ERK1 AND ERK2 IN HEMATOPOIESIS, MAST CELL FUNCTION, AND THE MANAGEMENT OF NF1-ASSOCIATED LEUKEMIA AND TUMORS

ERK1 AND ERK2 IN HEMATOPOIESIS, MAST CELL FUNCTION, AND THE MANAGEMENT OF NF1-ASSOCIATED LEUKEMIA AND TUMORS

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Abstract:

Neurofibromatosis type 1 is a genetic disease that results from either heritable or spontaneous autosomal dominant mutations in the NF1 gene, which encodes a protein serving, at least in part, to accelerate the intrinsic hydrolysis of active

Ras-GTP to inactive Ras-GDP. A second-hit NF1 mutation precedes predominant NF1 neoplasms, including juvenile myelomoncytic leukemia (JMML) and plexiform neurofibroma formation, potentially fatal conditions with no medical therapy. While NF1 loss of heterozygosity (LOH) in myeloid progenitor cells sufficiently engenders leukemogenesis, plexiform neurofibroma formation depends on LOH in Schwann cells and Nf1 heterozygosity in the hematopoietic system. Specifically, recruited Nf1+/- mast cells accelerate tumorigenesis through secreted cytokines and growth factors. Nf1+/- mast cells depend upon deregulated signaling in c-kit pathways, a receptor system conserved in hematopoietic stem cells (HSCs). Accordingly, Nf1-/- myeloid progenitor cells, which can induce a JMML-like disease in mice, also demonstrate deregulated c-kit receptor signaling. C-kit-activated Nf1+/- mast cells and Nf1-/- myeloid progenitors both show increased latency and potency of active Erk1 and Erk2, the principal cytosolic-to-nuclear effectors of canonical Ras-Raf-Mek signaling. Thus, Erk represents a potential regulator of leukemogenesis and tumor-associated inflammation. However, single and combined Erk1 and Erk2 roles in HSC function, myelopoiesis, and mature mast cell physiology remain unknown, and recent hematopoietic studies relying on chemical Mek-Erk inhibitors have produced conflicting results. Here, we show that hematopoietic stability, myelopoiesis, and mast cell generation require Erk1 or Erk2, but individual isoforms are largely dispensable. Principally, Erk-disrupted hematopoietic stem cells incorporate BrdU but are incapable of dividing, a novel and cell type-specific Erk function. Similarly, mast cell proliferation requires Erk but cytokine production proceeds through other pathways, elucidating molecule-specific functions within the c-kit cascade. Based on these findings, we have reduced tumor mast cell infiltration by treating genetically-engineered tumor model mice with PD0325901, a preclinical Mek-Erk inhibitor. Moreover, we have devised a quadruple transgenic HSC transplantation model to examine dual Erk disruption in the context of Nf1 nullizygosity, testing whether diseased hematopoiesis requires Erk. These insights illuminate cell-specific Erk functions in normal and Nf1-deficient hematopoiesis, informing the feasibility of targeting Mek-Erk in NF1-associated disease.

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