

Langerhans Cells at the Interface of Medicine, Science, and Industry

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The 10th International Workshop on Langerhans Cells,* held 3–4 September 2007 in Berne, Switzerland, was organized by Lasse Braathen, Robert Hunger, and Nikhil Yawalkar (all of Berne) and Sem Saeland (Lyon, France). This report emphasizes some of the cutting-edge research and several key issues discussed at this meeting.

Langerhans cells ontogeny

In the past few years, it has become evident from the study of mouse models that the dendritic cells (DCs) of the epidermis, Langerhans cells (LCs), have a life cycle quite distinct from that of many other types of DCs. They self-renew locally throughout life and require input from bone marrow precursors only after severe skin injury that may deplete local LC precursors (Merad *et al.*, 2002). When such bone marrow precursors are needed, they appear to derive from monocytes (Ginhoux *et al.*, 2006). New work presented by Julia Ober-Blobaum from Martin Zenke's laboratory (Aachen, Germany) further explored an observation that the inhibitor of DNA binding (Id2) is induced by transforming growth factor- β and that mice deficient in Id2 lack LCs (Hacker *et al.*, 2003). Dr. Ober-Blobaum observed a differential dependency on Id2 for local LC establishment at birth and ongoing maintenance in the steady state and the replenishment of LCs in injured skin because the repopulation of injured skin with LCs was independent of Id2. These data suggest that LC replenishment in highly inflamed skin uses a completely different pathway

from the one followed during development. These findings fit well with new data presented by Miriam Merad (New York, NY) that corroborated the concept that the embryonic LC precursor was distinct from circulating blood leukocyte populations present in adult mice.

Identification of langerin-positive dendritic cells, distinct from Langerhans cells, in the mouse dermis

To understand LCs, one must be able to trace them definitively. Langerin, a protein associated with the distinctive Birbeck granules of LCs, has been thought to selectively identify LCs in skin (Valladeau *et al.*, 2000). When langerin-positive cells were detected in the dermis in the past, it was suggested that they were LCs that had left the epidermis and were on their way to downstream lymph nodes (LNs), passing through the dermis. At the conference, it became clear that this is not the case. Instead, a proportion of the dermal langerin-positive cells comprise a distinct population on their own. Three talks, given by Sandrine Henri from Bernard Malissen's group (Marseille, France), Florent Ginhoux from Miriam Merad's laboratory (New York, NY), and Dan Kaplan in collaboration with Kristin Hogquist (Minneapolis, MN) discussed the characterization of a population of langerin-positive DCs independent of migratory LCs in mice dermis. Using a knockin mouse obtained from Dr. Malissen, in which diphtheria toxin receptor (DTR) is expressed under the langerin promoter (DTR-langerin mice) (Kissenpennig *et al.*, 2005), Henri,

Ginhoux, and Kaplan showed that after DT treatment langerin-positive DCs reappear in the dermis and in the LNs weeks before LCs reappear in the epidermis, suggesting that at least some langerin-positive DCs in the dermis can develop independently of LCs and differ from migratory LCs en route to the LNs. Additional data from Ginhoux showed that, in contrast to LCs, dermal langerin-positive DCs derive from blood precursors that are recruited to the skin in the steady state. He also showed that dermal langerin-positive DCs capture and present skin-derived antigens in the draining LNs. These results indicate that care must be taken in identifying LCs beyond the epidermis and that truly unique markers to LCs remain to be identified. These results also reveal for the first time the capacity of blood-derived DCs to constitutively patrol the skin, uncovering a previously unappreciated element of skin immunosurveillance that is likely to impact the design of vaccine strategies.

Regulation of Langerhans cell migration to the lymph nodes

Several studies established CCR7 as a key element in the migration of LCs to the LNs in inflamed state (Förster *et al.*, 1999). CCR7 is not expressed on immature LCs present in quiescent skin but can be triggered by inflammatory cytokines (Cyster, 2000). These observations led to the concept that inflammatory cytokines upregulate CCR7 expression on LCs, allowing them to migrate toward CCR7 ligands expressed by the lymphatic endothelium and LN stromal

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cells. However, LCs can also leave the skin and migrate to the LNs in the steady state, and the mechanisms that regulate LC steady-state migration remain unclear. Reinhold Förster (Hannover, Germany) discussed the importance of CCR7 in regulating LC migration to the draining LNs in the steady state (Ohl *et al.*, 2004), but how CCR7 is induced on quiescent LCs remains a puzzle.

