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Histiocytic Neoplasms in the Era of Personalized Genomic Medicine

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Abstract

Purpose of Review—Since the discovery of *BRAF*V600E mutations in histiocytic neoplasms, diverse kinase alterations have been uncovered in *BRAF*V600E-wildtype histiocytoses. The purpose of this review is to outline recent molecular advances in histiocytic neoplasms and discuss their impact on the pathogenesis and treatment of these disorders.

Recent Findings—Activating kinase alterations discovered in *BRAF*V600E-wildtype Langerhans (LCH) and non-Langerhans cell histiocytoses (non-LCH) result in constitutive activation of the mitogen-activated protein kinase (MAPK) and/or PI3K/AKT pathways. These kinase alterations include activating mutations in *ARAF*, *MAP2K1*, *NRAS*, *KRAS*, and *PIK3CA* kinases in LCH and non-LCH; *BRAF*, *ALK*, and *NTRK1* fusions, as well as the *ETV3-NCOA2* fusion in non-LCH; and mutations in the *MAP3K1* and *HRAS* kinases in LCH and histiocytic sarcoma, respectively. These discoveries have refined the understanding of the histiocytoses as clonal, myeloid neoplasms driven by constitutive MAPK signaling and identified molecular therapeutic targets with promising clinical responses to RAF and MEK inhibition.

Summary—Genomic analyses over the last 6 years have identified targetable kinase alterations in *BRAF*V600E-wildtype histiocytic neoplasms. However, despite this progress, the molecular pathogenesis and therapeutic responsiveness of non-*BRAF*V600E kinase alterations are still poorly defined in these disorders.

Keywords

Langerhans Cell Histiocytosis; Erdheim-Chester Disease; *ARAF*; *MAP2K1*; Kinase Fusions

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Introduction

Histiocytic disorders represent a class of diseases with heterogeneous clinical courses and prognoses. They encompass disorders including Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), Rosai-Dorfman disease (RDD), juvenile xanthogranuloma (JXG), histiocytic sarcoma (HS), and indeterminate cell histiocytosis (ICH). All of these conditions are believed to share a common pathologic characteristic: the accumulation and infiltration of macrophages, monocytes, dendritic cells, interdigitating reticulum cells, or Langerhans cells in the affected tissues. The pathophysiology of these diseases has long been obscure, and it was previously unclear as to whether or not they represented autoimmune or clonal, neoplastic disorders [(1), (2)]. However, starting 6 years ago, a series of recurrent activating mutations involving the MAPK and PI3K-AKT pathways (**Figure 1**) have been discovered in a large proportion of patients affected by this disorder. Here we review the molecular features of these disorders and the implications of these findings for therapy.

Current Clinical and Histological Categorization of Histiocytoses with Insights into the Cell-of-Origin

Currently, histiocytic neoplasms are divided into LCH and non-LCH. LCH is the most common histiocytic neoplasm and most commonly occurs in children. LCH is found in 5 out of 1 million children, which is a similar frequency to acute myeloid leukemia and Hodgkin lymphoma in children [(3)]. In 2008, the World Health Organization (WHO) defined LCH as a “clonal neoplastic proliferation of Langerhans-type cells that express CD1a, langerin, and S100 protein, and shows Birbeck granules by ultrastructural examination” [(1)]. LCH originally derived its name due to the fact the Birbeck granule was identified in mononuclear phagocytic cells of LCH lesions. Since the Birbeck granule had only been seen in epidermal Langerhans cells previously, LCH was historically thought to arise from epidermal Langerhans cells [(3), (4)]. However, recent evidence suggests that LCH is actually derived from myeloid precursor cells bearing somatic mutations in MAPK pathway members. Expression profiling studies of the purified CD207+ dendritic cells from human LCH neoplasms demonstrate a significant transcriptional overlap with immature myeloid dendritic cell precursors while there is only minimal overlap with the expression profiles of human Langerhans cells [(5)]. Additionally, *BRAF* V600E mutations were identified in CD11c+ myeloid dendritic cell precursors and CD14+ monocytes in systemic LCH while *BRAF* V600E mutations were not present in the peripheral blood of patients with multifocal-tissue-restricted or single-lesion LCH. Furthermore, *BRAF* V600E mutations were identified in CD34+ hematopoietic progenitor cells in several systemic LCH patients. Moreover, enforced *BRAF* V600E expression in mouse Cd11c+ cells results in a phenotype resembling systemic LCH while enforced *BRAF* V600E expression in more differentiated, langerin+ dendritic cells in mice resembled multifocal-tissue-restricted or single-lesion LCH. These data led to the proposal of the “misguided myeloid dendritic cell model of LCH pathogenesis” where the clinical severity and distribution of the LCH lesion(s) are defined by the cellular stage of myeloid differentiation during which the somatic *BRAF* V600E or other activating kinase mutation arises and results in pathological ERK activation [(3)]. Further work will be needed

to verify these results by attempting to understand the self-renewal potential of CD34+ cells bearing the *BRAF* V600E mutation in LCH patients and to clarify in which exact cell type within the CD34+ compartment the *BRAF* V600E mutations occur within LCH.

