

Functions of post-translational modifications of key proteins involved in DNA repair.

Lay summary

In this project we are aiming to understand how mammalian cells deal with the damage to its genetic material – the DNA. Damage to DNA, if left unrepaired, could cause a variety of problems for the cell. For example, the cell might not be able to divide with damaged DNA, as in order for DNA to be copied (duplicated) it cannot have any interruptions. In addition, generally speaking defective DNA repair has a strong contribution to disease development, which is particularly clear in the case of cancer. In order for a normal cell to become cancerous it has to acquire many mutations that rewire its genetic programme into an uncontrolled growth that is one of the cancer hallmarks. This process of stepwise mutation acquisition often is accelerated by defective mechanisms of DNA repair.

DNA can be damaged in many ways. One of the most difficult types of DNA damage to repair are so-called double strand DNA breaks (DSBs). These lesions completely sever the DNA in such a way that it causes a type of a large interruption in the genetic material of the cell. In order for these type of lesions to be repaired cells have evolved a number of repair mechanisms. One important such mechanism is so-called non-homologous end joining (NHEJ). In this pathway a collection of seven proteins (named Ku70, Ku80, DNA-PKcs, XLF, XRCC4, Ligase IV and PAXX) work together to seal the DNA damage and restore uninterrupted DNA structure.

NHEJ pathway of DSB repair is very important and the survival of the organism is not possible without it. We are interested in understating how NHEJ is regulated in cells, as this knowledge will allow us for developing new cancer drugs and also potentially improve the way we classify and diagnose the cancer. Therefore, we will be studying so-called post-translational modifications of key NHEJ proteins – PAXX and DNA-PKcs. Post-translations protein modifications are typically small molecular marks added physically to already produced and functional cellular proteins that can modulate their function in a variety of ways. For example, proteins can be modified by the addition of a methyl mark, which that could serve as a signal for recognition for other proteins (methyl mark readers) facilitating protein-protein interactions to functionally integrate the activity of DNA repair pathways. In this research proposal will investigate the functions of posttranslational modifications of PAXX and DNA-PKcs.

In addition to defining the function of PAXX and DNA-PKcs modifications in NHEJ we will investigate what happens to these modifications in cancer cells. We anticipate that in selected cancers the levels of PAXX/DNA-PKcs modifications might be very different than in healthy cells. Should this be the case than these modifications might serve as so-called biomarkers in certain tumors allowing for prediction of tumor therapeutic potential in relation to the NHEJ marks.

In summary, we aim to provide new knowledge on the regulation of one of the key pathways of DNA repair and to facilitate efforts in cancer diagnostics.