frontiers | Frontiers in Tropical Diseases

OPINION
published: 30 June 2022
doi: 10.3389/fitd.2022.874081

Have We Ignored Vector-Associated Microbiota While Characterizing the Function of Langerhans Cells in Experimental Cutaneous Leishmaniasis?

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neglected Tropical Diseases, a section of the journal Frontiers in Tropical Diseases

Received: *11 February 2022*
Accepted: *04 April 2022*
Published: *30 June 2022*

Citation:
Nerb B, Dudziak D, Gessner A, Feuerer M and Ritter U (2022) Have We Ignored Vector-Associated Microbiota While Characterizing the Function of Langerhans Cells in Experimental Cutaneous Leishmaniasis? Front. Trop. Dis. 3:874081. doi: 10.3389/fitd.2022.874081

Keywords: Langerhans cells, dendritic cells, microbiome, skin, experimental cutaneous leishmaniasis, T cell-mediated immunity, lymph node

THE SKIN-ASSOCIATED LYMPHOID TISSUE IS CRUCIAL FOR PARASITE CONTROL

The skin represents one of the largest organs in mammalians and accomplishes complex physiological and immunological functions (1). The most outer epidermal layer of this cutaneous shield is pivotal to protect the body from invading microorganisms. However, this barrier is futile, once pathogens are incorporated into deeper dermal compartments by bloodsucking arthropods. In this case, arthropod-associated pathogens such as fungi, protozoans, viruses, and bacteria are transmitted into the dermis of mammalians (2). After such a barrier-breakdown, a promptly reacting innate immune response is crucial to eliminate most of the arthropod-associated pathogens at the site of infection (3).

Pathogens have learned to evade some mechanisms of innate immunity (4–6). Thus, a precise pathogen-specific adaptive immunity has to be generated, to avoid an uncontrolled spreading of pathogens and tissue damage. This highly evolved immune response combines a network of cellular and humoral components capable of recognizing foreign antigens to eliminate pathogens and pathogen-harbouring cells (7, 8). In the case of bloodsucking arthropods, most of these host-pathogen interactions take place within the skin-associated lymphoid tissue (SALT) that combines three major components: First, the cutaneous microenvironment equipped with immune cells capable of accepting, processing, and presenting antigens at the site of adaptive effector cell function. Second, the efferent lymphatics connecting the dermal compartment with skin-draining lymph nodes (SDLN). Third, the paracortex within the SDLN where T cell-mediated immunity against skin-derived antigens is generated (9).

A coordinated interaction of immune cells is a precondition for efficient adaptive immunity within the SALT. In this context, the experimental cutaneous leishmaniasis (ECL) of mice has to be emphasized. In the model, promastigote *Leishmania* (L.) *major* parasites are mostly incorporated by a syringe into the dermal compartment to mimic the natural transmission by bloodsucking sand flies (10). Ground-breaking aspects of T cell-mediated immunity, such as T helper (T_h) 1 and T_h2 polarization arose from studies in ECL (11, 12). It has been shown, that healing of ECL correlates with the presence of a profound T_h1 cell expansion and the production of IFN-γ that activates macrophages to eliminate intracellular parasites (13). IL-12 has been identified as the T_h1-polarizing cytokine important for T_h1 cell differentiation (14, 15). By contrast, IL-4 promotes T_h2 cell development and susceptibility for ECL (16).

LANGERHANS CELLS ARE INVOLVED IN ADAPTIVE IMMUNITY AGAINST *LEISHMANIA* PARASITES

A subset of specialized myeloid cells, the epidermal Langerhans cells (LCs), has been favoured to generate *Leishmania*-specific T cells *in vivo*. In 1992, studies revealed that epidermal cells, including LCs, can activate the *Leishmania*-specific T cell clone L1/1 and antigen-primed T cells derived from susceptible BALB/c mice (17). Furthermore, DEC-205/CD205/NLDC-145$^+$ LCs can transport *L. major* antigens (L-Ag) to the SDLNs of susceptible BALB/c mice (18). Flohé *et al.* demonstrated that a single i.v. treatment with epidermal-derived LCs, that had been pulsed with L-Ags, induces adaptive immunity and resistance against a *L. major* (MHOM/IL/81/FE/BNI) infection (2×10^5 stationary-phase promastigote parasites/i.d.) in normally susceptible BALB/c mice (19). The release of T_h1-polarizing cytokines by LCs has also been proven by other groups using *L. major* clone V1 (MHOM/IL/80/Friedlin) and low-dose models of ECL (20, 21). Thus, LCs have been in the spotlight as decisive cells to induce a protective adaptive immunity in ECL for a long time.

