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Cell(s) of Origin of LCH

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Synopsis

Langerhans cell histiocytosis (LCH) is a diagnosis encompassing a wide spectrum of clinical manifestations, characterized by the common finding of inflammatory lesions containing clonal CD1a+ Langerin+ (CD207) histiocytes or LCH cells. Based on phenotypic similarity of LCH cells and epidermal Langerhans cells (LCs), models of pathogenesis have focused on aberrations in the differentiation of epidermal LCs. Recently, activating somatic mutations in the MAPK pathway have been discovered in the majority of cases of LCH and ERK phosphorylation appears to be universal in LCH cells. Using the BRAF V600E mutation as a lineage marker, emerging data support a model in which MAPK activation in self-renewing hematopoietic progenitors may drive disseminated high-risk disease, whereas MAPK activation in more differentiated committed myeloid precursors or peripheral tissue myeloid populations may induce multifocal or unifocal low-risk LCH. The heterogeneous clinical manifestations with shared histology may therefore represent the final common pathway of an acquired defect of differentiation, initiated at more than one point. Implications of this model include re-definition of LCH as a myeloid neoplasia and re-focusing therapeutic strategies on the cells and lineages of origin.

Keywords

Langerhans cell histiocytosis; BRAF; MAPK signaling; dendritic cell; myeloid differentiation

Introduction to LCH

The Histiocytoses

The spectrum of histiocytic diseases is characterized by collections of abnormal histiocytes or literally 'tissue cells' related to myeloid cells of the mononuclear phagocyte system¹⁻⁴. LCH is defined by the presence of a large pale-staining histiocyte with high expression of

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CD1a and Langerin (CD207) and containing Birbeck granules (Figure 1). These features, shared with Langerhans cells (LCs) of the epidermis, are the basis of classifying the disease as a ‘Langerhans cell’ histiocytosis. Prior to this, LCH was known as Histiocytosis X, a disease entity incorporating historically described syndromes: Hand-Christian-Schüller disease, characterized by lytic bone lesions and mucosal lesions; Letterer-Siwe disease, a fatal hepatosplenomegaly; and eosinophilic granuloma of bone. The discovery of the Birbeck granule in LCs in 1961 and identification of the same organelle in Histiocytosis X by Basset and colleagues in 1965 formed the basis for modern models of LCH⁵. Another influence driving this model of LCH at the same time, was the recently conceived ‘Mononuclear phagocyte system’ (MPS) in which peripheral macrophages were thought to be continually renewed from bone marrow derived monocytes¹. LCs had recently joined the MPS, by virtue of their expression of MHC class II, complement and Fc receptors and repopulation by bone marrow derived cells after transplantation. The formation of LCH was therefore perceived to be an aberration of this development leading to the accumulation of abnormal LC-like cells in inappropriate locations.

Clinical Overview

The clinical spectrum of LCH ranges from a trivial single lesion to aggressive and potentially lethal disseminated disease (Figure 1). Almost every organ system has been reported to be involved by LCH lesions. In infants, skin lesions are common and may represent skin-limited disease that resolves without therapy; alternatively, skin “rash” may be part of a constellation of lesions in disseminated multisystem disease. In older children and adults, presenting symptoms may include pain from bone lesions, dyspnea from lung lesions, failure to thrive from intestinal involvement, or uncontrolled thirst from pituitary infiltration and resulting diabetes insipidus. The range of presenting symptoms and overlapping clinical features with more common childhood conditions make LCH a challenging diagnosis. However, once biopsy is performed, the unique features of LCH cells and the inflammatory context of lymphocytes, eosinophils and macrophages are pathognomonic. While the number of pathologic histiocytes and relative contribution of infiltrating leukocyte populations may be variable, the overall pattern is conserved across the spectrum of clinical manifestations of LCH (Figure 1).

Rationale for current approaches to LCH

Clinically, LCH has been categorized as having a “high-risk” of mortality when it involves bone marrow, spleen or liver or “low-risk” in any other site. Treatment regimens are empiric, as summarized by Dr. Arceci and colleagues in the last *Clinics of North America* issue dedicated to LCH (1998): “The variety of different treatment approaches to such patients has prompted some individuals to believe that LCH treatment “strategy” is based more on a roulette wheel than on scientifically based logic. Certainly, part of the confusion and lack of consensus is derived from a persisting ambivalence as to whether LCH is primarily a neoplastic disorder, an immunodysregulatory disorder, or a disorder with characteristics of both”⁶. Vinblastine and prednisone have been the standard induction therapy for decades, though LCH-II and LCH-III trials demonstrated improved outcomes with dose intensification and therapy prolongation^{7;8}.

