immune cells can help to promote normal tissue function, as the complex circuitry between immune cells and the resident epithelial, mesenchymal, and endothelial cells of the "stromal" compartment have been increasingly appreciated across multiple systems (36). In this review, we discuss recent findings in the pathogenesis of lupus photosensitivity from the framework of circuitry. First, we discuss SLE in terms of anatomic circuitry to identify potential loci for pathogenesis. Second, we discuss immune cell–stromal circuitry that has recently been shown to contribute to pathogenesis at some of these loci. We propose this framework to help us all think about tissue injury and autoimmunity in disease.

Photosensitivity and SLE pathogenesis as an anatomic circuit

Viewing SLE pathogenesis through the lens of anatomic immune circuitry (37–39) leads to the identification of several potential loci in which dysfunction could contribute to disease (Fig. 2). Assuming that response to UVR exposure in part stimulates lymph nodes and are not solely dependent on tissue activities of resident lymphocytes such as skin-resident memory T cells (40), the sensitive keratinocytes will apoptose and release autoantigens. These autoantigens then are brought from the skin via lymphatic vessels in association with DCs or as soluble molecules to the draining lymph node, in which autoimmune T and B cells become activated and develop into effector cells. The effector T cells and Abs secreted by plasma cells will leave via the efferent lymphatics, pool into the blood circulation by way of the thoracic duct and then home from the blood into affected tissues. In a healthy host, inflammation at the site of injury likely leads to tissue repair and subsequent regulation of the immune response. A potential scenario in SLE is that mechanisms that turn off the response fail, leading to continued inflammation and tissue damage. The autoantibodies, potentially in the form of immune complexes (ICs), may also circulate to other tissues such as the kidneys, where they can deposit and cause inflammation. Similarly, lymphocytes can enter these tissues, especially in chronic inflammation perhaps caused by IC deposition or systemic inflammatory cytokines.

Although autoimmune lymphocytes are a prerequisite, they may be insufficient for disease manifestations. Pathophysiologic function of tissues in the immune circuit may additionally contribute. Below, we focus on the skin and the connection from events in the skin to systemic disease. Because SLE is fundamentally an immune disorder and the importance of immune cells in tissue function is increasingly appreciated,

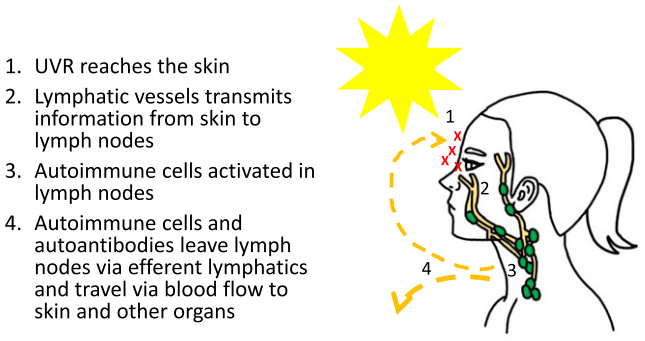

FIGURE 2. SLE as an anatomic immune circuit. The circuitry that may contribute to propagating information from the skin to draining nodes and systemically based on the principles of immune circuitry.

we discuss recent findings of immune cell–stromal circuitry that can contribute to disease pathophysiology.

Immune cell–stromal mechanisms in photosensitivity

Dysfunctional LC-keratinocyte circuit. We have recently shown that LCs protect UVR-induced skin injury by limiting keratinocyte apoptosis via epidermal growth factor receptor (EGFR) ligands. The key mediator in this axis is LC-expressed a disintegrin and metalloproteinase 17 (ADAM17) (24), a requisite sheddase for the activation of many EGFR ligands among other substrates (41). UVR activates LC ADAM17 to cleave EGFR ligands in a *cis*-dependent manner, providing these ligands to keratinocyte EGFR to limit UVR-induced keratinocyte apoptosis (24). Remarkably, LCs in photosensitive murine lupus models showed reduced ADAM17 mRNA expression and enzyme activity, suggesting that intrinsic LC dysfunction could contribute to photosensitivity. Nonlesional human SLE skin showed reduced epidermal EGFR phosphorylation and LC numbers, suggesting that SLE skin has an inadequate source of EGFR ligands perhaps from reduced LC numbers if not LC ADAM17 function. Together, our study suggested a mechanism whereby LC ADAM17 provides EGFR ligands that maintain skin barrier integrity (Fig. 3A), and a dysfunctional LC-keratinocyte axis leads to a propensity to photosensitivity. Topical EGFR ligand supplementation ameliorated photosensitivity in lupus models, pointing to the potential therapeutic use of EGFR ligands in photosensitivity.

