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. ■

REFERENCES

1. Hitzler JK, Zipursky A. Origins of leukaemia in children with Down syndrome. Nat Rev Cancer. 2005;5:11-20.
2. Gamis AS. Acute myeloid leukemia and Down syndrome evolution of modern therapy: state of the art review. Pediatr Blood Cancer. 2005;44:13-20.
3. Ge Y, Stout ML, Tatman DA, et al. GATA1, cytidine deaminase, and the high cure rate of Down syndrome children with acute megakaryocytic leukemia. J Natl Cancer Inst. 2005;97:226-231.
4. Wechsler J, Greene M, McDevitt MA, et al. Acquired mutations in *GATA1* in the megakaryoblastic leukemia of Down syndrome. Nat Genet. 2002;32:148-152.

IMMUNOBIOLOGY

Comment on Fuhlbrigge et al, page 1421

CD43, a novel lymphocyte ligand for E-selectin

M. Ursula Norman and Paul Kubes INSTITUTE OF INFECTION, IMMUNITY AND INFLAMMATION, UNIVERSITY OF CALGARY

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. ■

REFERENCES

1. Zanardo RC, Bonder CS, Hwang JM, et al. A down-regulatable E-selectin ligand is functionally important for PSGL-1-independent leukocyte-endothelial cell interactions. Blood. 2004;104:3766-3773.
2. Woodman RC, Johnston B, Hickey MJ, et al. The functional paradox of CD43 in leukocyte recruitment: a study using CD43-deficient mice. J Exp Med. 1998;188:2181-2186.
3. McEvoy LM, Sun H, Frelinger JG, Butcher EC. Anti-CD43 inhibition of T cell homing. J Exp Med. 1997;185:1493-1498.
4. Drew E, Merzaban JS, Seo W, Ziltener HJ, McNagny KM. CD34 and CD43 inhibit mast cell adhesion and are required for optimal mast cell reconstitution. Immunity. 2005;22:43-57.
5. Kunkel EJ, Ley K. Distinct phenotype of E-selectin-deficient mice: E-selectin is required for slow leukocyte rolling in vivo. Circ Res. 1996;79:1196-1204.
6. Katayama Y, Hidalgo A, Chang J, Peired A, Frenette PS. CD44 is a physiological E-selectin ligand on neutrophils. J Exp Med. 2005;201:1183-1189.