Identification and Targeting of Kinase Alterations in Histiocytic Neoplasms

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KEYWORDS

• ARAF • BRAF • Erdheim-Chester disease • Langerhans cell histiocytosis
• MAP kinase • MEK

KEY POINTS

- Nearly every patient with Langerhans cell histiocytosis and Erdheim-Chester disease has ERK activation owing to activating mutations in ARAF, BRAF, MEK1/2, or N/KRAS, or kinase fusions.
- BRAF inhibition results in dramatic and durable responses in patients with *BRAF* V600E mutant histiocytosis.
- MEK inhibitors may be efficacious for treating *BRAF*-wild-type histiocytosis.
- The safety and therapeutic usefulness of targeted therapy versus conventional therapy for children with Langerhans cell histiocytosis remains to be determined.
- Further genomic analyses are needed to define fusions in patients without point mutations in kinases and those alterations that cooperate with kinase mutations in histiocytoses.

INTRODUCTION

The histiocytoses are a diverse group of disorders defined by the pathologic infiltration of normal tissues by cells of the mononuclear phagocyte system. Owing to biologic variability of the cells of the mononuclear phagocyte system and the tissues they inhabit, histiocytic disorders are among the most intriguing yet complex areas of modern hematology and can be tremendously difficult to diagnose. Until recently, the mechanisms of pathogenesis of the histiocytoses have been speculative and debate

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has focused on the classification of these conditions as reactive versus neoplastic. However, starting 6 years ago, a series of recurrent, activating mutations in genes encoding kinases of the mitogen-activated protein (MAP) kinase (MAPK) system have been discovered in a large proportion of histiocytosis patients. These discoveries have resulted in potently effective therapies in genetically defined subsets of adults with these disorders. Here, we review the recent molecular advances in the systemic histiocytoses and their impact on treatment.

SYSTEMIC HISTIOCYTIC NEOPLASMS AND THEIR CURRENT CLASSIFICATION

According to the fourth edition of the World Health Organization (WHO) classification, histiocytic disorders can be classified into 2 main categories based on the phenotype of cells present within the lesions: (1) Langerhans cell histiocytosis (LCH) and (2) non-Langerhans cell histiocytoses (non-LCH) (**Fig. 1**A). LCH received its name as the tumoral cells share unique ultrastructural features of normal Langerhans cells (LCs). However, comparisons of gene expression between LCH cells and LCs indicate that LCH cells are considerable less mature than LCs and are phenotypically closer to myeloid dendritic cells than they are to LCs.[1,2] These data question LCs as the cell-of-origin of LCH, a hypothesis that has largely been discarded in recent years in favor of the idea that LCH arises from either myeloid dendritic cells, their progenitors, or cells even before dendritic cell, monocyte, or macrophage differentiation.[3]

In the WHO classification system, Langerhans cell lesions are divided into 2 subgroups based on the degree of cytologic atypia and clinical aggressiveness: LCH and Langerhans cell sarcoma. In contrast, non-LCH are a heterogenous group of disorders including Erdheim-Chester disease (ECD), juvenile xanthogranulomatous disease (JXG), Rosai-Dorfman disease (RDD), histiocytic sarcoma (HS), indeterminate cell histiocytosis, and others defined by the accumulation of histiocytes that do not meet the diagnostic criteria for LCH, Langerhans cell sarcoma, or hemophagocytic lymphohistiocytosis (see **Fig. 1**A).[4]

In addition to the WHO Classification, the Histiocyte Society has recently proposed a new classification of histiocytosis incorporating clinicopathologic, prognostic, and new genetic findings that have not been accounted for in the WHO classification. This new classification system categorizes the histiocytoses into 5 groups: "L" (Langerhans), "C" (cutaneous and mucocutaneous), "M" (malignant), "R" (Rosai-Dorfman), and "H" (hemophagocytic) groups[5] (see **Fig. 1**B). One important motivation of this effort to regroup the histiocytoses was to take into considerable new molecular genetic information that has revealed the unexpected genetic similarity between LCH and the non-LCH neoplasms (see **Fig. 1**C, D). Thus, in the revised Histiocyte Society classification, the L group includes LCH and ECD, entities that share mutations in the MAPK pathway in greater than 80% of cases[6,7] and may coexist.[8] This review focuses on the biological and therapeutic importance of MAPK mutations in diseases within this L category. The pathophysiology of hemophagocytic disorders of the H group seem to be distinct from those of the L group disorders and the conditions within the C, M, and R groups do not have clearly defined molecular characteristics of pathophysiology currently.

DISCOVERY OF *B-RAF* PROTOONCOGENE MUTATIONS IN HISTIOCYTOSES

In 2010, Badalian-Very and colleagues[6] identified that 57% of LCH patients carry the *BRAF* V600E mutation, thereby identifying a clonal marker of the disease and suggesting that LCH is driven by activation of the MAPK pathway. This high frequency of *BRAF* V600E mutations was then validated in a subsequent study in LCH[7] and also found in a