

Preface

In recent years, the pathogenesis of hematological disorders in children has been clarified, which has led to remarkable progress in the treatment outcome for these disorders. In particular, molecular targeted therapy has been shown to have an effect on childhood leukemia refractory to conventional therapy. Further development of these strategies will enable us to use more effective and less toxic therapies for hematological disorders in the future. Here we describe the pathogenesis and treatment (present and future) of several representative hematological disorders in children, especially focusing on the genetic and molecular aspects.

Most hematological disorders in children arise from intrauterine endogenous or exogenous exposures, genetic susceptibility, or several factors after birth. A good example is the case of infant leukemia. Greaves et al. [1] clarified the etiology of infant leukemia; analysis of *MLL* gene rearrangements in identical leukemic twins suggested that the *MLL* gene undergoes prenatal rearrangement and leukemic cells are present in the blood of newborns. In utero exposure to some drugs and foods that possess functional similarity to topoisomerase-II inhibitors and certain environmental factors may affect *MLL* gene rearrangements, which contribute to leukemogenesis [2]. This conclusion can be expanded to B-cell precursor acute lymphoblastic leukemia (ALL) with *TEL-AML1* [3] or hyperdiploidy [4], acute myeloid leukemia (AML) with *AML1-ETO* [5], and acute megakaryocytic leukemia with *GATA1* mutations in Down syndrome [6]. Clarification of leukemogenesis after birth is needed to establish more appropriate treatment modalities in childhood leukemia. We have recently shown that the *MLL-miRNA let7b*-oncogene HMGA2 pathway plays an important role in the proliferation of leukemic cells and could be a possible molecular target for the therapy of infant leukemia [7].

Congenital bone marrow failure syndrome in children is an inherited disease, including Fanconi anemia (FA), dyskeratosis congenita, Shwachman–Diamond syndrome, Diamond–Blackfan syndrome, severe congenital neutropenia, and congenital amegakaryocytic thrombocytopenia, which are characterized by cytopenias in different hematologic lineages and several congenital abnormalities [8]. Early diagnosis of bone marrow failure syndrome is important for optimizing clinical management, anticipating possible complications that may develop later in life, and

providing appropriate genetic counseling for the family [9]. Many of these syndromes require multidisciplinary and multispecialty medical care for appropriate surveillance and management. As a representative disease, FA is caused by germline mutations in DNA repair genes with autosomal recessive inheritance. A major problem of FA is its high risk of cancer, which increases with age. In particular, the risk of myelodysplastic syndrome or AML is relatively high, indicating that most patients with FA need hematopoietic stem cell transplantation (HSCT) before the onset of malignancy [10]. However, the rate of treatment-related side effects and graft-versus-host disease, as well as the risk of head and neck cancers, is high in FA patients after HSCT, demonstrating the need for a more appropriate conditioning regimen [8].

A high risk of malignancy can also be seen in other types of congenital bone marrow failure syndrome, and the molecular pathology will be similar and sometimes overlap between different subtypes. Genetic advances have already led to improved diagnosis, particularly in cases wherein the presentation is atypical. These advances may also lead to new treatments. In the meantime, it is important to obtain accurate information on the incidence and natural history of each disorder in order to provide a more rational basis for the optimal provision of clinical services [11].

Acquired aplastic anemia (AA) is an uncommon, life-threatening disorder in childhood. Because of major advances in diagnosis and therapeutic approaches, nowadays AA is a disease that results in long-term survival in more than 90% of cases [12]. In recent years, an immune-mediated pathogenesis for AA has been suggested because immunosuppressive therapy is usually effective and bone marrow lymphocytes from patients can suppress normal marrow cells *in vitro* [13]. Numerous studies have established that HSCT, especially bone marrow transplantation, from HLA-matched donors is highly successful, with five-year survival rates of >90% [14]. Unfortunately, horse antithymocyte globulin (ATG) is no longer available and an alternative agent, rabbit ATG, is associated with a lower response rate for AA in children [15].

Hemophagocytic lymphohistiocytosis (HLH) is characterized by fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and infiltration of histiocytes with hemophagocytic activity. HLH can be classified into two distinct forms, primary and secondary HLH; primary HLH includes familial hemophagocytic lymphohistiocytosis and several immunodeficiencies, while secondary HLH is usually associated with infections [especially Epstein–Barr virus (EBV) infection], immune disorders, or malignancy (especially non-Hodgkin lymphoma). In primary HLH, uncontrolled T lymphocyte activation by impairing defects of genes, such as *perforin* (*PRF1*) and *MUNC13-4*, results in large quantities of inflammatory cytokines that promote macrophage infiltration and formation of the cytokine network [16]. The pathogenesis of secondary HLH, especially EBV-HLH, is not fully understood. In EBV-HLH, inflammatory cytokines produced by EBV-infected T cells or natural killer cells are responsible for macrophage activation and subsequent development of HLH [17].

The treatment of HLH has been established in recent years. Immunochemotherapy followed by HSCT can be used for primary HLH, while the clinical course of

EBV-HLH varies among patients and treatment that is more appropriate should be organized for secondary HLH. Identification of all instigating mechanisms may prompt the development of novel approaches, including gene therapy, for this disorder in the future.

Langerhans cell histiocytosis (LCH) is a rare clonal disorder characterized by the proliferation of clonal CD1a-positive LCH cells in the skin, bone, lymph nodes, and other organs. LCH cells are immature dendritic cells, and the JAG-mediated Notch signaling pathway may play an important role in maintaining LCH cells in an immature state [18]. More than half of the LCH patients have the oncogene *BRAF* mutation, suggesting that LCH is a neoplastic disorder [19]. The outcome of LCH varies depending on the extent of organ involvement, and treatment should be planned according to the clinical subtype. In single-system disease, local corticosteroid therapy can be used for patients with single bones affected by lesions with no CNS risk [20], while chemotherapy is available for those with multiple affected bones or with CNS-risk lesions. In multisystem disease, on the other hand, chemotherapy including vincristine, cytarabine, and corticosteroid has been used with great success, with a mortality rate of only 10% [21].

Despite their successful treatment, LCH patients often develop long-term sequelae, including diabetes insipidus, orthopedic problems, hearing loss, neurological problems, growth-hormone deficiency, pulmonary fibrosis, and biliary cirrhosis [22]. The incidence of these sequelae increases with follow-up time. Further novel therapeutic measures are required to reduce these permanent sequelae.

Hematological disorders in children are usually rare, but clarifying their pathogenesis has progressed and appropriate treatment has been established in the recent years. More effective and less toxic therapies for these hematological disorders need to be developed in the near future.

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