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Setting up a new experimental system to studying the link between functional histone PTMs and double strand break repair

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In our cells the DNA is packed to a protein backbone which is called chromatin. Specific regions of this compacted structure open and close when different process like information transmission of the DNA to RNA (transcription) takes place. This opened or closed chromatin structure affects the probability of damage the DNA and has also impact on the repair of these DNA breaks as well. Slower repair speed or improper repair can also increase the probability of chromosome rearrangement by causing genome instability which is one of the early steps of cancer development. The DNA repair pathways are essential to minimize the chance of cancerous malformations. During the DNA repair processes histone post-translational modifications are important to open chromatin structure. Our goal is to set up a novel experimental system where we can follow the chromatin changes during DNA repair.

Our goal is to understand what makes eukaryotic cells able to recognize the appearance of a DSB, and how does the chromatin structure change around the break during repair and after it took place. The answers to these questions will provide information on whether specific chromatin structures predispose sites for chromosome breakage and whether memory of previous DSBs is retained in the chromatin structure. We are setting up an experimental system by which we will be able to study how do unique histone modifications affect the DSB repair. A powerful model for studying these aspects of chromatin structure changes has not been established in any other experimental system until now. A better understanding of DSB repair mechanism can lead to identification of novel potential therapeutic targets in cancer treatment.

Using an engineered histone cluster in cancer research

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The chromatin structure affects the probability of the damaging agents to cause DNA breaks and the recruitment of the repair proteins. The improper repair or persistence of breaks leads to translocations and genome instability which often results in tumour formation. To allow repair of these damages, the repair proteins must assess the damage site, so the condensed DNA needs to be looser. Our group is interested in to understand chromatin changes during DNA repair processes by using novel experimental system.

In our cells the DNA is packed to a protein backbone which is called chromatin. The base of the chromatin structure are the evolutionarily conserved histone protein family members. The histone proteins are necessary for nucleosome assembly by forming a heterooctamer with two copies of H2A, H2B, H3 and H4. The linker histone H1 requires for the proper chromatin condensation. All of the histone proteins can be post-translationally modified. These PTMs are the main rulers of epigenetic regulation. To study chromatin changes during DSB repair we plan to take advantage of a *Drosophila melanogaster* model system which allows generating targeted single point mutations at the N-terminal tail of a histone protein. Our aim is to understand how does the chromatin structure change around the break during the DNA repair and what is the link between unique histone PTMs and the mechanisms of the repair. We're setting up a new experimental system by which we will be able to study how do unique histone modifications affect the DSB repair. The base of this new experimental system is a clone of the histone cluster which contains all of the canonic (H2A, H2B, H3, H4) and linker (H1) histone genes in *Drosophila melanogaster*. Using the engineered histone cluster with gene deletions and unique base-modified histones can lead us to understand the regulation of the changes in chromatin structure during the DNA repair.