Microreviews in Cell and Molecular Biology
An undergraduate science journal
2023

The Interplay of BRAF and MAPK Pathways Inducing Senescence in Langerhans Cells Histiocytosis

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Key Words:
Langerhans, hematopoietic cells, senescence, mutation

A rare disease characterized by aberrant function, divergence, and uncontrolled proliferation of mononuclear phagocyte cells, Langerhans histiocytosis, and its concomitant granulomatous lesions within histiocytes can occur in any organ but has a rapport for the skin, bone, and the lungs. While it is known that somatic mutations in the MAPK pathway, specifically $BRAF^{V600}$, are common in most LCH cases within LCH lesions, the mechanisms underpinning $BRAF^{V600}$ mutation progenitor cells and its consequence of LCH lesions are wholly indefinite. Furthermore, gene expression between epidermal Langerhans cells and CD207+ lesional cells of LCH share a consistent signature parallel with immature myeloid precursors in LCH cells, implying a basis for hematopoietic provenance of such cells. So, while LCH is likely a result of clonally expanding neoplasm, the question remains if Langerhans cells are truly normal cells responding to immune signals gone awry or if it is an actual anomalous variant. Recent findings have illuminated the BRAFV600E mutation and its ability to influence multipotent hematopoietic cells in LCH disease. Scientists discovered the expression of the $BRAF^{V600E}$ mutation guides to a senescence program that results in growth arrest in hematopoietic progenitor cells, anti-apoptosis, and a secretory phenotype in mice that leads to the growth of LCH lesions. Conversely, the ablation of these senescent cells via induced apoptosis and SASP inhibitors ameliorated LCH disease in mice. Such results allude to senescent cells being a target that can potentially advance LCH treatment.

Introduction

Langerhans Histiocytosis (LCH) is the most common histiocytic disorder; it is a rare disease characterized by the clonal expansion of myeloid precursors that discern into tissue infiltration of clusters of CD1a+ cells, langerin-positive CD207 cells, and Langerhans cells, resulting in subsequent surrounding inflammation, encompassing a population of noteworthy T cells and inflammatory cytokines, that leads to a gamut of organ system dysfunction. Langerhans cells, a group of hematopoietic cells in lymphoid organs and tissues, are immature dendritic cells (DCs) in the epidermis. These cells are unique in dendritic cells because they arise from yolk-sac progenitors and fetal liver-derived monocytes rather than myeloid progenitor cells in the bone marrow. LCH can be present in any organ but concomitates with bone, skin, pituitary, and lungs. LCH can result in myriad phenotypes ranging from skin lesions to fatal metastasized disease. Adding to the pathogenesis of LCH in a study of 2013, Bates and colleagues discovered the identification of a gain-of-function mutation in $BRAF^{V600E}$ in most LCH patients (Bates et al., 2013). Additionally, further studies demonstrated that 100% of LCH cases exhibit ERK phosphorylation (Kobayashi & Tojo., 2018). Mutations in such signaling cascades involving the Ras/Raf/MEK/ERK pathways accompanied by the mutual exclusivity of these mutations in a given patient indicate a role in activating these oncogenic pathways in the LCH state. Furthermore, when introduced in the mutant, oncogenic form, this kinase cascade can evoke most of the transformation phenotypes that the Ras oncoprotein induces. Hence, in such cells, the Raf pathway is mainly responsible for the transforming powers of Ras oncoproteins, which include loss of contact inhibition and anchorage independence. This cascade's biology posits that Ras activation stimulates the Mitogen-activated protein kinase (MAPK) relay and induces

expression of the transcription factor AP-1. Activated Ras will trigger a 3-kinase relay that activates a serine/threonine kinase known as mitogen-activated protein kinase (MAP kinase). The first member of the relay is a MAPK kinase called Raf. Raf is a serine/threonine kinase that phosphorylates MEK1. This dual specificity protein kinase phosphorylates a tyrosine and a threonine residue on the last member of the relay, a MAPK, which in T cells and B cells is an extracellular signal-related kinase (ERK). Phosphorylation of transcription factors by ERK results in new gene transcription and thus novel gene expression via promoting the transcription of many target genes and growth-regulating genes, such as AP-1, which is in the hyperactivated form in cancer cells. Comprehending how $BRAF^{V600E}$ mutations affect Langerhans cells raises the question of the mechanisms underlying this mutation on multipotent progenitor cells.

