Biologic and clinical consequences of the BRAF^{V600E} mutation in langerhans cell histiocytosis

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Langerhans cell histiocytosis (LCH) is caused by mutations of the MAP Kinase pathway (*BRAF*^{V600E}, *MAPK1, BRAF* insertions, deletions, and others) It is hypothesized that mutations in the least differentiated (bone marrow stem) cells lead to diffuse disease especially in the liver, spleen, and bone marrow resulting in the clinical category of high risk disease (high risk of treatment failure and death). Mutations in more differentiated cells can lead to multiple lesions in a single organ system, such as bone or skin, or single lesions. Targeted therapy of patients with BRAF or MEK inhibitors can bring rapid clinical responses, but a majority of patients will relapse when the inhibitors are withdrawn. Over the past 3 years some important discoveries have uncovered some mysteries of the pathologic LCH cells and why these patients have poor responses to standard chemotherapy or MAPKinase inhibitors. MAPKinase mutations have wide-spread effects on the biology of histiocytes and lymphocytes. The pathologic dendritic cells accumulate in lesions because of down-regulated CCR7 which is supposed to direct antigen presenting cells to lymph nodes. BCLX is also down-regulated leading to inability of the caspase cell death program to be activated by therapies. A senescence program is activated which makes cells resistant to inhibitors. The histiocytes in LCH express elevated levels of the Programmed Cell Death Ligand (PDL-1) and the lymphocytes express Programmed Death Receptor (PD-1) leading to an exhausted phenotype for CD8 lymphocytes. The dysfunctional state helps explain why all of the neoplastic histiocytes are not eliminated with MAPKinase inhibitors alone.