Molecular Insights into Pathogenesis of LCH

Langerhans Cell Histiocytosis: The debate

The fundamental nature of LCH as neoplastic versus reactive disorder has been an ongoing debate^{6;9}. The granulomatous histology with quiescent histiocytes suggested potential autoimmune or infectious etiology¹⁰ but the unique appearance of LCH cells and destructive nature of lesions hinted at dysplastic development. Although Nezelof and colleagues described LCs as the ‘stem cell’ of LCH, they also acknowledged the prevailing view that elements of the MPS including LCs, were continually replenished by the differentiation of bone marrow derived precursors. Many hypotheses emerged that LCH might arise from LC precursors in a state of arrested development, misguided to inappropriate sites by a pathological cytokine or chemokine milieu^{11;12;13;14}, but no unifying ‘extrinsic’ explanation for pathological LCH cell differentiation was ever achieved (Reviewed in¹⁵). A neoplastic origin for LCH was suggested by the coincidence of LCH with myelodysplastic syndrome and other malignancies^{16;17} and a major breakthrough came with the finding the LCH cells are clonal^{18;19}. However, persistent failure to identify genetic abnormalities in systematic analysis of LCH lesions tempered classification of LCH as a “cancer”²⁰⁻²³.

Somatic MAPK mutations in LCH

In 2010, Rollins and colleagues reported the seminal finding of recurrent BRAF V600E point mutations in approximately 60% of LCH lesions²⁴. BRAF is a central kinase which transduces signals through the MAPK pathway that regulates numerous essential cellular functions (Figure 2A). The *BRAF* mutation encoding the V600E substitution leads to constitutive activation of downstream MEK and ERK kinases²⁵ and is observed at high frequency in melanoma, in approximately 7% of human cancers overall and also in a number of benign neoplastic conditions including epidermal nevi and colon polyps^{26;27}. Subsequently, whole exome sequencing of LCH lesions has revealed recurrent mutations in *MAP2K1* (encoding MEK1) in another 20% of patients and cases of mutations in other MAPK pathway genes *ARAF* and *ERBB3*, on a very low overall mutation rate background (0.03 mutations per Mb) (Figure 2)²⁸⁻³⁰. These mutations all induce ERK activation, a universal feature of LCH cells^{24;29}. The genomic landscape of LCH is discussed in more detail elsewhere in this issue.

Branches of DC Differentiation

The insight of Nezelof and colleagues identified commonality between LCs and LCH but by their own reckoning, could not fully explain the histogenesis of LCH³¹. The identification of MAPK pathway mutations provides a genetic neoplastic etiology and an important investigational tool with which to track potential LCH precursor cells. However, the problem of understanding exactly how potential LCH precursors differentiate abnormally remains unsolved.

The phenotype of LCH DCs

In order to understand how aberrant DC differentiation might give rise to LCH cells, it is necessary to consider the phenotype of LCH cells in more detail. Breathnach, Basset and

Nezelof noted that in addition to Birbeck granules, acid-phosphatase, non-specific esterase, and alpha-D mannosidase were expressed by LCs and LCH cells⁵. The advent of monoclonal OKT6, binding CD1a was a major advance both conceptually and diagnostically, as was the description of Langerin³². Expression of CD1a is universal in LCH, and typically CD1a and Langerin are highly co-expressed. Birbeck granules are associated with high CD1a and Langerin and are most abundant in the skin but may be absent in the liver and in old 'xanthomatous' lesions³³. Similarly, several reports describe heterogeneous states of differentiation of LCH cells within lesions, including variable CD1a +/Langerin-subpopulations³³⁻³⁵. Antibody recognizing BRAF V600E (VE1), has also demonstrated that the mutation is present in some Langerin-negative cells within LCH lesions³⁶.

Despite these similarities, gene expression studies have demonstrated many differences between LCH cells and LCs: LCH cells express relatively less EpCAM, E-cadherin and CD36; they also express higher levels of CD2, CD11b, CD11c, CD13, CD33, CD66c, and CD300LF, markers associated with myeloid DCs at all states of maturation. LCH cells also express high levels of cytokines and chemokines including SPP1 (osteopontin), together with receptors CCR1, and NRP1 that influence capacity to recruit and interact with T cells³⁷. When isolated from lesions, they are somewhat immature, promoting a Th2-rich environment enriched with eosinophils and Tregs²¹. These observations support a hypothesis that aberrant differentiation of a myeloid progenitor leads to a series of LC-like differentiation steps that are time and location dependent. The nature of this precursor remains undefined although the low expression of S100A8/9 indicates that LCH cells are unlikely to be recently derived from monocytes³⁷.