The non-Langerhans cell histiocytoses (non-LCH) are a heterogeneous group of disorders defined by the accumulation of histiocytes believed to be of monocytic/macrophage origin that do not meet the diagnostic criteria for LCH or hemophagocytic lymphohistiocytosis [(1), (6) ,(7)]. Non-LCH histiocytes are immunoreactive for CD68, CD163, Factor XIIIa, and CD14 but negative for CD1a and CD207 (langerin). Some non-LCH express S100 while others do not. The non-LCH consist of ECD, JXG, RDD, HS, ICH, and others [(1),(8)*,(6), (7)]. Currently, whether or not non-LCH neoplasms share a similar or different cell-of-origin than LCH is unknown and will need to be an active area of research.

Somatic Mutations of Genes in the MAP Kinase and PI3K-AKT Signaling Pathways in Histiocytoses

Despite the distinct clinical and histological characteristics of many of the histiocytoses as defined by the WHO, molecular characterization of these disorders has identified molecular alterations, which are recurrent across histological subtypes. The plethora of recurrent genetic alterations recently discovered across histiocytoses encompass somatic kinase alterations affecting members of the canonical MAPK and/or PI3K-AKT signaling pathways (**Figure 1**). These genetic alterations are detailed below.

BRAF

BRAF (B-Raf Proto-Oncogene) encodes the BRAF serine/threonine protein kinase that belongs to the Raf family of serine/threonine kinases. The RAF family includes the ARAF, BRAF, and CRAF kinases, which transduce mitogenic signals from the cell membrane to the nucleus and regulate the MEK-ERK signaling cascade of the MAPK pathway. *BRAF* mutations were first described in histiocytic neoplasms in 2010 when recurrent *BRAF*V600E mutations were discovered in 57% of LCH [(9), (10)] (**Figure 2A**). This was followed by the discovery of *BRAF*V600E mutations in 54% of ECD patients [(11)], 62.5% of HS [(12)], and in a proportion of patients deemed to have ICH [(13)]. These findings provided strong evidence that these disorders are clonal neoplastic conditions driven by constitutive MAPK signaling [(11)].

In contrast to recurrent *BRAF*V600E mutations, other mutations in *BRAF* have been found only rarely in histiocytoses. These include *BRAF*V600D in LCH [(10),(14)], *BRAF* F595L in HS [(15)], and *BRAF* V600insDLAT in LCH [(16)] (**Figure 2A; Supplementary Table 1**).

ARAF

The knowledge that *BRAF*V600E-wildtype histiocytoses consistently showed overexpression of phospho-MEK and phospho-ERK in pathological histiocytes [(9), (18)*, (19)], resulted in a search for other mutations, which might result in MAPK activation in *BRAF*V600-wildtype histiocytoses. Surprisingly, this led to the discovery of rare, activating

ARAF mutations in LCH in 2014 (**Figure 2A; Supplementary Table 1**) [(10),(17)*, (19)]. ARAF (A-Raf Proto-Oncogene) is a serine/threonine kinase like BRAF but differs from BRAF in its potential to become activated by RAS and stimulate MEK due to biochemical differences in the N-terminus of the protein [(26)]. *ARAF* mutations were also found to be recurrent in non-LCH and are present in 21% of ECD [(8)*] and 12.5% of RDD patients [(8)*]. Although *BRAF*V600E mutations have not been identified in JXG, 18% of JXG cases have been found to have an *ARAF* mutation. However, these activating *ARAF* mutations were found to co-occur with activating *NRAS* mutations in those cases [(8)*]. Further work will be needed to understand the functional contribution of *ARAF* mutations to MAPK signaling given their frequent co-occurrence with other activating mutations such as *BRAF* and *RAS* mutations (**Supplementary Figure 1**).

MAP2K1

Shortly after the discovery of rare *ARAF* mutations in histiocytoses, several groups discovered *MAP2K1* mutations in *BRAF*V600E-wildtype LCH [(18)*,(19),(10),(20),(8)*]. *MAP2K1* (Mitogen-Activated Protein Kinase Kinase 1) encodes the MEK1 kinase, which activate Extracellular Signal-Regulated Kinases 1 and 2 (ERK1/2) through phosphorylation of threonine and tyrosine residues in ERK1/2. Across 4 studies, *MAP2K1* mutations appear to be recurrent in LCH and are present in 10-40% of LCH patients [(18)*,(19), (20) (8)*]. *MAP2K1* mutations are also present in non-LCH and occur in 14% of ECD and 27% of *BRAF*V600E-wildtype JXG cases [(8)*]. Based on the above studies, it appears that *MAP2K1* mutations in histiocytoses cluster in the N-terminal negative regulatory domain encoded by exon 2 and the N-terminal catalytic core of the kinase domain encoded by exon 3 (**Figure 2B; Supplementary Table 1**) [(18)*,(19),(10),(20),(8)*]. Some of these *MAP2K1* mutations have been biochemically characterized as activating; however, several need to be evaluated functionally. Furthermore, these *MAP2K1* mutations need to be systematically evaluated for their response to diverse MEK inhibitors.