The LC-keratinocyte axis is consistent with the idea that immune cells, especially at barrier surfaces, can be tissue-protective. Keratinocyte ADAM17 expression and generation of EGFR ligands are critical for skin barrier maintenance during development but seem to play a minor role at homeostasis in adults (42). We also showed that LCs do not seem to play a major role in homeostatic adults, suggesting that LCs act as a dominant EGFR ligand source in times of stress, including UVR exposure. These data echo the role that DCs have in promoting the survival of mesenchymal cells in inflamed lymph nodes and fibrotic dermis (43, 44) and the role the EGFR ligand amphiregulin plays in protecting the epithelial barrier in inflamed lung and gut by regulatory T cells (T_{regs}) and ILC2, respectively (45, 46). Immune cells can serve as guardians of tissue function, shoring up stromal cells in times of stress by providing extra resources. Dysfunction of this protective immune cell–stromal circuitry, then, can lead to tissue injury and damage.

Keratinocytes can also regulate LC function. Keratinocytes are known to provide IL-34, which is required for LC differentiation and continued self-renewal at homeostasis (47). IL-34 has also been shown to activate TGFβ to retain LCs in the skin (48). Additionally, keratinocyte MyD88, IL-1β, and TNF-α have been implicated in the regulation of LC migration in murine models of atopic dermatitis and aged human skin, respectively (49, 50). Although the causative factors that drive LC dysfunction in SLE models are not fully understood, it is possible that altered keratinocyte phenotypes contribute to LC dysfunction, fueling a pathogenic feed-forward circuitry that contributes to photosensitivity.

Monocyte- and neutrophil-mediated tissue injury. Monocytes have been implicated to play a pathogenic role in photosensitivity. In humans exposed to UVR, monocytes are among the first cells that accumulate in the skin (51), although the cellular infiltrate in established CLE lesions largely consists

