Discovering the regulators of interferon-induced transcriptional memory through targeted approaches and unbiased epigenome screens

Abstract for the general public (Dr Paweł Mikulski)

Pathogen-infected or cancer-transformed cells in your body trigger inflammation. Various immune or non-immune cell types respond to inflammation signals as part of immune signalling. It is commonly known that cells of adaptive immune system (such as T cells and B cells) respond to inflammation and memorize previously encountered infections as exemplified by action mode of vaccines. Adaptive immune cells have been long believed to be the only cell types capable of such memory. However, recent research suggests that the other immune cells, innate immune (such as macrophages and dendritic cells) and non-immune cell types (fibroblast, stem cells or cancer cells) show the memory of previous inflammation events. However, the mechanism behind such memory is unknown.

The aim of this proposal is to discover what proteins and mechanisms regulate the memory of inflammation in human non-immune cancer cells. Specifically, human cells exposed to cytokine, interferon-γ (IFNγ), i.e. during infections or cancer transformations, transiently activate immune response genes. While the majority of these genes revert to their naïve state when IFNγ diminishes, a subset of them is maintained in a poised, but inactive state. This state allows rapid and bigger re-activation upon subsequent IFNγ exposures. In other words, some genes maintain the memory of prior IFNγ induction. What is fascinating is that such memory is passed from parental to daughter cells through multiple cell divisions and the memory is stable even in the daughter cells which did not previously undergo inflammation.

We have been investigating what molecular mechanisms underlie interferon memory. In contrast to a multitude of factors, IFNγ memory is regulated by unique chemical modifications of proteins, where DNA is tightly wrapped around (so called “histones”). Through machine learning approach, we found that these factors are necessary, but insufficient, to determine memory mechanism. In proposed project we aim to discover further regulators of interferon memory at immune response genes. To this end, we will investigate modes of action of particular histone modifiers which control expression of immune response genes in our preliminary data. Importantly, we will also modern genetic screens and identify previously unknown memory regulators in unbiased manner. Lastly, we will identify the role of IFNγ memory regulators in immune surveillance of cancer cells. To achieve project goals, our team will employ cutting-edge methodology with the blend of bioinformatics and molecular biology. We will use our collaborative experience in modern genomic methods, next-generation sequencing, quantitative proteomics and high throughput epigenome engineering.

Overall, our proposal aims to discover of the mechanism of cellular memory to inflammation based on unique chromatin modifiers and new regulators. Given crucial role of interferon in response to infections or cancer transformations, anticipated outcomes will form knowledge base to improve cancer immunotherapies, control infections and modulate autoimmunity-related toxicities in patients.