Origin and homeostasis of Langerhans cells in the steady-state

It is now appreciated that LCs are unique not only in their residence in the epidermis and mucosae but in their origin and homeostasis³⁸. Contrary to the MPS model, LCs are not continually replenished from blood-borne progenitors in the steady-state. The first LCs are derived from myeloid precursors during fetal life^{39;40} which differentiate under the influence of the CSF-1R cytokine IL-34^{41;42} and autocrine production of TGFβ⁴³. Ultimately, fetal LC progenitors are derived from primitive waves of hematopoiesis that are c-myb and flt3-independent and precede definitive hematopoiesis in the fetal liver⁴⁴⁻⁴⁶. Once seeded in the epidermis, LCs are able to undergo homeostatic self-renewal, as first suggested in humans⁴⁷ and proven by elegant experiments in mice²². The independence of LCs from monocytes and blood DCs in the steady state is also demonstrated by the preservation of these cells in patients with genetic deficiency of monocytes and DCs^{48;49} and in patients who have received limb transplants⁵⁰. The development and subsequent self-renewing potential of a tissue macrophage/DC network during fetal life raises new possibilities for the origin of LCH cells. It is conceivable that somatic mutation could arise in these cycling cells and could result in LCH or that activation of a more widely-distributed fetal precursor could occur (Figure 2B).

Replenishment of LCs during inflammation

While fetal-derived LCs are self-renewing in epidermis during steady-state, bone marrow-derived precursors are recruited during inflammation, such as graft versus host disease after human stem cell transplantation^{51;52}. In mice, the epidermis is initially infiltrated by classical monocytes⁵³, but a second wave of more long-lived LC precursors has recently been described^{54;55}. In a recapitulation of embryonic development, IL-34 is also required to maintain long term LC repopulation⁵⁴.

Dual inflammatory LC precursors

The duality of inflammatory LC precursors in mice also finds resonance with *in vitro* experiments in humans. A two phase kinetic was observed many years ago in serial skin biopsies of DTH reactions⁵⁶. Langerin+ cells can be derived from monocytes⁵⁷⁻⁵⁹, from CD14+ cells appearing in CD34+ cultures⁶⁰ and from dermal CD14+ cells that are now known to be monocyte-derived^{61;62}. All these may represent the monocyte pathway of short term recruitment. In addition, CD1a+ CD14-negative intermediates with restricted LC potential can be generated from CD34+ progenitors^{63;64}. This suggests potential for an alternative pathway of LC differentiation, a conclusion that was recently supported by direct comparisons of CD14 monocytes and CD1c+ blood DCs exposed to LC differentiation conditions. In these experiments, surprisingly, CD1c+ DCs expressed much higher levels of CD1a and Langerin than monocytes and only CD1c+ DCs rapidly formed Birbeck granules^{65;66}. Either GM-CSF or TSLP was able to induce CD1a expression and high Langerin was promoted by TGF β or BMP7. The role of IL-34 was not explored. Together these results suggest that the DC differentiation pathway may contribute to long term LC precursors observed in mice and furthermore, that both bone marrow-derived monocytes and myeloid DCs can express Langerin and are candidate precursors for LCH cells.

Langerhans cells are not the only fruit: other human dendritic cells

LCs are the paradigmatic migratory DC, but blood and interstitial tissues contain two other populations of myeloid DCs: a minor subset of CD141+ cells and a major subset of CD1c+ cells⁶⁷⁻⁶⁹. (Table 1) Representatives of both are found in the blood and lymph nodes and are evolutionarily conserved in mammals, corresponding to the two subsets of classical or conventional DCs described in mice^{2;4}. The term 'myeloid' is quite specific in humans and refers to the expression of antigens typically seen on granulocytes or monocytes including CD13, CD33, CD11b and CD11c. Plasmacytoid DCs, typically lack myeloid antigens and are morphologically and functionally quite distinct, providing a major source type 1 interferon in response to viral infection (Reviewed in⁷⁰). They are typically only found in lymph nodes and inflamed tissues. In addition, a number of monocyte-derived DCs and macrophages are found in human tissues^{61;71;72}.

Langerin-positive dendritic cells

It is now known that other DC lineage cells expression Langerin. A small population of CD1c+ DCs (the major myeloid DC), distinct from LCs and from CD141+ DCs, expresses a low level of Langerin *in vivo*^{68;73}. Confusingly, Langerin is also found on mouse DCs but restricted to the minor classical DC population which is not the direct homologue of human

CD1c+ DCs⁷⁴ (Table 1). The presence of Langerin+ CD1c+ DCs in human tissues is consistent with the ability of blood CD1c+ DCs to up-regulate Langerin *in vitro* and reinforces the idea that CD1c DCs could function as LC precursors during inflammation and potentially give rise to LCH cells. Intriguingly, some of the key differences in gene expression profile between LCH cells and LCs are lost when LCH cells are compared with Langerin+ CD1c+ DCs. For example, Langerin+ DCs are EpCAM and E-Cadherin negative and have higher CD11b and CD11c, unlike LCs⁷³. Direct comparison of the transcriptional profiles of LCH with blood CD1c+ DCs and epidermal LCs indicates similar proximity⁵⁹ but further studies are required to compare LCH with tissue CD1c+ DCs and Langerin+ *in vitro*-derived CD1c+ DCs in detail.