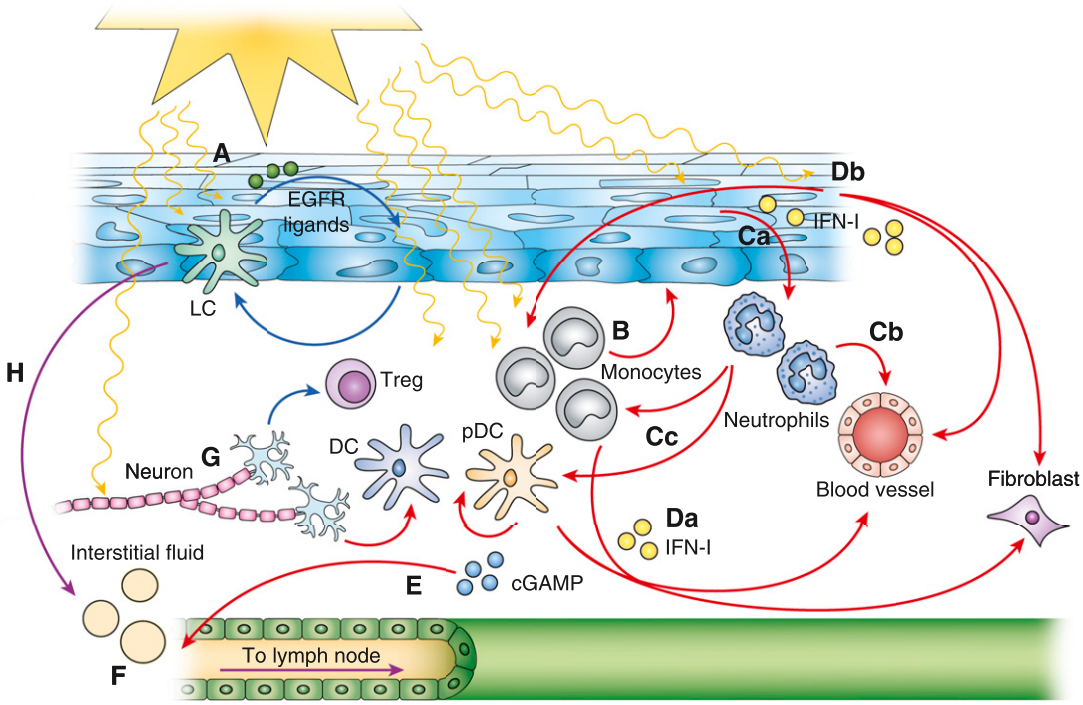

FIGURE 3. Immune-stromal circuits in the skin that may contribute to photosensitivity. Protective circuits are denoted by blue arrows, pathogenic circuits by red arrows, and circuits that can have dual roles by purple arrows. (**A**) LC-keratinocyte circuit. (**B**) Monocyte-epidermal circuit. (**Ca**) Keratinocyte-neutrophil circuit; (**Cb**) neutrophil-endothelial cell circuit; (**Cc**) neutrophil–immune cell circuit. (**D**) IFN-I circuits involving IFN-I originating from (**Da**) immune cells and (**Db**) stromal cells. (**E**) cGAMP originating from skin for systemic signal transmission. (**F**) Lymphatic flow and function that connects skin to draining lymph nodes and systemic circulation. (**G**) Neuronal control of immunity. (**H**) Migration of skin-derived LCs and DCs connects skin events to draining lymph nodes. See text for details.

of T lymphocytes (52). In the MRL/lpr lupus model, UVR caused keratinocytes and dermal fibroblasts to secrete CSF-1, and experimental deletion of CSF-1 and the associated reduction in myeloid cell accumulation prevented UVR-induced lesion development (53). These results suggested that myeloid cells are important contributors to lesion development. In wild-type mice on a B6 background, UVR-induced monocyte accumulation corresponded with an upregulation of IFN-stimulated genes (ISGs), and monocyte depletion in CCR2-DTR mice prevented ISG expression. These data are consistent with the idea that monocytes can be major producers of pathogenic IFN-I (54, 55). Monocyte depletion also prevented UVR-induced increases in epidermal permeability (24), suggesting that monocytes contribute to skin damage in part by disrupting barrier integrity (Fig. 3B). In tissues, monocyte phenotype and function are in part modulated by stromal cells. For example, fibroblast-derived CCL2, in addition to recruiting monocytes to the tissue, can modulate monocyte reactive oxygen species production (56). Additionally, notch ligands, potentially from endothelial cells, can act with TLR ligands to modulate monocyte phenotype and differentiation (57, 58). The fate of monocytes in skin [as monocytes, monocyte-derived DCs, macrophages, or LCs (59, 60)] and how these cells interact with epidermal and dermal stromal cells in photosensitivity remain to be better understood.

Neutrophils are also recruited to skin early after UVR exposure. There, they phagocytose Ags released by dying keratinocytes and are stimulated by UVR along with ICs of autoantibodies with nuclear autoantigens from dead cells to release neutrophil extracellular traps (Fig. 3Ca) (61). Netting neutrophils can directly damage endothelial cells (Fig. 3Cb) and the neutrophil extracellular traps, comprised in part by oxidized nucleic acids known to be more resistant to degradation, can induce pDC and other cells to upregulate IFN-I production (Fig. 3Cc) (62, 63).

