Novel factors involved in cell cycle control after DNA damage.

In this project, we will focus on studying the mechanisms of cellular response to DNA damage. In every cell of the body, as a result of the generation of free radicals (a by-product of oxidative metabolism) and the action of enzymes such as nucleases or topoisomerases, a damage to DNA occurs every day. Also, exposure of tissues to high-energy radiation (for example, during cancer radiotherapy) leads to complex damage to DNA. Damage to DNA, in addition to the threat of mutation fixation, also constitutes a barrier to a number of physiological processes of the cell, such as genome replication or transcription, and therefore it must be quickly repaired. In cells where DNA damage has occurred, mechanisms collectively known as DNA damage response (abbreviated as DDR) are activated. They include the initiation of the DNA repair process and the arrest of the cell cycle (induction of the so-called checkpoint). The role of the cell cycle arrest is to prevent cells from starting the genome duplication process (entry into the S phase of the cell cycle) or the division process (entry into the M phase) having a lot of unrepaired DNA in the genome. Checkpoint induction is initiated by kinases activated as a result of DNA damage (ATM, ATR and DNA-PK) that phosphorylate the so-called Chk1/2 effector kinases. Effector kinases block cell cycle progression by inactivating cyclin-dependent kinase complexes (e.g., Cdk1). These processes are also regulated by complexes of phosphatases that antagonize the activity of the above-mentioned kinases.

The checkpoint induced at the G2/M transition of the cell cycle is particularly important because in cancerous cells, due to mutations of the p53 gene, functional inactivation of the G1 checkpoint occurs frequently. Thus, tumor cells are strongly reliant on the G2/M checkpoint in order to avoid the consequences of DNA damage. Therefore, studying the mechanisms of G2/M checkpoint induction is very important for understanding the cellular response to DNA damage in general and for discovering new possibilities for developing effective anti-cancer drugs.

For years, our laboratory had specialized in studying the composition and function of protein complexes involved in DNA repair. We recently identified two new proteins, LZIC and LYAR, which are involved in the induction of the G2/M checkpoint in response to DNA damage induced by high-energy radiation.

In this project, we will address the following questions:

- what is the molecular mechanism of action of LZIC/LYAR proteins ?
- can these proteins be somehow utilised in cancer diagnostics as biomarkers of radiotherapy effectiveness ?
- are the genes encoding LZIC/LYAR genetically interacting with other genes involved in DDR in such a way that it will be possible to create new drugs for cancer based on mutations in the genes responsible for DDR ?