MAP3K1

While performing whole exome sequencing (WES) on LCH neoplasms, Nelson *et al.* also discovered 2 somatic mutations in *MAP3K1* (Mitogen-Activated Protein Kinase Kinase Kinase 1), which encodes an enzyme with both E3 ubiquitin ligase activity, as well as serine/threonine kinase activity. MAP3K1 can phosphorylate MEK1 of the ERK MAPK cascade or MAP2K4 in the JNK (c-Jun N-terminal kinase) MAPK cascade. However, the mutations identified in MAP3K1 in LCH were frameshift mutations (*MAP3K1* T799fs and *MAP3K1* L1481fs), with *MAP3K1* L1481fs occurring in the kinase domain. These mutations are therefore presumed to result in loss-of-function (**Figure 2B; Supplementary Table 1**) [(10), (20)], and the role of these *MAP3K1* mutations in LCH and how they might promote neoplastic growth is currently unknown [(10)].

RAS Isoforms

The RAS isoforms include *NRAS* (Neuroblastoma RAS Viral Oncogene Homolog), *KRAS* (Kirsten Rat Sarcoma Viral Oncogene Homolog), and *HRAS* (Harvey Rat Sarcoma Viral Oncogene Homolog), which encode small GTPases that regulate the MAPK and PI3K-AKT

signaling pathways. As with other hematological malignancies, recurrent mutations in *N/KRAS* but not in *HRAS* have been found in systemic histiocytoses. This includes *NRAS* mutations in 3-7% of ECD [(23), (24), (8)*] and *NRAS* and *KRAS* mutations in 18% of JXG patients, respectively (**Figure 2C**). However, *RAS* mutations frequently co-exist with activating *ARAF* mutations in JXG (**Supplementary Figure 1**), as discussed above [(8)*]. Similarly, *NRAS* and *KRAS* mutations are present in 12.5% and 25% of RDD patients, respectively [(8)*]. In contrast to non-LCH, rare *RAS* mutations have been reported in LCH patients in the setting of concomitant juvenile myelomonocytic leukemia [(21)] and have not been reported in patients with LCH alone. The sole exception to the lack of *HRAS* mutations in histiocytosis has been the report of an *HRAS* mutation in HS (**Figure 2C; Supplementary Table 1**) with a concomitant *BRAF* F595L mutation [(15)] (**Supplementary Figure 1**).

PI3K Isoforms

The PI3K isoforms include *PIK3CA* (Phosphatidylinositol-4,5-Bisphosphate 3 Kinase, Catalytic Subunit Alpha) and *PIK3CD* (Phosphatidylinositol-4,5-Bisphosphate 3 Kinase, Catalytic Subunit Delta). These genes encode subunits of the PI 3-Kinases (phosphoinositide 3-kinases), which belong to a family of lipid kinases that play a role in a diverse range of cellular functions that include proliferation and survival and are part of the PI3K-AKT signaling pathway. Consistent with the potential activation of the PI3K-AKT signaling pathway downstream of RAS mutations in non-LCH, *PIK3CA* mutations have been described in 17% of *BRAF*V600E-wildtype ECD [(8)*]. These mutations cluster in the α-helical and kinase domains of PIK3CA [(8)*, (23)]. Consistent with the rarity of *RAS* mutations in LCH, activating mutations in *PIK3CA* have only been identified in 1.2% of LCH patients [(10),(22)]. In addition to *PIK3CA* mutations, rare *PIK3CD* mutations have been identified in JXG (**Figure 2D**) [(19)]. The expression of *PI3K* isoforms and the role of constitutive PI3K-AKT signaling needs to be further evaluated in the pathogenesis of the histiocytoses.

Other Mutations in Genes Influencing the MAP Kinase and PI3K-AKT Signaling Pathways

Other potentially relevant mutations identified in LCH [(19)] based on WES include non-recurrent mutations in *PICK1*, an adaptor protein that organizes the subcellular localization of a variety of membrane proteins, and *PIK3R2,* a regulatory component of PI3K. Although these proteins are not directly in the MAPK cascade, they could affect ERK activation. A non-recurrent mutation in *ERBB3*, a member of the epidermal growth factor receptor family of receptor tyrosine kinases, has also been reported in LCH [(19),(10)]; however, it is not clear if ERBB3 is even expressed in histiocytes.

