Human Langerhans Cells with Pro-inflammatory Features Relocate within Psoriasis Lesions

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Psoriasis is a common skin disease that presents with well-demarcated patches of inflammation. Recurrent disease in fixed areas of the skin indicates a localized disease memory that is preserved in resolved lesions. In line with such concept, the involvement of tissue-resident immune cells in psoriasis pathology is increasingly appreciated. Langerhans cells (LCs) are perfectly placed to steer resident T cells and local tissue responses in psoriasis. Here, we present an overview of the current knowledge of LCs in human psoriasis, including findings that highlight pro-inflammatory features of LCs in psoriasis lesions. We also review the literature on conflicting data regarding LC localization and functionality in psoriasis. Our review highlights that further studies are needed to elucidate the molecular mechanisms that drive LCs functionality in inflammatory diseases.

Keywords: Langerhans cells, human, psoriasis, microenvironment, inflammation, Langerhans cell function, Langerhans cell localization

SELF-RENEWING LCs FORM A CELLULAR NETWORK IN HEALTHY EPIDERMIS

The human skin forms a sophisticated barrier in which resident immune cells orchestrate immune responses against foreign antigens, while maintaining tolerance to commensals (1). In focal inflammatory skin diseases, tissue homeostasis is unevenly disturbed, and patches of intense inflammation are surrounded by apparently normal skin. Local alterations of resident immune cells are increasingly appreciated in these diseases. Langerhans cells (LCs) form a stable pool of professional antigen-presenting cells resident in healthy epidermis with distinct ontogeny and phenotypes compared to dermal dendritic cells (DCs) (2, 3). The CFS-1 receptor ligand IL-34, abundantly produced by keratinocytes, is crucial for LC development within the skin (4), whereas LC residency is strongly dependent on the constitutive expression of TGF-β (5). In contrast, replenishment of dermal subsets of DCs is dependent on the differentiation of circulating precursors and is driven by the tyrosine kinase FLT3 ligand (6, 7). LCs predominately self-renew within murine (8) and human skin, with donor-derived LCs detected up to 10 years after human hand transplantation (9, 10). However, in murine models of inflammation and infection, short-lived and bone marrow-derived CCR2-expressing myeloid precursors fill up the epidermal niche following LC depletion, indicating heterogeneity within the pool of LCs in resolved skin lesions (8, 11). Human LCs form a network capable of sensing the entire skin surface (12) and comprise 2–4% of epidermal cells with a surface density of 500–1,000 cells per mm^2 (13, 14). Apart from their ability to sense danger and present antigens, the function of human LCs remains debated after more than a century of studies in healthy and diseased conditions.

Functional studies in murine models have provided fundamental insights into LC biology in different settings of tissue immunity and inflammation. However, profound anatomical and immunological differences are obvious when comparing murine and human skin. Human epidermis comprises several layers of keratinocytes (14) and is dominated by interfollicular epithelium, whereas murine epidermis comprises 2–3 cell layers and is covered by dense hair follicles (1). Although many aspects of LC biology and functionality are comparable between mouse and man (15), epidermal lymphocyte populations differ, with αβ T cells populating human epidermis and dendritic epidermal T cells and γδ T cells dominating the murine epidermis (16). Finally, albeit inflammatory models have provided valuable information on LC biology, the full complexity of human inflammatory skin diseases cannot be captured in murine models (17).

PSORIASIS OCCURS IN FIXED PATCHES OF THE SKIN

Psoriasis is one example of a focal inflammatory skin disease where disturbance of LC biology has been reported. Psoriasis affects 2–3% of the human population and typically presents with macroscopic well-demarcated, red, and scaly plaques. Genetic predisposition increases the risk of psoriasis (18), and several psoriasis-associated genes are linked to the immune system. In particular, *HLA-Cw6* is strongly associated with psoriasis and genome-wide association studies link psoriasis to polymorphisms of genes belonging to MHC class I pathway (*ERAP1*), IL-23 signaling pathway (*IL12B*, *IL23A*, and *IL23R*), cytokines pathways and Th17 polarization (*STAT3*), or NF-kB pathway (*CARD14*) (19). Epidermal hyperplasia, focal immune cell infiltration, and vascular changes dominate the microscopic disturbances in affected sites, whereas nonlesional and resolved skin at large appears normal. Contemporary immunological findings support the idea that psoriasis plaques are maintained by interactions between aberrantly differentiated keratinocytes and immune cells, both resident and recruited. Myeloid and lymphoid immune cells including T cells, innate lymphoid cells, inflammatory DCs, and neutrophils accumulate in psoriasis lesions and produce disease-driving effector molecules such as IL-23, TNF, IL-17, IL-22, granzyme A, and IFN-γ *in situ* (20–34). Both genetic and therapeutic studies imply that cytokines originating from DCs are involved in psoriasis pathogenesis. The influx of several subsets of inflammatory DCs into psoriasis lesions is discussed in several recent reviews (35, 36). In contrast, few studies have characterized LCs in psoriasis. Nevertheless, these few studies have shed some light on the complexity and plasticity of human LCs. As of yet, less can be concluded regarding pathologic consequences of such LC alterations.

