cells having the immunophenotype of dendritic cells. These dendritic cells were in close association with developing megakaryocytes and contained $CD61^+$ intracellular material indicative of phagocytosis of megakaryocyte cytoplasm. In addition, these dendritic cells were capable of activating autologous T lymphocytes in vitro. They went further to investigate the type of phagocytic cells in bone marrow smears from patients with the hemophagocytic syndrome and identified a significant percentage of these cells as having the immunophenotypic characteristics of dendritic cells. Previous work by the same group has shown phagocytosis of immature erythroid cells by dendritic cells in cultures of $CD34^+$ cells in the presence of erythropoietin (EPO) and TNF-α.[4]

These observations shed more light on the role of dendritic cells in the hemophagocytic syndrome, in particular their contribution to the process of hemophagocytosis and its propagation through further activation of autologous T lymphocytes. In addition, they raise the possibility that dendritic cells with phagocytic activity may contribute during their development in the bone marrow to the development of tolerance to molecules released from dying or damaged hematopoietic cells. ■

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NEOPLASIA

Comment on Ge et al, page 1570

Up and down in Down syndrome: AMKL

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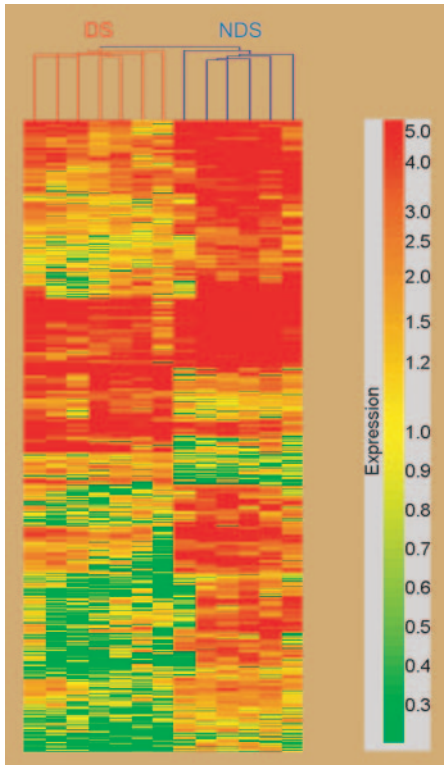
Children with Down syndrome (DS) show a remarkable predisposition to develop acute megakaryocytic leukemia. In this issue of *Blood*, Ge and colleagues identify a set of genes that are differentially expressed in DS versus non-DS megakaryocytic leukemias. These findings may help explain many of the unique features of DS malignancies.

It is well established that children with Down syndrome are at an elevated risk of developing leukemia.[1] In particular, the risk of acute megakaryocytic leukemia (AMKL) in children with DS is increased 500-fold over that of children without DS. It has become clear in the last 10 years that DS children with acute myeloid leukemia (AML) have a significantly better outcome than non-DS children with AML, with event-free survival (EFS) approximating 70% to 80%.[2] This improved outcome has been attributed to the increased sensitivity of DS megakaryoblasts to cytosine arabinoside (ara-C) therapy.[3]

In addition, AMKL patients with DS, but not those without DS, harbor somatic mutations in the X-linked hematopoietic transcription factor GATA-1.[4] In all patients, the mutations lead to loss of full-length GATA-1, but persistent expression of a shortened isoform, GATA-1s, that lacks the N-terminal transactivation domain. Thus, it is likely that these mutations contribute to leukemia by leading to altered expression of GATA-1 target genes. The identification of these genes that are misexpressed in DS-AMKL blasts is an essential step in understanding the mechanism of leukemogenesis in DS.

In order to determine the effect of *GATA1* mutations and trisomy 21 on gene expression in AMKL, Ge and colleagues performed gene expression profiling of leukemia samples from DS and non-DS children with AMKL. Using Affymetrix U133A microarray chips, they identified 551 differentially expressed genes, consisting of 105 genes overexpressed in the DS group and 446 genes in the non-DS group (see figure). Of note, these genes were widely localized to different chromosomes, with only 7 genes located on chromosome 21. One of these genes, bone marrow stromal cell antigen (*BST2*) was chosen for further study because previous reports have suggested that bone marrow stromal cells exert a protective effect on leukemic cells. BST2 expression was reduced 8.5-fold in the DS-AMKL group. Using multiple approaches, Ge et al confirmed that *BST2* is a bona fide GATA-1 target gene and showed that full-length GATA-1, but not GATA-1s, could efficiently activate *BST2* transcription in vivo. Next, they demonstrated that ectopic expression of *BST2* in a DS-AMKL cell line, which does not endogenously express this gene, resulted in a significant reduction in ara-C–induced apoptosis when cells were cocultured with bone marrow stromal cells. Thus, restoration of *BST2* expression likely facilitated an association with the stromal cells, leading to protection from ara-C–induced cytotoxicity. Decreased expression of *BST2* in DS-AMKL may act in conjunction with alterations in expression of genes that govern the metabolism of ara-C, such as cytidine deaminase,[3] to elicit the remarkable



Cluster analysis of differentially expressed genes between DS and non-DS megakaryoblasts; chromosomal localization of genes in cluster analysis. See the complete figure in the article beginning on page 1570.

hypersensitivity of DS megakaryoblasts to therapy.