Gene Fusions Influencing the MAP Kinase Signaling Pathway in Histiocytoses

In addition to somatic mutations, structural alterations and gene fusions represent important somatic alterations driving the pathogenesis of common cancers. However, no gene fusions

had been uncovered in the histiocytic neoplasms until 2015 when 2 studies described gene fusions in *BRAF*V600E-wild type, non-LCH neoplasms [(8)*, (25)**]. The activating or recurrent gene fusions found in the histiocytoses to date are described below.

BRAF Fusions

In addition to *BRAF* mutations, fusions involving *BRAF* have been identified in non-LCH. These include an *RNF11-BRAF* fusion in JXG and a *CLIP2-BRAF* fusion in a patient with a non-LCH resembling HS. Both fusions were found using RNA-seq and confirmed by RT-PCR followed by Sanger sequencing and interphase FISH [(8)*]. In both cases, exons 11-18 of *BRAF* were involved in the fusion, leading to loss of the N-terminal regulatory, RAS-binding domain of BRAF with placement of the intact BRAF kinase domain under the aberrant regulation of another promoter (**Figure 2E**). It is not clear what role, if any, the N-terminal fusion partner to BRAF may play in these cases.

ALK Fusions

In addition to *BRAF* fusions, 2 fusions involving *ALK* have been described in ECD (both *KIF5B-ALK*). In both cases, the N-terminal coiled-coil domain of KIF5B was fused to the intact kinase domain of ALK resulting in inappropriate expression and constitutive activation of ALK (**Figure 2F**) [(8)*]. KIF5B (Kinesin Family Member 5B) serves as a microtubule-dependent motor involved in the normal distribution of mitochondria and lysosomes while *ALK* (Anaplastic Lymphoma Receptor Tyrosine Kinase) encodes a neuronal orphan receptor tyrosine kinase whose expression is normally limited to the nervous system. *KIF5B-ALK* fusions therefore result in inappropriate ALK expression and constitutive activation of the MAPK and PI3K/AKT pathways within histiocytes. The *KIF5B-ALK* fusions have similar configurations to previously described *KIF5B-ALK* fusions in non-small cell lung cancer (NSCLC) [(27)] and are functionally activating kinase fusions that show sensitivity to ALK inhibition *in vitro* [(8)*].

NTRK Fusions

Thus far, fusion of a single NTRK member (*NTRK1*) has been described in a case of ECD. This alteration was confirmed to lead to fusion of the N-terminal coiled-coil domain of LMNA to the intact kinase domain of NTRK1 resulting in inappropriate expression and constitutive activation of NTRK1 (**Figure 2G**) [(8)*]. *LMNA* (Lamin A/C) encodes lamins, which are components of the nuclear lamina, a fibrous layer on the inner nuclear membrane that provides a framework for the nuclear envelope. *NTRK1* (Neurotrophic Tyrosine Kinase, Receptor Type 1) encodes the TrkA receptor tyrosine kinase, which is a membrane-bound receptor that phosphorylates itself and members of the MAPK pathway leading to cellular proliferation and differentiation. Similar to ALK, expression of NTRK1 is normally restricted to the nervous system, but *LMNA-NTRK1* fusions result in inappropriate expression and constitutive activation of MAPK and P3K/AKT pathways within histiocytes. The *LMNA-NTRK1* fusion has a similar configuration to previously described *LMNA-NTRK1* fusions in spitzoid neoplasms [(28)].

ETV3-NCOA2

In addition to activating kinase fusions, recurrent *ETV3-NCOA2* fusions have now been described in ICH [(25)**]. This fusion juxtaposes the N-terminal ETS domain of ETV3, a winged helix-turn-helix DNA-binding domain [(25)**, (29), (30)], to the C-terminal transcriptional activation domains AD1 (Transcriptional Activation Domain 1), CID (CBP/p300 Interaction Domain), and AD2 (Transcriptional Activation Domain 2) of NCOA2 (**Figure 2H**). This configuration is consistent with previously described *NCOA2* fusions in cancer [(25)**, (29), (31), (32), (33), (34)]. Previous studies of *NCOA2* fusions have demonstrated that the AD1 and CID domains are required for transformation of NCOA2 fusion proteins [(29), (32), (34)]. The involvement of the same NCOA2 C-terminal domains and the evidence that the AD1 and CID domains are necessary for NCOA2 fusion protein transformation supports a model where the NCOA2 C-terminal transcriptional activation domains are aberrantly targeted by the DNA-binding domain provided by an N-terminal fusion partner [(25)**, (29), (31), (32), (33), (34)]. It is not yet clear how the *ETV3-NCOA2* fusion relates to the persistent MAPK activation known to be present in these ICH cases. Further functional characterization of the *ETV3-NCOA2* fusion in the pathogenesis of histiocytic neoplasms is therefore needed.