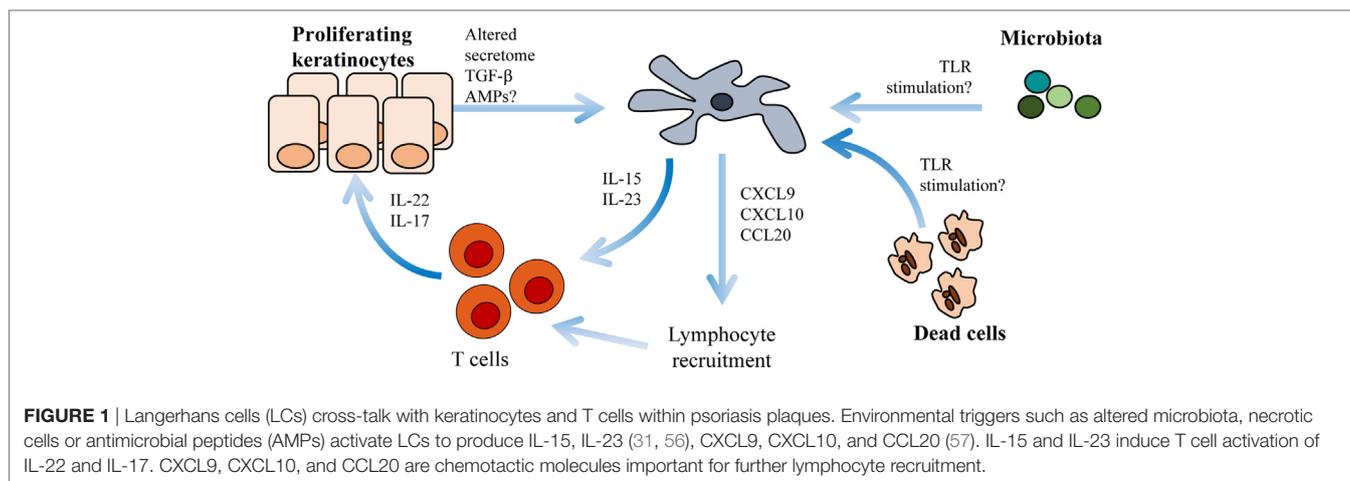## MICROENVIRONMENTAL ALTERATIONS ASSOCIATED WITH PSORIASIFORM INFLAMMATION IMPACT ON LC FUNCTIONALITY

LCs sense the external environment and the microbiota covering the human body through dendrites protruding all the way to the apical part of epidermis (12). Compared to dermal DCs, LCs express fewer Toll-like receptors (TLRs) (37–39), which indicates impaired capacity to respond to TLR signaling (39). It is plausible that LCs maintain tolerance to commensals during homeostatic conditions (40). Within psoriasis lesions, LCs are exposed to a complex plethora of inflammatory signals that might affect the expression pattern and the activation threshold of TLRs. In contrast to atopic dermatitis, the few available reports on the psoriasis microbiome have not been able to highlight striking alterations from healthy skin (41–45). Higher resolution analysis using shotgun metagenomics, ideally combined with genetic and transcriptomic analysis, may shed light on psoriasis–dysbiosis. It would be of particular interest to investigate the fungal microbiome in psoriasis, taken that IL-17 is associated with fungal responses (46). Another source of external influence on LCs functionality is systemic medication. Angiotensin II inhibitors, a common treatment for hypertension, dampen TGF-β signaling and reduce the density of LCs in human skin (5). In a number of case reports, losartan is implicated as a triggering factor for psoriasis (47, 48), and it would be interesting to investigate the activation status and functionality of LCs in such patients.