CHANGING VIEWS ON LC FUNCTIONS IN ECL

Inspired by novel markers, useful for the dissection of LCs and dendritic cell (DC) subsets, it has been shown by different *in vivo* configurations, varying in *L. major* strains and dose of application, that LCs are not the only "antigen-presenting cells" that are involved in orchestrating T cell-mediated immunity (22–26). L-Ag-specific T cell proliferation is predominantly driven by Langerin/CD207$^-$ DC subsets (epidermal LCs are Langerin/CD207$^+$), suggesting that Langerin/CD207$^-$ dermal-derived DCs (dDCs) are crucial for protective immunity in ECL using different *L. major* strains [MHOM/IL/81/FE/BNI or clone VI (MHOM/IL/80/Friedlin)] and applications (low- or high-dose) for needle infections (27–30). Indeed, LCs can present L-Ags to T cells under certain conditions (17–21). However, the question remains, which pathways of T cell development and immunity are induced by LCs in ECL? To address this aspect, *in vivo* models of inducible ablation of LCs and other DC subsets have been used (31). It has been proven that C57BL/6-LangDTR mice remain resistant against *L. major* (MHOM/IL/81/FE/BNI) high-dose infection even after depleting LCs (29). Protective T_h1 cells are also induced in SDLNs in the absence of LCs (29). Other groups using low-dose models and the *L. major* strain clone VI (MHOM/IL/80/Friedlin), were able to confirm that finding - mice depleted for LCs can still control the disease (28). Consequently, the presence of lymph node resident or dDCs is sufficient to generate a protective immunity in *in vivo* ECL (28, 29).

One should not get the impression that epidermal LCs represent a kind of rudimental or redundant myeloid subset, without specific immunological functions. Speculations in this field assumed that LCs are involved in dampening the immune response against *Leishmania* parasites (32, 33). This hypothesis has been confirmed some years later, by demonstrating that LCs participate in expanding regulatory CD4$^+$ T cells (T_{reg}) [low-dose model; *L. major* strain clone VI (MHOM/IL/80/Friedlin) (28)] and other IL-10 and IFN-γ expressing CD4$^+$ T cells [high-dose model; *L. major* MHOM/IL/81/FE/BNI (29)] with regulatory capacity (34). Consequently, LCs are involved in balancing immune responses within the SALT. This aspect has also been supported by other experimental systems, showing that LCs are involved in the maintenance of tolerance to peripheral skin-associated antigens (35–37).

Apart from this tolerance promoting functions, LCs are also crucial in ECL for priming and differentiation of follicular helper T cells (T_{fh}) and the subsequent formation of early germinal centres (GC) within SDLNs [high-dose; *L. major* MHOM/IL/81/FE/BNI (38)]. A number of other immunization-based and disease models, such as atopic dermatitis, have also confirmed that LCs promote T_{fh} differentiation and GC formation (39–42). This general "LC attribute" of T_{fh} polarization, needs to be examined in more detail. In ECL, B cell-deficient μMT mice develop severe lesions, compared to WT mice. However, the absence of B cell-mediated immunity does not affect the final

outcome of ECL (43). These facts might explain why LC-depleted C57BL/6-LangDTR mice can control ECL, even in the absence of early GC formation and restricted T_{fh} development (38).

NATURAL TRANSMISSION OF *LEISHMANIA* PARASITES IS NOT STERILE

In ECL, LCs contribute to the differentiation of distinct $CD4^+$ T cell subsets such as $Foxp3^+$ T_{reg} cells, IL-10 and IFN-γ producing $CD4^+$ T cells, and T_{fh} cells. However, the absence of LCs does not affect the generation of protective immunity in ECL. Are LCs really "sufficient but not necessary" for protective immunity? Most of the studies involved in the decoding of LCs function in ECL have been performed under standardized conditions such as defined parasite numbers, sterile needle injection and animal housing under specific pathogen free (SPF) conditions (21, 27–29). This standardization is crucial to compare data between studies and in terms of reproducibility, but have we underestimated some vector-associated important factors while decrypting the function of LCs in ECL?

This question is more than justified, because all metazoans coexist intimately with a community of commensal microorganisms (44). Sand flies can harbour fungi, bacteria and viruses (44). In addition, there are sand fly-associated components, such as the saliva and others, that can also influence immune cells (45). The elaboration of all these "vector additives" in ECL is very ambitious. We nonetheless are of the opinion that these factors, most prominent the microbiota-associated side effects, should not be ignored while decrypting the function of LCs in ECL. Given the fact that *L. major* parasites are transmitted selectively by *Phlebotomus* (P.) *papatasi* (46), this vector-parasite constellation will be considered in the following paragraphs.

