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Gene regulation and deregulation by MAL/MRTF coactivators

G Posern

Address: Max-Planck-Institute of Biochemistry, Department of Molecular Biology, Munich, Germany
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Proteins of the MRTF family play a key role in regulated gene expression downstream of Rho family GTPases. MAL/MKL1/MRTF-A is a transcriptional coactivator of serum response factor (SRF) and is bound and inhibited by G-actin in the non-induced state. In acute megakaryocytic leukaemia in infants, a recurrent translocation t(1;22) results in the OTT-MAL/RBM15-MKL1 fusion oncoprotein. How it contributes to the malignancy is unknown. We tested by biochemical analysis whether OTT-MAL is functionally deregulated. We showed that OTT-MAL is a constitutive activator of SRF and target gene expression. This requires the SRF binding motif and the MAL-derived transactivation domain. OTT-MAL localises to the nucleus and is not regulated by upstream signalling. OTT-MAL deregulation reflects its independence from control by G-actin, which fails to interact with OTT-MAL in co-immunoprecipitation experiments. OTT-MAL also caused a delayed induction of the MAL-independent, TCF-dependent target genes c-fos and egr-1, and the MAPK/Erk pathway. In addition, RBPJ/CBF-1 regulated gene expression was activated by OTT-MAL but not by MAL. Our data suggest that the deregulated activation of MAL-dependent and independent promoters results in tissue-specific functions of OTT-MAL.

When tested in heterologous tissue culture systems, however, we observed strong anti-proliferative effects of OTT-MAL. Similarly, overexpression of MAL exhibited antiproliferative and pro-apoptotic effects requiring transcription through SRF. To gain insight into the molecular mechanisms involved, we performed gene expression analysis. By using a combination of actin binding drugs, which specifically interfere with the actin-MAL complex, we identified on a genome wide basis 210 genes primarily regulated by G-actin. We found many known MAL-dependent SRF target genes, as well as novel directly regulated genes. Several putative antiproliferative target genes were newly identified. We showed that a group of MAL regulated genes negatively interferes with the EGFR-MAPK pathway, thereby reducing proliferative signalling. Our results show the existence of negatively acting transcriptional networks between pro- and antiproliferative signalling pathways towards subsets of SRF target genes.