Meeting Report of the 16th International Langerhans Cell Workshop: Recent Developments in Langerhans Cell and Skin Dendritic Cell Biology and their Therapeutic Application

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Introduction

The 16th International Workshop on Langerhans Cells (LCs) was organized by Björn E. Clausen with the help of Patrizia Stoitzner and Nikolaus Romani in Budenheim near Mainz, Germany. From 3rd through 6th October 2019, more than 100 scientists from all over the world presented their cutting-edge work and technological advances in the field of skin immunity with a special focus on LCs and dermal dendritic cells (DCs). Novel insights into the development and homeostasis of LCs and dermal DCs and their respective functional roles in health and disease were discussed. Regarding translation into the clinic, several therapeutic interventions using DC for the treatment of skin diseases and cancer were presented. The workshop gave particularly young researchers a great opportunity to meet and interact with leading experts in the field of myeloid cell biology and skin immunology.

LC ontogeny or development, skin DC network, and skin homeostasis

Muzlifah Haniffa (Newcastle University, Newcastle-upon-Tyne, United Kingdom), a member of the Human Cell Atlas consortium (Regev et al., 2017), reported on the perspectives and possibilities of mapping human development at single-cell resolution (Behjati et al., 2018). She presented single-cell RNA-sequencing data of fetal and adult skin and demonstrated how the tissue influences marker expression on immune cells already in the fetal tissue, at a time when innate immunity dominates over adaptive immunity (Popescu et al., 2019). Florent Ginhoux (Singapore Immunology Network, Singapore) gave an overview on his recent work on tissue niche-specific subsets of macrophages, exemplary in the lung (Chakarov et al., 2019). He put forward the notion that the main function of macrophages may be maintenance of tissue homeostasis rather than phagocytosis of bacteria. Moreover, he extended our perception of cDC1s in skin bacterial infection beyond antigen presentation to the regulation of neutrophil recruitment (Janela et al., 2019) and presented a novel monocyte fate mapping mouse model on the basis of *Ms4a3* expression (Liu et al., 2019). Kristin Seré (RWTH Aachen University, Germany) emphasized that LCs undergo mesenchymal-epithelial transition for long-term residency in the epidermis (Hieronymus et al., 2015). Id2 is required for mesenchymal-epithelial transition in LCs, and consequently, lack of Id2 mediates LC emigration from the skin. Further novel insights on LC homeostasis came from Vincent Flacher (University of Strasbourg, France), who demonstrated that LCs require autophagy for their maintenance in the skin and unperturbed lipid metabolism. Anna Brand (University of Mainz, Germany) discovered that E-cadherin–deficient LCs display a dramatically altered morphology with more rounded cell bodies as well as less and shorter dendrites. Unexpectedly, these LCs persist in the epidermis, indicating that lack of E-cadherin alone does not trigger LC emigration (Brand et al., 2020). Using a mouse model, in which neoantigen ovalbumin is expressed exclusively in LCs (Strandt et al., 2017), Helen Strandt (University of Salzburg, Austria) proved that LCs in steady state induce tolerance that is able to suppress allergic airway responses. Dan Kaplan (University of Pittsburgh, PA) presented a possible explanation for the longstanding, unresolved discrepancy in the intensity of contact hypersensitivity (CHS) responses between the various LC-depletion mouse models available (Clausen and Stoitzner, 2015). Specifically, long-term depletion of LC by repeated diphtheria toxin injections in Langerin-DTR or constitutively, in Langerin-DTA mice (Kaplan, 2017) leads to a loss of epidermal sensory afferent nerves. The absence of these nerves results in hyperactive mast cell function. As a consequence, mice with long-term ablation of LCs or mice specifically lacking just these neurons develop exaggerated irritant dermatitis, CHS, and host defense against *Staphylococcus aureus*. These observations support Florent Ginhoux's notion that LCs, which have a common embryonic origin with macrophages, contribute to maintain skin homeostasis (see above), in addition to their well-known antigen-presenting DC function. Moreover, the novel data put forward by the Kaplan laboratory extend initial reports that long-term absence of LCs impairs