DS-AMKL blasts are distinct from those in non-DS AMKL in that they harbor both trisomy 21 and a *GATA1* mutation. This new study by Ge and colleagues suggests that the *GATA1* mutations themselves may lead to the differential regulation of target genes that contribute to the unique features of DS-AMKL, such as the increased susceptibility to ara-C and high EFS rates. Surprisingly, their data provide few insights into the causative role of trisomy 21 in the disease. Future studies to determine the contributions of trisomy 21 to the initiation and/or progression of AMKL will be necessary to further advance our understanding of this malignancy. ■

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IMMUNOBIOLOGY

Comment on Fuhlbrigge et al, page 1421

CD43, a novel lymphocyte ligand for E-selectin

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An elegant analysis of potential E-selectin binding ligands from extracts of CLA-expressing T lymphocytes reveals a novel role for the sialomucin CD43.

The selectins (L-, P-, and E-selectin) are a group of adhesion molecules that play a pivotal role in the migration and homing of various leukocyte populations under inflammatory and noninflammatory conditions. In particular, migration of lymphocytes to the skin appears to be heavily dependent upon the endothelial selectins (E- and P-selectin). Cutaneous lymphocyte antigen (CLA) is a carbohydrate epitope presented by specialized glycoprotein scaffolds such as PSGL-1, and it binds E-selectin. PSGL-1 has been shown to account for all P-selectin–dependent leukocyte rolling and the majority but, importantly, not all, E-selectin–dependent rolling. Although, the identity of the ligand responsible for PSGL-1–independent, E-selectin–dependent leukocyte rolling remains unclear, this residual E-selectin–dependent rolling was recently shown to be physiologically relevant, as the few remaining rolling cells were able to entirely reconstitute a normal contact hypersensitivity response.[1]

In this issue of *Blood,* Fuhlbrigge and colleagues have used a very elegant, unbiased biopanning technique (blot-rolling assay) that involves the rolling of E-selectin–expressing CHO cells over a Western blot containing lysates from CLA-positive T cells to identify E-selectin binding ligands. This approach revealed a novel CLA-containing ligand for E-selectin, namely the high-molecular-weight isoform of the sialomucin CD43 (leukosialin). Fuhlbrigge et al have also shown that unlike PSGL-1, CD43 supports only E-selectin–dependent rolling and not P-selectin–dependent rolling. Interestingly, in vivo, CD43 has been shown to have both antiadhesive[2] and proadhesive[3] properties. This study goes a long way in resolving this dichotomy. CD43, because of its long, negatively charged structure, would function as an antiadhesive molecule on unactivated or naive cells, but through activation of the cell and posttranslational modification, CD43 would switch to a proadhesive E-selectin ligand. Interestingly, CD34, a related sialomucin to CD43, has also been recently reported to be an antiadhesive molecule on hematopoetic cells[4] despite its well-known proadhesive function on lymph node endothelium following posttranslational modification. Whether CD34 can become proadhesive on hematopoetic cells remains to be elucidated.

Numerous critical issues arise. For example, a major characteristic of E-selectin is its ability to cause leukocytes to roll very slowly (< 10 μm/sec), presumably allowing for more effective firm adhesion.[5] Rolling velocity can be several-fold higher in the absence of functional E-selectin,[5] but not in the absence of PSGL-1,[1] suggesting that other E-selectin ligands, perhaps CD43, may mediate the slow rolling in lymphocytes. Recently, it was reported that CD44, another posttranslationally modified molecule, may also function as a ligand for E-selectin in neutrophils.[6] However, since the rolling velocity in the absence of CD44 increased only 30% to 50%, this leaves plenty of room for other molecules such as CD43 to also mediate rolling velocity. Whether only T cells use CD43 to roll, or whether this also extends to other CD43-expressing cells—including neutrophils—following activation, remains to be established. Finally, it will be very important to study the contribution of CD43 relative to other E-selectin ligands in skin inflammation. This study reminds us of the difficulties of targeting inflammation and adds an additional twist: what is antiadhesive in one situation could be contributing to inflammation in another. ■

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