Activated keratinocytes represent another LC-trigger in the skin milieu (49, 50). Both keratinocytes and T cells secrete the psoriasis triggering cytokine granulocyte–macrophage colony-stimulating factor (GM-CSF) (51). GM-CSF induces LC maturation and exacerbates their stimulatory capacity (52). It is plausible that activated keratinocytes interact with LCs in evolving psoriasis lesions. In psoriasis plaques, keratinocytes upregulate the antimicrobial peptide LL-37 (53) that theoretically should activate LCs (54). Activated LCs could potentially present antigens *in situ* to T cells infiltrating the skin. IL-22 and IL-17 produced by T cells in psoriasis plaques amplify the production of the antimicrobial peptide LL-37 in keratinocytes (55), thereby perpetuating this potential inflammatory loop (**Figure 1**).

ALTERED LOCALIZATION OF LCs WITHIN PSORIASIS LESION

Conflicting data regarding the density of LCs in psoriasis have been debated since the seventies with reports detecting increased (57, 59, 60), decreased (61–63), or stable (22, 31, 64–66) densities of LCs in psoriasis-afflicted epidermis. Interindividual variation in LC density is considerable in healthy and psoriasis-affected subjects, and thus, the variable results may be a consequence of underpowered studies. In addition, local redistribution of LCs and shared surface markers with inflammatory DCs complicate the assessment of LC density within psoriasis plaques. In active psoriasis, LCs co-localize with T cells and inflammatory DCs in epidermal aggregates and relocate within epidermis to the basement membrane and to the apical part of the dedifferentiated epidermis (**Figures 2A–C**) (67). To add a further layer of complexity, increased density of LCs in perilesional skin, close to the border of active psoriasis lesions, has been reported (60, 68, 69), and the conflicting results obtained by different investigators might be affected by the location within the psoriatic lesion that was sampled. Increased (60, 64, 68) or similar (70) numbers of LCs in non-involved psoriasis skin in comparison to healthy skin

FIGURE 1 | Langerhans cells (LCs) cross-talk with keratinocytes and T cells within psoriasis plaques. Environmental triggers such as altered microbiota, necrotic cells or antimicrobial peptides (AMPs) activate LCs to produce IL-15, IL-23 (31, 56), CXCL9, CXCL10, and CCL20 (57). IL-15 and IL-23 induce T cell activation of IL-22 and IL-17. CXCL9, CXCL10, and CCL20 are chemotactic molecules important for further lymphocyte recruitment.

have been described. In resolved psoriasis lesions, the LC number is reduced after PUVA treatment (64, 71, 72) and increased during anti-TNF treatment (69, 73, 74). Despite the experimental challenges in enumerating LCs, the wealth of conflicting studies suggests dynamics in the survival or migrational patterns of LCs in psoriasis.

More than 10 years ago, elegant studies from the Griffith laboratory identified migrational impairment in LCs in response to IL-1β and TNF injection in non-lesional psoriasis skin (70). Reduction in the number of epidermal LCs was measured 2–4 h after injection, and follow-up studies further stratified LC responses to the time of onset of psoriasis (58, 70, 76). Reduced migration of LCs toward inflammatory cytokines is attributed to the IL-17-induced keratinocyte secretome (77). A possible consequence of this migrational impairment is the accumulation of LCs in the dermis (67, 78–82), where they form dermal aggregates with T cells outside lymphatic vessels (**Figures 2A–C**). The localization of LCs in dermis and basal epidermis, adjacent to the basement membrane in areas where dermal immune cells are entering the epidermis, raises questions on the nature of interactions between LCs and other inflammatory cells, questions that at large remain to be answered.

FUNCTIONAL PROFILING REVEALS INFLAMMATORY PROPERTIES OF LCs IN PSORIASIS PLAQUES

Functional studies on human LCs in psoriasis lesions are scarce in comparison to the wealth of studies that have investigated the properties of blood-derived lesional immune cells. In line with the pro-inflammatory microenvironment within the psoriasis lesions (83), and despite the tolerogenic potential of LCs in healthy skin (40), LCs seem to play an active role in sustaining the inflammation in psoriasis. Transcriptional profiling of LCs sorted from lesional psoriasis revealed expression of several immune cell attracting chemokines including *CXCL1* and *CXCL10* and inflammatory chemokines such as *CCL18* and *CCL20* (57).