IFN-I in immune cell–stromal circuitry. IFN-I can be key mediators in interactions between immune cells and stromal cells in many settings and seems to play a role in photosensitivity. An IFN-I signature is observed in both lesional and nonlesional SLE skin (21, 64, 65), and UVR can upregulate IFN-I in skin in humans and mice (51, 54, 66). Recently, clinical trials in SLE patients have shown that anti-IFNAR1, anifrolumab, improves CLE (67, 68). Although IFN-I appears to play a pathogenic role in humans, the data in mice are less clear. Topical application of TLR7 agonist imiquimod that drives IFN-I to wild-type B6 mice was sufficient to cause autoimmunity and photosensitivity (69), but global IFNAR deficiency exacerbated UVR-induced skin lesions in otherwise wild-type (i.e., nonlupus) mice (54). Whether this phenotype of global IFNAR deficiency reflects in part the protective role of IFNAR in epithelial maintenance and wound healing (70) remains to be seen. However, recent efforts delineating the exact roles, sources, and regulation of IFN-I at different time points after UVR exposure are starting to paint a picture as discussed below.

Nucleic acids, likely from cell injury or death, seem to be a key driver of the IFN-I response to UVR exposure. Elkon and colleagues have shown an important role for cyclic GMP-AMP synthase (cGAS), which detects cytosolic dsDNA and produces cGAMP that binds to the stimulator of IFN genes (STING). STING then activates, via TBK1, IFN regulatory factor 3 (IRF3) along with NF-κB, which function together to turn on and amplify the transcription of IFN-I and other proinflammatory cytokines (71, 72). In mice, global cGAS and STING deficiencies were both associated with reduced UVR-induced skin IFN-I signatures (54, 66). cGAS activity was especially important at the earliest time point, 6 h, after a single dose of UVR (66). Whether STING is important during the same period of time was not tested, but STING was required for both IFN-I signature and inflammatory cytokine expression with a subacute multiday regimen. This suggested that other DNA and RNA sensors that can also activate STING (73, 74) may be involved at later time points. In addition to potential involvement of different pathways over time, the key cellular sources of cGAS and STING still need to be worked out.

Immune cells may be important expressors of IFN-I (Fig. 3Da) and pDCs in lesional skin have been implicated as a major source (64). Consistent with this idea, depleting pDCs in SLE patients with anti-BDCA2 led to reduced skin IFN-I signatures and improved skin scores (75). In mice, pDCs were necessary for tape stripping–induced lesions in the NZBxNZW lupus model (76). However, other studies have emphasized the importance of inflammatory monocytes over pDCs in producing IFN-I (Fig. 3Da). In UVR-exposed lupus patients, an increase in skin ISG expression correlated with T cell and monocyte infiltration but not pDC accumulation (51). Furthermore, a monocytic signature was observed in lesions of CLE patients (77), and inflammatory monocytes, but not pDCs, were also shown to be necessary for a UVR-induced IFN-I signature in wild-type mice (54). Together, the data point to monocytes and pDCs as the likely immune cell that are key sources of or are necessary for IFN-I, although work remains to better understand disease type and stage-specific contributions.

Stromal cells may also be critical sources of IFN-I (Fig. 3Db). UVR induced keratinocytes cultured from nonlesional lupus skin to upregulate IFN-κ (78), the only IFN-I besides IFNA10 that was detected to be upregulated in CLE lesions (29). In situ, IFN-κ was expressed in both the epidermis and dermis. Keratinocytes were a major source in healthy skin and expressed IFN-κ at higher levels in nonlesional SLE skin. Michelle Kahlenberg and colleagues (29) recently showed that the keratinocyte IFN-κ overexpression contributed to their increased sensitivity to UVR-induced apoptosis, amplified responses to other IFN-I, and could stimulate DC activation. Keratinocytes are among the first cells to sense UVR exposure, and their subsequent upregulation of IFN-I may be one of the critical early events in photosensitive responses. Although TLR stimulation will upregulate keratinocyte IFN-I expression (78), cGAS and STING are also functional in keratinocytes (79), and the early cGAS-dependent upregulation of IFN-I after UVR (66) may reflect keratinocyte rather than immune cell activity.

