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# Langerhans Cells: Not Your Average Dendritic Cell

**Daniel H. Kaplan** and **Elizabeth C. Thompson**

The skin acts a first line of defense against cutaneous pathogens and environmental insults. It offers protection not only as a barrier, but also through surveillance by a complex system of immune cells. Langerhans Cells (LCs) were first identified as residents of the skin's outermost layer – the epidermis – more than 140 years ago by Paul Langerhans. He was convinced that these were peripheral nerve cells, based on their dendritic processes and network-like distribution. It was not for almost another 100 years that LCs were appreciated as dendritic cells (DCs), which function as skin-resident antigen presenting cells (APCs)[2,3]. After this discovery, LCs featured as the prototypical DC in much of the work that defined the concept of DCs as professional APCs. These studies led to the DC or LC paradigm which proposes that, in the steady-state, LC are highly specialized in antigen uptake. In this model, LC become activated in response to pathogen products and migrate from the skin to the regional lymph node (LN). During migration, LCs process the antigen acquired in the periphery and then present it to naïve and memory T cells in the LN, resulting the initiation of an adaptive immune response.

In the past decade, the pace of LC research has accelerated after the discovery that LCs express Langerin, a C-type lectin[4]. Langerin is responsible for the formation of Birbeck granules – the ultrastructural hallmark of LC – and is a valuable marker for LC identification. Development of LC-specific antibodies has allowed LCs to be easily identified in locations other than the epidermis, and several groups have exploited Langerin to develop lines of LC-deficient mice. These new tools have helped transform the view from LCs as the only DC in the skin to LC as one subset of several skin-resident DC populations. In addition, LCs can no longer be considered representative of all peripheral DCs but instead have a unique and highly specialized biology. This themed issue of *Trends in Immunology* collects reviews that examine advances in understanding of LC biology, which have emerged as a result of these new tools.

Most DCs are ablated by irradiation and can be reconstituted from donor bone-marrow. LCs, however, are radio-resistant, and are only transferred with bone-marrow under strong inflammatory conditions[5]. This was the first indication that LCs are distinct from other DC subsets and might have a unique ontogeny. More recent studies have demonstrated that LCs seed the epidermis during embryogenesis and form a self-renewing population. In this issue, Chorro and Geissmann examine how the epidermal LC network is established during development and discuss the factors involved in maintaining LC homeostasis in the steady-state and during inflammation.

By using the *langerin* gene to drive expression of the diphtheria toxin receptor, diphtheria toxin or cre recombinase specifically in LCs, several groups have generated mice with absent or defective LCs. These mice, as well as the radio-resistance of LCs, have led to the discovery that Langerin is also expressed by a DC subset in the dermis. We now appreciate that there are at least three (and probably more) functionally distinct DC subsets in the skin. On pages XXX, these skin DC subsets are explored, as well as the phenotypic and functional differences between the LC-deficient mouse strains. Although there is still controversy regarding LC function, mounting evidence supports a model in which Langerin-expressing

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DCs in the dermis are required for initiation of adaptive immune responses, while LCs modulate the response.

De Jong and Geijtenbeek review data supporting an innate anti-viral function for LCs situated at mucosal sites. In addition to being a convenient marker for LCs, Langerin is also part of a large family of C-type lectins that are antigen-uptake receptors. Langerin binds and sequesters HIV, and thus LCs might act as a barrier, capturing the virus to attenuate infection. But in situations where Langerin function is compromised (for example, in activated LCs) HIV might exploit LCs to promote infection. This raises important considerations for design of mucosal anti-HIV microbiocide or vaccine strategies.

In addition to serving as a physical and immunologic barrier, the skin is also a site of frequent neoplasms. Lewis et al., examine the role of LC in cutaneous malignancy. Although the immune system is generally thought to recognize and eliminate nascent transformed cells, it can have the opposite effect. Unexpectedly, recent data found LCs promote formation of squamous cell carcinomas in a chemical carcinogenesis model.

As evident from the reviews in this issue, despite the recent and considerable progress in the field of LC biology, many questions remain. It has become clear, however, that LCs are a unique cell type with a variety of features and functions that are distinct from other DC subsets. How LC affect the development of systemic immunity and impact local skin responses based on interactions with pathogens and other stimuli should prove an exciting area for further research.

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