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epidermal barrier function (Lee et al., 2019) and alters the gene expression profile of keratinocytes and dendritic epidermal T cells (Su et al., 2020). On the other hand, why acute depletion of LCs in essentially the same mice also leads to enhanced CHS responses (Bobr et al., 2010), in contrast to other inducible LC-depletion models (Clausen and Stoitzner, 2015), remains elusive. Not only is the LC network important in homeostasis; the T cells present in the skin are too. Iris Gratz (University of Salzburg, Austria) analyzed the life cycle of tissue-resident memory T cells. Using a skin xenograft model, she reported that human tissue-resident memory T cells can leave skin grafts, recirculate in mouse blood, and home to another human skin transplant (Klicznik et al., 2019). Moreover, tissue-resident memory T cells are *Candida*-specific, and they proliferate locally in response to immunization with *Candida*-loaded DCs. Sangbum Park (Yale University, New Haven, CT) investigated the conspicuous spatial organization and homeostasis of immune cells in the skin, specifically LCs in the epidermis. By cutting-edge two-photon live imaging techniques combined with cell ablation models, he revealed and strikingly visualized a mutually repulsive behavior of LCs that ensured their typical network pattern. The molecular mechanism for this behavior remains to be determined. Another novel aspect of skin homeostasis was presented by Shruti Naik (New York University, NY), who reported that inflammation-linked cutaneous insults instruct tissue cells, such as keratinocytes, to retain open chromatin areas where genes for tissue regeneration, cancer, and apoptosis are located (Naik et al., 2017). Thus, this "inflammatory memory" can be beneficial because tissue regeneration and healing occur faster, but it can also harm the skin because after resolution of inflammation, subsequent chemical carcinogenesis is accelerated.

Microbiota and pathogen interactions with skin and mucosal DCs

LCs are located in the outmost layer of the skin and thus have access to microorganisms on the skin surface or during infection. Several other immune cell types are also present in the skin, including innate lymphoid cells (ILCs), as emphasized by Tetsuro Kobayashi (RIKEN, Center for Integrative Medical Sciences, Yokohama, Japan). Investigating the various ILC subtypes in the skin, he observed a preferred localization of ILC3s in the epidermis and ILC2s in the dermis. ILC3s are recruited to the epidermis through hair follicles and regulate sebaceous glands and as a consequence, the composition of the microbiota (Kobayashi et al., 2019). LCs are also present in the oral mucosa where they are even more exposed to commensals and pathogens. Interestingly, in the tongue, LCs accumulate in germ-free mice, indicating that they might leave the epithelium owing to contact with commensals as shown by Yael Horev (Hebrew University, Jerusalem, Israel). Moreover, they are lost during aging due to upregulation of inflammatory cytokines and chemokines, although the epithelium can be repopulated by monocytic precursors.

LCs are exposed to multiple pathogens, such as viruses, fungi, and bacteria. As outlined by Teunis Geijtenbeek (University of Amsterdam, The Netherlands), LCs have developed smart ways to eliminate viruses. The restriction factor TRIM5a prevents HIV replication only in LCs but not in other DC subtypes as it is located in the Birbeck granules. This elimination process is insufficient for many of the so-called transmitted founder viruses, that is, those HIV strains that, among a variety of other strains, finally enter the patients (Hertoghs et al., 2019). This underscores the dual function of LCs in HIV infection: virus elimination and virus transmission to CD4 T cells. Interestingly, during experimental coinfection with the bacterium *Prevotella*, occurring in the vaginal microbiota during bacterial vaginosis, LCs take up HIV but do not eliminate but rather store it intracellularly for subsequent transmission to other immune cells. Leanne Helgers from the same working group reported that Dengue virus infects LCs and can be transmitted to other DCs, partly mediated by langerin. Yonatan Ganor (Cochin Institute, Centre National De La Recherche Scientifique, Paris, France) unraveled a role for capsaicin, the spicy ingredient in chili peppers that stimulates cutaneous nociceptors to secrete CGRP, which in turn inhibits infection of LCs by HIV-1. *S. aureus* is a common cutaneous pathogen that binds to — interestingly only human — langerin, leading to activation of LCs as recently published by Nina van Sorge (Utrecht University, The Netherlands) (van Dalen et al., 2019). Moreover, skin LCs are activated by Pam3Cys from *S. aureus,* promoting a T helper 2 (Th2) response as reported by Yi Pan (University of Bonn, Germany). The application route for *S. aureus* determines the subsequent immune response as illustrated by Sandrine Henri (Aix Marseille University, France). While topical application leads to mild inflammation and mixed Th1 and/or Th17 responses, intradermal injection triggers a Th1 response after translocation of bacteria to lymph nodes. Both LCs and cDC1s are dispensable for the T-cell response against *S. aureus*, whereas cDC2s induce the Th17 response. A novel Malassezia infection mouse model to investigate the rapid Th17 response mediated by αβ and γδ T cells as well as ILCs was presented by Florian Sparber (University of Zürich, Switzerland) (Sparber et al., 2019). Nevertheless, the main DC subset inducing these Th17 responses has not been elucidated yet. Many workshop presentations emphasized the need for novel infection models, not least for the purpose of a desirable reduction in animal experimentation. Indeed, such a prototypic model has been established by Doris Wilflingseder (Medical University of Innsbruck, Austria). It is a human three-dimensional lung epithelial cell culture model that can be seeded with immune cells to investigate DC- and/or macrophage-pathogen interactions ex vivo (Chandorkar et al., 2017).