Revisiting the Cell of Origin in LCH

Lineage tracing LCH

Somatic mutations in LCH have provided a foothold with which to study the cell of origin of LCH. From the previous discussion it is evident that LCH cells could arise from more than one source. In an attempt to more precisely identify candidate precursor populations, we asked whether the mutation encoding BRAF V600E was present in circulating mononuclear cells in patients with active LCH. In our series of 100 patients, peripheral blood mononuclear cells with the BRAF V600E point mutation were identified in all patients with high-risk LCH in whom BRAF V600E was detected in lesion LCH cells⁷⁵. No circulating cells with BRAF V600E were identified in patients with single system disease, and only in a small number of patients with presumed multifocal low-risk disease. Furthermore, the presence of circulating cells in high-risk patients correlated with disease activity. Lineage analysis of the circulating cells in high-risk patients identified cells with BRAF V600E in CD14+ monocyte and CD11c+ myeloid DCs (which includes CD1c+ DCs, CD141+ DCs, CD16+ non-classical monocytes) fractions in all cases, suggesting the somatic mutation arose in a myeloid progenitor.

Continuing the search upstream for the hematopoietic origin of LCH, analysis of bone marrow aspirate demonstrated that the BRAF V600E mutation was present in CD34+ hematopoietic stem and progenitor cells (HSPC) in some, but not all, cases of high-risk patients. It should be noted that in half of the cases where BRAF V600E was identified in bone marrow aspirate, histology was reportedly normal, suggesting the mutation arose in morphologically normal precursor cells. Interestingly, in cases where BRAF V600E was identified in CD34+ HSPCs, it could also be identified in circulating CD19+ B cells, suggesting the involvement of a pluripotent stem cells. CD3+ T cells were not affected in keeping with their relative independence from the bone marrow⁷⁵. BRAF V600E was also recently identified in CD34+ cells of patients with hairy cell leukemia⁷⁶. It is not clear why the same presumed driver mutation occurring in HSC leads to distinct conditions. Potential explanations include epigenetic imprinting of individual stem cells towards different fates or additional modifying somatic mutations⁷⁷ or acquisition of mutations at different stages of hematopoietic development.

An updated model of LCH

These data suggest a revised model of LCH pathogenesis in which the developmental stage at which an ERK activating mutation arises determines the clinical manifestations (Figure 2B). The common histology observed by Lichtenstein could represent a common final pathway from many different starting points. This hypothesis is further supported by the observation that enforced expression of BRAF V600E in Langerin+ cells in mice resulted in formation of localized LCH-like lesions with no BRAF V600E expressed in cells in circulation, where enforced expression of BRAF V600E in CD11c+ cells resulted in a more aggressive phenotype similar to disseminated high-risk LCH⁷⁵.

JXG and ECD: Cousins or siblings of LCH?

Juvenile xanthogranuloma (JXG) and Erdheim-Chester disease (ECD) are histologically similar diseases characterized by CD14+, CD68+, fascin+, factor XIII+, CD1a-, CD207- histiocytes. JXG is a disease of childhood that, like LCH, ranges from trivial skin-limited lesions to life-threatening disseminated disease. JXG has been reported to co-present with juvenile myelomonocytic leukemia as well as with germline mutations in *NF1* that implicate potential role for MAPK hyperactivity in pathogenesis (Reviewed in ⁷⁸). ECD is a very rare disease of adults that typically presents with more clinically ominous systemic lesions. Like LCH, BRAF V600E and other activating MAPK mutations are reported in the majority of cases^{79;80}. Furthermore, both JXG and ECD have been reported to co-present with LCH, either with mixed histology in the same lesion or with distinct histology in different lesions (Reviewed in ⁷⁸). Together, the common trigger of MAPK hyperactivity and consistent mutations across lesions in patients with mixed histiocytic disorders^{29;75;81} suggest potential for a common origin and blurs the distinction between the neoplastic histiocytoses.

LCH as a myeloproliferative disorder

Activating somatic mutations in hematopoietic stem cells and myeloid precursors in LCH patients, coupled with the formation of lesions driven by BRAF V600E in mouse models, support the classification of LCH as a myeloid neoplasia. Transformed DC clones presumably recruit inflammatory cells, resulting in a cytokine rich milieu that promotes LCH cell survival. We therefore propose that LCH and related JXG and ECD represent a class of histiocytic inflammatory myeloproliferative neoplastic (MPN) disorder. Other MPNs, such as chronic myelogenous leukemia and myelofibrosis, also share the features of a genetically quiet landscape with single driver mutations in kinase pathways and a prominent inflammatory component to disease.