Sonja Zahner (Björn Clausen's laboratory, Amsterdam, The Netherlands) may have a key to this question. Zahner's hypothesis suggests that the E-cadherin- β -catenin complex plays a key role in CCR7 expression. β -Catenin is the central, nonredundant component of the canonical Wnt signaling pathway and mediates regulation of gene expression. β -Catenin is also a member of the E-cadherin-catenin complex and contributes to cell adhesion. In particular, LCs and keratinocytes form adherens junctions containing E-cadherin, and downregulation of E-cadherin coincides with LC maturation and emigration from the epidermis. Zahner's hypothesis is that E-cadherin- β -catenin signals may play a critical role in the control of LC function in immune regulation. This is based on work from Ira Mellman's lab (New Haven, CT) demonstrating that disrupting E-cadherin binding or overexpressing β -catenin *in vitro* induces DC maturation and DC expression of CCR7 without secretion of proinflammatory cytokines (Jiang *et al.*, 2007). To unravel the capacity of the Wnt and E-cadherin pathways to govern LC/DC function *in vivo*, Dr. Zahner recently generated mice with LC/DC-specific expression of constitutively active β -catenin and with LC/DC-specific β -catenin or E-cadherin deficiency. Surprisingly, the LC network in these mice was still intact and indistinguishable from that of wild-type animals. Nevertheless, all three LC/DC-specific mutants demonstrated dysregulated contact hypersensitivity (CHS) responses to topical haptens, and, in particular, the β -catenin-stabilization mutant failed to mount any measurable ear-swelling response.

Gwendalyn Randolph (New York, NY) reported that two contact sensitizers, fluorescein isothiocyanate (FITC) and tetramethylrhodamine isothiocya-

nate (TRITC), that are often assumed to trace DC migration from skin identically in fact behave distinctly and may not label precisely the same populations of DCs. The use of TRITC as a tracer of migration has become popular as the use of green fluorescent protein (GFP)-positive mice, including langerin-GFP mice, has increased. These data raise the possibility that the large body of literature on the regulation of DC migration after FITC painting may not apply fully to TRITC-based assays. Dr. Randolph also presented data illustrating that some DCs that carry fluorescent tracers to the LNs are, surprisingly, found in the adipose tissue outside of the draining LNs. These DCs may be skin DCs that miss the target of the LNs and instead prematurely migrate out of the lymphatics into adipose tissue. Alternatively, the adipose tissue may serve as a source of migratory DCs, because there is no formal proof that the contact sensitizer-bearing DCs all derive from skin after its application epicutaneously.

Langerhans cells and innate immunity

The roles of LCs in immune responses—and how these roles differ, if at all, from those of other populations of DCs—is a matter of intense research in skin immunology. Matthias Gunzer (Braunschweig, Germany) presented an interesting model with which to assess microbial capture by LCs in clinically relevant conditions. He showed that DCs are very efficient at capturing fungi in a 3D *in vitro* model, in contrast with how they performed in a 2D culture model, indicating that LCs likely have a role in capturing parasites in the skin and that the design of any *in vitro* experiments conducted to assess LC function should take into account the normal 3D structural properties of the skin. Jürgen Harder (Kiel, Germany) examined the potential role of antimicrobial cutaneous proteins in skin immunity. By culturing psoriatic-scale extracts with bacterial components to search for antimicrobial properties, he identified the first antimicrobial peptide: β -defensin 2, a peptide expressed in the upper layer of inflamed epidermis with activity against *pseudomonas*, *Candida albicans*, and *Staphylococcus aureus* (Harder *et al.*,

1997). Using the same strategy, Harder discussed the recent identification of several other antimicrobial peptides (Glaser *et al.*, 2005).

