Abstract

The presented data of this doctoral thesis suggest that the transcription factor GFI1/Gfi1 plays an important role in the progression and manifestation of AML. AML patients with low *GFI1* expression in their blasts showed an inferior prognosis and a shortend EFS and OS. Furthermore, the KD of *GFI1* resulted in a block of differentiation in the bone marrow of mice. The KO and the KD of *GFI1/Gfi1* lead to an enhanced AML progression in the *MLL-AF9* mouse model. In addition, upregulation of *Gfi1* resulted in an increase of differentiation of bone marrow cells and a decrease of monocytosis in a persisting AML.

It could be shown that the KO of *Gfi1* impeded AML progression whereas the KD of *GFI1* accelerated AML progression in the *NUP98/HOXD13* mouse model. In cooperation with the the IRCM in Canada it could also be shown that H3K9 acetylation at GFI1 target genes is increased in the bone marrow of *GFI1*-KD-*NUP98/HOXD13* mice. Further analysis of gene expression (Gene Set Enrichement Analysis) showed an upregulation of those genes that belong to "cluster 5" which were defined by Valk et al. as a subgroup of AML patients with poor prognosis. These data suggest, that the *GFI1*-KD-*NUP98/HOXD13* mice recapitulate the situation of AML patients with an inferior prognosis very well.

Moreover, the essential role of GFI1/Gfi1 for AML progression and manifestation in *AML1-ETO9a*- and *CBFB-MYH1*- mouse models could be demonstrated.

Furthermore the here depicted results open up new vistas in treating AML patients with epigenetic drugs. As well as in murine as in human leucemic bone marrow cells it could be shown that cells with low *GFI1* expression responded better to the treatment with the HATi CTK7a. This could be also confirmed in first *in vivo* experiments.

Taken together, the presented data suggest that GFI1/Gfi1 plays a level- and dose-dependent role in progression of AML in the here used mouse models and that different GFI1/Gfi1 expression levels could be exploited as new prognostic factor in order to establish a new epigenetic therapy for MDS/AML patients.