infection rates) of lenalidomide-Dex treatment with lower versus higher Dex dose[9]; and the high rates and durability of responses to lenalidomide-bortezomib in a study where most patients did not receive Dex.[10]

This study by Hsu et al triggers captivating new questions. What is the impact of Dex on patients' NK-cell activity against autologous MM cells and does it correlate with clinical outcome after lenalidomide-Dex treatment? Does the impact of Dex on lenalidomide-induced immunostimulation depend on disease stage, underlying degree of MM-associated immunoparesis, status of prior treatment(s), or concomitant use of other therapeutics (eg, proteasome inhibitors)? Will this study's results differ quantitatively or qualitatively in MM patients who are younger or without renal impairment (ie, in patient populations different from those of the current study) or with thalidomide or pomalidomide treatment? Do the in vivo interactions of the tumor cells with their microenvironment alter the balance between the opposing immunologic effects of lenalidomide versus Dex? Can doses or schedules of lenalidomide and/or Dex be adjusted to preserve their synergistic direct proapoptotic activity against MM cells, while minimizing Dex-induced immunosuppressive effects? Which clinically applicable marker(s) can identify such potential optimal settings to help individualize the use of these agents?

Until these questions are answered, a key message from this stimulating study is that, in clinical settings where lenalidomide use aims to augment the anti-MM activity of immunotherapeutics, caution should be exercised with concurrent use of potent glucocorticoids.

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## REFERENCES


1. Hsu AK, Quach H, Tai T, et al. The immunostimulatory effect of lenalidomide on NK-cell function is profoundly inhibited by concurrent dexamethasone therapy. *Blood*. 2011;117(5):1605-1613.
2. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*. 2001; 98(1):210-216.
3. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol*. 2009;27(30):5008-5014.
4. Anderson KC. Lenalidomide and thalidomide: mechanisms of action–similarities and differences. *Semin Hematol*. 2005;42(4 suppl 4):S3-S8.
5. Gandhi AK, Kang J, Capone L, et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. *Curr Cancer Drug Targets*. 2010;10(2):155-167.
6. Attal M, Cristini C, Marit G, et al. Lenalidomide maintenance after transplantation for myeloma [abstract]. *J Clin Oncol*. 2010;28(suppl):4402. Abstract 8018.
7. McCarthy PL, Owzar K, Anderson KC, et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104 [abstract]. *J Clin Oncol*. 2010;28(suppl):4402. Abstract 8017.
8. Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood*. 2009;114(4): 772-778.
9. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol*. 2010;11(1):29-37.
10. Richardson PG, Weller E, Jagannath S, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. *J Clin Oncol*. 2009;27(34):5713-5719.


● ● ● LYMPHOID NEOPLASIA

Comment on Hosking et al, page 1633

# When the negative is positive

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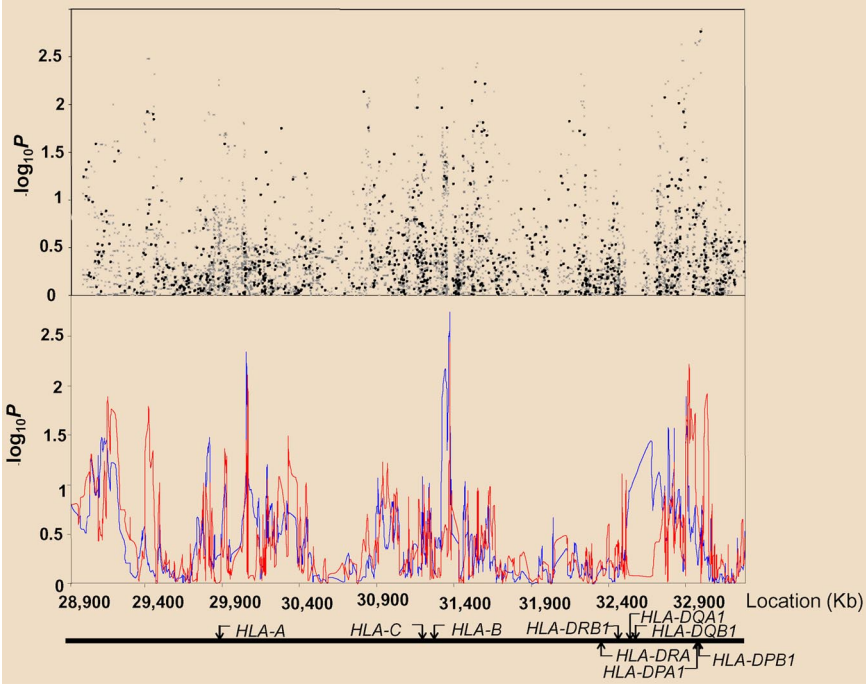
In this issue of *Blood*, Hosking and colleagues report the lack of correlation between genetic variants within the MHC and the risk of ALL.[1]

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. It is a biologically heterogeneous disease with B-cell precursor ALL as the most common subtype accounting for ~ 70% of childhood ALL. There is now conclusive evidence that the risk