Recent Progress

Recently, scientists have discovered the $BRAF^{V600E}$ mutation in CD34+ (a biomarker for HPC and HSC) bone marrow hematopoietic cells in patients with LCH. This revelation leads to the consideration of the codification of multifocal LCH as myeloid neoplasia. Additionally, this recent discovery warrants the exploration of the mechanisms by which the BRAF mutation could usher multipotent hematopoietic progenitor to form lesions in LCH. The search for this unknown means led to the finding that manifestation of this mutation in both human and mouse multipotent hematopoietic progenitor cells (HPCs) generated a senescence program that resulted in growth arrest, anti-apoptosis, and senescence-associated secretory phenotype induction (SASP). As a result of SASP, the promotion of multipotent HPC furthering away from other hematopoietic lineages led toward mononuclear phagocytes. Therefore, the BRAF mutation yielded a senescence program that perpetuated and lasted in differentiated mononuclear phenotypes that amassed in interface tissues (Merad, 2020). Here, scientists showed that SASP induction and prolonged mononuclear survival contributed to the development of LCH lesions. Conversely, scientists discovered that genetically ablating senescent cells via apoptosis resistance (INK-ATTAC) through specific activation in transgenic mouse models ameliorated LCH conditions. As cellular senescence is fundamentally a barrier to tumorigenesis, it can result in lesions in LCH. Scientists have also made progress in developing and framing utilizing a senescence-associated secretory phenotype inhibitor.

Discussion

By generating $BRAF^{V600E}$ WT and mutant mice using a genetically engineered mouse model expressing a Cre-recombinase under the Scl promoter, the authors displayed that presentation of the expression of the $BRAF^{V600E}$ mutation in human and mouse hematopoietic progenitor cells is adequate to cause the appearance of LCH lesions. This model is also sufficient to be comparable for systematic LCH human application. By also showing that hematopoietic progenitor cells in mice and humans with a somatic mutation of $BRAF^{V600E}$ and CD34+ cells that are isolated from LCH patients, evident is the fact that these are indeed in a senescent program. Likewise, the induction of senescence via $BRAF^{V600E}$ contributes to LCH pathology. Lastly, using a transgene of INK-ATTAC, another mouse model that enables the elimination of selective senescent cells, the authors verified the collection of senescent cells in the bone marrow. They exemplified that ablation of such senescent cells in LCH-afflicted mice ameliorates disease conditions. Additionally, within this current study, the authors show that when the $BRAF^{V600E}$ mutation occurs in pluripotent hematopoietic progenitors upstream of mononuclear phagocyte progenitors, skin lesions and granulomatous come to be present in the dermis in the mice that draw a parallel to human LCH lesions in humans, indicating that the impression of the mutation at the hematopoietic stem cell level triggers a more steady LCH phenotype than the disease formed via induction of the mutation at the mononuclear progenitor site. Therefore, the expression of the $BRAF^{V600E}$ mutation in HPCs facilitates the installation of a senescence program that permits the shaping of the LCH phenotype. Hematopoietic progenitor cells also are more inclined to distinguish into $BRAF^{V600E}$ pathogenic senescent mononuclear phagocytes, which remain in tissue for an extended duration, where results show how they continuously emit (senescence-associated secretory phenotype) SASP-triggered cytokines. Thus, the senescence highlights a central feature of the LCH disease burden, including the build-up of proliferative mononuclear phagocytes guided by the expression of SASP inhibitor INK and a corresponding immune infiltrate in LCH lesions. Comparatively, while the deletion of CDKN2A (tumor suppressor genes) or any variant is unclear, clonal elimination of these genes is associated with Langerhans cell sarcoma. Hence, BRAF-induced senescence can likely link to protecting LCH cells from malignant change. Overall, $BRAF^{V600E}$ mutations in HPCs can, directly and indirectly, lead to LCH through internal and external cues impacting cell differentiation to mononuclear phagocytes and oncogene-induced senescence, which fuels telomere shortening, DNA damage, and the activation of oncogenes, such as Ras, all things advantageous to the formation and development of cancer. The primary root of the inflammatory infiltrate in LCH lesions is obscure in its exact origin; however, the authors reveal the induced SASP pathway that sparks inflammatory cytokines in bone marrow HPCs. As a result, these released cytokines

advance the differentiation of HPCs into mononuclear phagocytes and contribute to assembling granulomatous lesions in surrounding tissues.

LCH possesses many clinical manifestations, from single lesions to multi-system disease (Allen et al., 2020). While LCH in adults is less severe and more treatable, LCH in children poses a far greater risk. Nonetheless, systemic LCH continues to be challenging to treat, but BRAF or MEK inhibition can potentially improve clinical outcomes in individuals suffering from LCH. The MAPK pathway is the most standard dysregulated route in cancer, and 8% of all cases consist of the mutation of $BRAF^{V600E}$ (Rodriguez-Galindo & Allen., 2020). Thus, altogether, these results divulge the assistance of $BRAF^{V600E}$-driven senescence to LCH pathology and physiology and illuminate senescent cells as an operative target for treating systemic LCH.

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