DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

The molecular secret of life lies in the regulation of gene expression: expression of the right gene, at the right time, and in the right place.

Gene expression is a process which allows to decode the genetic information contained in a DNA fragment called a gene, and translate it into a gene product: usually a protein. This process is very tightly regulated. DNA contains all the information how to make a protein, but gene expression requires the intermediate of messenger RNA (mRNA). mRNA is the matrix for protein synthesis and is made by RNA polymerase II (Pol II) in a process called transcription.

Human DNA contains besides genes also long non-coding stretches. In order to transcribe RNA correctly, Pol II has to recognize the beginning and the end of the gene. This is aided by proteinaceous initiation, elongation and termination (i.e. stopping) factors. The process of transcription termination is the least understood aspect of gene expression. However, proper termination is crucial for efficient production of a correct mRNA molecule, for functional separation of neighbouring genes, and for recycling of the available Pol II pool. Additionally, termination restricts non-coding RNA transcription, which is prevalent in the human genome.

My recent research has shown that in human cells, as well as in other vertebrates, transcription stops prematurely on selected genes. This is triggered by the transcription termination factor PCF11. PCF11-mediated premature transcription termination lowers the levels of many important proteins, which are responsible for gene expression regulation both at the level of transcription and RNA processing. This suggests the existence of a previously non-appreciated mechanism of gene expression control by premature transcription termination. The proposed project aims to better understand this new mechanism.

The project is divided into three specific aims and its implementation will involve the following research tasks:

1) Elucidation of the mechanism of PCF11-mediated premature termination. We will determine the contribution of various PCF11 activities to triggering premature termination: binding of Pol II, binding of RNA, or RNA cleavage stimulation by interactions with other factors.

2) Genomic characterization and comparative analysis of premature and normal transcription termination regions in respect to their epigenetic chromatin environment and binding of transcription factors.

3) Determining the prevalence of premature termination in human tissues and during developmental processes in model vertebrate organisms, and the identification of novel factors triggering premature termination.

The acquired knowledge will be published in international scientific journals and used by researchers world-wide, both involved in basic science as well as in applied research. Gene expression regulation is of paramount importance in all cellular, physiological and pathological processes. Therefore uncovering new mechanisms of this regulation will lead to better diagnostics and treatment of human disease, as well as to practical applications in biotechnology.