

Review Article

Langerhans Cell Histiocytosis: Revisited

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Abstract:

Langerhans cell histiocytosis (LCH) combines in one nosological category a group of diseases that have widely disparate clinical manifestations but are all characterized by accumulation of proliferating cells with surface markers and ultrastructural features similar to cutaneous Langerhans cells (LCs). In particular, careful molecular analyses of mouse models and human LCH samples suggest that LCH's cell of origin may not be the epidermal LC itself but a myeloid-derived precursor. Advanced genomic technologies have revealed the presence of activating, somatic BRAF mutations in the majority of patient specimens. Together, these observations have produced a new picture of LCH as a myeloid neoplasm.

Key words: Antigen presenting cells; dendritic cell; histiocytosis; neoplasia.

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Introduction

Langerhans cells (LCs) were first described by Paul Langerhans, in 1868, as dendritically shaped cells, which were located in the squamous epithelia of epidermis. Later on, these cells were identified in all stratified squamous epithelium of mammals. Dendritic cells (DCs) play an important role in local defense mechanisms in the epithelium. LCs are situated usually in the suprabasal layer of stratified squamous epithelia of oral mucosa and epidermis of skin. They constitute 3% of the cell population in epidermis. LCs are thought to act as antigen presenting cells (APCs) during initiation of immune responses. With the help of APCs, the lymphocytes are able to recognize and respond to specific microbes.^[1]

Langerhans cell histiocytosis (LCH) is a rare disease involving clonal proliferation of Langerhans cells, abnormal cells deriving from bone marrow and capable of

migrating from skin to lymph nodes. Clinically, its manifestations range from isolated bone lesions to multisystem disease. LCH is part of a group of clinical syndromes called histiocytoses, which are characterized by an abnormal proliferation of histiocytes (an archaic term for activated dendritic cells and macrophages). These diseases are related to other forms of abnormal proliferation of white blood cells, such as leukemias and lymphomas.^[2]

Langerhans Cells: Origin

The Langerhans cells (LCs) originate from the bone marrow and then migrate into the epithelium to perform the function of antigen recognition and presentation. Studies have shown that the dendritic cells (DCs) are developmentally similar. They share a common origin and then differentiate into different types in response to different environmental stimuli. (Zuniga et al. 2004. Earlier studies of DCs in the rat (Klinkert, 1984; Bowers and Berkovitz,

1986), the mouse (Steinman and Cohn, 1973), and humans (Caux et al., 1992) suggested the presence of cell types of progenitor cells, which were developmentally distinct, the myeloid and the lymphoid series.^{[1],[3]} These cells can then differentiate into distinct DC subtypes and perform distinct functions.^[1]

Langerhans Cells: Mechanism of Action

The DCs and other antigen presenting cells (APCs) must quickly respond to the invading bacterial structures (e.g. lipopolysaccharides, proteoglycans) called pathogen-associated molecular patterns. This function is accomplished through toll-like receptors (TLRs), which are a major class of signaling receptors. Receptors involved in antigen recognition are toll-like receptors (TLRs) and C-type lectin receptors. The LCs migrate via the afferent lymphatics as veiled cells, into the paracortex of the draining lymph nodes. Within the para-cortex, the cells interdigitate with many T cells. This migration carries the antigen from the skin or mucosa to the TH cells of the lymph nodes. The LCs express Class II MHC molecules for communicating with CD4+ T cells. Antigens are then degraded by proteolytic enzymes in specialized intercellular organelles. The linear fragments of antigenic peptides associate with class II MHC molecules as they are moved to the cell surface.^[1]

Langerhans cells histiocytosis: Recognizing the disease

Langerhans cell histiocytosis (LCH) is a clonal proliferative disease of Langerhans cells (LCs), the primary antigen-presenting cells of the skin. It occurs predominantly, but not exclusively, in children and is quite rare. Recent estimates infer an incidence of 2-9 cases per million children under the age of 15.^{[4],[5]} The clinical manifestations of LCH are highly variable and depend to a large extent on the number of body sites infiltrated by the pathologic LCs, the specific organs involved, and the precise anatomical location of the cellular

infiltration. Limited disease involving a single infiltration site can present as a skin rash, bone pain or soft tissue swelling. More extensive disease can present with symptoms of specific organ failure, such as diabetes insipidus which results from invasion of the pituitary stalk or respiratory insufficiency which results from pulmonary involvement; an example of the former is described in the accompanying case study. Extensive disease may also be associated with systemic signs of illness including fever or lymphadenopathy, as well as multiple organ failure. Pulmonary LCH is non-clonal and, in many cases, appears to be a reactive inflammatory disease that is primarily seen in adult smokers: this disease is probably distinct from the childhood form of LCH and will not be considered here further.^[4]

Historically, three distinct clinical syndromes have been described: eosinophilic granuloma, characterized by the presence of one or more lytic bone lesions in which the proliferating histiocytes are accompanied by a prominent infiltrate of eosinophils; Hand-Schüller-Christian disease, comprising the clinical triad of bone defects, exophthalmos, and polyuria, the latter due to histiocytic infiltration of the pituitary stalk; and, Letterer-Siwe disease, a fulminant disorder marked by hepatosplenomegaly, lymphadenopathy, skin rash, bone lesions, and haematological compromise.^[6-8]

