Concept Evolution of Hemophagocytic Syndrome

The concept of hemophagocytic syndrome (HPS) evolved from the ambiguous histiocytic medullary reticulosis (HMR) adopted by Scott and Robb-Smith in 1939,1 to malignant histiocytosis proposed by Rappaport in 1969,2 and finally to the reactive nature of virus-associated HPS reported by Risdall et al in 1979.3 Patients with this disorder usually present with prolonged fever, hepatosplenomegaly, pancytopenia and coagulopathy. The presence of atypical histiocytes (now, transformed lymphoid cells) and macrophages with phagocytosis of blood cells in bone marrow, lymph nodes, and spleen establishes the diagnosis. The ambiguity in terminology, either with regard to benignancy versus malignancy or cell origin, reflects our lack of understanding of the exact nature of this disease. HPS now represents a common epiphenomenon of an immune disorder associated with a diverse spectrum of underlying illnesses such as viral infections, genetic disorders or malignancies. Recently, the development of HPS in H5N1 avian influenza virus infection has increased the urgency to resolve the pathogenesis and therapy of HPS.4,5

Gene Mutations in Patients with Familial History of HPS

Our understanding of the pathogenesis of HPS comes mainly from studies on X-linked lymphoproliferative disorder (XLP). XLP occurs in children around 1 year of age.6 The discovery of mutations in the SH2D1A/SAP gene, the negative regulator of the SLAM/ERK pathway for T cell activation, represents a milestone in the pathogenesis of XLP.7–9 Mutations in this gene lead to overt T cell activation and secretion of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) in response to Epstein-Barr virus (EBV) infection.10,11 Similar to XLP, cases of childhood HPS with familial clustering were found to have mutations in perforins, Munc13-4 and others.12–14 They are now classified as familial hemophagocytic lymphohistiocytosis (FHL). The mutations in the perforin gene in FHL highlight the reduced innate (NK) immunity in response to virus infections.

EBV-associated Hemophagocytic Lymphohistiocytosis and Disease Progression

In Asian countries and Taiwan, we noted the prevalence of a childhood entity of “HMR” or EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) showing entirely similar findings to XLP or FHL, except that no familial linkage was demonstrated.15 In 1993, Kawaguchi et al and our group noted that EBV unexpectedly infects T cells in EBV-HLH, instead of the B cells in XLP.15,16 EBV latent membrane protein-1 can transduce the signals through TRAFs/NF-κB to activate T cells through suppression of the SH2D1A/SAP
gene, thereby providing a cross talk between XLP and HLH.

EBV causes the majority (60–80%) of childhood HPS/HLH, but other viruses may also be associated with HPS, usually with relatively benign disease.

Based on the underlying immunopathogenesis associated with XLP, FHL and HLH, HPS can be categorized into two main entities (Table 1). FHL represents the primary or hereditary defect of innate (NK or cytotoxic cells) response to virus infections, while XLP and HLH represent the overt adaptive Th1 response to virus infections. The common outcome in both categories is the enhanced Th1 cytokine secretion, which will subsequently activate macrophages.10,11 In severe viral infections such as H5N1 avian influenza, NK cells were noted to be reduced, leading to high viral replication and enhanced proinflammatory cytokine secretion.4,5 Similar to the progression of XLP to Burkitt’s lymphoma, EBV-HLH may progress to chronic active disease or T cell lymphoma in about 10–20% of cases after therapy.17 EBV LMP-1 could suppress TNF receptor-1 to survive from TNF-α-induced apoptosis and then progress to T cell lymphoma due to constitutive activation of NF-κB signals.17

### Mechanism of Blood Cell Phagocytosis by Activated Macrophages in HPS

One important phenomenon of HPS is the engulfment of blood cells by activated macrophages. The phagocytic process is a non-random biologic event and involves sophisticated ligand-receptor interaction.18 Why hemophagocytosis occurs in HPS is still mysterious. In an animal model of rabbit HPS by Herpesvirus papio infection, we observed the emergence of autoantibodies to red cells as a precipitating factor for the subsequent phagocytosis of red cells.19 The development of autoantibodies is presumed to result from an imbalanced switch between Th1 and Th2 cells, leading to the emergence of polyclonal autoreactive B cell response and autoantibody production.

### Diagnosis and Therapy of HPS

In the past 10 years, we have witnessed the improved survival of HPS patients for several reasons. First, the proposal of the criteria guidelines by the International Society of Histiocytes (Table 2) has contributed significantly to the diagnosis and therapy of HPS patients.14 The current regimens are designed to control T cell activation (steroids, cyclosporine, etoposide) and macrophage activation (intravenous immunoglobulin, etoposide) in HPS. Bone marrow transplantation is recommended for patients with hereditary disorders such as XLP or FHL.

### Challenging Issues in HPS

Considering the high mortality of HPS and the potential threat of H5N1 avian influenza, proper management of patients with HPS is becoming a challenging issue. To clarify the nature of underlying diseases remains the critical event. However, the common clinical presentations and rapidly progressive diseases of HPS usually make the early recognition of HPS difficult. Rapid tests for viral etiology using a combination of serologic

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**Table 1.** A comprehensive classification of hemophagocytic syndrome (HPS)

<table>
<thead>
<tr>
<th>Reduced or absent innate immunity (NK/CTL) associated with HPS</th>
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<tbody>
<tr>
<td>Primary or familial: FHL1-4 (mutations in perforin, Munc13-4, others)</td>
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<tr>
<td>Severe viral infections with reduced NK activities: H5N1, dengue, adenovirus</td>
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<tr>
<th>HPS associated with overt adaptive T cell (Th1) response</th>
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</thead>
<tbody>
<tr>
<td>Primary or familial: XLP (SH2D1A/SAP gene mutations)</td>
</tr>
<tr>
<td>EBV-HLH (EBV infections of T cells)</td>
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<tr>
<td>Autoimmune disorders (lupus erythematosus)?</td>
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<tr>
<td>Others: malignancy (solid tumor)-associated HPS</td>
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FHL = familial hemophagocytic lymphohistiocytosis; XLP = X-linked lymphoproliferative disorder; EBV-HLH = Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis.
and molecular tests should establish the etiology in the majority of cases. Finally, an ideal regimen for the control of HPS, especially the management of chronic active or relapsing diseases, remains to be developed. Since NF-κB plays a pivotal role in the initiation of proinflammatory cytokine storm in HPS,17,20 NF-κB inhibitors or peroxisome proliferator-activated receptor agonists are potential agents to be developed.21,22

References