IFN-I can act on multiple immune and stromal cell types. DCs, macrophages, B cells, and T cells can all respond to IFN-I, stimulating downstream programs that can promote autoimmunity when effects are unbalanced (80–82). Stromal cells respond as well, with IFN-I presumably acting on keratinocytes to promote epithelial integrity during wound healing (70) but, likely at higher levels, promoting sensitivity to UVR-induced apoptosis and IL-6 expression (29, 78). Similar

to the epithelium, endothelial cell barrier integrity is mediated by IFN-I, but high IFN-I levels can induce vascular activation and vasculopathy (83, 84). Fibroblasts can be activated by IFN-I to adopt a proinflammatory phenotype (80). Successful targeting of IFN-I in photosensitivity may have to be titrated, leaving enough tonic IFN-I signaling to maintain proper homeostatic tissue function, and consideration of IFN-λ, which can have similar effects (82, 85), may be needed.

From UVR exposure at the skin to systemic flare

A longstanding enigma has been how UVR exposure triggers not only skin lesions but also flares of systemic disease. Supporting the idea that the link between skin lesions and systemic disease reflects similar pathogenic mechanisms in all affected tissues is that the IFN-I gene expression signature found in SLE blood cells (86–88) is also found in lesional skin and kidney (21, 65, 89, 90). Remarkably, vascular activation in even nonlesional skin of SLE patients with kidney disease paralleled vascular activation in kidneys (23), suggesting nonlesional skin was not only abnormal but also a potential barometer of and accessible window into the systemic state. This concept was further reinforced recently by the Accelerated Medicines Partnership consortium that showed via single-cell RNA sequencing that epithelial cells from both nonlesional skin and diseased kidneys in SLE patients had IFN signatures (65). Although these studies showed a clear connection between skin and systemic disease, the results do not establish that skin lesions beget systemic disease.

In mice, there is evidence that UVR will induce systemic effects that are relevant for SLE. BXSB male mice are a model of severe SLE that developed high autoantibody levels, nephritis, and eventually death after UVR exposure (91). The NZM2328 lupus model also showed immune activation with UVR, developing lymphadenopathy, increased IFN-β and IFN-κ in skin, and IFNAR-dependent activated T cell accumulation and T_{reg} suppression in lymph nodes (92). Keith Elkon and colleagues (66) recently showed that UVR treatment can lead to a rapid IFN-I response in skin that is propagated to blood and kidneys of wild-type mice. The systemic IFN-I response, like the early skin response, was dependent on cGAS, and manipulation of extracellular cGAMP levels modulated the systemic IFN-I response. These results suggest a scenario whereby cGAMP generated in the skin after UVR exposure could enter the circulation and induce a systemic IFN-I response (Fig. 3E). It will be interesting to further understand how the T_{reg} effect in NZM2328 mice is disseminated beyond the draining lymph nodes and how the cGAMP circuit may operate differently in lupus models to contribute to pathology.

Circuitry to be explored in photosensitivity

Lymphatics. The lymphatic system functions to reduce inflammation in part by removing fluid from inflamed tissues and propagating tissue-specific information to the draining lymph node via Ags, APCs, and cytokines. Increased vessel permeability and/or reduced lymphatic flow increases the magnitude and duration of UVR-induced skin inflammation as seen with inhibition of lymphatic-dependent VEGFR3 or VEGF-A overexpression–mediated vascular permeability (93, 94). Supplementation of VEGFR3 ligands VEGF-C or VEGF-D partially reduced UVR-induced damage (95, 96). Interestingly, lymphatic function can also be modulated by immune cells, with inflammatory cells including T cells contributing to lymphatic dysfunction (97, 98) and IRF4-dependent DCs maintaining lymphatic vessel integrity (99). Although lymphatic vessels are not known to be dysfunctional in SLE (100), the association of lymphatic dysfunction with inflammation suggest the possibility of lymphatic-specific contributions to lupus photosensitivity.