Unification

Lichtenstein's unification of the three clinical forms of 'Histiocytosis X' was the culmination of nearly a decade of observations made by several discerning pathologists, including T.B. Mallory and Sidney Farber,^{[9],[10]} who noted that the proliferating cells in all of these disorders had the morphology of histiocytes. Although the origin of these cells was obscure [Lichtenstein wrote that they were derived from 'adventitial reticular cells of blood vessels']^[11] this novel nosological

category provided a new way of thinking about these unusual diseases.^[6]

Arvid Wallgren^[12] of Goteborg should be better recognized as a towering figure in this field because he marshaled substantial evidence from published case reports that Hand-Schuller-Christian disease is not a cholesterol-storage disorder. In particular, he cited several cases in which reticular cell proliferation was not associated with cholesterol, and he suggested that the appearance of foam cells is simply a late-stage phenomenon associated with tissue destruction. Furthermore, he cited cases in which the clinical boundaries between Hand-Schuller-Christian and Letterer-Siwe diseases seemed fluid: exophthalmos and diabetes insipidus accompanied by progressive anemia in some cases, Letterer-Siwe disease accompanied by lipid-laden foam cells in others.^[13]

Etiopathogenesis

Initial attempts to understand the pathobiology of LCH were focused on the immune and inflammatory nature of the LC, the presumed cell of origin. The primary function of LCs is to use the dendritic processes they extend in their resting state to survey the epidermis for foreign antigens. The appearance of these antigens usually occurs in association with immune activators, such as cytokines secreted by epidermal keratinocytes (e.g. TNF- α) or pathogen-associated ligands recognized by immune cell receptors (e.g. Toll-like receptor ligands). Upon activation, LCs take up and process antigen. The activated LCs then migrate to regional lymph nodes where they initiate an adaptive immune response by presenting processed antigen to T lymphocytes.^[6]

Some of the molecular mechanisms underlying LC migration are understood. In particular, the process appears to be controlled, at least in part, by sequential expression of chemokine receptors on the surface of LCs. In their resting state, LCs express the chemokine receptor CCR6 whose ligand, CCL20, is secreted by

epidermal keratinocytes. This ligand/receptor interaction is thought to keep resting LCs in the skin.^[6]

A feature of some forms of LCH, such as Letterer-Siwe disease, is the presence of pathological LCs in multiple organs at the same time, including both skin and lymph nodes. This observation led to the hypothesis that patterns of tissue infiltration in LCH might be explained by dysregulated expression of chemokine receptors.^[6]

One of the most significant conceptual breakthroughs in the understanding of this disease was the discovery of a link between the pathologic cells of LCH and normal epidermal LCs on the basis of shared surface markers and ultrastructural features. The simplest pathogenetic inference that was drawn from this connection is that the normal epidermal LC is the precursor cell for LCH. Whether the disease arises in

response to an external inflammatory stimulus or as the result of a cell-autonomous genetic event (see the section titled Neoplasm Versus Immune Disorder, below), the cellular target of these changes has been assumed to be the epidermal LC.^[13] The idea that the epidermal LC is the cell of origin for LCH has also been

questioned because LCs are a stable, localized cell population and are therefore unlikely to be responsible for disseminated forms of LCH. Again, there are different ways to interpret these facts, but an understanding of LC homeostasis can inform the discussion. LCs are phenotypically related to classical DCs, and both classical DCs and LCs are derived from circulating hematopoietic precursor cells. The bone marrow source of classical DCs is convincingly demonstrated by the wholesale replacement of host DCs, including those residing in mucosal sites, by donor cells after hematopoietic stem cell transplantation. Similarly, donor bone marrow cells can replace a significant proportion of host LCs when transplanted into lethally irradiated recipients, although there is a caveat: The replacement of host LCs is not complete. Approximately 20%

of LCs retain host markers, which may be a consequence, in part, of the relative radio-resistance of LCs compared with that of classical DCs. The lineage of the bone marrow-derived replacement cell is monocytoid, according to the finding that blood monocytes can replenish cutaneous LCs following UV irradiation; this process requires expression of both the chemokine receptor CCR2, for cells to enter the dermis, and CCR6, for the cells to reach their final destination in the epidermis.^[13]

Conclusion

After decades of careful work and molecular characterization, a clearer picture of LCH is beginning to emerge. The fact that LCH is a clonal disease in which the majority of cases carry an activating allele of an authentic oncogene indicates that it is a neoplasm. While some of its clinical manifestations may be related to an accompanying inflammatory state, and while it is possible that some of its behaviour may be exacerbated by inflammatory stimuli, the pathogenesis of a majority of LCH cases lies firmly within the paradigm of a cell-autonomous proliferative disorder that arises from a somatic mutation of a cell proliferation gene.^[6] Although recurrent genetic abnormalities have not been identified in LCH, it may be reasonable to use rodent models to test the relevance of other molecular abnormalities that have not necessarily been demonstrated to be pathogenic.^[4]

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