Re-branding LCH as a *bona fide* myeloid neoplasia has some practical as well as political implications. First, understanding LCH as a “stem cell” disease may explain the very high rate of relapse in patients treated with local or minimally myelotoxic therapeutic strategies⁸². If approached as a stem cell disease, optimal therapy for patients with systemic disease would focus on eradicating the transformed precursor rather than treating individual lesions or tolerating frequent “reactivations”. Further, chemotherapy agents with efficacy against myeloid lineages may have superior efficacy in LCH, compared with traditional ALL-based therapies. In keeping with this, small cohort studies report that clofarabine, a nucleoside analogue with efficacy in AML, has cured some patients with aggressive,

refractory LCH⁸³⁻⁸⁵. Finally, direct targeted therapy with RAF inhibitors such as vemurafenib has shown early promise in adults with ECD and LCH, further demonstrating the critical role of MAPK activation in driving pathogenesis⁸⁶.

Summary/Future Directions

LCH is a complex disease with a fascinating history. Individual reports of highly variable intriguing presentations merged into eponymous classifications that were later unified as Histiocytosis X, due to common histology. Subsequently, “Langerhans cell” histiocytosis shifted focus to the aberrant development of LCs. New data support a model that once again deconstructs this single diagnosis into its many facets each caused by a repertoire of mutations acting at multiple stages of myeloid cell development. The common molecular pathway is MAPK hyperactivation and the common endpoint is a CD1a+ CD1c+ neoplastic cell, but it now seems that every patient has their own private route to developing LCH.

The pace of progress since the last LCH edition of *Clinics* has accelerated, though patients continue to have suboptimal outcomes, and many fundamental aspects of pathogenesis remain unanswered. Politically, new understanding of the nature of LCH is highly significant in placing LCH in the disease family embraced by funding agencies including the National Cancer Institute as well as by cooperative clinical trial and translational research groups that advocate for patients with cancer and related disorders. Scientifically, the mechanisms by which MAPK activation drives differentiation of the precursor and subsequent recruitment of inflammatory infiltrate are not known. Improved understanding of mechanisms of pathogenesis will further inform general clinical approaches as well as opportunities for personalized approaches to risk stratification, targeted therapy and monitoring disease burden. While much remains to be learned, we believe that there is now a more rational path to develop “strategy” to improve outcomes for patients with LCH beyond the luck of the roulette wheel.

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Key Points

- Dendritic cells are immune cells that arise from different lineages with the shared function of presenting antigen and activating adaptive immunity.
- LCH arises from myeloid dendritic cell precursors. MAPK activation is a universal feature of CD1a+ Langerin+ LCH cells. The clinical extent of LCH is related to the stage of development in which somatic MAPK mutations arise; either self-renewing progenitors or committed precursors.
- Activating MAPK mutations in hematopoietic stem cells and committed myeloid precursors support classification of LCH as a myeloid neoplasia.

