32nd Nikolas Symposium

Tissue inflammation and the Langerhans cell histiocytosis lesion

Summary of the 32nd Nikolas Symposium, Athens, May 16-19, 2024

The Nikolas Symposium

The Nikolas Symposium is an annual meeting hosted by Paul and Elizabeth Kontoyannis, whose son Nikolas developed Langerhans Cell Histiocytosis (LCH) in infancy. Their motivation to initiate the Nikolas Symposium in 1989 was the lack of knowledge on the pathogenesis of this rare disease. The symposium is an interactive forum of basic scientists and clinicians who discuss a different topic each year that is related either to the clinical presentation of LCH, the spectrum of its complications (late effects), the neoplastic cells involved and new therapeutic targets (PMID **31831887)**. The meeting also provides an opportunity for Greek physicians to present difficult histiocytosis cases or their research. Traditionally, the scientific program is opened by Steering Committee members presenting the concept and history of the meeting, clinical and pathophysiological features of LCH and the summary of the previous symposium.

Introduction to the 32nd symposium

After the discovery of somatic driver mutations in genes encoding various components of the MAPK pathway, targeted therapy was shown to be a breakthrough therapeutic options for (refractory) histiocytosis. Despite their efficacy, these drugs have significant limitations, as adults particularly experience off-target side effects. Moreover, patients exposed to these drugs often display mutated cells in their blood in the absence of active lesions. It is therefore questionable whether targeted therapy eradicates the stem/progenitor cells wherefrom tissue-accumulating neoplastic histiocytes arise. Preliminary data also show that neurodegeneration, a much feared late complication of LCH, can still occur in RAF inhibitor-exposed patients. This Hence, we need an exit strategy which aims at blocking pathogenic function of circulating mutated cells. One plausible way of targeting LCH could be the niche(s) where its mutated cell of origin resides. The 2024 symposium brought together experts in the field of (hematological) malignancies and innate cell-driven inflammation to discuss how various hematopoietic and non-hematopoietic cells can foster malignant (stem)cells.

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What can we learn from human and murine brain tissue?

Histiocytic neoplasms can affect many organ systems including the bone marrow and central nervous system (CNS). The lesions comprise many different types of hematopoietic cells besides mutation-expressing myeloid cells. Their role in the pathophysiology of these disorders is unclear. Likewise, we have no clue on how tissue stromal cells affect the pathologic function of mutation-expressing cells. In human brain specimen collected from patients who died from progressive neurodegeneration, monocytic-macrophage like cells can be found in close proximity to blood vessels; some of these cells also express the mutated BRAF protein. Similar observations were made in a mouse model wherein both the wildtype and mutated BRAFV600E protein is expressed under the Scl promotor (Dr. Merad, New York). Scl is essential for hematopoietic stem cell specification at different levels including erythrocyte maturation. Besides inflammation in lungs, spleen and liver, these mice demonstrated accumulation of a specific type of myeloid cells in distinct areas of the brain (Wilk et al, Immunity 2023). These intra-vascular CD11a+ myeloid cells showed a senescent phenotype marked by BcL-xL expression. Combining drugs which specifically target cells expressing anti-apoptotic proteins (senolytic drugs) and a MAPK pathway-activating driver mutation significantly reduced BRAF mutation expressing myeloid cell influx in aforementioned organs and restored the behavior of the mice.

Production and nurture of malignant cells

Tissue-accumulating neoplastic histiocytes are thought to be derived either from myeloid-committed precursor cells produced in the bone marrow during definitive hematopoiesis or from precursor cells which are formed and seeded to various tissues and organs during fetal hematopoiesis. As thymic involvement is occasionally seen in infant LCH, Dr. Staal (Leiden) shared single-cell gene expression data on hematopoietic populations isolated from neonatal human thymus tissue, including diverse thymic seeding progenitors (TSP) which originate in the bone marrow (Cordes et al, Sci Immunology 2022). These TSP transcriptomically resemble the well-known hematopoietic stem/progenitor cell populations present in the bone marrow. This may explain the presence of many different lineage committed precursor as well as mature lineage cells in the thymus. Three additional speakers discussed how tissue stromal cells and co-infiltrating hematopoietic cells can foster malignant cells. First, Dr. Cupedo (Rotterdam) shared recent single-cell RNAseq data generated on bone marrow samples derived from healthy donors or from patients with newly diagnosed multiple myeloma (MM) cells (de Jong et al, Nat Immunol 2024).

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Production and nurture of malignant cells

The BM of the latter patients contains a specific type of activated IL1β+ neutrophilic granulocytes (MatNeu2) which prime mesenchymal stromal cells to produce factors that support MM cell outgrowth.

This neutrophil – iMSC axis persist after induction and consolidation chemotherapy, which could explain the high relapse rates in this patient population. Dr. Arnold (Zurich) presented transcriptomic differences between circulating and tissue-invading eosinophils. Dr. Sherman (New York) showed that the presence of high numbers of eosinophils in pancreatic cancer biopsies - whose migration is driven by eotoxin-1 (CCL11) - is associated with a better overall survival. Eosinophil influx is modulated by autotaxin produced by stromal cells present in cancerous pancreatic tissue. This is another example of malignant cell fostering by non-hematopooietic stromal cells. Dr. Becher (Zurich) discussed how locally produced GM-CSF - a growth factor produced by neutrophils, eosinophils and macrophages – modulates the inflammation induced influx of monocytes from the blood into the CNS. A second pro-inflammatory cytokine (IFNγ) regulates monocyte transition into pathological dendritic cells or macrophages.

Targeting niches preferred by malignant (stem) cells

LCH most frequently presents as lytic lesions in the bone. Like in multiple myeloma, these lytic lesions are the result of increased osteoclast activity. Dr. Makras (Athens), explored the impact of 4 subcutaneous injections with denosumab – a monoclonal antibody which prevents RANK- RANK signaling in osteoclasts via binding with high avidity to RANKL – in 10 patients with systemic disease and involving the bone. This treatment is well tolerated and PET-CT imaging showed that 8/10 patients had either non-active disease (n=5) or regressed bone lesions (n=2) at 12 months after last dose. Two patients had progressive bone disease and received additional injections. With follow up period of up to 4.5 years, this study showed sustained efficacy without the need of additional therapy (Makras et al, Am J Hematol 2023).

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