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Review

# Epidermal Langerhans cells—Changing views on their function *in vivo*

Nikolaus Romani [a,b,*], Susanne Ebner [b], Christoph H. Tripp [a], Vincent Flacher [a], Franz Koch [a], Patrizia Stoitzner [a,c]

[a] *Department of Dermatology and Venereology, Innsbruck Medical University, Austria*
[b] *Kompetenzzentrum Medizin Tirol, Innsbruck, Austria*
[c] *Malaghan Institute for Medical Research, Wellington, New Zealand*

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**Abstract**

New experimental models and methods have rendered the field of Langerhans cells very lively. An interesting and productive scientific debate as to the functions of Langerhans cells *in vivo* is currently going on. We have not yet reached the point where the "pros" would weigh out the "cons", or vice versa. There is good evidence for a lack of Langerhans cell function and for down-regulatory Langerhans cell function in some models. On the other hand, there is also evidence for an active immunogenic and tolerogenic role of Langerhans cells. These recent developments will be discussed.


*Keywords:* Langerhans cells; Dendritic cells; *In vivo*; Function; Skin; Epidermis; Contact hypersensitivity; Ablation; CD207; Langerin

## 1. Introduction

Microbes are constantly threatening the organism. In most cases they attempt to enter the body through the skin and different mucous epithelia. Innate immunity, as a first line of defense, utilizes an array of anti-microbial peptides and proteins that are mainly produced by epithelial cells to build up an effective "chemical barrier" [1]. In addition, the adaptive immune system operates with lymphocytes and antibodies. Cells of the immune system have regularly been observed in epithelia including the skin. This led to the concepts of the skin immune system (SIS [2]) and the skin-associated lymphoid tissue (SALT [3]). They emphasized that the different leukocytes did not just accidentally reside in or pass through epithelial tissues but rather played a systematic role in the immunologic surveillance of skin and other epithelia.

*Langerhans cells* have been positively associated with the immunological control of skin homeostasis ever since they had entered the realm of immunology, that is in 1977, when three groups reported for the first time the expression of immune molecules (Fc receptors, complement receptors, MHC II molecules) on Langerhans cells [4–6]. The concept evolved that Langerhans cells represent the afferent limb of cutaneous immune responses, and lymphocytes are the efferent (effector) limb. This concept was enriched by another seminal finding, namely that keratinocytes were able to produce "ETAF" (epidermal thymocyte activating factor, i.e., IL-1)[7]. This, and the wealth of additional data that came in the wake of that work, made keratinocytes an equally important contributor to adaptive skin immunity by virtue of their potential to produce a wide array of cytokines, chemokines and other mediators.

## 2. Langerhans cells and dermal dendritic cells

*Langerhans cells* have always been the prototype dendritic cell of the skin. They were described almost 140 years ago [8]. They can easily be visualized by different labeling techniques (Fig. 1A) as well as by electron microscopy by virtue of their characteristic tennis-racket-shaped Birbeck granules (Fig. 1B). And, as will be discussed below, they are quite well characterized in terms of phenotype and function [9–12].

*Dermal dendritic cells* were identified more than 120 years after the description of Langerhans cells [13,14]. In spite of some 25 years of research, they are still less well characterized

* Corresponding author.
*E-mail addresses:* nikolaus.romani@uibk.ac.at (N. Romani), patrizia.stoitzner@uibk.ac.at (P. Stoitzner).

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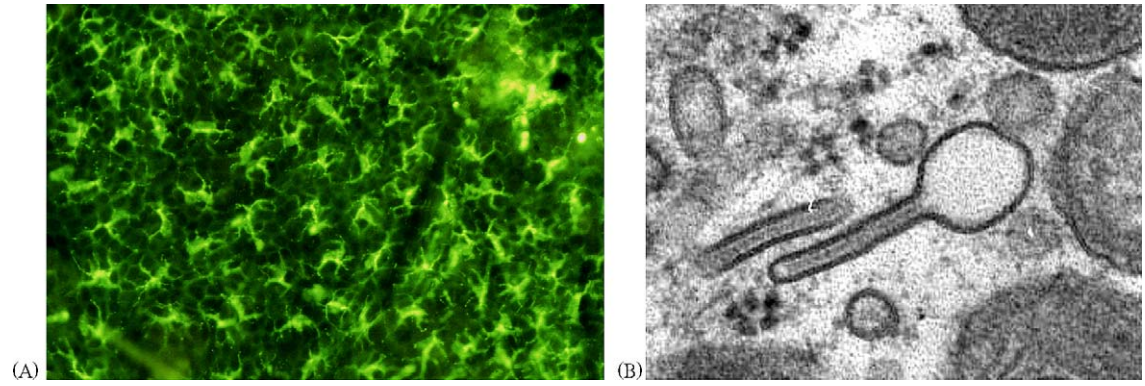