Role of Molecularly Targeted Therapy in the Histiocytic Neoplasms

The initial discovery of the *BRAF*V600E mutation in ~50% of patients with LCH [(9), (8)] and ECD [(11)] and the other molecular advances summarized in this review (**Figure 3**; **Supplementary Table 1**) have led to the advent of clinical trials of targeted molecular therapeutics in these orphan hematopoietic neoplasms [(8)*] (**Figure 3; Supplementary Table 2**) [(35)]. The outcome of reported trials and case series of histiocytosis patients treated with molecularly targeted therapies are described below.

RAF Inhibitors

Thus far, there have been 2 major studies of the RAF inhibitor vemurafenib in *BRAF*V600E-mutant histiocytoses. These include a case series of 8 adult patients with severe, treatment refractory, *BRAF*V600E-mutated ECD or ECD/LCH hybrid disease [(36)*] and a phase II clinical trial with 18 adults with *BRAF*V600-mutant ECD or LCH [(37)**]. In the study by Haroche *et al.*, all patients had a significant and sustained clinical response to vemurafenib as measured by PET scanning during a 6-16 month follow up period with a mean follow up period of 10.5 months [(36)*]. In the study by Hyman *et al.,* 14/18 patients were evaluated, and there was a 43% response rate with 86% of patients (12 of 14) showing disease regression. All patients had improvement in disease-related symptoms. There was a median treatment duration of 5.9 months (0.6-18.6 months) with no ECD or LCH patients experiencing progression while on treatment. The 12-month progression-free survival rate was 91% with a 100% overall survival for this study cohort. These data suggest that BRAF inhibition may have a clinically significant effect on the natural history of ECD and LCH [(37)**].

In contrast to the case series and clinical trial in adults, there is only a single report of a child with histiocytosis treated with vemurafenib. In this case, an 8-month-old with *BRAF*V600E-

mutated, high-risk LCH, whose disease failed to respond to multiple rounds of prior therapy, experienced dramatic clinical efficacy to vemurafenib with a sustained response during the 10-month follow up period [(38)*]. With the success of vemurafenib treatment in clinical studies of adult ECD and LCH [(39), (40), (36)*, (37)**], the efficacy of RAF inhibitors should be investigated in clinical trials of infants and children with severe, high-risk, treatment-refractory, *BRAF*V600E-mutated LCH and other histiocytic neoplasms.

Given the frequency of *ARAF* mutations in histiocytoses, several studies have investigated therapies to target these alterations. Given a prior report of a patient with *ARAF* S214C-mutant non-small lung cancer who had a dramatic response to single-agent sorafenib, we treated one *ARAF* S214A-mutated refractory ECD patient with sorafenib with remarkable results [(8)*]. This patient experienced regression of lesions in the retina and cavernous sinuses with a >50% decrease in *ARAF* S214A-mutant DNA in the plasma cell-free DNA after 12 weeks of sorafenib. Sorafenib is a multi-kinase inhibitor that inhibits all 3 Raf isoforms (BRAF, CRAF, ARAF), in addition to inhibiting a host of additional kinases (including vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, c-Kit, Flt-3, RET, and platelet derived growth factor receptor beta (PDGFRβ)). The clinical activity of sorafenib is thought to be due to its capacity to inhibit multiple kinases that are part of ubiquitous signaling pathways dysregulated in neoplastic disease [(41)]. However, pre-clinical studies are needed to evaluate the responsiveness of sorafenib and other RAF inhibitors to different *ARAF* mutations in the histiocytic neoplasms, and clinical studies on larger series of *ARAF*-mutated, histiocytosis patients is warranted.

MEK Inhibitors

At present, there has been a single report of the clinical use of MEK inhibitors in *MAP2K1*-mutated, histiocytosis patients [(8)*]. We treated 2 non-LCH patients with *MAP2K1* K57N and *MAP2K1* Q56P mutations with trametinib and cobimetinib, respectively. Both patients experienced dramatic radiologic improvements, as well as clinical improvements, and both have been sustained for nearly 6 months. These encouraging results will need to be followed with pre-clinical studies to evaluate MEK inhibitor responsiveness of different *MAP2K1* mutations in the histiocytic neoplasms, as well as clinical studies on cohorts of *MAP2K1*-mutated, histiocytosis patients.

Conclusion

Since *BRAF*V600E mutations were first described in LCH, there have been tremendous molecular advances in our understanding of histiocytic neoplasms. These discoveries have directly resulted in wider use of RAF inhibitors for the treatment of *BRAF*V600E mutant histiocytoses and indicate the importance of comprehensive molecular analysis in routine clinical practice. It will now be important to determine how relevant the mutations in these kinases are to histiocytic disorders such as RDD and HS, which have been less systematically studied to date. Moreover, it will be important to determine the clonal composition of histiocytoses using studies of purified lesional histiocytes and surrounding cells from histiocyte tissue biopsies. In addition, currently, the therapeutic relevance of activating *ARAF*, RAS, and *MAP2K1* mutations, as well as activating fusions in *BRAF*,

ALK, and *NTRK1* in the histiocytoses remains to be systematically studied in clinical trial settings. Given the relative rarity of these conditions, the wider use of histology-independent clinical trials of molecularly targeted therapeutics ("basket trials") will hopeful allow inclusion of histiocytosis patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Recurrent somatic mutations in Langerhans cell histiocytosis (LCH) and non-LCH have refined our understanding of these enigmatic disorders as clonal, myeloid neoplasms driven by constitutive MAPK signaling.

