Title: eIF4E3, a regulator of monocytic differentiation in AML?

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Purpose:
Acute myeloid leukemia (AML) is characterized by an overwhelming accumulation of immature myeloblasts in the patient blood with impaired differentiation programs caused by recurrent mutations. Despite a high efficiency for front line chemotherapy on leukemia cells, relapses often occur and new therapeutic strategies are dramatically needed.¹ eIF4E3 belongs to the eIF4E family of mRNA translation initiation factors. Like the prototypical and well studied eIF4E1, it possesses mRNA cap-binding properties. eIF4E3 has been however described as a tumor suppressor competing with the growth-promoting functions of eIF4E1 likely through a distinct interactome.² We therefore decided to investigate eIF4E1 and eIF4E3 roles in AML.

Experimental Design: eIF4E1 and eIF4E3 expressions were measured by RNAseq in a cohort of AML patients and in normal differentiation ex vivo. Naïve HL60 cells or cells engineered to stably express either a non-targeting (NSi) or an eIF4E3-targeting (sh4E3) shRNA were used as a model for myeloid promyelocytic cell differentiation and proliferation. The expression of translation initiation factors was visualized by RT-qPCR and Western-blotting. The expression of monocytic differentiation markers (cd14 and cd11b) was monitored by flow cytometry.

Results: RNAseq analyses revealed a significant decrease of eIF4E3 mRNA in AML samples but a strong induction during normal monocytic differentiation ex vivo. eIF4E1 mRNA showed an opposite tendency. In naïve HL60 cells, monocytic differentiation was accompanied by a decrease in eIF4E1 expression and an induction of eIF4E3 at both mRNA and protein levels. A decrease in the global rate of protein synthesis was also observed. The use of HL60-NSi and HL60-sh4E3 cells then demonstrated that eIF4E3 is actually involved for monocytic differentiation.

Conclusion: Thus, monocytic differentiation seems to rely on a specific eIF4E3 translational program. Genome-wide analysis of the mRNAs bound to polysomes in cells overexpressing eIF4E3 should reveal some eIF4E3 specific targets and might lead to new therapeutic strategies in AML.

References:
2. Osborne MJ., et al., PNAS, 2013; 110(10) 3877-82