Regarding HIV treatment, Sylvain Cardinaud (Vaccine Research Institute, Créteil, France) has developed an LC-based immunotherapy with anti-langerin antibody conjugated to HIV envelope antigen that was tested in human Langerin-DTR mice and non-human primates (macaques). Without addition of adjuvant, a strong activation of T follicular helper cells and antibodies specific for HIV-1 could be detected. In contrast, no cytotoxic T-cell response could be measured. This sheds new light on a possible role of LCs in the humoral response (Bouteau et al., 2019).

In summary, workshop contributions emphasized that the understanding of

commensal and/or pathogen interactions with LCs and other skin DCs is crucial to develop future strategies for immunization and therapy. LCs interact with multiple pathogens with very diverse, context-dependent immunologic outcomes; however, Th17 responses seem to be crucial for clearing bacterial and fungal infections. Novel three-dimensional epithelium models will help to further elucidate the close interactions between (human) immune cells and pathogens in the tissue.

LCs and/or DCs in the pathogenesis and regulation of inflammatory skin diseases

LCs and dermal DCs also play crucial roles in various inflammatory skin diseases, such as CHS, psoriasis, and systemic lupus erythematosus. Michel Gilliet (University Hospital, Lausanne, Switzerland) highlighted the importance of plasmacytoid DCs, which are recruited to inflamed skin through the neutrophil-produced chemokine CXCL10 (IP-10) during psoriasis (Conrad and Gilliet, 2018). He presented a novel feature of this chemokine as it binds directly to DNA, thus forming CXCL10-DNA complexes that trigger the pathogenic type-1 IFN response. I-hsin Su (Nanyang Technological University, Singapore) reported that the essential integrin adaptor talin1 was required for the formation of novel preassembled TLR complexes in DC at steady state through direct interaction with MyD88 and PIP5K, which were required for the MyD88-dependent toll-like receptor signalosome assembly during DC activation in CHS and antibacterial responses (Lim et al., 2020). Karsten Mahnke (University of Heidelberg, Germany) stressed the decisive role of adenosine, produced by DCs and/or LCs through surface CD73, for the generation of hyporeactive (tolerant) T cells during CHS (Silva-Vilches et al., 2019). Kenji Kabashima (Kyoto University, Kyoto, Japan) characterized the skin T-cell pool in more detail and revealed that, intriguingly, it contains up to 30% regulatory T cells (Tregs), which can recirculate through the lymph nodes and suppress CHS. These Tregs produce IL-10 that blocks DC migration, and their depletion from the skin improves $CD8^+$ T-cell and humoral responses. Furthermore, he reported that tertiary lymphoid structures, originally detected in inflammatory experimental settings ("iSALT") (Natsuaki and Kabashima, 2016), also develop in the upper dermis of human atopic dermatitis and psoriatic skin. The high endothelial venules in these structures are surrounded by DCs and recruit memory T cells. In systemic lupus erythematosus-affected skin, Theresa Lu (Hospital for Special Surgery, New York, NY) investigated the reasons for the higher photosensitivity. LCs protect UVR-damaged keratinocytes from apoptosis by providing EGFR ligands and in systemic lupus erythematosus this function is impaired causing photosensitivity (Shipman et al., 2018). Further dissecting the mechanisms of LC-induced immunosuppression, Karin Loser (University of Münster, Germany) observed that in a murine UV-irradiation model, LCs upregulate PD-L1, and aryl-hydrocarbon receptor leading to their migration to lymph nodes where they induce Tregs. Sayuri Yamazaki (Nagoya City University, Nagoya, Japan) reported that Tregs are expanded in UV-exposed skin by $langerin^-$ $CD11b^+$ dermal DC subsets (Yamazaki et al., 2018) and that the UV-expanded Tregs play a key role in skin homeostasis. The expression of CD5 in subsets of human DCs and/or LCs indicates that these cells are superior in CTL, Th1, and Th22 induction and higher numbers of $CD5^+$ LCs and dermal DCs are present in psoriatic lesions as shown by Eynav Klechevsky (Washington University School of Medicine, St. Louis, MO) (Korenfeld et al., 2017). BMP7, a new player in psoriasis, was reported by Tommaso Sconocchia (Medical University of Graz, Austria) to be expressed by keratinocytes. Known to be a growth factor that is important for human LC differentiation (Borek et al., 2020), BMP7 may thus contribute to psoriatic inflammation.