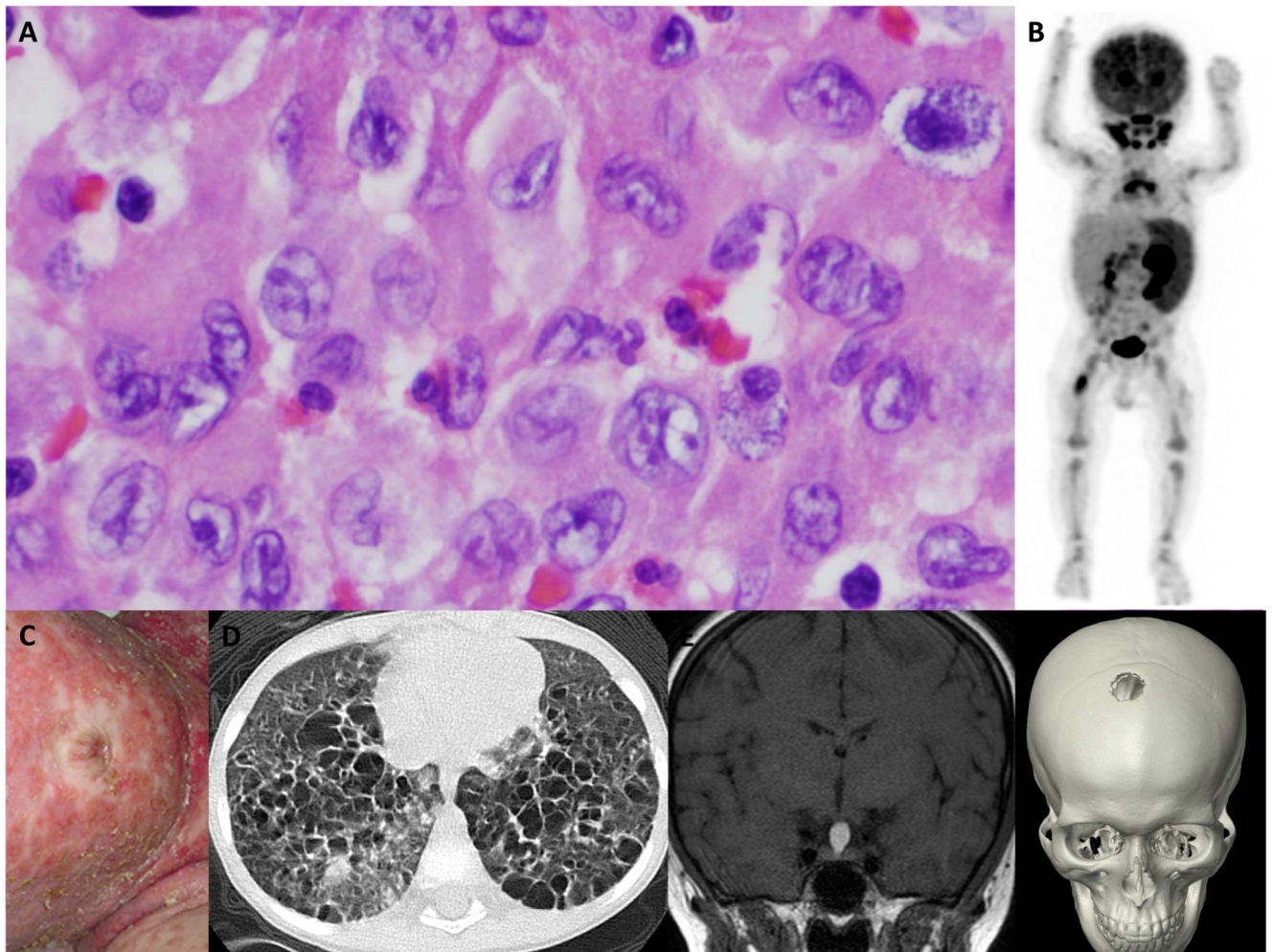


Figure 1. LCH: Common histology and clinical heterogeneity

A. Hematoxylin and eosin staining of a typical LCH lesion, demonstrating the classic large histiocytes with grooved “coffee-bean” nuclei and abundant eosinophilic cytoplasm. The inflammatory infiltrate varies, but typically includes lymphocytes, eosinophils and macrophages. Histologic features have not been associated with specific clinical presentations. This biopsy could have come from any of the cases presented in B-F.

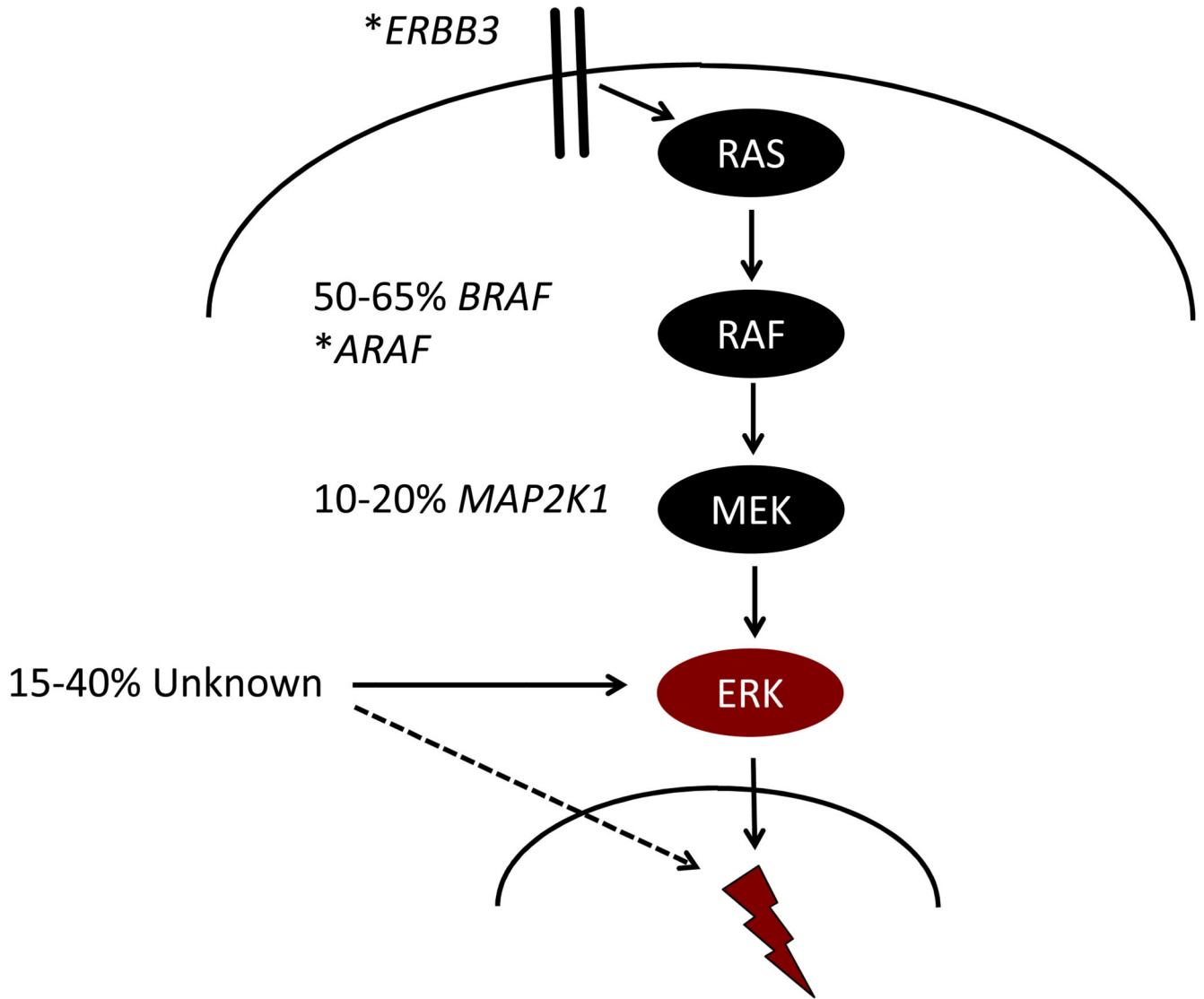
B. PET scan of a 1 year old with high-risk LCH: PET-avid R femur lesion, spleen, bone marrow and cervical lymph nodes are evident in this image.

