Introduction to the Review Series. Looking back and to the future: the Histiocyte Society blueprint for research in histiocytic disorders

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Introduction to the Histiocyte Society Review Series

Histiocytic disorders encompass a diverse and rare group of conditions including histiocytic neoplasms such as Langerhans cell histiocytosis (LCH) and non-LCH, and hyperinflammatory diseases like hemophagocytic lymphohistiocytosis (HLH). Over the years, significant progress has been made in our understanding the pathogenesis, and treatment of these disorders, leading to improved outcomes for patients. This three-article series, commissioned by the Histiocyte Society, highlights progress in histiocytosis research and care.

The Histiocyte Society (*https://histiocytesociety.org*), founded in 1985, is the scientific organization that has played a pivotal role in advancing the study and treatment of histiocytic disorders. With a global network of physicians and scientists, the Society has been instrumental in establishing consensus classifications, leading clinical trials, and fostering collaboration to improve patients' outcomes. Recognizing the importance of nurturing the next generation of experts, the Society has actively engaged young investigators in its activities over the past decade. Shortly after the Society's formation, the Histiocytosis Association (*https://histio.org*), a worldwide non-profit organization, emerged to provide vital support for patients and families, advocate for research, and raise awareness. Complementing these efforts, the Erdheim-Chester Disease Global Alliance (*https://erdheim-chester.org*) has played a key role in advancing research and care for this ultra-rare histiocytic neoplasm. Together, these organizations have significantly shaped the modern landscape of histiocytosis research and care (Figure 1).

For this review series, the Histiocyte Society's President, Dr. Kim Nichols, proposed to senior members of the community that a group of articles be developed to highlight progress and future directions in each of the three main subtypes of histiocytic disorders. The concept was reviewed and approved by the Society's Steering Committees in the summer of 2024 and followed a structured process developed by the Society's Executive Board.

The classification of histiocytic disorders has evolved considerably since the initial description in 1987, with a landmark 2016 revision by J.F. Emile and colleagues refining disease categorization into five distinct groups based on histology and molecular features in conjunction with clinical and imaging characteristics: Langerhans-related (L group), cutaneous and mucocutaneous (C group), malignant histiocytoses (M group), Rosai-Dorfman disease and variants (R group), and HLH/macrophage activation syndrome (H group).[1] These refinements, along with discovery of pathological somatic mutations primarily affecting the RAS-MAPK pathway in LCH and non-LCH lesions, as well as germline mutations impairing CD8 T-cell and natural killer-cell cytotoxicity in familial HLH, have facilitated a paradigm shift in the diagnosis and management of patients with histiocytic disorders. At the same time, these advances have raised more questions and identified new gaps in knowledge that encourage the community to continue working toward improving the outcomes of the individuals affected by these disorders.

Advancements in Langerhans cell histiocytosis

LCH is the most well-recognized histiocytic disorder, affecting multiple organs, including bones, skin, lymph nodes, lungs, liver, pituitary gland, and brain. Historically, LCH was