Role of Langerhans cells in contact allergies

Bettina Jux from Charlotte Esser's laboratory (Düsseldorf, Germany) discussed the role of LCs in allergies to low-molecular-weight chemicals. Jux and colleagues discovered that LCs express the arylhydrocarbon receptor, a transcription factor that controls the enzymes needed for the biotransformation of harmless low-molecular-weight chemicals, and that LCs isolated from mice that lack the arylhydrocarbon receptor poorly upregulate CD40 and CD80 after *in vitro* maturation. Based on these data, Jux discussed the possibility that arylhydrocarbon-receptor mutations might interfere with the potential of LCs to tolerize against low-molecular-weight chemicals.

Role of Langerhans cells in viral immunity

Teunis Geijtenbeek (Amsterdam, The Netherlands) discussed the importance of C-type lectin receptors (CLRs) as part of the pattern recognition receptor family and discussed their role in cutaneous immunity. Focusing on two CLRs—DC-SIGN and langerin—Geijtenbeek explained that both can be involved in the recognition of similar pathogens, including HIV. However, the differential expression of DC-SIGN and langerin by DC compartments in the skin select for preferential recognition *in vivo*. Langerin expression is restricted to epidermal LCs, whereas DC-SIGN is expressed on dermal DCs and dermal macrophages. In addition, CLRs can have opposite functions in viral immunity. While DC-SIGN binds to HIV-1 to facilitate its transmission to CD4 T cells, langerin captures and targets HIV to the Birbeck granules, where it gets degraded, preventing T-cell infection. Lot de Witte, from Geijtenbeek's group, demonstrated that a similar fate awaits measles viruses that are captured by langerin. Marein de Jong, also from the Geijtenbeek group, illustrated that HSV facilitates HIV transmission through downregulation of langerin on

LCs. Downregulation of langerin on LCs favors HIV capture by the viral receptors CD4 and CCR5 (also expressed on LCs) and prevents HIV routing to the Birbeck granules and its degradation, thereby facilitating its transmission to T cells.

Targeting Langerhans cells *in vivo* to manipulate the immune response

Targeting Langerhans cells with monoclonal antibodies. A strong effort is being made to target specific DC subsets to tune the immune response. Vincent Flacher from Nikolaus Romani's laboratory (Innsbruck, Austria) discussed *in vivo* targeting approaches using intradermal injection of antigens coupled to two different lectin-binding monoclonal antibodies, including antibody to DEC-205 and langerin (also called L31). Flacher found that these antibodies can reach the epidermis less than an hour before being internalized by LCs. Targeted LCs migrate to the dermis to form dermal cords and upon injection of proinflammatory signals are induced to migrate to the skin draining LNs. L31 targets LCs very efficiently but does not target CD8⁺ langerin^{low} DCs in the LNs. These studies are very relevant to the design of targeting-approach strategies for modulating specific immune responses *in vivo*.

Deleting Langerhans cells: what we have learned from the DTR-langerin transgenic mice? The DTR-langerin transgenic mouse model has been used in a large number of studies, thanks to the generosity of Bernard Malissen (Marseille, France) and Björn Clausen (Amsterdam, The Netherlands) (Kissenpfennig *et al.*, 2005; Bennett *et al.*, 2005).

Several groups reported that conditional ablation of LCs after DT administration does not affect adaptive immune responses. For example, Fabienne Anjuère (Nice, France) examined the contribution of vagina LCs to CD8-specific immune responses induced after intravaginal administration of a cholera toxin-based vaccine. She noted that the response was identical in the presence or absence of LCs. Likewise, Angelika Stöcklinger (Salzburg, Austria) showed that gene-gun-induced immune responses remained unchanged in the presence or absence of LCs.

