Immune Strategies in the Histiocytoses

Summary of the 29th Nikolas Symposium, Athens, May 16-19, 2019

The 29th Nikolas Symposium organized discussion around mechanisms of inflammation in LCH and related histiocytic disorders. The granulomatous character of LCH lesions led to recurrent historical debate regarding the nature of LCH as a disorder of immune dysregulation versus a neoplastic disease. Discoveries from Nikolas Symposium alumni including clonality of the pathologic histiocyte[1;2], *BRAF-V600E* and other MAPK pathway activating mutations[3-9] in LCH lesions and myeloid stem cells[10;11], and promising clinical response rates with MAPK inhibitors[12-16] focused much of the scientific attention in the past decade on neoplastic features of LCH. However, the sparks inciting inflammation and the role of immune activation in pathogenesis remain poorly understood. The long-standing mission of the Nikolas Symposium is to "search for a rationale cure" for children and adults with LCH. This symposium sought to explore the causes of inflammation in LCH in order to identify new therapeutic opportunities.

Introduction.

The meeting was opened by **Dr. Maarten Egeler** (Toronto, Leiden), who introduced the history of the Symposium and tasked the participants to commit to present provocative data, share ideas and argue. **Dr. Milen Minkov** (Vienna) provided a clinical overview of LCH. He framed the scope of the problem with respect the range of clinical presentations, current therapeutic strategies, and areas of greatest unmet needs. Frontline therapy has improved through a series of clinical trials organized through the Histiocyte Society that demonstrate the benefit of intensified and prolonged chemotherapy.[17-19] He reviewed the framework and progress of the ambitious 5-armed global LCH-IV trial that is currently underway. Dr. Minkov also discussed recent clinical studies describing experiences with MAPK inhibition in children with relapsed and refractory LCH.[15;16] As with adults, MAPK inhibition evokes high response rates in children. However, MAPK inhibition alone may not be curative, and sustained responses appear to be dependent on continued therapy. **Dr. Carl Allen** (Houston) summarized the 2018 Nikolas meeting which focused on myeloid cell programming and differentiation: Indelible and inducible aspects of the LCH cell were analyzed in search of Achilles heel(s).

Lumping and Splitting

Dr. Kenneth McClain (Houston) was recognized for his scientific contributions and dedication to improving outcomes of patients with LCH as a ***Life Member of the Nikolas Symposium.*** He reviewed the competing hypothesis and evolving views of LCH pathogenesis and changes in treatment strategies over the past several decades *"From Nezelof to Now"*. **Dr. Jennifer Picarsic** (Pittsburgh/Cincinnati) discussed pathologic approaches to LCH and related disorders. Historically, classification systems organized histiocytic disorders based on characteristic features such as CD207 (langerin) expression, with comparison to physiologic cells (e.g. epidermal LC) that share similar features.[20] Revised models of pathogenesis suggest that LCH acquires langerin expression and other characteristics as lesions develop, with terminal differentiation dependent to some degree on the tissue "neighborhood". Updated classification strategies that incorporate age, tissue distribution, and molecular lesions as well as histology are required for accurate diagnosis, predict risk and identify optimal therapy for patients with LCH and related disorders.[21]

Targeting the Target

LCH and related disorders display universal activation of MAPK signaling, with *BRAF-V600E* as the most common mutation.[3] *BRAF-V600E* arises in approximately 7% of all human cancers.[22] However, unlike melanoma or colon cancer which harbor hundreds or thousands of additional mutations, the genome in LCH cells is largely intact with few other mutations.[5] **Dr. Gideon Bollag** (Berkely) described his seminal work applying combinatorial drug design to create vemurafenib, which specifically blocks signaling of BRAF-V600E monomers.[23] In a paradigm-changing study, targeted therapy with vemurafenib achieved superior survival in patients with metastatic BRAF-V600E+ melanoma than chemotherapy.[24] Ultimately, vemurafenib was FDA-approved for BRAF-V600E cancers.[25] While vemurafenib is effective in blocking BRAF-V600E monomers, it paradoxically activates BRAF signaling in cells without this specific mutation, leading to some toxicities

