UKE Paper of the Month October 2013

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Aberrant ZNF423 impedes B cell differentiation and is linked to adverse outcome of ETV6-RUNX1 negative B precursor acute lymphoblastic leukemia

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ABSTRACT: Differentiation arrest is a hallmark of acute leukemia. Genomic alterations in B cell differentiation factors such as PAX5, IKZF1, and EBF-1 have been identified in more than half of all cases of childhood B precursor acute lymphoblastic leukemia (ALL). Here, we describe a perturbed epigenetic and transcriptional regulation of ZNF423 in ALL as a novel mechanism interfering with B cell differentiation. Hypomethylation of ZNF423 regulatory sequences and BMP2 signaling result in transactivation of ZNF423α and a novel ZNF423β-isoform encoding a nucleosome remodeling and histone deacetylase complex–interacting domain. Aberrant ZNF423 inhibits the transactivation of EBF-1 target genes and leads to B cell maturation arrest in vivo. Importantly, ZNF423 expression is associated with poor outcome of ETV6-RUNX1–negative B precursor ALL patients. Our work demonstrates that ALL is more than a genetic disease and that epigenetics may uncover novel mechanisms of disease with prognostic implications.

STATEMENT: *We believe that our work qualifies as the paper of the month since it emphasizes the importance of epigenetics in a genomic era of cancer research. As an unanticipated finding we provide novel experimental evidence that transregulatory and epigenetic mechanisms interfere with the B-lymphopoietic transcriptional program in ALL. Specifically, we identified the multifunctional Krüppel-like C2H2 zinc finger factor 423 (ZNF423) in ALL, which is also highly expressed in embryonic stem cells, suggesting a reactivation of transcriptional programs in ALL physiologically encountered during development. We believe that our findings provide novel insight into specific mechanisms of B-cell maturation arrest, which could have important implications for epigenetic therapies of ALL.*
The biological significance of our work will be of interest to a broad readership in the field of molecular biology and medicine.

BACKGROUND: This work was performed at the Research Institute of the Children's Cancer Center Hamburg and Clinic of Pediatric Hematology and Oncology at the UKE in the group of Martin A. Horstmann who holds a professorship at UKE since 2008. It was part of the PhD thesis of Dipl. Biochem. Lena Harder. Martin Horstmann's group focuses on mechanisms of leukemogenesis at childhood. The work was performed in close collaboration with the Institute of Clinical Chemistry, the department of Experimental Pharmacology and Toxicology, and the Heinrich Pette Institute on the UKE campus. Funding was provided by Fördergemeinschaft Kinderkrebs-Zentrum Hamburg, Burkhard Meyer Stiftung, Hans Brökel Stiftung für Wissenschaft und Kultur, and Madeleine Schickedanz Kinderkrebs-Stiftung.