Abstract

Background:
Glucocorticoids (GC) have pronounced effects on metabolism, differentiation, proliferation and cell survival in many tissues. In cells from the lymphoid lineage they induce massive apoptosis which led to their inclusion in essentially all chemotherapy protocols for lymphoid malignancies, particularly childhood acute lymphoblastic leukemia (ALL).
MicroRNAs (miRNAs) are $\sim$22 nucleotide RNA molecules that control essential biological functions including proliferation, differentiation and apoptosis. miRNAs act as post-transcriptional repressors of their target genes by either inhibiting their translation, or by directly cleaving and thus degrading their mRNA.
Essentially all effects of GCs are mediated via its receptor, the glucocorticoid receptor (GR), a transcription factor regulating a plethora of genes. Whether also miRNA genes are regulated by GCs is not known. Thus we investigated miRNA expression and regulation at the various stages of miRNA biogenesis in GC treated CCRF-CEM T-ALL cells and performed GO analysis on their target genes to reveal their potential functional role.

Results:
Three miRNAs, miR-15b, miR-16 and miR-223 were identified to be regulated at pri-, pre- and mature levels after GC treatment. Two other miRNAs, miR-19a and miR-92-1, were regulated at pri- and pre-miRNA levels, but no regulation was detected at mature level, implicating a high stability of the mature miRNA, or failed detection on the Ambion due to technical problems. Prediction of target genes resulted in 1208 genes potentially post-transcriptionally repressed by the GC regulated miRNAs. Target genes did not show significantly decreased mRNA levels indicating that most target genes are repressed by translational repression rather than by mRNA cleavage. GO analysis of the target genes led, in concordance with previous observations, to the conclusion that the GC regulated miRNAs are involved in cell cycle arrest, cell differentiation and apoptosis. Identification of *regulation of transcription* among the enriched biological processes could indicate a potential regulatory feedback loop of the GR mediated by the induced miRNAs.

Conclusion:
For the first time it has been shown that GCs induce expression of miRNAs. The comprehensive analysis of pri- pre- and mature miRNA expression revealed 3 miRNAs, miR-15b, miR-16 and miR-223 to be induced by GCs in ALL cells. GO analysis and previous reports suggest the involvement of the GC regulated miRNAs in GC apoptosis and cell cycle arrest. Whether their contribution is required for, or facilitates or accelerates, GC induced apoptosis has to be revealed by experimental investigations.

Keywords: glucocorticoids, acute lymphoblastic leukemia, microRNA, expression profiling