- Activating kinase mutations in *BRAF*, *ARAF*, *MAP2K1*, *N/K/HRAS*, and *PIK3CA* have now been described in LCH and non-LCH histiocytic neoplasms due to the implementation of next-generation sequencing technologies.

- Kinase fusions involving *BRAF*, *ALK*, *NTRK1*, and *ETV3-NCOA2* have been discovered in non-LCH histiocytic neoplasms.

- Significant clinical responses to RAF inhibitors have been documented in adult and pediatric patients with *BRAF*V600E-mutated LCH and non-LCH marked by a prolonged durability when compared to *BRAF* inhibition in more common *BRAF*V600E-mutated malignancies.

- *MAP2K1*- and *ARAF*-mutant histiocytosis patients have been reported to have clinical responses to MEK inhibition and sorafenib, respectively.

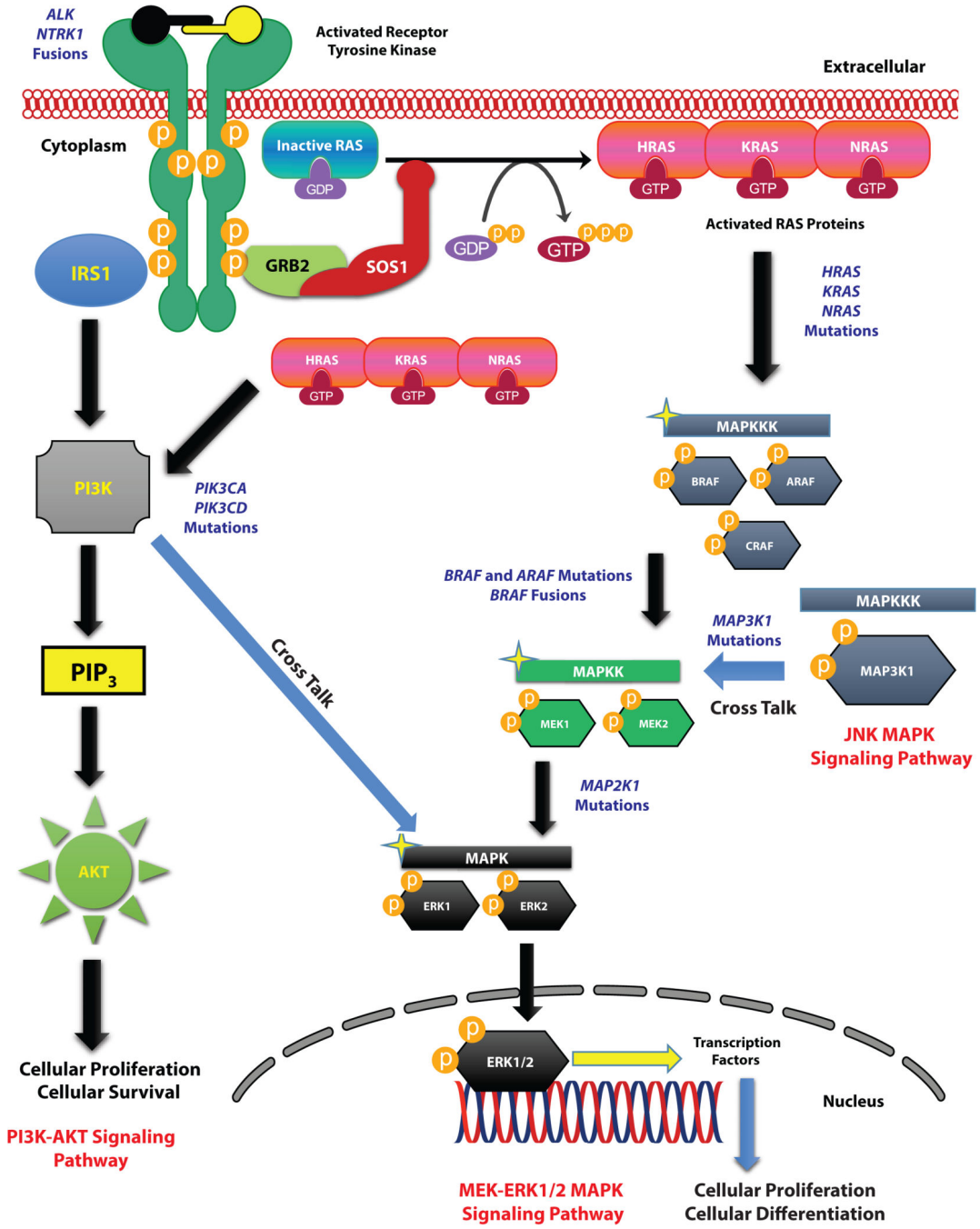

Figure 1. Overview of the MEK-ERK signaling cascade of the MAPK pathway and the PI3K-AKT pathway