Skin DCs in cancer and DCs-based therapeutic strategies

Carl Allen (Texas Children's Cancer Center, Houston, TX) reported on the latest developments in understanding the pathogenesis of LC histiocytosis. $BRAF^{V600E}$ or other activating somatic *MAPK* mutations are detected in almost all cases. MAPK hyperactivation in myeloid precursors recapitulates an LC histiocytosis-like phenotype in mice, and MAPK inhibitors are now clinically used for treatment (reviewed in Allen et al., 2018). Cells in LC histiocytosis lesions express langerin and CD1a and develop from different cell types, primarily $CD1c^+$ myeloid DCs, but possibly also from $CD14^+$ cells (Lim et al., 2020). The functional role of skin DC in tumor immunity was discussed by Tanja de Gruijl (University Medical Center Amsterdam, The Netherlands). Owing to the recruitment of suppressive $CD14^+$ macrophage-like cells, melanoma tumors exert an early negative effect on anti-tumor immunity in the sentinel lymph nodes that can be overcome by intratumoral injection of the TLR9 ligand CpG, leading to prolonged recurrence-free survival (van den Hout et al., 2017; Koster et al., 2017). Thus, TLR ligation could be an alternative approach to checkpoint blockade therapy in an early adjuvant setting. Avi-Hai Hovav (Hebrew University, Jerusalem, Israel) described LCs in the tongue epithelium (Hovav, 2018) and reported that they play an essential role in inhibiting oral squamous cell carcinoma in a chemical carcinogenesis model as has been reported before in the skin (Ortner et al., 2017). A continuous decline of LCs in the tongue of aged mice could be a reason for the higher susceptibility to carcinogenesis in elderly individuals.

With regard to DC-based therapeutic strategies, James Young (Memorial Sloan Kettering Cancer Center, New York, NY) reported that most patients in a previously published clinical study using human $CD34^+$-derived LCs transfected with mRNA encoding murine TRP2, many of whom had received additional interventions like checkpoint inhibitors, were still alive and exceeding expected outcomes with either modality alone. This highlights the continued relevance of LCs as immunogens for cancer immunotherapy (Chung et al., 2017). Similarly, promising results are being observed in an ongoing study of patients with myeloma treated with LC electroporated with mRNAs encoding three myeloma antigens. Still, in vitro generated LCs or dermal DCs are not entirely overlapping with their counterparts in situ, as determined by CyTOF and single-

cell RNA-sequencing. Anastasia Prokopi (Medical University of Innsbruck, Austria) discussed a spontaneous melanoma mouse model with a specific loss of skin cDC2s in tumors that could be overcome by treatment with Flt3L and a DC-activating adjuvant. In combination with checkpoint blockade antibodies, T-cell function in tumors and draining lymph nodes could be boosted. An alternative approach developed by Christoph Rademacher's laboratory (Max Planck Institute of Colloids and Interfaces, Potsdam, Germany) uses a glycomimetic langerin ligand conjugated to liposomes that can carry any drug or antigen (Wamhoff et al., 2019). These langerin-liposomes are specifically incorporated into LCs and represent a promising novel approach for LC-based immunotherapy of skin diseases or cancer. Besides this, exploiting these liposomes, cytostatic drugs could be specifically delivered to LC histiocytosis lesions to destroy proliferating tumor cells. The question about the best means of delivering DC-adjuvant was addressed by Juliana Idoyaga (Stanford University School of Medicine, Stanford, CA). As a rational basis, she presented a detailed CyTOF analysis of DCs and defined a subset of transitional DCs (Axl^+ DCs) in humans and mice (Leylek et al., 2019). As a novel twist of targeting strategies, not only antigens but also adjuvants are being coupled to DC-specific antibodies (e.g., DEC205). Indeed, double-stranded DNA linked to anti-DEC205 boosted tumor immunity in a mouse model.

Conclusion

The presence of more than 100 scientists from all over the world working on various aspects of LC and DC biology made LC2019 a very exciting meeting. The functions of LCs in the skin immune system in vivo seem to be manifold. Clearly, they are involved in immune responses against pathogens and skin tumors, but also perform a regulatory role by down-modulating immune responses or even promoting disease progression. These abilities make them attractive targets for therapeutic interventions through the skin. Nevertheless, there are still many unresolved questions that need to be addressed before one can harness LCs and/or other skin DCs for immunotherapy at a large scale. With new mouse models, new sorting strategies for the various skin DC subsets, new analytic tools for the analysis of minute-cell populations and even single cells, and most importantly, with more studies on human cells and with human diseases and patients, we will be able to illuminate these remaining mysteries in the future. Ultimately, this will benefit medicine and thus industry as well as society.

The 17th International Workshop on Langerhans Cells, organized by Avi-Hai Hovav (Jerusalem) and Eynav Klechevsky (St. Louis) with the help of Yonatan Ganor (Paris), will take place in the fall of 2021 in Jerusalem, Israel. (www.lc2021.org)

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Conflict of Interest

The authors state no conflict of interest.

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Author Contributions

All authors equally contributed to the conceptualization and writing of this Meeting Report.

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