Prostate Cancer

Major finding: A prostate cancer risk allele increases *RFX6* expression by enhancing HOXB13 DNA binding affinity.

Concept: *RFX6* upregulation promotes cell growth and invasion and correlates with prostate cancer aggressiveness.

Impact: A prostate cancer risk allele functionally interacts with a prostate cancer susceptibility gene product.

A PROSTATE CANCER–ASSOCIATED SNP INCREASES HOXB13 BINDING

Germline mutations in *HOXB13*, encoding a homeobox transcription factor that is expressed during prostate development, are associated with an increased risk of hereditary prostate cancer. To identify HOXB13 targets in prostate cancer cells, Huang and colleagues performed chromatin immunoprecipitation sequencing and observed that prostate cancer susceptibility alleles identified by genome-wide association studies (GWAS) were significantly enriched for HOXB13-occupied sites. One such prostate cancer risk–associated single-nucleotide polymorphism (SNP), rs339331, was located on chromosome 6q22 in a highly conserved active enhancer region within intron 4 of *RFX6*. The risk-associated T allele strongly increased the DNA-binding affinity of HOXB13 compared with the reference C allele *in vitro*, and HOXB13 preferentially bound the risk allele in prostate cancer cell lines that were heterozygous at rs339331. Moreover, HOXB13 was required for risk-associated allele-specific *RFX6* expression in prostate cancer cell lines, suggesting that the prostate cancer susceptibility allele at 6q22 promotes *RFX6* expression by increasing HOXB13 binding to the transcriptional enhancer within this locus. Knockdown of either *HOXB13* or *RFX6* significantly reduced prostate cancer cell proliferation, migration, and invasion, raising the possibility that increased *RFX6* expression may underlie the increased prostate cancer risk conferred by the T allele of rs339331. In prostate cancer samples, the risk-associated T allele was significantly associated with elevated *RFX6* expression, and, consistent with the findings suggesting that *RFX6* upregulation promotes phenotypes associated with prostate cancer progression, RFX6 expression was significantly higher in prostate cancer samples than in benign or normal prostate samples and was significantly correlated with Gleason score, prostate-specific antigen level, and increased probability of biochemical recurrence. Together, these findings not only identify *RFX6* as a potential prostate cancer susceptibility gene but also uncover a functional interaction between HOXB13 and GWAS-identified SNPs that may explain mechanisms underlying hereditary prostate cancer risk. ■

Huang Q, Whitington T, Gao P, Lindberg JF, Yang Y, Sun J, et al. A prostate cancer susceptibility allele at 6q22 increases RFX6 *expression by modulating HOXB13 chromatin binding. Nat Genet 2013; 46:126–35.*

Leukemia

Major finding: Constitutive activation of β-catenin in murine osteoblasts leads to AML with complete penetrance.

Mechanism: β-catenin increases jagged 1 expression in osteoblasts, which activates Notch signaling in HSCs.

Impact: AML can be induced by dysfunctional niche signals mediated by osteoblasts in the bone marrow.

OSTEOBLAST-SPECIFIC GENETIC ALTERATIONS CAN INDUCE AML

Osteoblasts are key facilitators of hematopoietic stem cell (HSC) homing, mobilization, and lineage specification. Previous studies have connected osteoblasts to preleukemic characteristics in mice, but it is unclear whether they play a direct causative role in leukemogenesis. Kode and colleagues sought to determine whether a single genetic alteration in osteoblasts could induce leukemia by generating mice expressing a constitutively active β-catenin allele in osteoblasts (*Ctnnb1*^{CAosb}). Prior to death by 6 weeks, *Ctnnb1*^{CAosb} mice developed hematopoietic dysfunction indicative of acute myeloid leukemia (AML), with splenic myeloid cells harboring recurrent cytogenetic abnormalities orthologous to those commonly observed in human AML and myelodysplastic syndrome (MDS). Transplantation of bone marrow cells from *Ctnnb1*^{CAosb} mice into lethally irradiated recipients induced AML and early lethality, with long-term repopulating HSCs (LT-HSC) acting as leukemia-initiating cells. Strikingly, transplantation of wild-type bone marrow cells to lethally irradiated *Ctnnb1*^{CAosb} recipients also resulted in lethal AML, providing support for a role of osteoblasts in leukemogenesis. Microarray profiling to identify osteoblast β-catenin targets that might alter HSC function revealed that the Notch ligand jagged 1 (*Jag1*) was highly upregulated in *Ctnnb1*^{CAosb} osteoblasts in association with increased Notch signaling in LT-HSCs. Deletion of one *Jag1* allele in osteoblasts or pharmacologic inhibition of Notch signaling prevented AML development in *Ctnnb1*^{CAosb} mice, suggesting that osteoblast-induced Notch signaling in HSCs drives AML formation. Consistent with these findings, 41 of 107 (38%) bone marrow biopsies from patients with AML or MDS showed increased β-catenin nuclear localization in osteoblasts and increased Notch signaling in hematopoietic cells, whereas nuclear β-catenin staining and Notch pathway activation were not observed in osteoblasts and hematopoietic cells of healthy controls. Together, these findings establish that genetic alterations in osteoblasts can drive the malignant transformation of myeloid progenitors, a finding that may have implications for the treatment of AML. ■

Kode A, Manavalan JS, Mosialou I, Bhagat G, Rathinam CV, Luo N, et al. Leukaemogenesis induced by an activating β-catenin mutation in osteoblasts. Nature 2014 Jan 15 [Epub ahead of print].