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GATA1 – A Player in Normal and Leukemic Megakaryopoiesis

A review of: Wechsler J, Greene M, McDevitt MA, *et al*. 2002 Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. Nat Genet 32:148–152

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Acute megakaryoblastic leukemia (AMKL), a subtype of acute myeloid leukemia, is rare in the general pediatric population but highly prevalent in children with Down syndrome (1). Other forms of megakaryoblastic leukemia occur in childhood (2) however the AMKL of Down Syndrome is unique in many respects, including an association with abnormal megakaryopoiesis (myelodysplasia) (3). Little is known about this genetic predisposition to AMKL in Down syndrome and the preceding myelodysplasia. At the same time, the crucial role of transcription factors such as GATA1 (GATA binding protein 1 or globin transcription factor 1) during normal megakaryopoiesis (and erythropoiesis) have been established by gene inactivation experiments (reviewed in (4)) and the detection of inherited *GATA1* mutations in several types of congenital dyserythropoietic anemia and thrombocytopenia (5). The report by Wechsler *et al*. (6) now merges the investigation of normal and malignant megakaryopoieis by providing exciting evidence linking AMKL of Down syndrome with the loss of normal GATA1 function.

Searching for *GATA1* mutations in blasts of several subtypes of acute myeloid leukemia, the authors discovered nucleotide insertions, deletions or point mutations in all six samples of patients with AMKL and Down syndrome that they examined. The mutations clustered in the first coding exon of *GATA1* and in each case resulted in a premature stop codon preventing the synthesis of full length GATA1 protein. Instead, a truncated protein was detected that lacked the N-terminal activation domain and showed reduced transcriptional activation. The mutant protein, however, did not differ from its wildtype counterpart in the ability to bind DNA and interact with the essential cofactor FOG1 (Friend of GATA1). All mutations were somatic and specific for AMKL in Down syndrome. They were neither found in non-Down syndrome AMKL nor in samples from patients with Down syndrome and lymphoblastic leukemia or other subtypes of acute myeloid leukemia.

This report by Wechsler *et al*. provides the second example in human leukemia, of how point mutations of a hematopoietic transcription factor gene generate a truncated gene product. In acute myeloid leukemia heterozygous mutations in the gene encoding C/EBPα, a transcription factor crucial for granulocytic differentiation, were previously shown to result in truncated proteins interfering with the function of the wildtype protein (7). The mutations found in *GATA1*, however, prevent the synthesis of wildtype GATA1 altogether. Previous experiments show that lack of Gata1 function during murine hematopoiesis results in excessive proliferation and impaired differentiation of megakaryocytes without leukemic transformation (4). If malignant transformation in acute myeloid leukemia is the result of at least two cooperating mutations - one promoting proliferation and a second impairing differentiation (8), the loss of GATA1 may well provide the differentiation block. The authors have defined an important pathogenic event in the disordered megakaryopoieis and malignant transformation of AMKL in Down syndrome. The next challenge will be to define the contribution of the gene(s) on chromosome 21 that cooperate with mutations of *GATA1* to cause AMKL.

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