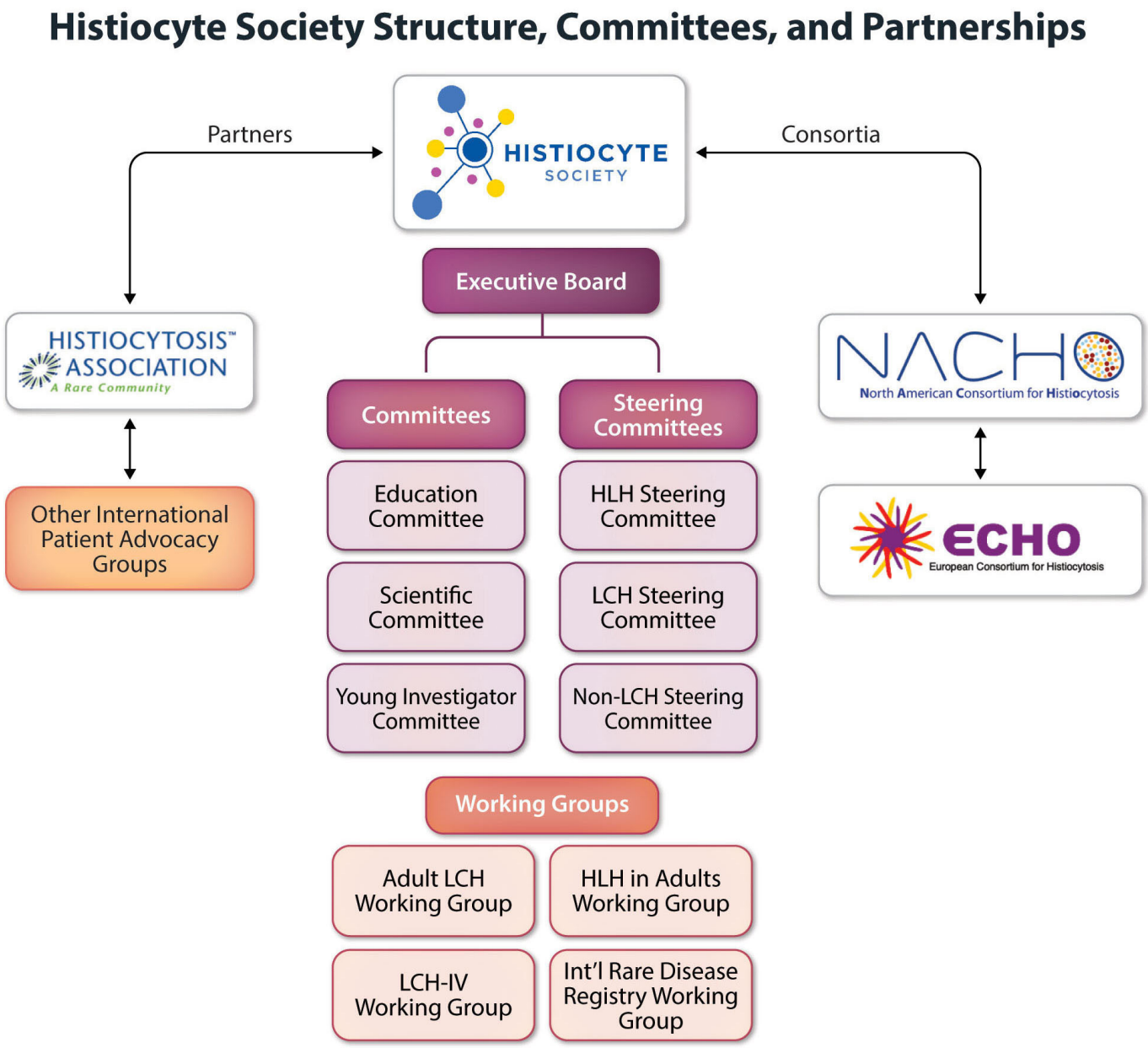

Figure 1. The Histiocyte Society structure, committees, and partnerships. HLH: hemophagocytic lymphohistiocytosis; LCH: Langerhans cell histiocytosis; Int'l: international.

described through different clinical presentations: eosinophilic granuloma (solitary bone lesions), Hand-Schüller-Christian disease (chronic disease with a characteristic triad), and Letterer-Siwe disease (severe multisystem involvement). The term histiocytosis X was introduced by Lichtenstein to unify these entities, and later, the Histiocyte Society formally adopted the name Langerhans cell histiocytosis to reflect the lesional cell's phenotype.

A major breakthrough came in 1994 when LCH was recognized as a clonal disease,[2] shifting the perspective from an immune disorder to a neoplastic condition. The discovery of the *BRAF* V600E mutation in over 50% of LCH cases[3] further revolutionized disease understanding and therapeutic strategies. LCH is now classified as a clonal hematopoietic neoplasm in both the International Consensus Classification[4] and the World Health Organization classification.[5]

In the article "*Histiocyte Society blueprint of Langerhans cell histiocytosis research: improving outcome and quality of life by understanding its 'cell-of-origin'*," Pegoraro *et al.*[6] explore the biological underpinnings of LCH and the implications of emerging technologies such as peripheral blood *BRAF* V600E monitoring. The review also highlights key areas for future research, including deciphering mechanisms of treatment resistance and mitigating long-term complications such as neurodegeneration.

