ABSTRACT FOR GENERAL PUBLIC

The role of 3D genome folding in the establishment of keratinocyte-specific promoter-enhancer network.

The epidermis is the outermost tissue, a self-renewing part of the skin. It consists of several layers of keratinocyte cells differentiated to various extent. The epidermis is crucial for survival – it protects the body from dehydration, entering of pathogens, and serves as a sense organ. Intriguingly, a big part of keratinocyte-specific genes is grouped within three distinct places (loci) in the genome, including epidermal differentiation complex (EDC).

Genome folding is important for the cell. The mammalian genome consists of ~2-meter-long DNA which must fit into the cell nucleus with diameter of 10 μM: approximately 200 thousand times smaller. DNA, while highly packed, needs to be at the same time easily accessible for the enzymatic complexes participating in reading and copying of the genetic information – this requires highly coordinated spatial organization.

My research is focused on understanding how changes in genome folding control gene activation. I have shown previously that one of keratinocyte-specific genomic regions, EDC, changes significantly as epidermis maturates: it re-locates from the periphery of cell nucleus towards its interior, whereas its central part becomes more compacted. The observed changes proved to be crucial for proper expression of genes located in EDC. Those findings showed that activation and control of genes important for epidermal development depends on genome organization. Yet, we don't understand how this works.

Gene activity is regulated by interactions between the control region at its beginning of (called the promoter) and other regulatory regions which may be located far away from the gene (called enhancers). The **main goal of the proposed project is to investigate the changes in keratinocyte-specific promoter-enhancer networks and their importance for gene activity during mouse development**. This will be possible by using Capture-HiC methodology which can detect interactions between promoters and enhancers with high sensitivity and resolution.

To achieve this goal, I will use a comprehensive, inter-disciplinary approach that combines genome-wide (NGS) methods, bioinformatics, cutting-edge microscopy and advanced 3D image analysis. I will compare differences in the shape of loci at different developmental stages with Capture-HiC. Capture-HiC allows to study the genome folding at high resolution and relatively low cost. This approach will be complemented by a number of genome-wide molecular biology assays. To gain single-cell insight into loci re-modelling, I will use set of experiments visualizing localization of epidermis-specific loci as well as their genetic activity. Experiments will be visualized besides conventional methods with SIM super-resolution which allows to observe and quantify much smaller details than light diffraction limited regular microscopes. Finally, I will check which features are biological significant by switching off either enhancers or removing some genomic structural elements.

The proposed research will first of all enhance our understanding of keratinocyte differentiation and epidermal morphogenesis. It will provide a comprehensive and high-resolution characterization of interactions within epidermal loci, and broader nuclear architecture during differentiation of keratinocytes. It will be of interest not only for cellular and skin biology but also for clinical research. In a broader perspective, this study will give an important insight into the establishment of promoter-enhancer interactions, as well as the role of genomic compartmentalization in gene regulation and in cell differentiation. Those topics are currently the subject of huge scientific interest and debate in the field of developmental epigenetics, higher-order chromatin structure, genome biology and also gene expression control.