The discovery of multifactorial regulation at epigenetic memory of active gene expression state

Abstract for the general public (Dr Pawel 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 dependent on inflammation. However, recent research suggests that the other immune cells, innate immunity cells (such as macrophages and dendritic cells) or even some non-immune cell types (fibroblast, stem cells or cancer cells) show the memory of previous inflammation events. However, the mechanism behind such memory is largely unknown.

The aim of this proposal is to discover what proteins and mechanisms regulate the memory of inflammation in human non-immune cancer cells. I will build on my 12 year-long experience in research on cellular memory and use experimental system of human interferon-mediated immunity ("interferon memory") which I gained experience in in recent years. Specifically, human cells exposed to cytokine, interferon-γ (IFNγ), i.e. during infections or cancer transformations, transiently activate certain set of 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 were not previously exposed to IFNγ at all.

Me and my colleagues went on the search for factors which can regulate and underlie the mechanism behind interferon memory. However, most of the tested factors, proteins and RNA, had a role in gene activation during IFNγ exposure, but not the memory. Finally, I discovered that two chemical modifications of proteins where DNA is tightly wrapped around (so called "histones") are retained after IFNγ induction and are stably maintained on target genes until subsequent stimulation. This means that these chemical modifications could potentially underlie the mechanism which determines and controls interferon memory.

This proposal aims to address aforementioned hypothesis and find regulators behind interferon memory based on previously identified modifications. I plan to test interferon memory under perturbations of proteins controlling the function of these modifications using genome editing and transcript depletions. I propose to investigate which important part of the genome are bound by such proteins by employing epigenomic next-generation sequencing and bioinformatics. Lastly, I plan to dissect how identified modifications change during phases of cell division and whether they have capability to maintain information passed across cell generations.

This project could lead to discovery of the mechanism behind cellular memory of inflammation. Given crucial role of interferon as response to infections or cancer transformations, anticipated outcomes could form knowledge base to improve cancer immunotherapies, control infections and modulate autoimmunity-related toxicities in patients.