Fig. 1. The *left panel* depicts the network of Langerhans cells as visualized in an epidermal sheet from mouse skin. Monoclonal antibodies against MHC II were used. The right panel shows typical rod- and tennis racket-shaped Birbeck granules in a Langerhans cell from human skin.

than Langerhans cells. There is no exclusive marker for dermal dendritic cells comparable to langerin/CD207 or Birbeck granules for Langerhans cells. It is also more difficult to obtain enriched populations of dermal dendritic cells for phenotypical and functional analyses. Some data suggest that dermal dendritic cells and Langerhans cells may subserve somewhat different functions. Both cell types are equipped with different sets of C-type lectins, molecules that facilitate and regulate the uptake of microorganisms. DC-SIGN/CD209 is expressed on dermal dendritic cells and langerin/CD207 on Langerhans cells [11] (see Table 1.). Similarly, the CD1a molecule, that is involved in the presentation of lipidic microbial antigens [15,16], is abundant on Langerhans cells but low or absent on dermal dendritic cells [13]. It is not yet known whether such differences also extend to the repertoires of toll-like receptors [17].

A recent report by Angel at al. [18] showed that a dermal dendritic cell population expressing CD1a at intermediate levels migrates rapidly in response to CCL19 and CCL21 chemokines due to their CCR7 expression. They efficiently stimulate proliferation of allogeneic T cells *in vitro*, and they reside in the upper dermis near lymphatic vessels. The other subset of dermal antigen-presenting cells ($CD14^+$) did not migrate in response to CCR7-ligands. These data suggest that this $CD1a^+$ dermal dendritic cell subset might be supporting Langerhans cells in inducing immune responses.

The observed differences in receptor expression indicate that Langerhans cells and dermal dendritic cells (or subsets thereof) may recognize and react to different spectra of pathogens. These spectra, however, are still far from being defined for skin dendritic cells. Also in general terms, knowledge on pathogen binding properties of the various receptors is limited. Whereas many pathogens have been reported to bind to DC-SIGN/CD209 [19], very little is known with regard to the other receptors such as langerin/CD207 or DEC-205/CD205 [11,20]. Another hint to functional specializations of Langerhans cells and dermal dendritic cells is provided by the observation that dermal dendritic cells appear to be better capable of stimulating B cells [21]. This is underscored by the finding that after application of a contact allergen Langerhans cells migrated preferentially to the deeper T cell area of the lymph nodes whereas dermal dendritic cells were found in the paracortex adjacent ot the B cell follicles [22]—a strikingly divergent migration pattern.

A frequent source for misunderstandings in discussions on skin immunity is the false (mostly inadvertent) assumption that "skin" equals "epidermis". The epidermis is a relatively simple system that consists of keratinocytes, Langerhans cells and few melanocytes and T cells. The underlying dermis, however, is much more complex as can be illustrated in a well known example of human skin: in healthy epidermis, the expression of MHC II molecules is specific for Langerhans cells and has therefore been used as a reliable Langerhans cell marker for many years. In the dermis, MHC II is expressed not only on dermal dendritic cells but also on a variety of other cells such as macrophages and endothelial cells of blood vessels. Therefore, much of the existing data on Langerhans cells needs to be critically evaluated with regard to possible additional, perhaps confusing contributions by dermal dendritic cells. In the past, this aspect has been often overlooked, unknowingly, though. Still today, it is sometimes not considered appropriately.

For the sake of completeness it should be mentioned that other types of dendritic cells can also be found in the skin, albeit in much lower numbers. Plasmacytoid dendritic cells, inflammatory dendritic epidermal cells ("IDECs") and TNF and iNOS-producing dendritic cells ("Tip DC") are mostly associated with disease states (see Table 2).

Table 1
Expression of C-type lectin receptors on dendritic cells of healthy skin

| | Langerhans cells | Dermal dendritic cells |
|---|---|---|
| CD205/DEC-205 | + | + |
| CD206/mannose receptor | − | + |
| CD207/langerin | + | − |
| CD209/DC-SIGN | − | + |

## 3. Functional properties of Langerhans cells *in vitro*

There is abundant evidence from *in vitro* models that Langerhans cells possess outstanding immunostimulatory capacities. It began with the groups of S.I. Katz and G. Stingl who showed that Langerhans cells were immunostimulatory in the allogeneic mixed leukocyte reaction [31] and induced cytotoxic T lym-