Diagram of activation of the RAS proteins (HRAS, KRAS, NRAS), the MEK-ERK signaling cascade, and the PI3K-AKT signaling pathways with annotation of the signaling proteins affected by mutations in histiocytic neoplasms is shown. Key highlights of cross talk involving members of the JNK MAP Kinase signaling cascade and the PI3K-AKT signaling pathway with the MEK-ERK signaling cascade are also shown.

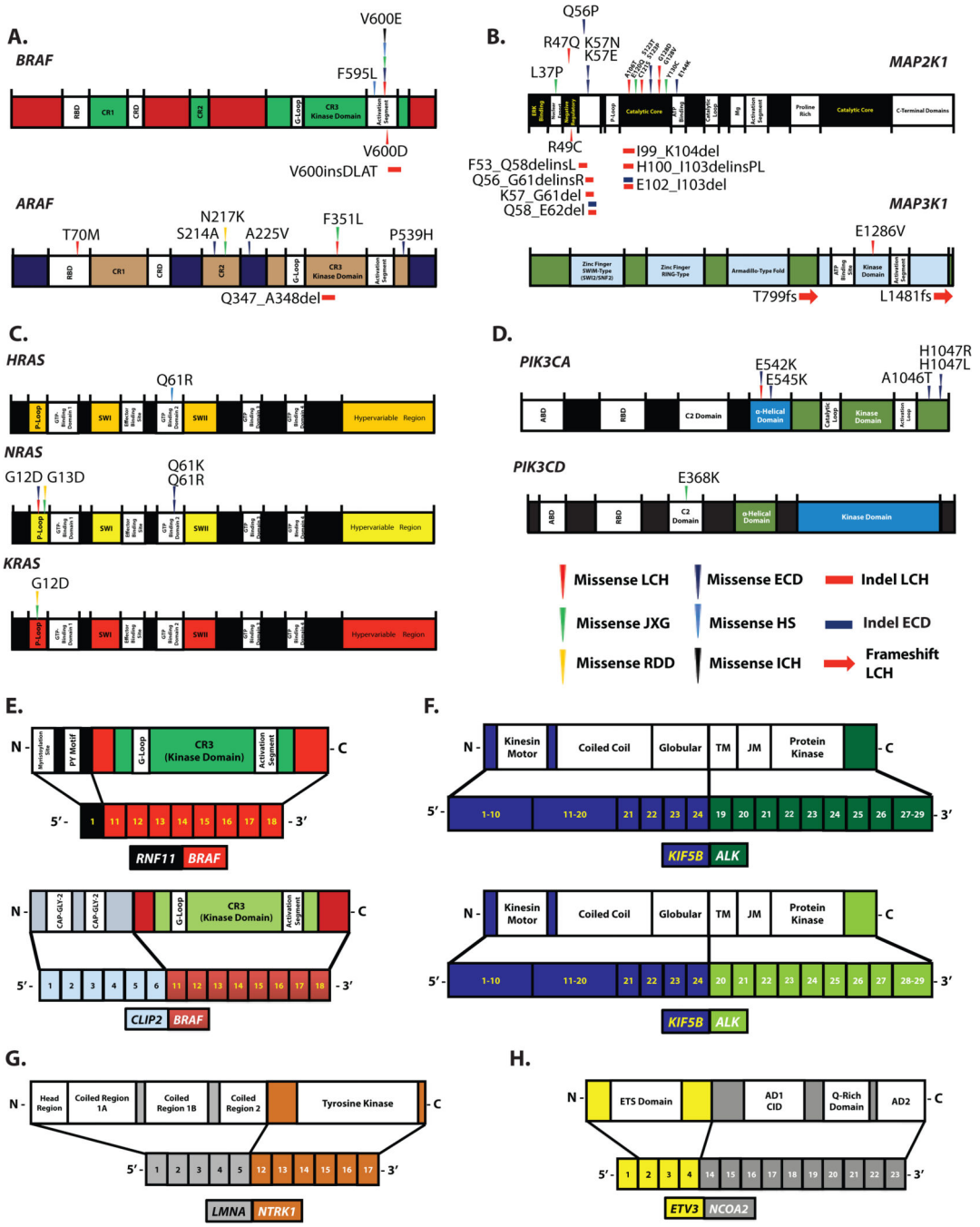

Figure 2. Summary of kinase alterations documented in histiocytic neoplasms

Somatic mutations described in (A) *BRAF* and *ARAF,* (B) *MAP2K1* and *MAP3K1*, (C) *H/N/KRAS,* and (D) *PIK3CA* and *PIK3CD*, as well as fusions in (E) *BRAF,* (F) *ALK,* (G) *NTRK1* and (H) *ETV3-NCOA2.*