Progress in non-Langerhans cell histiocytosis

Non-LCH comprises a heterogeneous group of disorders, including Rosai-Dorfman disease, Erdheim-Chester disease, and juvenile xanthogranuloma. Rosai-Dorfman disease, first described by Dr. Destombes as adenitis with lipid excess[7] and later by Drs. Rosai and Dorfman in 1969 as sinus histiocytosis with massive lymphadenopathy,[8] has since been recognized to include diverse extranodal manifestations. Erdheim-Chester disease was initially identified as 'lipid granulomatosis' involving the long bones of the legs by Drs. Erdheim and Chester in 1930[9] and later coined by Dr. Ronald Jaffe, with its definition subsequently expanding to include unique imaging and histological features such as hairy kid-

ney, coated aorta, and posterior fossa involvement. Juvenile xanthogranuloma is traditionally thought to be a benign skin condition, but systemic forms have been reported as well. The histopathological features of Erdheim-Chester disease are similar to those of juvenile xanthogranuloma, highlighting overlap between these entities.

While historically challenging to classify and treat, recent molecular insights have uncovered shared pathogenic mechanisms across non-LCH subtypes, including alterations in the MAPK and PI3K pathways. The recognition of these commonalities has not only improved diagnostic precision but has also paved the way for novel targeted therapies, such as BRAF- and MEK-inhibitors.

The non-LCH review in this series "*Histiocyte Society blueprint for non-Langerhans cell histiocytosis research: unraveling complex diseases through collaboration*" by Hershkovitz-Rokah *et al.*[10] provides a critical assessment of the current classification system, arguing that it does not fully account for the clinical and molecular overlaps among subtypes. It proposes a re-evaluation of the classification framework to enhance patients' care, facilitate drug development, and advance research in these rare disorders. The review also emphasizes the importance of natural history studies in early diagnosis and prognostication.

Deciphering hemophagocytic lymphohistiocytosis

HLH represents a distinct and often life-threatening hyperinflammatory syndrome, manifesting with fever, cytopenia, hepatosplenomegaly, and multi-organ dysfunction. HLH can occur in individuals of all ages and in hereditary (also known as primary; familial) and non-hereditary (secondary; sporadic) forms. In 1939, Scott and Robb-Smith described a fatal adult disorder characterized by fever, wasting, cytopenia, hepatosplenomegaly, and histiocytic proliferation, which they termed histiocytic medullary reticulosis.[11] This condition likely corresponded to secondary HLH associated with malignancies. Familial HLH was first formally described in 1952 by Farquhar and Claireaux,[12] although earlier reports suggest that cases identified as familial Letterer-Siwe disease in 1951 were also likely HLH.[13] The recognition of virus-associated HLH (secondary HLH) in 1979 further expanded the understanding of the disorder.[14] A landmark discovery in 1999 identified *PRF1* as the first genetic cause of familial HLH.[15] Subsequent research has linked familial HLH to mutations in *UNC13D*, *STX11*, and *STXBP2*, which encode essential proteins for natural killer-cell and cytotoxic T-cell functions. The role of defective lymphocyte cytotoxicity in the pathogenesis of primary HLH is now well established but the mechanisms driving secondary HLH remain poorly understood. Nevertheless, the various forms of HLH share common immunological features, notably the overproduction of pro-inflammatory cytokines, a finding that has opened doors to the use of cytokine-directed therapies for individuals with these conditions.

In their article, "*Histiocyte Society blueprint for hemophagocytic lymphohistiocytosis research: deciphering underlying disease mechanisms to optimize therapy*," Meyer *et al.*[16] outline current gaps in HLH pathogenesis and the challenges they pose for diagnosis and treatment.The review identifies six priority areas for research, including efforts to refine diagnostic criteria, develop biomarkers for disease stratification, and improve global collaboration to enhance treatment outcomes.

Conclusion

The field of histiocytosis has witnessed remarkable progress over the past few decades, driven by advances in molecular biology, targeted therapies, and international collaborative efforts spearheaded by the Histiocyte Society. The review series in this issue of *Haematologica* provides an in-depth examination of LCH, non-LCH, and HLH, highlighting key discoveries and future research directions that will continue to shape the field. By integrating biological insights with clinical applications, these articles aim to foster innovation and further collaborative investigations to improve the outcomes for patients affected by these rare but impactful disorders worldwide.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally to this article.

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