Genomic Alterations in Langerhans Cell Histiocytosis

Barrett J. Rollins, MD, PhD[a,b,*]

KEYWORDS

• Langerhans cell histiocytosis • LCH • BRAF • MAP2K1 • MEK1

KEY POINTS

- Recurrent somatic genomic abnormalities occur in Langerhans cell histiocytosis (LCH), indicating that it is a neoplastic disease.
- Most mutations activate signaling enzymes that result in extracellular-signal-regulated kinase (ERK) activation.
- More than 50% of cases carry *BRAF* mutations and 10% to 28% carry *MAP2K1* mutations, but all cases show activation of ERK.
- Significant clinical responses to RAF family inhibitors have been reported in patients whose LCH cells carry *BRAF* mutations, indicating that these mutations are authentic drivers of disease in LCH.

INTRODUCTION

Long considered an enigmatic disease, LCH defies simple categorization. Its 4 clinically distinct syndromes (Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma, and Hashimoto-Pritzker disease) were unified by observations in the mid-twentieth century of a characteristically abnormal histiocyte with distinctive morphology, subcellular structures, and staining patterns that appears in all forms of the disease.[1–3] Although this categorization has helped clarify thinking about LCH, it has not explained its pathogenesis or its impressively protean clinical manifestations.

The author has no commercial or financial conflicts of interest to declare. The author's work has been supported by the Histiocytosis Association, Team Ippolittle/Deloitte of the Boston Marathon Jimmy Fund Walk, Stichting 1000 Kaarsjes voor Juultje, the Say Yes to Education Foundation, and Mr George Weiss.

[a] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215, USA; [b] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

* Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215.

E-mail address: barrett_rollins@dfci.harvard.edu

Hematol Oncol Clin N Am 29 (2015) 839–851
http://dx.doi.org/10.1016/j.hoc.2015.06.004 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

Further progress in characterizing LCH has been impeded by a paucity of samples, a consequence both of the low prevalence of LCH[4,5] and the small size of most tissue samples obtained for clinical purposes. However, technical advances in the genomic analysis of clinical material have been applied to LCH and have revolutionized the understanding of the fundamental nature of the disease. One of the most enabling innovations is the ability to perform robust multiplexed genetic testing on small amounts of archived clinical material, that is, formalin-fixed, paraffin-embedded samples acquired for diagnostic purposes.[6–8] This ability has opened the archives of pathology departments around the world to genomic analyses, and the application of these technologies has revealed some of the first evidence for recurrent and pathogenetically relevant mutations in LCH. To date, these have been somatic mutations rather than germline alterations affecting risk. The result has been a clearer understanding of LCH as a neoplastic disease and the identification of therapeutically important molecular targets.

MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY ACTIVATION

BRAF

One of the first technologies capable of testing archived human samples for multiple alleles simultaneously was the Sequenom mass spectrometric genotyping platform.[6] A modification specific for oncology applications known as OncoMap, which tests 983 specific mutations in 115 cancer-related genes, was applied to 61 LCH clinical samples.[9] Overall, very few mutations were detected, a common finding in all subsequent studies (see later discussion) attesting to the stability of the LCH genome. However, a mutation in *BRAF* encoding the substitution of glutamate for valine at amino acid 600 (BRAF V600E) was observed in 57% of the samples.[9] This mutation, which produces a constitutively active BRAF kinase, is the most commonly observed *BRAF* variant in cancer and is found in a variety of different cancer types in which it often plays a driver role in pathogenesis.[10–14] The effect of mutationally activated BRAF is to stimulate signaling through the RAS/RAF/MEK/ERK pathway leading to constitutive transcription of genes involved in a variety of cellular responses including proliferation (**Fig. 1**).

The presence in LCH of recurrent activating mutations in *BRAF* has been confirmed in several studies using a variety of different detection techniques (**Table 1**). Among them are immunohistochemical studies with a V600E-specific antibody, which confirms that the variant is present specifically in LCH histiocytes,[15] a fact that could previously be inferred only indirectly by molecular means.[9] *BRAF* mutations occur in all clinical settings, including pediatric, adult, single system, and multisystem disease, and their overall prevalence in reported studies is 45% to 65%.[9,15–24] Surprisingly, *BRAF* mutations appear at a nearly similar frequency in pulmonary LCH, a disease of adult smokers that has generally been thought to be polyclonal. However, about one-third of pulmonary LCH cases are clonal.[25] It is also possible that cases that are polyclonal in the aggregate actually comprise several clones of *BRAF* mutant disease that arose independently.

In the original OncoMap analysis, the median age of patients whose histiocytes contain BRAF V600E was less than the median age of patients whose histiocytes did not, and younger age was associated with the presence of the mutation in an unadjusted exact logistic model but not in the adjusted model.[9] The presence of mutated *BRAF* did not correlate with any other clinical features, although the clinical annotation of that sample set was limited. In contrast, in the largest sample set analyzed to date, clinical annotation was much more complete and the presence of BRAF V600E