Comparable to the human gut microbiome (47), wild caught *Phlebotomus* species (sp.) host distinct microbiomes (2) (**Figure 1B**). During the blood meal of sand flies, gut microbes are egested into the skin - alongside with *L. major* parasites (89). This "multicomponent infection" triggers early inflammatory responses within the dermal compartment, such as inflammasome activation and neutrophil infiltration (89). The potential impact of microbes on innate and adaptive immunity in ECL has been already demonstrated. In this case, a needle infection of C57BL/6 mice using a combination of *Staphylococcus* (S.) *aureus* plus *L. major* (90) supports the recruitment of neutrophil granulocytes, γδ T cells, and IL-17 releasing T_h17 cells to the dermal compartment (90). These microbiome-associated side effects seem beneficial for parasite replication and spreading, based on three reasons: First, *L. major* parasites have the ability to maintain infectivity in neutrophil granulocytes. Second, the parasites use granulocytes as "Trojan horses" before they enter their definitive host cells, the macrophages (91, 92). Third, IL-17 favours the recruitment of additional "Trojan horses" such as neutrophil granulocytes (93). This suggests that the inflammatory micro milieu mediated by *S. aureus* is responsible for exacerbating lesion development (90). Arthropod-associated microbiota might therefore represent "natural adjuvants" capable of catalysing parasite spreading. Whether functional capacities of LCs are also affected, needs to be analysed. Additionally, it remains speculative whether such an exacerbation of lesion development is crucial for long-lasting immunity.

Given the fact that most cell types at the infection site including LCs, dermal macrophages and keratinocytes, are equipped with pattern recognition receptors (PRRs), capable of sensing the bacterial PAMPs (**Figure 1A**), it is plausible that microbiota-associated PAMPs strongly influence adaptive immunity in ECL (**Figure 1B**). For instance, application of isolated PRR ligands, in parallel to *Leishmania* parasites or antigens, displayed beneficial effects. In addition, C57BL/6 mice treated intradermally with *L. major* and the TLR9 ligand CpG oligodeoxynucleotides developed little or no dermal lesions (94) and the treatment of BALB/c mice with L-Ag fractions plus the NOD2 ligand muramyl dipeptide induced resistance against cutaneous leishmaniasis (85). Moreover, an administration of the TLR2/TLR6 agonist BPPcysMPEG in combination with fixed *L. major* parasites protected BALB/c mice against *L. major* infection (95). Based on these and other data, it is obvious that arthropod microbiota might represent important additional parameters in orchestrating immunity in ECL (96, 97) (**Figure 1**).

CONCEIVABLE IMPACT OF ARTHROPOD-ASSOCIATED MICROBIOTA ON LC FUNCTIONS IN ECL

LCs and other cells associated to the SALT are equipped with PRRs sensing microbial PAMPs (**Figure 1**). It is obvious that LCs must get in contact with bacterial compounds during the blood meal of vectors, harbouring microbiota and *Leishmania* parasites. In this context, LCs will be "stimulated" by PAMPs based on the expression of the corresponding PRRs (compare **Figure 1B**). Additionally epidermal LCs, while migrating through the dermal compartment, will be exposed to a micromilieu of soluble factors including cytokines, chemokines and other metabolites, that are released by keratinocytes or other dermal immune cells in response to microbial compounds. This natural *Leishmania*-infection, in the presence of additional vector-derived microbes, is might be capable to modify the transcriptome and proteome of LCs. The consequence remains still speculative. Many scenarios are conceivable based on the given expression PRRs and immune receptors sensing the environment. Here just one example: After PRR-ligation, LCs can release cytokines such as IL-17 (98), IL-12 (49) and TNF-alpha (99) - known to support T_h-cell polarization and LC maturation programs (99). Consequently, it is feasible that LCs might lose their "tolerogenic capacity" (23, 32) and support T_h-cell programs, resulting in adaptive immunity against *L. major* parasites (**Figure 1B**).

