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Target Genes of WT1 in Leukemic Cells

Helena Jernmark Nilsson, Giorgia Montano, Tove Ullmark, Karina Vidovic, Kristina Drott, Urban Gullberg
Division of Hematology and Transfusion Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden

Conclusion
Overexpression of the oncogene WT1 is common in acute myeloid leukemia (AML). QPRT, NAB2, and possibly FSCN1 have been found to be direct target genes of the transcription factor WT1. QPRT, NAB2 and FSCN1 may be important for the leukemic phenotype.

Introduction
Wilms’ tumor is a childhood kidney cancer, in which the gene Wilms’ tumor gene 1 (WT1) is involved in about 20% of the cases. The transcription factor WT1 is also recurrently mutated in acute myeloid leukemias (AMLs). Mutations and high expression of WT1 associate with a poor prognosis in AML (1). In mice, overexpression of WT1 contributes to the induction of acute leukemia (2), further emphasizing a role for WT1 in leukemia development. Molecular mechanisms and target genes for WT1 in leukemia are, however, incompletely understood.

Background to the study
High expression of the transcription factor WT1 is found in leukemic blasts from most AML patients (1). To identify putative novel target genes for WT1 in leukemia, we identified partial correlations in gene expression between WT1 and other genes in a large cohort of 3,844 AML patients. We found that QPRT (quinolinate phosphoribosyltransferase), NAB2 (NGFI-A binding protein 2), and FSCN1 (fascin) were genes with high transcriptional correlation to WT1. This finding led us to investigate functional relationships between WT1 and putative target genes.

References

Helena Jernmark Nilsson, Division of Hematology and Transfusion Medicine, Department of Laboratory Medicine, Lund University, Klinikgatan 26, Lund. helena.jernmark_nilsson@med.lu.se

Figure 1. QPRT overexpression in K562 cells reduces sensitivity to imatinib. QPRT, encoding a key enzyme in the de novo NAD+ synthesis pathway, was transfected into K562 cells. Cells stably overexpressing the QPRT protein and control cells, were then exposed to imatinib for 96 h. There was a significant difference in survival between QPRT overexpressing cells and controls.

Figure 2. WT1 binds to the NAB2-promoter in vivo. NAB2, encoding a zinc-finger protein influencing cellular differentiation, proliferation, and cell death, was analyzed by ChIP to evaluate if its promoter has binding sites for WT1. Nuclear extracts from K562 cells, expressing endogenous WT1 and NAB2, were precipitated and the DNA was amplified by PCR (A). Fold enrichment was determined by densitometry (A, lower). GAPDH and anti-HA were used as negative controls.

As shown by others (3), NAB2 and the transcription factor EGR1, with similarity to WT1, bind directly to each other (4). To investigate the situation of NAB2 and WT1, 293T/17 cells were cotransfected with WT1+NAB2, co-immunoprecipitated, and analyzed by Western blot (B), demonstrating binding of NAB2 to WT1 (5).

Figure 3. FSCN1 levels rise in U937 cells overexpressing WT1 and cells show higher migration. FSCN1 is a globular actin-binding protein, involved in cancer cell migration, invasion, and metastasis. We decided to look into its possible influence on WT1 and its potential role in migration of leukemic cells.

When we overexpressed WT1 in U937 cells, the FSCN1 levels rose (A). Moreover, U937 cells overexpressing WT1 migrated to a higher extent compared to control (B), possibly due to FSCN1 modulation of WT1.

Further investigations into the functional role of FSCN1 in leukemia are ongoing.