Although moving interstitial fluid out of the skin may reduce inflammation, reducing lymphatic flow may serve protective purposes. Experimentally, reduction of lymphatic flow with viral infection helped to limit systemic dissemination (101). Lymphatic flow may play a critical role in connecting skin pathology to systemic disease flares by transmitting pathogenic signals such as IFN-I to the draining lymph node, where it could help to activate responses or inhibit regulatory responses (92, 102). Or, taking the example of cGAMP discussed above, lymphatic vessels would bring cGAMP from the interstitial fluid to the draining lymph node to be sent via the efferent lymphatics to the blood circulation. Additionally, once brought to the lymph node, soluble molecules can be sent into the conduit system comprised by fibroblastic reticular cells (FRCs) to the basement membrane of postcapillary venules. From the basement membrane, molecules can traverse the endothelium to the vessel lumen and be delivered to the blood stream (103). Lymphatic vessels that drain the skin, then, critically bridge skin signals to the systemic circulation and may contribute to the induction of systemic disease flares after UVR exposure (Fig. 3F).

In addition to transmitting proinflammatory signals, the lymphatics transmit regulatory signals that act directly on immune cells. Regulatory signals such as IL-10, T_{regs}, and DCs with regulatory functions are all carried by lymphatic vessels to the draining nodes (104–106). Interestingly, fluid transport and DC migration to the lymph node are differentially affected by lymphatic flow disruption (107), suggesting that altered flow can lead to unbalanced information reaching the lymph node. Lymphatic endothelial cells can also directly promote T cell tolerance (108, 109) and induce DCs to adopt a regulatory phenotype (110). Lymphatic flow or phenotypic alterations, then, can modulate the information that reaches the lymph node, which could potentially result in immune dysregulation.

Neuronal-immune cell circuit. The skin is rich in sensory nerves that innervate both the epidermis and dermis. Sensory nerves with nociceptors that sense noxious stimuli can release neuropeptides and neurotransmitters to modulate skin-resident and immune cells (111). For example, α-melanocyte-stimulating hormone (α-MSH) induces expansion of tolerogenic DCs and T_{regs} and can dampen skin inflammation in a psoriasis-like model. Ex vivo, α-MSH can reduce the activity of pathogenic Th17 cells from psoriasis patients (112). Similarly, the neurotransmitter dopamine can activate T_{regs} (113). In contrast, nociceptor neurons activated by imiquimod can induce dermal DCs to express IL-23, subsequent skin-resident γδ T cell expression of IL-17, and psoriasis-like inflammation (114). This effect may reflect neuronal expression of CGRP, which mediated a similar IL-17 response to *Candida albicans* infection (115). Interestingly, UVR activates nociceptor neurons that can then mediate vasodilation and other features of inflammation (116).

Whether there is a role for nociceptor neurons in lupus photosensitivity and UVR-induced systemic disease flares remains to be determined (Fig. 3G).

LC and other APC migration. Although LCs and dermal DCs migrate constitutively to draining lymph nodes to modulate T cell responses, our findings that LCs can modulate keratinocytes directly to limit UVR-mediated skin injury raise the possibility that LCs may directly modulate lymph node stromal cells (Fig. 3H). Classical DCs can modulate vascular-stromal proliferation, growth, and survival with lymph node stimulation and expansion (44, 117–119) as well as FRC contractility to accommodate the expanding lymph node (120, 121). Footpad injection of DCs can stimulate lymph node endothelial and FRC proliferation, and depletion of migratory DCs reduces OVA/CFA–induced vascular-stromal expansion (118, 122, 123), supporting the idea that migratory APCs contribute to this modulation. As such, LCs could have contributed to studies that implicated migratory APCs that used CD11c-DTR, CD11c-cre, or CCR7-deficient mice (118, 120, 121, 123). How LC ADAM17 dysfunction, in addition to its contributions in photosensitivity, can affect lymph node function through the vascular-stromal or lymphoid compartments remains to be determined.

Conclusions

In this review, we have discussed and speculated on how immune cell–stromal circuits in the skin can contribute to photosensitivity and how UVR-induced effects on skin can be associated with flares of systemic disease. The state of the immune system and the tissues are inextricably linked, and there is much to be better understood about the extent to which tissue-modulating functions of immune cells and their interactions with stromal cells contribute to disease.

Disclosures

The authors have no financial conflicts of interest.

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