including development of squamous cell carcinoma or potentially more serious second malignancies.[26] Dr. Bollag described early data for a second-generation "pan-RAF" inhibitor (PLX8394) which blocks signaling of a broader range of BRAF mutations. This is being tested now in clinical trials, which includes eligibility for patients with refractory LCH.[27] Dr. Bollag's team has also developed an inhibitor that blocks signaling through CSF1R (PLX3397), which is upstream of BRAF, and plays a critical role in development of monocytes, macrophages and microglia in normal development. PLX3397 has been approved for treatment of giant cell synovitis.[28] Evaluating potential activity of PLX3397 alone or in combination with other MAPK inhibitors in histiocytic disorders merits further consideration.

Dr. Julian Haroche (Paris) described the molecular landscape of systemic histiocytoses (LCH, Erdheim-Chester Disease (ECD), juvenile xanthogranuloma (JXG) and Rosai-Dorfman-Destombes Disease (RDD)). Mutually exclusive activating mutations in MAPK pathway are observed in very high frequency across the histiocytic histologies. In adults, these somatic mutations may arise as part of the process of accumulation of mutations in a shrinking pool of stem cells (clonal hematopoiesis).[29] Drugs that inhibit MAPK signaling show high response rates, unfortunately with high rates of rapid relapse upon cessation of MAPK blockade.[12] **Dr. Eli Diamond** (New York) presented updated results of genomic landscape across histiocytic disorders, reinforcing a theme of mutually exclusive activating MAPK pathway mutations.[30] Based in large part on data from the French and Memorial Slone Kettering teams, vemurafenib has been approved by the US Food and Drug Administration (FDA) for use in adults with BRAF-V600E+ ECD. Recurrent mutations in *CSF1R* in juvenile xanthogranuloma represent a notable addition, especially in light of efficacy of PLX3397 in other tumors driven by CSF1R activation.[28] Specific activity of vemurafenib against BRAF-V600E, and potential for mutation-specific blockade of CSF1R or other tyrosine kinase mutations demonstrates potential for personalized therapeutic approaches for histiocytic neoplasms. However, Dr. Diamond also presented 1 year overall response rate of 100% in 18 patients with diverse histiocytic disorders and diverse molecular drivers by aiming downstream at MEK blockade with cobimetinib.[13] The revolutionary advance of small molecule inhibitors arrived around the same time of discovery of activating MAPK mutations in LCH. Early trials clearly demonstrate remarkable activity. In potentially fatal conditions such as ECD, MAPK pathway inhibition strategies are clearly indicated.[31]

MAPK inhibitor monotherapy remains an imperfect arrow, with high rates of toxicity and apparent inability to achieve cure. One-size-fits-all or bespoke approaches to therapy require continued tailoring, but MAPK blockade offers opportunities for progress that have been absent until now. Finding "the cure" for a rare disease is challenging. In the case of LCH, defining optimal therapy for a heterogeneous class of disease driven by distinct pathogenic triggers adds an order of complexity. **Dr. Michel Zwaan** (Utrecht) reviewed the regulations, challenges and opportunities involved in developing a specific drug for approval by the European Medical Authority (EMA).[32;33] One mechanism that may be relevant for LCH is the "PIP" (Pediatric Investigation Plan) which is now required for development of any drug. Pediatric LCH could represent a strategic population to achieve PIP requirements for companies seeking to develop agents that target MAPK pathway activation. Organizational ingenuity fostering relationships between industry, investigators, clinicians and patients is also required to perform clinical trials. The complexity of executing clinical trial from conception through pre-clinical testing, early phase testing, and pivotal trial is compounded in rare pediatric disease and have limited the ability of a volunteer organization such as the Histiocyte Society to bear the sole responsibility for organizing clinical trials for LCH. Despite the scientific progress over the past decade, empiric chemotherapy that cures <50% of patients with multisystem disease remains the standard of care.[19] Prioritizing LCH within organizations such as ACCELERATE (ITCC-Europe) and COG-NCI MATCH (US) is a strategy to develop, test and implement rationale cures for children and adults with LCH.

