MODELING GENETIC ABERRATIONS PRESENT IN RELAPSED ALL BY CRISPR/CAS9 AND THEIR METABOLIC PROFILE

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One of the most common genetic aberrations present in relapsed pediatric patients with acute lymphoblastic leukemia (ALL) is mutation in histonacetyltransferase CREBBP. One potential way relapse can occur is through the metabolic rewiring of leukemic cells. The role of CREBBP in relapsed ALL has not yet been clarified.

The primary objective is to create a suitable cell line model with a *CREBBP* mutation and investigate the metabolic alterations resulting from this genetic modification.

We generated models of CREBBP KO in both, leukemic and healthy cell lines. The introduction of an additional mutation on a leukemic background did not seem to reprogram the metabolic processes. In case of cell line model of CREBBP KO in healthy progenitor B-cells the knockout was confirmed on DNA and protein level. Lower glycolytic capacity and reserve were observed in CREBBP edited cells. Surprisingly, when activating signaling pathways by cAMP induction, those differences have been diminished, possibly by activating other partners of transcription regulation as p300. Unexpectedly, targeted DNA cleavage by Cas9 led to exon 8 skipping while all the other exons were transcribed as in control cells. Exon 8 is needed for KIX domain providing docking region for transcription factors.

These data show that editing the genes encoding proteins of significant importance in biological systems poses numerous challenges. Cells can activate different rescue mechanisms when edits are introduced. Moreover, redundant proteins could compensate for loss of target; in our case it is possibly protein p300. Our project is the first to study a metabolic phenotype of CREBBP KO. Further investigation is needed in order to describe the role of CREBBP in generating ALL relapses and initiate targeted therapeutic strategies.

Supported by GAUK 198623, AZV NU22-07-00087, NPO (Programme EXCELES, LX22NPO5102).