In contrast with the studies above, several groups were able to identify a role for LCs in cutaneous immunity. Simone Zimmerli (Geneva, Switzerland) discussed the role of thymic stromal lymphopoietin (TSLP) and LCs in CHS. TSLP is known to prime DCs (Soumelis and Liu, 2004), including LCs (Ebner *et al.*, 2007), to induce pro-allergic cytokines by T cells. Dr. Zimmerli demonstrated that TSLP mRNA increases after epicutaneous FITC sensitization and CHS response to FITC was reduced in TSLP receptor-deficient mice. Interestingly, CHS to FITC was also strongly decreased after conditional ablation of LCs. Patrizia Stoitzner (Innsbruck, Austria) examined the role of LCs in antitumor immunity induced by an ovalbumin-containing cream applied onto a barrier of disrupted skin using a B16 tumor melanoma mouse model. She showed here that the antitumor response was strongly reduced in the absence of LCs and that the need for LCs was most stringent when a low dose of antigen was present in the vaccine. This argument was further discussed by Björn Clausen (Amsterdam, The Netherlands), who pointed out that LC contribution to CHS is directly correlated with the amount of hapten painted onto the skin. Using langerin-DTR mice, Clausen demonstrated that CHS reactions in the absence of LCs were more strongly reduced when a low dose of oxazolone was applied to the skin, most likely due to limited dissemination of the antigen into the dermis (Bennett *et al.*, 2007).

Carlos Ardavin (Madrid, Spain) summarized recent published data showing that after leishmania infection of the skin, freshly recruited circulating monocytes that differentiate into DCs in the dermis are responsible for the induction of T-cell-specific immune response (Leon *et al.*, 2007). It is therefore likely that depletion of LCs and dermal DCs in this model will not alter antileishmania immunity.

All together, these studies suggest that LCs are required to induce CHS or antigen-specific CD8 response when antigens are delivered exclusively to the epidermis. In contrast, DCs other than LCs are able to induce adaptive

immune response, when antigens diffuse out of the epidermis. For example, gene-gun immunization strategies deliver antigens to the epidermis and the dermis, and it is likely that LCs, dermal DCs, and potentially freshly recruited monocyte-derived DCs are equally able to capture and present cutaneous antigens in this model. Antigens present in mucosal cholera toxin-based vaccine are also likely to diffuse beneath the epithelium, allowing both LCs and submucosal DCs to capture and present antigen-derived epitopes. The capacity of DCs other than LCs to present antigens will help explain why, in some models, ablation of LCs does not significantly alter the fate of the immune response.

Role of Langerhans cells in tolerance

Dan Kaplan (Minneapolis, MN) discussed the role of LCs in immune tolerance. The basis for this hypothesis was shown in an LC-deficient mouse model, in which an attenuated form of the DT is expressed under the human langerin promoter, leading to the specific killing of mouse LCs in the epidermis (Kaplan *et al.*, 2005). Unlike the langerin-DTR mice, only epidermal LCs are deleted and not langerin-positive DCs in the dermis and secondary lymphoid tissue. These mice have an increased CHS response to topical haptens compared with wild-type mice, leading to the hypothesis that LCs play a critical role in the modulation of cutaneous immune response. Consistent with this hypothesis and extending it to a different assay system, more recent data were presented that indicate that male → female grafts on the FVB background, which are normally accepted, are rejected if the donor skin lacks epidermal LCs.

In the last session of the meeting, Thomas Schwarz (Kiel, Germany) addressed the role played by LCs in UV-induced immune suppression and induction of T-regulatory cells. He discussed previous data showing that UV radiation mediates the induction of T-regulatory cells through LCs harboring UV-induced DNA damage (Schwarz *et al.*, 2005). However, more recent preliminary data using langerin-DTR mice suggest that UV-induced

T-regulatory cells may still develop in the absence of LCs.

New tools in Langerhans cell research

Another session was dedicated to the development of new tools to facilitate LC research. The DTR-langerin mouse model was much discussed. Jean Davoust discussed the importance of live imaging in LC biology and presented beautiful two-photon images illustrating that LCs can detach antigen cargo from keratinocytes in the steady state. Two presentations emphasized the importance of skin-equivalent models for the pharmaceutical industry. Françoise Rousset (L'Oréal Advanced Research, Aulnay-sous-Bois, France) discussed the relevance of reconstructed human skin for the cosmetics industry. Striking images of an epidermal equivalent containing keratinocytes, melanocytes, and CD34-derived LC-like cells were presented. LC-like cells that differentiate in this model contained Birbeck granules; they secreted inflammatory cytokines and were able to induce T-cell immune response. Rousset also argued that CD34-derived LCs represent a major limitation to the extended use of skin equivalents in drug screening and pointed out that LC-like cell lines are currently being examined as a potential replacement source. Nicolas Bechetoille (BASF, Lyon, France) described the first human reconstructed skin model system with an epidermal and dermal equivalent component containing LC-like and dermal DC-like cells. In this model, LC- and dermal DC-like cells segregated in the expected compartments. Both sources of DCs were able to upregulate CCR7 in response to inflammatory signals and secrete inflammatory cytokines (Bechetoille *et al.*, 2007).