In contrast, LCs derived from atopic dermatitis preferentially expressed *CCL17* and *CCL20*, underlying the disease specificity of LC function. In a recent publication, a subset of myeloid cells expressing CD5 promoting induction of IL-22, IFNγ, TNF, and granzyme B in mixed lymphocyte reaction assays was enriched in psoriasis epidermis (84). We and others have directly shown that that LCs from psoriatic lesions produce IL-23 following TLR activation (31, 56), thereby directly linking LCs to the pathogenic IL-23/IL-17 axis. Conversely, lesional LCs also display increased mRNA levels for several tolerogenic factors, including IDO-1, PD-L1, and PD-L2 (31), which complicates interpretations of their role in chronic psoriasis plaque. New techniques are needed to fully understand the overall role of LCs in psoriasis, but current data point toward an active participation in shaping the local inflammatory milieu (**Figure 1**).

LOCAL ANTIGEN PRESENTATION IN PSORIASIS LESIONS

Systemic administration of T cell-depleting antibodies temporarily normalizes psoriasis pathology in human patients (85). Epidermal T cells accumulate (86, 87) and co-localize with both LCs and inflammatory DCs within psoriasis lesions (**Figure 2B**) (31). The impressive inflammatory profile of epidermal T cells (30, 33, 34, 88) could result from *in situ* stimulation by epidermal LCs and DCs. Indeed, several studies have shown that DCs derived from psoriasis lesions sustain the inflammation by producing TNF, iNOS, and IL-23 (20, 22–24, 26, 29, 35, 75). Furthermore, lesional DCs are capable of activating allogenic T cells and induce production of IL-17, IL-22, and IFN-γ (29, 57, 80, 89). Intriguingly, LCs from psoriasis skin show similar ability to stimulate allogenic T cells compared to LCs sorted from atopic dermatitis-affected skin (57). Several autoantigens are proposed to be important to maintain psoriasis (53, 90–92), but the polyclonal pool of pro-inflammatory T cells in psoriasis plaques complicates the concept of psoriasis as a purely autoimmune disease (92, 93). Lipid antigens are presented by CD1a, highly expressed on LCs and on inflammatory DCs. The presence of
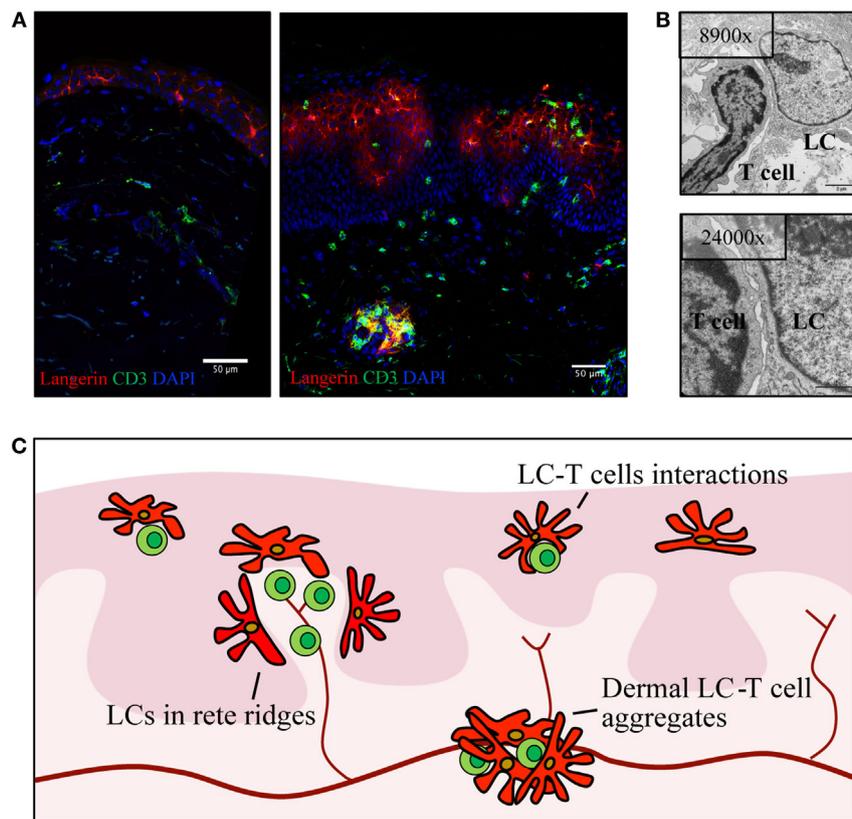
FIGURE 2 | Langerhans cells (LCs) relocate within psoriatic lesions and translocate into dermis. **(A)** Confocal image of healthy skin (left) and active psoriasis (right). LCs are visualized by Langerin (red) and T cells by CD3 (green) with mixed cellular aggregates present in both epidermis and dermis of psoriasis skin. **(B)** Transmission electron microscopy images depicting an example of LCs–T cell interaction in psoriasis epidermis. **(C)** Schematic highlighting localization of LCs (red) in active psoriasis skin, in relation to T cells (green) and blood vessels (dark red). Illustrations from the Eidsmo laboratory of previously published data (31, 75).

