Down Syndrome Preleukemia and Leukemia

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KEYWORDS

- Down syndrome • Preleukemia • Leukemia
- Myeloid leukemia of Down syndrome • B-ALL • GATA1
- Transient abnormal hematopoiesis/transient myeloproliferative disorder

KEY POINTS

- Children with Down syndrome manifest multiple hematologic manifestations: (1) transient myeloproliferative disorder (TMD)/transient abnormal myelopoiesis (TAM) at birth, (2) acute myeloid leukemia (ML-DS), and (3) acute lymphoblastic leukemia (ALL).
- The underlying primary basis for the varied hematologic manifestations is linked to the gene dosage effect of chromosome 21–encoded genes.
- TMD/TAM and ML-DS are characterized by the presence of truncating mutations in exon 2 of the hematopoietic transcription factor *GATA1*. Spontaneous resolution is common in TMD/TAM, and ML-DS is highly responsive to chemotherapy with resultant high cure rates compared with acute myeloid leukemia in non-DS children.
- DS-ALL is characterized by the presence of mutations in *JAK2* tyrosine kinase and *IKZF1*. In contrast to the high cure rates in ML-DS, the results in DS-ALL are same are inferior to non-DS ALL, in part, because of the lower frequency of good-response ALL subtypes and also the higher systemic toxicity of agents used in children with DS.

INTRODUCTION

For more than 150 years, Down syndrome (DS) has been linked to the English physician John Langdon Down. His essay published in 1866, "Observations on an Ethnic Classification of Idiots," described a group of cognitively impaired individuals with common physical features. DS is now recognized as the most common chromosomal

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abnormality, occurring in 1 in every 800 to 1000 live births. Neonates, children, and adults with DS develop multiple medical disorders; hematologic disorders being one of the most well known. It has long been recognized that children with constitutional trisomy 21 (DS) have a markedly increased risk of acute leukemia. The first description of a child with DS who developed acute leukemia was published in 1930. Subsequently, a national survey in the United States provided support to the notion that children with DS had an increased risk of developing leukemia.[1] Remarkably, children with DS are at an increased risk both of acute megakaryocyte-erythroid leukemia (known as myeloid leukemia of DS [ML-DS]) by 150-fold and of acute B-lineage lymphoblastic leukemia by 33-fold compared with children without DS.

In ML-DS, it is now clear that the initial event is perturbation of fetal hemopoiesis by trisomy 21 (T21) itself. This perturbation leads to complex defects in fetal hemopoiesis and newborn hematology. In up to 28% of fetuses/newborns with DS, hemopoietic cells acquire mutations in the gene encoding the key megakaryocyte-erythroid transcription factor GATA1. Acquisition of *GATA1* mutations can either be clinically silent or result in a clinically important preleukemic fetal/neonatal disorder transient abnormal myelopoiesis (TAM). Most cases of TAM resolve without long-term clinical sequelae; but in a proportion of cases with TAM, neonates/young children acquire additional genetic mutations that immortalize the TAM clone and result in frank ML-DS. There are parallel defects in DS fetal B-cell lymphopoiesis caused by T21 that most likely result in acquisition of a series of cooperating and transforming mutations in genes encoding key regulators of B-lymphopoiesis (eg, *JAK2* and *CLRF2*).

Thus, the unique features of DS-associated leukemias arise because of the crucial role played by T21 that then creates the right cellular and molecular environment for the acquisition of additional genetic mutations that together lead to acute leukemia. Thus, DS-associated leukemias represent potentially one of the most tractable human models to understand the biological basis of multistep leukemogenesis and the impact of aneuploidy on cancer. Next, the authors highlight some of the recent clinical and biological advances in these preleukemic and leukemic conditions.

TRISOMY 21 AND HUMAN FETAL HEMATOPOIESIS

Fetal Origin of Trisomy 21–Associated Leukemias

Human T21 itself perturbs second-trimester fetal liver hemopoietic stem/progenitor (HSPC) function.[2–4] T21 increases the frequency of immunophenotypic hemopoietic stem cell (HSC) that has a biased erythroid-megakaryocyte primed gene expression profile compared with disomic HSC. Furthermore, multiple HSPC populations show increased megakaryocyte-erythroid output in colony assays. Coupled with this, there is an expansion of megakaryocyte-erythroid progenitors themselves. Consistent with this increased megakaryocyte output, immunohistochemical studies of T21 fetal liver sections show increased megakaryocyte numbers. However, megakaryocyte differentiation may be compromised, as fetal liver megakaryocytes are morphologically abnormal. Corroborating data from human T21 embryonic stem cells and induced pluripotent stem cells show increased erythroid and possible megakaryocyte production.[5,6] In addition to increased, but likely perturbed megakaryocyte-erythroid differentiation, there is a severe impairment of B-lymphoid development in DS fetal liver; with an approximately 10-fold reduction in pre-pro B cells and B-cell potential of HSC, in tandem with reduced HSC lymphoid gene expression priming.[4]