Alternative Tactics

In additional amassing forces for head-on conflict, the ancient Greek navy used an array of techniques to paralyze advancing ships, penetrate lines of defense and expose vulnerable positions. The remainder of the scientific sessions focused on deciphering immune mechanisms with potential relevance to LCH pathogenesis that could also uncover furtive therapeutic opportunities. The nature of T cell interactions with pathogenic

dendritic cells (DC), or contributions of "bystander" immune cells to pathogenesis is not known. In his last manuscript on LCH, **Dr. Robert Arceci** documented presence of markers of immune activation and exhaustion on LCH lesion T cells. The potential to disarm pathogenic inflammatory cells or to activate effector immune cells against LCH DCs is not known. LCH DC and T cell interactions may have distinct characteristics compared to conventional T cell and tumor biology since the LCH DC itself may function as a "professional antigen presenting cell".[34;35]

Dr. Astrid van Halteren (Leiden) explored the intriguing possibility that the adaptive immune system might recognize "public antigens" derived from the BRAF-V600E protein in LCH DC. While her team noted mutation-specific density of CD4+ and CD8+ T cells, they did not identify effector cells "licensed to kill" BRAF-V600E-related antigen-presenting cells. By contrast, in melanoma and other cancers, T cells primed to kill BRAF-V600E+ cells are plentiful. The relatively low overall mutation burden in LCH may also play a role in potential for neoantigen formation.[36] Given previous descriptions of LCH lesion T cells, it remains to be determined what activates them and why they become exhausted. **Prof. Jolanda de Vries** (Nijmegen) reviewed clinical applications of immunotherapy using dendritic cells. Specifically, she discussed potential to harness adaptive immune responses against predicted mutations through vaccination with antigen loaded dendritic cells. To induce tumor-specific immune responses, DCs are loaded with relevant tumor antigens, then they must migrate to T-cell-rich areas of lymph nodes. Dendritic are highly sensitive to environmental cues, adding technical challenges to labor intensive vaccine production.[37;38] Beyond typical challenges in cancer vaccine development, for LCH there is also lack of obvious neo-antigen target and uncertain capacity for "host versus tumor" responses. However, one feature a DC that could be therapeutically appropriated is ability to phagocytose and concentrate drug-laden nanoparticles.[39] **Dr. Stephen Hodi** (Boston) discussed the evolving landscape of cancer immunotherapy strategies aimed at dis-inhibiting exhausted tumor-directed T cells by blocking checkpoint receptors (e.g. CTLA-4 and PD-1).[40;41] Checkpoint blockade strategies evoke encouraging responses in many cancers, but rarely are curative in the case of metastatic melanoma. Combination strategies that further enhance immune function (e.g. GM-CSF expression or VEGF blockade) or enhance cytotoxicity (e.g. chemotherapy) are under investigation. Biological characterization of tumors may predict responses to specific therapies. For example CTLA-4 blockade responses are dependent on MHC Class I expression where PD-1 blockade responses are improved by MHC Class II and IFN-γ expression.[42]

Identifying critical components of macrophage/DC function may identify therapeutic targets for LCH. **Dr. Laurie Glimcher** (Boston) investigated mechanisms of cell resilience that tumors may activate to promote survival. She described her work in regulation of cellular responses to stress and inflammation that regulate cell survival. The transcription factor XBP1 promotes cell survival by inducing expression of critical genes involved in protein folding and quality control. In malignant cells, XBP1 overexpression confers drug resistance by preventing drug-induced apoptosis. In DCs, XBP1 is required for differentiation and survival, but may also impair ability to present antigen to tumor-specific T cells. Therefore, cell-specific regulation of XBP1 or other master stress regulators may impact tumor susceptibility to chemotherapy and immunotherapy strategies[43;44]. **Prof. Burkhard Becher** (Zurich) discussed cellular mechanisms regulating expression of the master-regulators of tissue inflammation. Specifically, he investigated the identity of cells that produce the cytokine GM-CSF, a key communicator between tissue phagocytes and T-cells. His team identified central nervous system-infiltrating T helper cells as a source of GM-CSF that are crucial for phagocyte invasion and neuroinflammation. Pathogenicity was lost in the absence of GM-CSF expression despite IFN-γ and IL-17 producing T helper cells in the CNS.[45] Dissecting cellular and cytokine networks that mediate neuroinflammation may particularly relevant to therapeutic opportunities for LCH-associated neurodegeneration.