CD1a-restricted T cells polarized to IL-17 and IL-22 production in lesional psoriasis (91) is indicative of *in situ* antigen presentation of LCs to T cells, but formal proof of such events remains to be shown in human settings.

LCs IN RESOLVED SKIN SHOW POTENTIAL TO MAINTAIN PATHOGENIC RESIDENT T CELLS

Therapies for psoriasis range from topical treatments to UV therapy and systemic immunomodulatory treatments. Biologics targeting cell-to-cell signaling through TNF or the IL-23/IL-17 pathway have revolutionized the clinical management of severe psoriasis. This range of different treatment strategies offers a possibility to investigate LC biology in different settings of resolved psoriasis (94, 95). UV light induces LC migration from the epidermis, and a reduction in the number of LCs in the skin has been noted after UV treatment (59, 72). TNF inhibitors alter the balance of resident and infiltrating DCs in both epidermis and dermis (69, 73, 74). Despite complete resolution of macroscopic disease, the local transcriptome remains dysregulated following both UVB and anti-TNF treatment (96, 97), and resident T cells

poised to produce IL-17A and IL-22 accumulate in resolved lesions (30, 88). LCs sorted from resolved lesions after successful treatment with UVB therapy retain elevated *IL15* expression, whereas LCs from anti-TNF-treated lesions display residual *IL23* expression. Furthermore, LCs sorted from resolved lesions during TNF treatment, unlike healthy LCs, are able to respond to TLR stimulation with IL-23 production (31). These findings, together with their placement in close contact with T cells within active lesions (**Figure 2B**), put LCs both in the right place and perfectly equipped to induce IL-17 and IL-22 production in IL-23R-positive epidermal resident T cells (88).

LESSONS LEARNT FROM LC BIOLOGY IN MURINE MODELS OF PSORIASIS

Psoriasis is restricted to the human species; nevertheless, several murine models have been developed to mimic psoriasiform inflammation (17). These models provide an attractive tool to further explore findings from human studies in an *in vivo* setting (**Table 1**). Several mouse models support the idea that LCs have a pathogenic role in acute disease. In early studies using the flaky skin mouse, where mice develop scaling and vessel abnormalities

TABLE 1 | Alteration of LCs in human psoriasis and in mouse models.