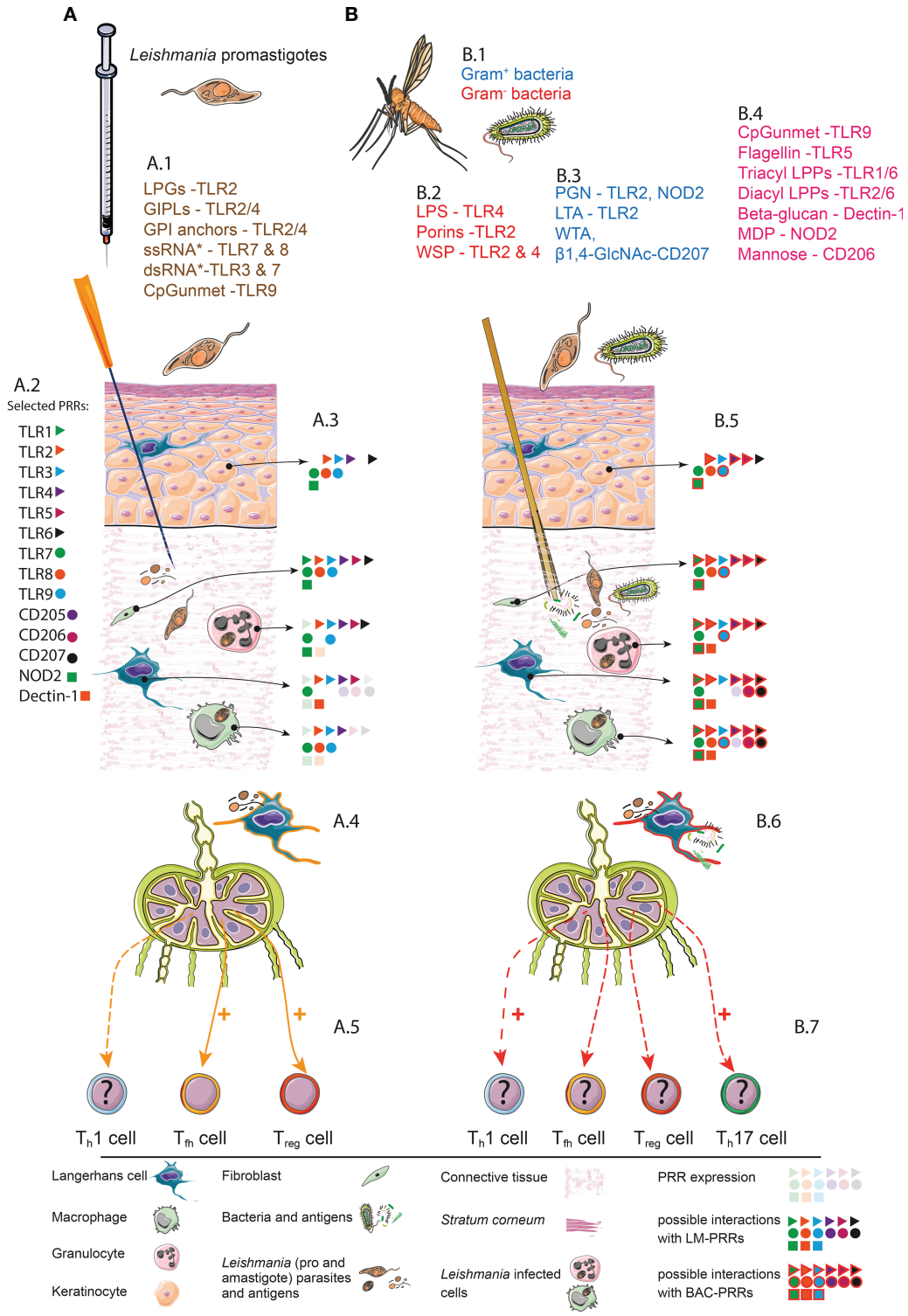

FIGURE 1 | Continued

FIGURE 1 | Simplified synopsis of LC-functions in experimental cutaneous leishmaniasis. Comparison of needle infection **(A)** and transmission by vectors **(B)**. **(A)** Needle infection. A.1. Selected PAMPs of *Leishmania* parasites and their possible interactions with PRRs. *single strand (ss) RNA and *double strand (ds) RNA from *Leishmania*-associated viruses (48). A.2. Representative PRRs and assigned symbols. A.3. PRRs expression and interaction with *Leishmania* (LM)-PAMPs. Pale symbols represent PRRs that are expressed by the indicated cell subset. Solid symbols represent a possible interaction between PRRs and LM-PAMPs. Keratinocytes (49–53), Fibroblasts (54–58), TLR8 (54, 59), Neutrophil granulocytes (60–69), Epidermal Langerhans cells (24, 70–73). Dermal Macrophages (69, 74, 75). A.4. Migratory LC that has been primed in a sterile context (orange contour). This subset can present LM-derived antigens. A.5. LC-driven immune responses in skin-draining lymph nodes. Documented LC functions such as the induction (highlighted by "+") of T_{fh} and T_{reg} cells are highlighted with solid orange arrows. So far unclear (highlighted by "?") involvement of LCs in T_h1 cells differentiation is depicted with a dashed orange arrow. **(B)** Natural transmission. B.1. Gut microbiome of *P. papatasi. Gram*$^-$ bacteria: *Wolbachia* sp. (2), *Klebsiella* sp., *Serratia* sp., *Stenotrophomonas gen.*, *Thauera* sp (76), *Pseudomonas* sp (77), *Brevundimonas* sp., *Ochrobactrum gen* (76). Gram$^+$ bacteria: *Spiroplasma* sp (2) *Staphylococcus* sp., *Micrococcus* sp., *Corynebacteriaceae* sp. (2) *Bacillus* gen (78), *Microbacteria gen* (77). Gram$^+$ or gram$^-$ *Paenibacillus gen* (2). B.2. PAMP/PRR-interactions of gram$^-$ bacteria (79–81). B.3. PAMP/PRR-interactions of gram$^+$ bacteria (82–84). B.4. PAMP/PRR-interactions with bacterial components in general (68, 79, 85–88). B.5. PRRs expression and interaction with LM and bacterial (BAC) PAMPs. Pale symbols represent PRRs that are expressed by the indicated cell subset. Solid symbols represent a possible interaction between PRRs and LM-PAMPs. Solid symbols highlighted with red lines represent possible interactions with BAC-PAMPs. B.6. Migratory LC that has been primed in a nonsterile context (red contour). A presentation of BAC- as well as LM-derived antigens is possible. B.7. Putative (highlighted by "?") LC-driven immune responses in SDLNs. The LC-driven T_h1 and/or T_h17 immune responses might be enhanced (+) by LCs that has been primed in a nonsterile context (solid red arrow). Whether LCs still prime *Leishmania*-specific T_{reg} or T_{fh} cell subsets under nonsterile conditions remains speculative (dashed red arrow). It is possible that LCs fulfill novel functions if conditioned within