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INVITED REVIEW ARTICLE

Role of Langerhans cells in cutaneous protective immunity: Is the reappraisal necessary?

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Summary Langerhans cells (LC) are constantly exposed to external antigens and pathogens, and they are the cutaneous counterpart of dendritic cells (DC). DC not only act as professional antigen presenting cells to induce antigen-specific T cells for adaptive immune responses, but they also initiate a cascade of innate immune responses by sensing these danger signals. However, recent studies challenge the classical paradigm to position LC in the center of cutaneous immunity. Although LC express toll-like receptors (TLRs) that recognize bacterial and viral products, exposure to pathogen-associated TLR ligands triggers neither sufficient LC maturation nor good production of cytokines and chemokines. LC also lack the ability to produce IFN-γ by any stimuli, and together with the characteristics of LC that are prone to produce Th2-type chemokines and to produce much less IL-12 in the presence of keratinocyte-derived GM-CSF, LC primarily may not have the character to induce Th1- and Tc1-type immune responses necessary for protective cellular immunity. Moreover, LC maturation is inhibited, rather than enhanced, by type I IFNs that are abundantly produced in viral infections in the skin microenvironment. Finally, recent data suggest that LC may not directly present viral antigens to T cells for their activation in mouse models of cutaneous viral infection. The alternative player in protective immune responses may be surrounding keratinocytes, which may modulate LC functions indirectly. Dermal DC may also participate in this scheme. Further studies are required to clarify the role of LC in their interplay with keratinocytes and other DC subsets, and to draw the entire picture of the cutaneous immune system against pathogens.

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1. Introduction

There is a long-standing belief that Langerhans cells (LC) play an important role in a multitude of cutaneous immune responses as the cutaneous counterpart of dendritic cells (DC). As dedicated antigen presenting cells (APC), DC sensitize the body against foreign antigens or pathogens that protrude through the skin by priming both CD4+ and CD8+ naive T cells for their proliferation and differentiation into cytokine-producing effector T cells. Recently, the role of DC to sense danger signals and to initiate innate immune responses also came to be acknowledged, and we now regard DC as the pivotal cells linking innate and adaptive immunity [1,2]. It is also evident that different DC subsets exist in various organs and have different roles and functions depending on their lineages, maturation status, and the microenvironment from which their phenotypes are greatly affected. In this context, LC are not the only DC in the skin, and the presence of dermal and submucosal DC, as interstitial DC, need to be taken into account when considering all cutaneous immune reactions *in vivo* (Fig. 1). Another concern is that most of the previous findings on LC biology were established by using LC-like cells generated from bone marrow-derived or monocyte-derived DC, but not by using genuine skin-resident LC. To overcome these limitations, we successfully purified mouse LC from the skin without contaminating keratinocytes by using the panning technique, and used these isolated LC for a number of *in vitro* studies to characterize LC functions. Moreover, new exciting *in vivo* data, specifically focusing on skin-resident LC, are now becoming available, owing to recent advances in methodology to identify LC by using novel specific markers.

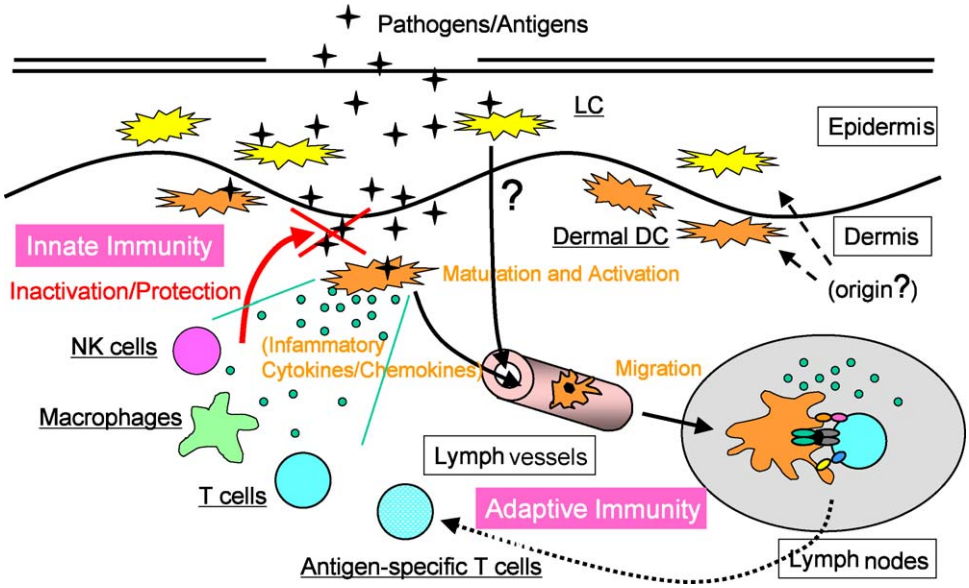

Fig. 1 Langerhans cells (LC) and dermal dendritic cells (DC) in innate immunity and adaptive immunity against pathogens. After encountering pathogens that invade the skin, LC and/or dermal DC are directly or indirectly activated with functional maturation, and they secrete inflammatory cytokines and chemokines to accumulate and activate other immunocompetent cells such as NK cells and macrophages for innate immune responses. At the same time, LC/dermal DC migrate to the draining lymph nodes to induce the differentiation and activation of antigen-specific T cells for the following adaptive immune responses. The actual contribution of LC in a series of responses is controversial.