Project 9.3 Ten eleven translocation 2 (TET2) in acute myeloid leukemia

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www: https://bit.ly/3xkvFR7

Background:

Ten eleven translocation 2 (TET2) is frequently mutated in acute myeloid leukemia (AML). TETs are dioxygenases that catalyze active-passive and active DNA demethylation, in conjunction with base excision repair. Their presence is known to facilitate cellular reprogramming, for example in experiments to restore pluripotency. Consequently, a TET gain of function would not be surprising in malignancies. However, the pattern of the frequent TET2 mutations in acute myeloid leukemia clearly suggests that these mutations cause a loss of function, not a gain of function. A possible explanation for the paradox could be that the anti-oncogenic properties of TETs are dependent more on its role as an epigenetic repair enzyme, and not on its role as an epigenetic reprogramming enzyme.

To test this hypothesis, we will artificially increase out-of-context “erroneous” DNA methylation by ramping up salvage of 5-methyl-2’-deoxycytosine taken up from the environment. First, we will characterize the extent of pinocytic 2’-deoxynucleotide uptake in leukemia cell lines using phosphorylated BrdU analogues as surrogate for 2’-deoxynucleotides. Next, we will use CRISPR-Cas9 genome engineering tools to create leukemia cell lines with externally controllable TET2 expression (in several different backgrounds of other AML mutations). We will then test whether loss of TET2 activity sensitizes cells to nucleotide pool driven perturbations, and whether this increased sensitivity contributes to epigenetic diversity that leukemia can play on to select more aggressive clones. Techniques used in the project will be CRISPR-Cas9 engineering to generate AML cell lines with externally (doxycycline) controllable TET2 expression, high throughput transcriptomics to characterize the response of AML cell lines to epigenome perturbations, and bisulfite, TOP-Seq and hmTOP-Seq sequencing to characterize DNA modifications.

Aim:

The goal of the project is to determine the role of TET2 perturbations in acute myeloid leukemia. The plan is to clarify whether TET2 activity aberrations affect the hematopoiesis predominantly via the defects in the epigenetic reprograming or in the repair of erroneously incorporated modified bases.

Requirements:

- Master's degree in biology, biochemistry or a related field,
- eligibility for PhD studies in Poland,
- theoretical knowledge of genetics and epigenetics,
- theoretical knowledge of hematopoiesis,
- practical experience with human cell cultures (an absolute requirement),
- experience with CRISPR-Cas9 engineering,
- experience with or theoretical knowledge of modification sensitive deep sequencing techniques and transcriptomic techniques,
- written and spoken fluency in English,
- willingness to learn and take new challenges, ability to work independently, analytical thinking,

- good interpersonal skills and a collaborative attitude

Number of positions available: 1

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