a nonsterile microenvironment such as the induction of T_h17 and T_h1 cells. All components and symbols are explained by the legend below the figure. LPG, Lipophosphoglycan; GIPLs, glycoinositolphospholipids; TLRs, Toll-like receptors; CpG, cytosine-phosphate-guanine; unmet, unmethylated; LPS, lipopolysaccharide; WSP, *Wolbachia* surface protein; PGN, peptidoglycan; LTA, lipoteichoic acid; WTA, wall teichoic acid; β1,4-GlcNAc, β 1,4-N-acetyl glucosamine; LPP, lipoprotein; NOD, nucleotide-binding oligomerization domain; MDP, muramyl dipeptide; LM, *Leishmania*; BAC, *Bacteria*; PRR, pattern recognition receptors.

CONCLUSION

It is very likely that LCs can support so far unknown immunological programs in the presence of distinct sand fly-associated factors. Up to now, no systematic studies have been performed comparing the immunological attributes of LCs under "microbiome-free" and "microbiome-containing" sand fly or syringe conditions. In our opinion, these aspects need to be deciphered to understand the role of LCs in adaptive immunity and the generation of long-lasting immunological memory in detail. This understanding is pivotal for the improvement of alternative rationally designed vaccination strategies, using novel vector-associated "natural" microbial adjuvants. This new studies are more than overdue based on two aspects: First, L-Ag plus classical adjuvants such as CpG does not protect mice from ECL after challenge with infected sand flies (100). Second, people living in endemic areas seem to be "vaccinated" by multiple sand fly bites in the absence of clinical symptoms of ECL (101). Let's get started to decrypt the impact of LCs in ECL under more physiological conditions.

AUTHOR CONTRIBUTIONS

Conceptualization and investigation, UR. Writing – Original Draft, UR. Writing – Review & Editing, BN, MF, AG, DD. Visualization, UR and BN. Funding Acquisition, UR, MF, AG, and DD. All authors contributed to the article and approved the submitted version.

FUNDING

The study was supported by the Bavarian Research Network (bayresq.net; Bavarian State Ministry for Science and the Arts, UR, MF, AG, and DD).

ACKNOWLEDGMENTS

Many thanks to Ingeborg Becker (Centro de Medicina Tropical, Unidad de Medicina Experimental, Facultad de Medicina, Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico) for helpful discussions and Lisa Schmidleithner (Department for Immunology, LIT - Leibniz Institute for Immunotherapy - Universitätsklinikum Regensburg Franz-Josef-Strauß-Allee 11, 93053 Regensburg) and Jordan Hartley (Department for Gene-Immunotherapy, LIT) for critical reading of the manuscript. Graphic abstract illustratiion credits from Servier Medical Art (https://smart.servier.com/), reproduced under Creative Commons License attribution 3.0 Unported License.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.