DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Mechanisms ensuring the stability of the cellular genome are crucial to the maintenance of life and are evolutionarily conserved. It is well known that DNA polymerases must be extremely faithful while replicating the DNA sequence, damaged DNA must be promptly and properly repaired, and the replicated chromosomes must be precisely segregated to daughter cells during mitotic division, otherwise a change in the genome can occur. While the term "genomic stability" may seem exotic or marginal, the closely related subjects "mutation" or "genetic instability" definitely do attract attention. This is hardly surprising, when one takes into account that genetic instability manifests, among others, in cancer cells, various mutations are the cause of many diseases, including familial ones, may also lead to non-susceptibility to pharmacological treatment, and are responsible for the variability and virulence of common viruses (e.g. influenza virus), and the ineffectiveness of previously used vaccines and the consequent need to design new therapies. Therefore, understanding the mechanisms shaped by evolution to maintain genetic stability of cells is critical to aid them in cases of failure, such as cancer, or to employ them to fight pathogens.

Recent introduction of large-scale methods of functional genomics allowed the identification of numerous genes important for maintaining genome stability. Also we have contributed to this progress. In an experiment involving collection of several thousand yeast strains, each with a single gene deleted from the genome, we indentified over one hundred strains that were oversensitive to zeocin, the DNA damaging compound, which is also used in cancer chemotherapy. Among those strains the largest group comprised, quite unexpectedly, 49 strains lacking genes encoding proteins involved in vesicular trafficking. Preliminary analysis showed that the involvement of vesicular trafficking in protection against DNA damage stress, is not related to the transport of zeocin either by removing it from cells or involving other detoxification mechanism but rather ensuring an effective response to DNA damage. Using a variety of genetics and molecular and cellular biology methods we will determine how the proteins engaged in vesicular trafficking indicated in the initial screen, modulate cellular response to genotoxic stress, affect the ability of cells to recognize and repair DNA damage. We will also establish, which of the analyzed proteins help prevent formation of mutations upon genotoxic stress, and determine the type of mutations occurring in cells lacking these proteins.

Our work will contribute to the deciphering of an important but previously unknown mechanism that protects cells against DNA damage and its harmful consequences and, in a broader perspective, to improving therapies based on genotoxic agents, e.g. anti-cancer therapies.