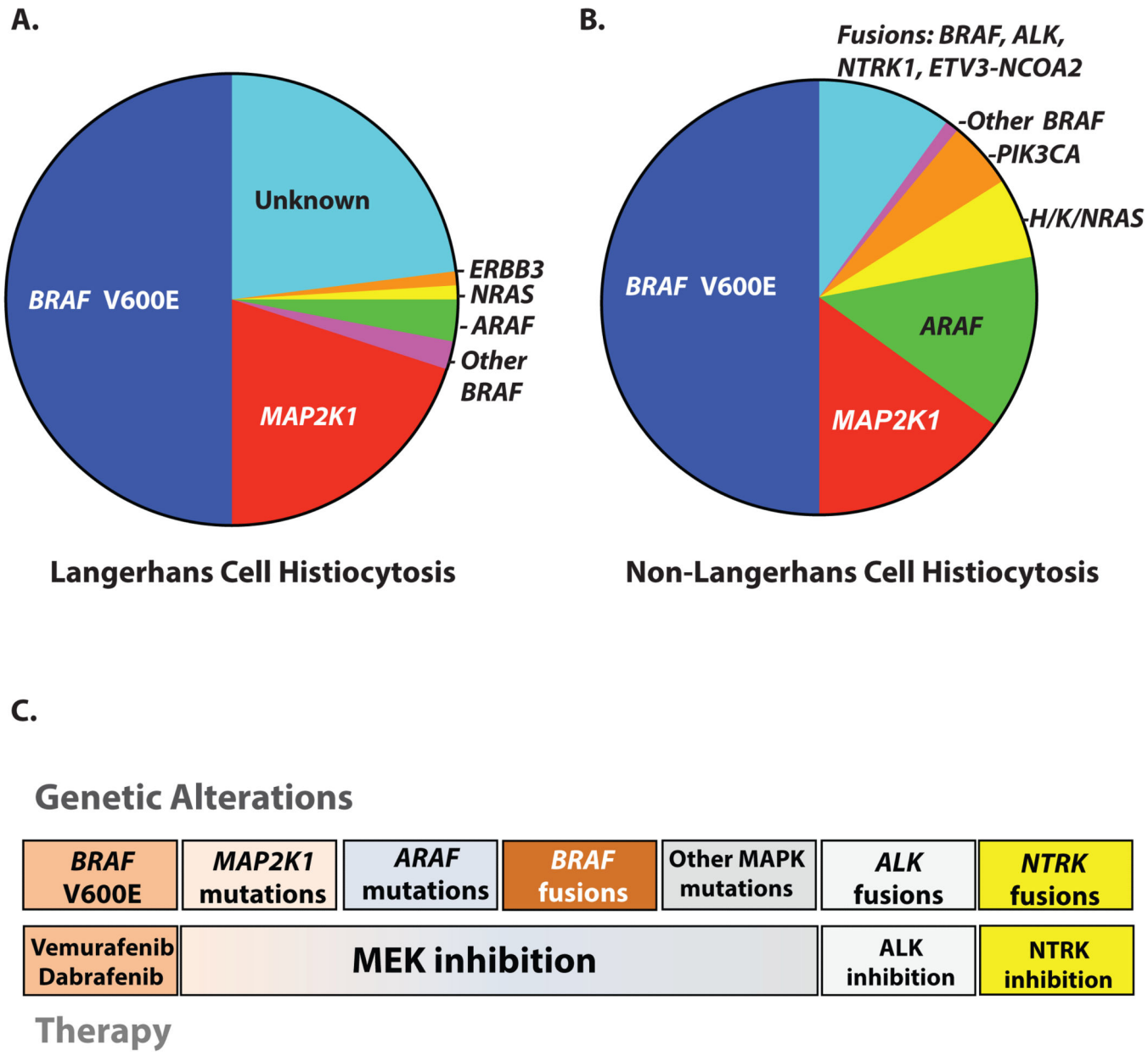

Figure 3. Summary of actionable genetic alterations in histiocytic neoplasms matched with a potential targeted therapy

Pie chart illustrating the known activating kinase alterations in (A) Langerhans cell histiocytosis and (B) non-Langerhans cell histiocytoses. (C) Diagram summarizing the potential targeted therapies that have or may demonstrate clinical efficacy in histiocytic neoplasms. The RAF inhibitors vemurafenib or dabrafenib have already demonstrated efficacy in *BRAF* V600E mutant histiocytoses. MEK inhibition may have an important role in histiocytoses, regardless of *BRAF* V600E mutational status. ALK and NTRK inhibitors need to be studied for the potential role in the therapy of *ALK* or *NTRK*-fusion histiocytoses specifically.