



Milestones in the Research on Skin Epidermal Langerhans/Dendritic Cells (LCs/DCs) from the Discovery of Paul Langerhans 1868–1989

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Abstract. Almost 100 years elapsed after the discovery of dendritic cells in the human skin epithelium by Paul Langerhans in 1868 until the initiation of research on those cells was reinitiated. The present paper provides the milestones in the research on Langerhans/dendritic cells (LCs/DCs) between 1960 and 1989. This historical review will explain how researchers gradually discovered the role of the bone marrow-derived dendritic cells in the immune response. The paper is an appendix to the manuscript entitled: “Immunological and regulatory functions of uninfected and infected immature and mature subtypes of dendritic cells” (Virus Genes 26: 119–130, 2003).

Key words: dendritic cells, Langerhans cells, milestones in dendritic cell research, Paul Langerhans

Introduction

Paul Langerhans observed dendritic cells in gold stained human skin, while studying medicine in Berlin. He assumed that they were nerve cells and published his findings in 1868 [1]. Almost 100 years were to pass before research on DCs was initiated in the 1960s. The progress of LC research on was relatively slow, as the LC population in the skin is relatively low (about 1–3% of the total skin cells), and special reagents had to be developed to identify these cells. However, the major obstacle in the research on LCs stemmed from the need to determine if indeed Paul Langerhans was correct in assuming that DCs are of neural origin or perhaps have a different tissue origin.

The aim of the present analysis is to define the major discoveries and breakthroughs achieved in the field of LC/DC research over a 30-year period, 1960–1989 (Table 1). The present review does not elaborate on the research of LCs/DCs that paved the way for studies on the immunological and

regulatory functions of uninfected and virus-infected immature and mature DC subtypes during the 1990s.

Milestones in the Research of LCs/DCs, 1960–1989

Electron microscopical studies that showed the presence of Birbeck granules in LC cytoplasm was the first step of the renewed activities in LC research [2,3,5]. These structures were used to identify LCs *in situ* [3]. However, the finding that LCs are present in mouse skin that were deprived of their neural crest [4] provided the first hint that LCs/DCs are not neurons with dendrites. During the 1970s, the discovery that LCs in the skin have ATPase on the cell surface [6] subsequently became a method to identify LCs in the skin epidermis. Furthermore, the discovery of Ia antigens (MHC class II) on the cell surface of LCs proved the latter's immunological significance [7,8,12,13]. It was also reported that LCs are involved in allergic contact sensitivity [9,10]. Cells containing Birbeck granules were found in lymph and lymph nodes [14,19], which were capable of antigen presentation [16] and lymphocyte activation

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Table 1. Milestones in the Research on LCs/DCs 1868–1989*

Discoveries or <i>Breakthroughs</i>	Year	Reference
<i>Discovery of DCs in human skin epidermis (gold staining) by Paul Langerhans</i>	1868	1
Birbeck describes granules in LCs	1961	2
Birbeck granules identify LCs	1966	3
<i>LCs are present in the skin of mice that are deprived of their neural crest</i>	1968	4
Cells containing Birbeck granules are present in human thymus DCs	1970	5
Cytochemical identification of ATPase-positive LCs in the skin	1975	6
<i>Immunological function of Ia antigen-bearing epidermal LCs are discovered</i>	1976	7
<i>LCs at the sites of vaccinia virus inoculation into human skin, virus is revealed by electron microscopy in the cells cytoplasm</i>	1976	8
The role of LCs in allergic contact sensitivity is discovered	1976	9
LCs form a reticuloepithelial trap of external antigens in the skin	1976	10
Epidermal LCs bear FC and C ₃ receptors	1977	11
Ia antigen expression by human epidermal LCs	1977	12
Ia antigens in mouse skin are predominately expressed on LCs	1979	13
The discovery of cells containing Birbeck granules that are present in the lymph and lymph nodes	1979	14
<i>Epidermal LCs are derived from cells originating from the bone marrow</i>	1979	15
LCs' antigen-presenting capacity is demonstrated	1980	16
<i>Ia positive DCs originating in the bone marrow are present in the medulla of rat thymus</i>	1981	17
Veiled cells are involved in lymphocyte reactivation	1982	18
Veiled cells, LCs, and interdigitating cells are proven to be related	1982	19
Depletion of epidermal LCs from tape-stripped mouse skin	1982	20
Human epidermal LCs induce a cellular immune response to trichophyton in dermatophytosis	1983	21
Epidermal LCs contain filaments of Vimentin	1984	22
LCs produce IL-1	1984	23
Cytologic identification of allogeneic LCs in bone marrow graft recipients	1984	24
Interferon enhancement of HLA-DR antigen expression on epidermal LCs	1985	25
LCs and lymphocyte subsets are present in the female genital tract	1985	26
The role of LCs in antigen presentation is demonstrated	1985	27
<i>A subset of human cord blood mononuclear cells resembles skin LCs</i>	1986	28
Leu3/T4 expression on epidermal LCs	1986	29
IL-2 receptors are present on cultured murine epidermal LCs	1986	30
Ia positive murine epidermal LCs express class I major histocompatibility complex (MHC)	1986	31
<i>A monoclonal antibody that is specific to mouse LCs, veiled cells, and interdigitating cells is developed</i>	1986	32
DCs are involved in the initiation of contact sensitivity to fluorescein isothiocyanate (FITC)	1986	33
Lymph node DCs localize FITC antigen	1987	34
LCs internalize antigens via receptor mediated endocytosis of T6, and Birbeck granules are involved in the intracellular traffic of antigen	1987	35
Immunostimulatory capabilities of highly enriched LCs <i>in vitro</i> were reported	1987	36
<i>Putative bone marrow precursors of LCs are cultured in vitro</i>	1988	37
Epidermal LCs release interferon γ	1988	38
<i>Viruses infect LCs</i>	1988	39
Murine DCs are invaded by <i>Leishmania major</i> and <i>L. mexicana</i>	1988	40
<i>Presentation of exogenous proteins by dendritic cells to T cell clones</i>	1989	41
Activated LCs release tumor necrosis factor (TNF)	1989	42

*The list of milestones in LC/DC research was compiled according to the review by Sprecher and Becker [43].

[18,20,21]. Moreover, F_C and C₃ receptors were located on the cell membranes of LCs [11].

The discovery of the origin of skin epidermal LCs, the antigen-presenting cells [15,16,21,27] from the

bone marrow, and that Ia⁺ cells in the medulla of rat thymus also originate from precursors that derive from the bone marrow [17] enabled scientists to determine the connection between LCs/DCs in