Prof. Gregory Petsko (New York) continued discussions around causes of neurodegeneration. He noted the apparently distinct features of cancer (uncontrolled proliferation and survival) and neurodegeneration (uncontrolled cell death). This fundamental difference is consistent with inverse comorbidity between most cancers and neurodegenerative diseases. However, a positive association of PD and melanoma has been reported that may elucidate common pathogenic mechanisms.[46] Genetic lesions in α-synuclein have been described in Parkinsons disease that drive formation of pathogenic Lewy bodies.[47] Additionally, caspase-1

causes truncation and aggregation of α-synuclein. Notably, inhibition of caspase-1 improved neuron survival in a cell model.[48] The role of inflammasome activation in LCH is not known and may merit investigation. Jon Pritchard Fellow **Thomas Burke** (Houston) presented his research on mechanisms of inflammation in LCH. Specifically, he reviewed exuberant production of TNF-α that corresponds to extent of disease and clinical risk. Disappointingly, TNF-α blockade does not seem to be effective in LCH, despite an early report of success.[49;50] Additionally TNF-α knock-out mice with enforced expression of BRAF-V600E in CD11c+ cells develop LCH-like lesions and succumb to disease with similar kinetics as "LCH" mice with intact TNF-α expression (unpublished). Continued investigation of immune regulators on the background of "LCH" mice may identify which cytokines/chemokines are sparks that incite inflammation and which are downstream bystanders.

In the Family/Physician session, Greek physicians presented challenging cases that highlight the ongoing unmet need for patients with LCH. **Prof. Petrikkos** (Athens) discussed the problem of managing arthralgias and bone pain that are sometimes discordant with extent of disease. **Dr. Tsipou** (Athens) presented a patient with aggressive histiocytic sarcoma without obvious molecular targets who responded to high dose chemotherapy (cytarabine/cladribine). **Dr. Yavropoulou** (Athens) presented an adult with fever of unknown origin with a variety of other long-standing symptoms that was ultimately found to have BRAF-V600E+ Erdheim Chester Disease. These cases demonstrate the difficulty supporting complicated patients with histiocytic disorders which present with wide range of clinical and histologic variability.

Jon Pritchard Fellow **Dr. Olive Eckstein** (Houston) presented data from retrospective evaluation of a cohort of pediatric patients with LCH treated with MAPK inhibition organized by the North American Consortium for Histiocytosis (NACHO).[16] Response rates in this group highly refractory disease was promising at >85%. However, as observed in adult series, MAPK inhibitor monotherapy did not clear BRAF-V600E+ cells from circulation and cessation of therapy was associated with disease progression. **Dr. Johannes Visser** (Cambridge) presented data from a cohort of children with high-risk LCH treated with vemurafenib in a coordinated strategy at multiple centers in Europe. This study also reported extremely high response rates and rapid relapse associated with cessation of therapy.[15] Dr. Visser went on to lead discussion on strategies to evaluate use of MAPK inhibitors now that we know 1)they are frequently effective and 2)are unlikely to cure. Children at risk of death from high-risk LCH that require improved early therapy and patients who are at risk for developing LCH-ND represent patients who may benefit most from targeted clinical trial strategies.

Summation

Profs. Barrett Rollins (Boston) and **Peter Beverley** (Oxford) reviewed the presentations and discussions of the 29th Nikolas Symposium. The pathogenic mechanisms driving LCH are now evident: MAPK activation in a myeloid precursor. Additionally, the potential performance of MAPK inhibition is increasingly clear. Excellent responses with incomplete cure and predictable toxicities require continued efforts to discover rationale cures. The group not only reflected on the scientific and clinical advances in LCH over the past 29 years, but also on the role of the Nikolas Symposium in catalyzing progress. The Steering Committee reviewed the history of the Nikolas Symposium and noted that scientists invited to the Symposium (n=173) experienced a 25-fold increase in LCH-associated research publications following attendance.[51] Nikolas and his Symposium have transformed outcomes for children and adults with histiocytic disorders.

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