**Association between SNPs and haplotypes mapping to 6p21 and BCP-ALL risk. The x-axis represents the position of each SNP; the y-axis, *P* values on a minus logarithmic scale. Cochran-Armitage trend test statistics are shown in black for directly genotyped SNPs and in gray for imputed SNPs in the top panel. Lines in the bottom panel correspond to haplotype test statistics: blue defined by 5 SNPs and red by 12 SNPs. Relative positions of the major *HLA* genes are also shown. Chromosomal coordinates were derived from the National Center for Biotechnology Information, build 36. See the complete figure in the article by Hosking et al beginning on page 1633.**

of ALL has an inherited genetic component.[2-4] There has been considerable interest in the major histocompatibility complex (MHC) locus on chromosome 6p21 due to the proposition that immune dysfunction or delayed infection has a role in ALL etiology. However, the results have been inconsistent with different class I and class II alleles implicated. Possible reasons for the inconsistencies include study design issues (limited sample sizes, confounded by population stratification), multiple testing, and disease definition of ALL. Hosking et al overcome several of these issues in their study. Using existing genotype data from a genome-wide association (GWA) study of ALL and imputed data based on the HapMap, they evaluated more than 8000 single nucleotide polymorphisms (SNPs) in the MHC region, spanning 4.5 Mb in 824 B-cell precursor ALL cases and 4737 controls. Both single SNP analyses as well as haplotype analyses lacked any evidence of association. The authors also estimated 2- and 4-digit human leukocyte antigen (HLA) alleles from the SNP genotypes and still found little evidence of association with B-cell precursor ALL risk, especially after accounting for multiple testing (see figure).

Although the reported findings are negative, they are important. First, with more than 800 cases and 4700 controls, this study is sufficiently powered to identify common variants with modest effects, even after adjusting for multiple testing. Second, this study focused on only 1 ALL subtype, B-cell precursor ALL. Although this limits generalizability of the findings to other subtypes, this reduces heterogeneity and therefore strengthens statistical power. Finally, this study was able to rule out confounding from population stratification or cryptic relatedness due to the available genotype data from the GWA study. Most candidate-gene association studies are only able to use self-reported race or ethnicity that can be inadequate. However, with the use of the GWA data, one can estimate race from the observed genetic data thereby providing an unbiased estimate of race.[5]

Do the results of Hosking et al mean that we can rule out any role of the MHC region on the risk of B-cell precursor ALL? Unfortunately, no. This study touches on only one aspect of the genomic complexity in the region by providing conclusive evidence that common genetic variants within the region lack any association with risk. However, other possible mechanisms may still exist, including interactions (eg, interactions between MHC variants and variants located on other chromosomes), epigenetics (eg, methylation of genes), or structural changes (eg, insertions or deletions of chromosomal regions). Further work still needs to be done to determine what role, if any, the MHC region has in ALL risk, but the reporting of negative results from strong studies is a positive thing.

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## REFERENCES


1. Hosking FJ, Leslie S, Dilthey A, et al. MHC variation and risk of childhood B-cell precursor acute lymphoblastic leukemia. *Blood*. 2011;117(5):1633-1640.
2. Trevino LR, Yang W, French D, et al. Germline genomic variants associated with childhood acute lymphoblastic leukemia. *Nat Genet*. 2009;41(9):1001-1005.
3. Papaemmanuil E, Hosking FJ, Vijayakrishnan J, et al. Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia. *Nat Genet*. 2009;41(9):1006-1010.
4. Prasad RB, Hosking FJ, Vijayakrishnan J, et al. Verification of the susceptibility loci on 7p12.2, 10q21.2, and 14q11.2 in precursor B-cell acute lymphoblastic leukemia of childhood. *Blood*. 2010;115(9):1765-1767.
5. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet*. 2006;38(8):904-909.


● ● ● THROMBOSIS & HEMOSTASIS

Comment on Haling et al, page 1719

# Talin's second act-ivation: retraction

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In this issue of *Blood*, Haling and colleagues demonstrate that in addition to talin-dependent integrin activation, talin is required for platelet fibrin clot retraction by physically linking integrins to the actin cytoskeleton.

Integrins are ubiquitous transmembrane α/β heterodimers that provide an essential link between the extracellular and intracellular environments, which is vital for both normal and pathophysiologic processes. The well-characterized platelet-specific integrin αIIbβ3 (like several other integrin receptors) is constitutively expressed on the cell surface in a low-affinity state. Agonist stimulation or exposure of platelets to extracellular matrix proteins generates intracellular signals that enhance integrin-binding affinity for ligands. Ligand binding to αIIbβ3, in turn, transduces signals from the extracellular environment into the cell leading to platelet adhesion and aggregation. Finally, integrin αIIbβ3-dependent clot retraction is necessary for normal thrombus stabilization and wound healing. In platelets, these bidirectional signaling events are tightly regulated processes; perturbation of this regulation can lead to pathologic conditions such as hemorrhage or occlusive platelet thrombi.

The integrin cytoplasmic domains are key regulatory sites for integrin bidirectional signaling. Multiple proteins have been identified that bind to integrin cytoplasmic domains and, as such, are likely to play a role in regulating integrin function.[1] One of these proteins, talin, binds to β-integrin cytoplasmic tails and is an important regulator of integrin activation (reviewed in Shattil et al[2]). Talin is an abundant (~ 3%-8% of total platelet protein[3]) cytoskeletal protein composed of a 220-kDa C-terminal rod domain and a 50-kDa N-terminal FERM (4-point-one/erzrin/radixin/moesin) head domain. This N-terminal FERM domain binds to β-integrin cytoplasmic domains and the C-terminal rod domain interacts with F-actin, thus providing a physical link between the actin cytoskeleton, integrins, and the extracellular matrix. Several elegant biochemical, mutational, and structural studies identified sites in both talin and the β-integrin cytoplasmic domains that mediate the interaction between these 2 binding partners.[2] Talin binds to a conserved membrane distal NPxY motif, which is hypothesized to be important for talin recruitment to β-integrin tails.[4,5] Key studies, however, revealed a second critical site of interaction between the β-integrin membrane proximal region and the talin head FERM domain that is necessary for talin-dependent integrin activation.[2] Of particular relevance to the study by