Review

The balance between immunity and tolerance: The role of Langerhans cells

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Received 6 August 2008; received after revision 18 September 2008; accepted 13 October 2008
Online First 11 November 2008

Abstract. Langerhans cells are immature skin-homing dendritic cells that furnish the epidermis with an immune surveillance system, and translate information between the internal and external milieu. Dendritic cells, in particular Langerhans cells, are gaining prominence as one of the potential principal players orchestrating the decision between immunity and tolerance. Langerhans cells capture aberrant self-antigen and pathogen-derived antigen for display to the efferent immune response. Recent evidence suggests redundancy in the antigen-presenting function of Langerhans cells, with dermal dendritic subsets capable of fulfilling an analogous role. There is mounting evidence that Langerhans cells can cross-prime T cells to recognize antigens. Langerhans cells are proposed to stimulate T regulatory cells, and are implicated in the pathogenesis of cutaneous T cell lymphoma. The phenotype of Langerhans cells, which may be tolerogenic or immunogenic, appears to depend on their state of maturity, inciting immunogen and cytokine environment, offering the potential for manipulation in immunotherapy.

Keywords. Langerhans cells, dendritic cells, immunity, tolerance, cutaneous T cell lymphoma, immunotherapy.

Introduction

Langerhans cells (LCs) were first described by Paul Langerhan in 1868 as star-shaped epidermal nerve cells [1]. LCs are now recognized as an immature subset of skin-homing dendritic cells (DCs), whose primary role is classically described as recognition of foreign invaders at the skin barrier and transfer of this information to the adaptive immune system. LCs comprise 3–8% of epidermal cells, with representation in the oral and genital mucosa, and perform immune surveillance by sampling the external milieu through a combination of phagocytosis, macropinocytosis, and receptor-mediated endocytosis [2, 3]. Foreign antigens encountered are internalized by these endocytic processes, with the foreign peptides processed and ultimately displayed on either class I or II major histocompatibility complex (MHC) molecules, allowing presentation to cytotoxic T cells and T helper cells, respectively [4]. In the accepted paradigm, antigen presentation to CD4+ T helper cells via MHC II molecules promotes expansion of antigen-specific CD8+ cytotoxic T cell populations, and antigen-nonspecific natural killer cells (NK), macrophages and eosinophils [5]. DC and possibly LC mediated secretion of type I interferon and IL-12 cytokine stimulates NK and γδT cell activation, which can destroy targeted cells that lack self-identifying MHC class I molecules. NK and γδT provide positive
feedback for DC and LC maturation, with propagation of both innate and adaptive immune responses [6]. Additionally, DCs are unique among antigen-presenting cells (APCs) in their ability to cross-prime exogenous antigens for presentation to T cells, and the LC subset appears to share this ability. Thus, LC mediated antigen presentation to CD8+ T cells via the class I MHC pathway results in CD8+ T cell cytotoxic effector function enabling destruction of both infected cells and tumor cells carrying the relevant cell surface peptides [7, 8]. Furthermore, DCs—alone among APCs—can elicit primary immune responses, resulting in the establishment of immunologic memory [9]. To come in contact with high concentrations of naive T cells, activated epidermal LCs must reach draining lymph nodes, guided by a chemotactic cytokine gradient and maturing during the migration process [10].

LCs are distinguished by their expression of Birbeck granules, ‘tennis-racket’ shaped cytoplasmic granules that are thought to play a role in endocytic function [11]. Constitutively associated with Birbeck granules is the transmembrane C-type lectin Langerin, which is involved in ligand internalization. LCs also express MHC I and II molecules, and the invariant chain Ii/CD74, a membrane localized MHC class II chaperone [1].

Ep-CAM, and the integrin CD11b, is highly specific for the LC population [14, 27, 28]. Originally, Langerin, which is involved in ligand internalization [12]. Until recently, Langerin was thought to be an LC-specific marker, but it has been discovered, makes them difficult to track such markers characteristic of LC populations, while TGF-β knockout mice are profoundly deficient in epidermal LCs [20, 21]. Therefore, LCs have an in vivo requirement for TGF-β, with keratinocytes providing a paracrine supply of TGF-β in the skin [22]. The transcription factors PU.1 and Id2, and the notch ligand δ-1 further mediate LC differentiation from monocytes [23]. In mice, lymphoid restricted precursors are able to differentiate into functional LCs, as determined by the isolation of pure populations of common lymphoid progenitors (CLPs) followed to terminal differentiation [24]. The identification of lymphoid lineage LCs indicates plasticity in LC development rather than lineage restriction, with the suggested evolutionary design of redundancy in maintaining an essential cell line [25].

The initial misconception that mouse-specific CD8a was a marker of lymphoid origin lead to the conclusion that CD8a+ LCs were of lymphoid origin, however CD8a expression appears to be an activation marker of mobilized, antigen exposed epidermal LCs [26]. Human and murine LCs express the leukocyte surface antigens CD45 and CD11c, the cutaneous lymphocyte-associated protein (CLA), and the myeloid markers CD33, CD13, CD1a, and CD11c. Adhesion molecules expressed by LCs include β1 integrins, CD44, CD54, E-cadherin, and the sialyl-Lewis X monoantigen carbohydrate antigen CD15s. FcyRII/CD32 and receptors for IgE and the IgE-binding protein play a role in allergen uptake, while the lectins dectin-1, DEC205 and Langerin are implicated in antigen internalization. LCs also express MHC I and II molecules, and the invariant chain li/CD74, a membrane localized MHC class II chaperone [1].

In humans, coexpression of Langerin, CD1a (which plays a role in presentation of lipid microbial antigens), E-cadherin (which mediates LCs attachment to keratinocytes), the membrane ATPase (CD39), the chemokine receptor CCR6, the adhesion molecule Ep-CAM, and the integrin CD11b, is highly specific for the LC population [14, 27, 28]. Originally, Langerin was thought to be an LC-specific marker, but it has now been identified in a population of DDC. The phenotype of murine L- DDC is distinct from epidermal LCs, with murine L- DDC expressing low/absent

**Ontogeny of Langerhans cells**

All DC subsets ultimately originate from hematopoietic stem cells (HSCs) in the bone marrow. In early embryonic life, LC precursors localize to the skin, and cell division maintains an autonomous epidermal LC population in the absence of active inflammation [16]. In humans, different subsets of monocytes with the capacity to generate LCs have been identified; CD14+ monocytes predominate, while 16+ monocytes are relatively rare [10, 17]. Murine monocytes exhibiting high expression of the monocyte marker Gr-1, are recruited to inflamed skin, and differentiate into LCs [18]. Historically, DC subsets including LCs were thought to be of myeloid lineage, and can be generated in vitro by culturing monocytes with granulocyte/macrophage colony-stimulating factor (GM-CSF) and IL-4 [19]. In murine studies, the addition of transforming growth factor β (TGF-β) to such cultures results in high levels of expression of the phenotypic markers characteristic of LC populations, while TGF-β knockout mice are profoundly deficient in epidermal LCs [20, 21]. Therefore, LCs have an in vivo requirement for TGF-β, with keratinocytes providing a paracrine supply of TGF-β in the skin [22].

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