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Target Gene Identification for the MLL Protein Towards the Understanding of the Pathomechanism of High Risk Leukemia

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Although most acute B-cell leukemia in children can be cured (80%), a minor portion of high risk leukemia still pose a major problem. 80 % of this type of leukemia is caused by a chromosomal translocation involving the MLL gene on chromosome 11 and the AF-4 gene on chromosome 4.

Our group has studied the reciprocal t(4;11) translocation. Cells carrying this translocation contain in addition to one copy each of the MLL and the AF-4 gene the two artificial gene fusions MLL•AF-4 and AF-4•MLL. We identified MLL target genes by DNA-microchip hybridization with cRNA isolated from $MLL^{+/+}$ and $MLL^{-/-}$ fibroblast cell lines. 197 differentially expressed (> 2,5 fold) genes were detected. In $MLL^{-/-}$ cells 136 genes are activated whereas 61 genes are inactivated. Uncovering the suppressive activity of MLL was surprising since so far MLL was only considered to be an activator of transcription. Several of the activated target genes are known to be oncogenes. Some of the deactivated genes are known to be involved in developmental processes.

Furthermore, it was planned to identify target genes for MLL•AF-4 and AF-4•MLL fusion genes in $MLL^{+/+}$ cells, which were stably transformed with derivative constructs. As it turned out no differences were observed in cells transformed compared to untransformed cell lines. Even more surprising was the observation that $MLL^{+/+}$ cells could not be "cured" by simply transfection. Apparently the established transcriptomes are epigentically fixed, which might lead to the conclusion that it could be much more difficult to cure such leukemias than probably anticipated.

Profile: Professor for Pharmaceutical Biology at the Goethe-University Frankfurt/Main, Germany. Vice-president of the Goethe-University from 1998 – 2000. President of the German Pharmaceutical Society (DphG) form 2000 – 2003.