C. Infant with severe LCH skin lesions. In infants, skin LCH may be self-limiting and spontaneously resolve or may be part of life-threatening multi-system high-risk disease.

D. CT scan demonstrating innumerable cysts and lung lesions in a 3 year old with LCH involving lung, pituitary and skin.

E. Brain MRI in a teenager with an isolated pituitary LCH lesion.

F. CT scan of a teenager with an isolated skull LCH lesion.



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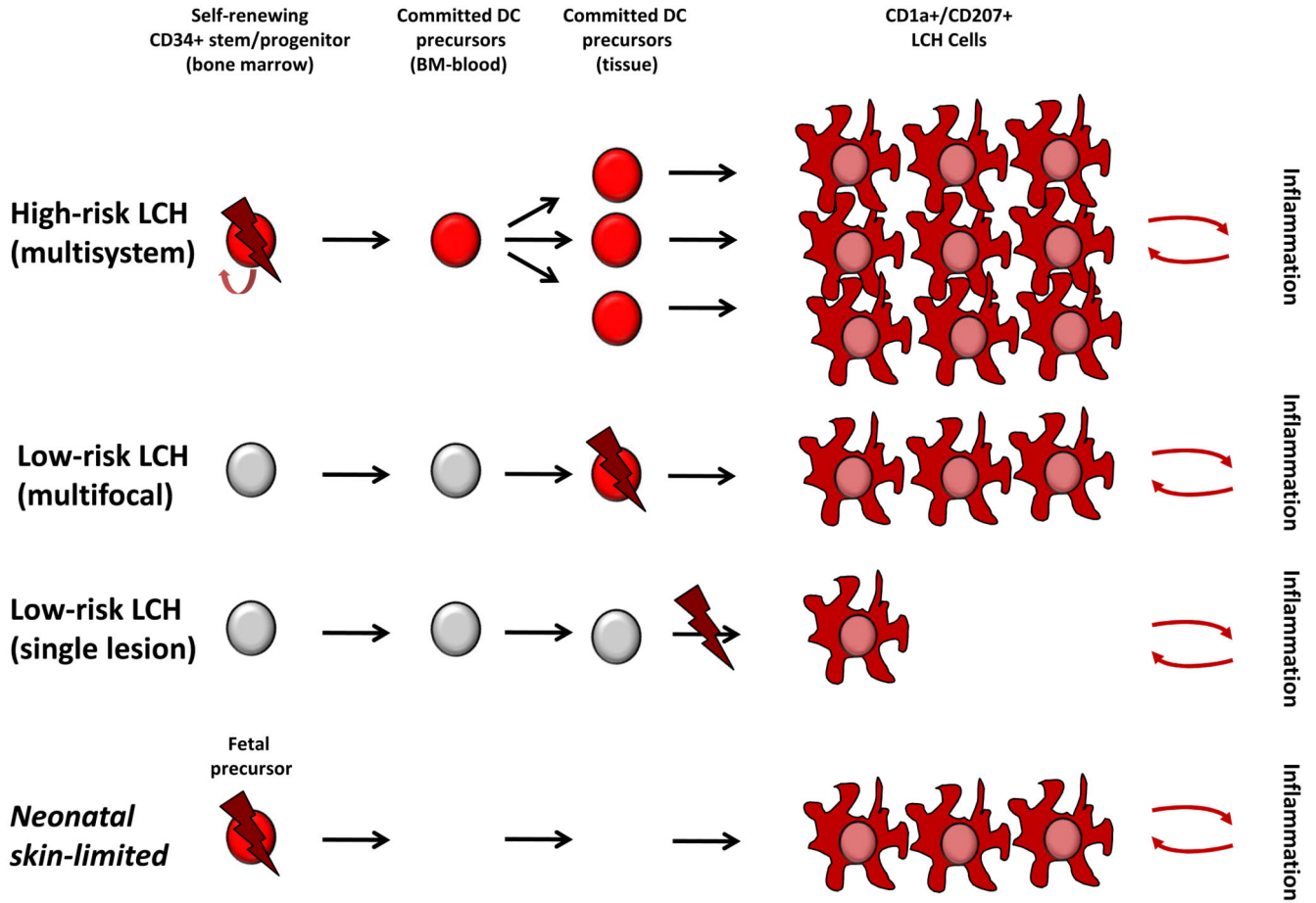