Personal views on Langerhans cells

In this session investigators were asked to summarize the impact of recent research—their own or others'—on what we know about LCs and to outline areas of LC research that need to be explored further.

Georg Stingl (Vienna, Austria) noted how much more needs to be learned about the role of LCs in the control of

keratinocyte proliferation and in diseases such as psoriasis. Stingl emphasized the multiple roles of langerin, including its role in the presentation of glycolipid antigens, its capacity to give access to the nonclassic CD1-dependent antigen pathway, and its role in viral recognition and antiviral immunity. Dr. Stingl also discussed his recent data on a somewhat unexpected innate defense function of DCs showing that tumoricidal dendritic cells were induced by imiquimod treatment of patients with basal cell carcinoma (Stary *et al.*, 2007).

Karolina Palucka (Dallas, TX) discussed the role of human LCs and dermal DCs in T-cell responses. Human LCs and dermal DCs were either generated from CD34⁺ progenitors or directly isolated from human skin, and DCs from both sources led to similar functional responses. Data strongly supporting the capacity of human LCs to cross-present soluble antigens to CD8 T cells and to induce very potent CD8 cytotoxic antitumoral response were presented. LCs were also shown to be very potent at inducing allogeneic T-helper 2 responses. In contrast, dermal DCs were shown to be unable to cross-present antigens and less efficient at priming CD4 and CD8 T cells while inducing potent T-helper follicular T cells. Dr. Palucka emphasized the similarity between these results and results obtained by Malissen's group (Kissenpfennig *et al.*, 2005) that demonstrate that in mouse-skin draining LNs, migratory LCs are located mostly in the T-cell areas, whereas dermal DCs localize near the B-cell follicle where T-helper follicular T cells are present.

Miriam Merad (New York, NY) reviewed past and recent studies on LC ontogeny, as indicated above (Merad *et al.*, 2002; Ginhoux *et al.*, 2006). She also discussed similarities between the properties and mechanisms that regulate human and mouse LC homeostasis. Data indicating that human LCs proliferate *in situ* in quiescent skin were presented. Also presented were results of prospective clinical trials examining the turnover of LCs and dermal DCs in patients who receive either a reduced-intensity or full-intensity

conditioning regimen prior to grafting of allogeneic hematopoietic cells.

Do Langerhans cells deserve a meeting on their own?

Nikolaus Romani (Innsbruck, Austria) summarized the main findings of the meeting and emphasized the importance of new tools in fostering LC research. LCs are attractive to a variety of physicians, scientists, and pharmaceutical organizations. Poised at the interface with the environment, LCs play a role in a variety of human diseases and are being studied by scientists with diverse interests.

In medicine, LCs are studied by dermatologist for their role in numerous skin diseases including psoriasis, atopic dermatitis, and skin allergies. They are also studied by specialists in infectious disease, because the skin is a frequent site of infection, and by oncologists because of their role in a number of prevalent cancers such as squamous- and basal-cell carcinoma and melanoma. They are of great interest to immunologists because LCs are the most accessible nonlymphoid DC population in mice and humans, and to photobiologists because LCs are a critical target of UV-induced injuries. LCs are also actively studied by the cosmetics industry for their potential role in cream-induced adverse responses and by the vaccine industry for their key role in vaccine-induced immunity. So, yes, LCs do deserve a meeting on their own, because it is through these diverse interactions that important discoveries are made.

The 11th International Workshop on Langerhans Cells will be held in Funchal, Madeira, Portugal, 3–6 September 2009 (<http://www.lc2009.at>).

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The interesting and valuable work of many of our colleagues could not be mentioned here due to space restrictions.

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