LCs	Observed effect		Observation in humans	Observation in murine models	Mouse model
Phenotype	Epidermal density of LCs	Increase	Baker et al. (59), Komine et al. (60), Fujita et al. (57)	Sundberg et al. (98), Schön et al. (99), Singh et al. (105), Xiao et al. (101)	Flaky skin mouse, IL-23 injection, IMQ
		Decrease	Lisi (63), Bos et al. (61), Glitzner et al. (62)	Suzuki et al. (100), Glitzner et al. (62)	IMQ
		Stable	Gommans et al. (65), Czernielewski et al. (64), Gunther et al. (66), Martini et al. (31)	–	–
	IL-23 and inflammatory chemokines production		Fujita et al. (57), Sweeney et al. (56), Martini et al. (31)	Yoshiki et al. (102), Sweeney et al. (56), Xiao et al. (101)	IMQ
	IL-10 and PD-L1 expression		–	Glitzner et al. (62)	DKO*
Function	Migratory capacity	Increased	–	Suzuki et al. (100), Glitzner et al. (62), Xiao et al. (101)	IMQ, DKO*
		Impaired	Cumberbatch et al. (70), Shaw et al. (76)	–	–
	Enhanced T cell stimulatory ability		Fujita et al. (57)	Yoshiki et al. (102), Xiao et al. (101)	IMQ
dDCs	**Observed effect**		**Observation in humans**	**Observation in murine models**	**Mouse model**
Phenotype	Density of dDCs	Increase	Summarized by Haniffa et al. (6), Jariwala (35), Kim et al. (36)	Glitzner et al. (62), van der Fits (107), Terhorst et al. (81), Singh et al. (105)	DKO*, IMQ, IL-23 injection
	Pro-inflammatory cytokine profile (production of IL-23, TNF, iNOS)			Wohn et al. (106), Massot et al. (103), Singh et al. (105)	IMQ, IL-23 injection
Function	Enhanced T cell stimulatory ability			Wohn et al. (106), Massot et al. (103)	IMQ

LC, Langerhans cell.

as a consequence of an autosomal recessive mutation of the *Ttc7* gene, the number of LCs increases in acute disease (98) and is reduced after administration of an IL-1β-neutralizing antibody (99). In the IMQ model, the density of epidermal LCs is reduced and coupled with enhanced LC emigration to the skin-draining lymph nodes (100). More strikingly, data from IMQ-induced psoriasiform inflammation show that LCs produce pro-inflammatory cytokines necessary to activate pathogenic T cells (56, 101, 102), whereas other studies focus on the role of dermal DCs in driving psoriasiform inflammation (103–106). Conversely, recent work attribute LCs a protective role with elevated levels of IL-10 mRNA and upregulation of PD-L1 in the *Jun^{f/f} JunB^{f/f} K5cre^{ER}* (DKO*) mouse (62). Moreover, after long-term application of IMQ, LCs are important to control the influx of neutrophils into the epidermis (81), indicating that LCs relocated to the border between epidermis and dermis may act as gate keepers that influence on epidermal tissue homeostasis. Collectively, it appears that the lack of clarity on LCs in human psoriasis is mirrored in the mouse models.

CHALLENGES IN PHENOTYPIC AND FUNCTIONAL STUDIES OF LC IN PSORIASIS PATHOGENESIS

Characterization of LCs in psoriasis lesions was initially performed by immunohistochemistry using markers such as HLA-DR, CD1a, and s100 proteins (59, 61, 108, 109). However, inflammatory epidermal DCs share many of the cellular markers previously used to define LCs (22, 31, 57). In humans, in both healthy skin and inflamed skin, the most reliable markers for epidermal LCs are Birbeck granules and Langerin. Langerin has an

extracellular domain and an intracellular domain located within the Birbeck granules (110), therefore choosing the right antibody is essential to optimize cell sorting. Although low expression of CD1a is detected on inflammatory DCs, flow cytometry can separate CD1a-bright LCs and CD1a-dim inflammatory DCs. Despite reliable protocols to sort LCs *ex vivo* (111), functional studies require substantial numbers of viable cells which complicates the analysis of clinical material. Decreased LC viability following tissue isolation procedures or even short-term culture (112–114) further impedes the study of human LC functionality. Instead, LC-like cells differentiated from blood CD34⁺ precursors have been used. Although these cells share some properties with primary LCs, they display a mature phenotype (115) with profound differential transcriptomic profiles (116). It is important to bear these methodologic challenges in mind when assessing the wealth of sometimes conflicting reports on LC biology.

CONCLUSION AND FUTURE PERSPECTIVES

In psoriasis lesions, LCs relocate both within the epidermis and to the dermis. Their localization in close contact with lesional T cells indicates that LCs may participate in focal immunopathology. Indeed, LCs are poised to produce IL-23 in active and resolved psoriasis lesions. However, despite considerable efforts in a multitude of models and settings, the role of LCs in psoriasis pathogenesis remains to be shown. With the current speed of development of experimental techniques combined with the wealth of novel immunotherapies, ample opportunities to fully elucidate the involvement of LCs in psoriasiform inflammation should present themselves over the years to come.

AUTHOR CONTRIBUTIONS

LE and EM planned the outline, reviewed the literature, and wrote this paper together. EM prepared figures and tables.

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