Figure 2. Model of LCH pathogenesis: ERK activation at specific stages of myelopoiesis determines clinical phenotype

A. Mutually exclusive activating mutations in MAPK genes have been reported in most cases of LCH, and ERK activation appears to be universal in LCH lesion CD207+ cells. Lightning bolt represents the downstream impact of ERK activation that presumably is essential for LCH pathogenesis.

B. Proposed “*Misguided Myeloid DC*” model of LCH pathogenesis in which somatic mutation (lightning bolt) and subsequent ERK activation (red cell) at specific stages of DC development determines clinical outcome. This model reflects interpretation of data from human and mouse studies⁷⁵, but leaves room for future refinement. According to this model, ERK activation in a self-renewing progenitor/stem cell in the bone marrow has the potential to form lesions in hematopoietic organs, liver, and virtually any organ system leading to MS LCH with somatic mutation detectable in BM and blood. In contrast, ERK activation in committed precursors may form multiple lesions in a limited number of organ systems, but somatic mutation is not usually detectable in the BM or blood at diagnosis, or subsequently. ERK activation at a later stages of differentiation, perhaps even in a single tissue cell, may form a single unifocal lesion. Based on recent data describing the pre-natal origin of tissue myeloid cells, it is also conceivable that ERK activating mutation may arise during fetal development. This is speculative but could explain “self-resolving” neonatal LCH (Hashimoto Pritzker syndrome) in which mutated fetal precursors would be replaced by

normal myeloid cells after birth. In all models, it is suggested that LCH cells recruit and activate inflammatory cells which may provide reciprocal survival signals and clearly play a role in clinical manifestations of LCH.

Data from Refs ^{28-30, 75}

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
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Table 1

Steady-state human dendritic cells

The principal DC subsets found in human blood, tissues and lymphoid tissues, together with their murine homologues. L.Cs are restricted only to human monocytes. *Collin et al.*

	Human	Mouse homologue	
Myeloid Langerhans cell 	Langerin CD1a EpCAM ECadherin CD11c ^{low} CD11b ^{low}	Langerin EpCAM CD24	
	Minor subset (DC1) 	CD141 XCR1 CLEC9A CD11c ^{low} CD1a/c ⁺ (tissue)	CD103 (tissues) CD8 (lymphoid) CLEC9A XCR1 Langerin ***
	Major subset (DC2) 	CD1c SIRPα CD11c ⁺ CD1a ⁺ (tissue) *** Langerin ***	CD11b ⁺ CD24- CD64- (tissues) CD11b ⁺ CD4 ⁺ (lymphoid) CD11c ^{low} ESAM
Plasmacytoid 	CD303 (CLEC4C) CD304 (neuropilin) CD123 (IL-3R)	B220 Siglec H	
Monocyte-related Mo-DC 	CD11c S100 A8/9? CD209 (DC-SIGN)? CD206?	CD11b ⁺ CD24 ^{low} CCR2 ⁺ CD64 ^{low} MerTK- CD209 (DC-SIGN)	
	Mo-Macrophage (formerly 'CD14 DC') 	CD14 CD209 (DC-SIGN) CD11b Factor XIIIa CD141 ^{low}	CD11b ⁺ CD24 ^{low} CD64 ⁺ CCR2 ^{low} MerTK ⁺ CD209 (DC-SIGN)