

Ionizing radiation is defined as all types of radiation – electromagnetic and corpuscular – having common characteristic: when passing through material medium they cause its ionization. Harmful effects of ionizing radiation to the living organisms was already observed during the first studies with X-rays and radioactive substances. Since those days the knowledge about natural and artificial sources of radiation, and also about chemical and biological consequences of its impact on living cells and entire organisms has increased considerably. Radiation effects and their mechanisms were defined: it is known that ionizing radiation is harmful to living organisms, because it causes the formation of free radicals, which in turn can damage the genetic material and other cell structures. This damaging effects are now used for medical purposes, including cancer therapy. Rigorous security systems were introduced and also the rules for radiotherapy planning were modified in order to minimize the negative effects. Still, recently it turned out that although the degradative processes to biological structures occur in fractions of a second, their final biological effect can appear even after many decades. The evidence was provided by long-term medical observation of people exposed to ionizing radiation, for example, mine workers, survivors of the bombings in Hiroshima and Nagasaki in Japan in 1945 and patients undergoing radiotherapy: in these groups increased the incidence of bone marrow diseases and cardiovascular disorders. Every exposure of the human body to ionizing radiation carries the risk and can lead to several undesirable effects: in case of bone marrow disorders we are talking about myelotoxicity and when the cardiovascular system is affected – cardiotoxicity.

While there is a consensus on the dangers of high doses of radiation, the ideas about negative impact of low doses are varied. Some researchers believe that small doses of radiation can even have health benefits (radiation hormesis theory), because can stimulate the natural DNA repair mechanisms. They also say that in the case of ionizing radiation the "dose makes the poison". Because the exposure to low doses of radiation increases in the modern world, primarily from medical sources, the knowledge is collected about the long-term effects to the health of persons exposed to low doses of ionizing radiation. According to these observations exposure to potentially "not harmful" ionizing radiation doses markedly increases the risk of morbidity and mortality from cardiovascular disorders. Although the appearance of clinical symptoms of heart failure may require many years, from the first moment in heart cells can take place small, accumulating changes resulting in the development of cardiotoxicity. At the moment, the exact mechanism of ionizing radiation low doses action on the heart cells is not known, but answer to this question could be provided by an analysis of changes in the metabolome of affected cells.

Metabolome is the set of all metabolites present in particular biological system (cell, tissue or body fluid). In comparison to the genome (the entire genetic material of cell) or the proteome (set of proteins present in the cell) metabolome reacts much faster to external factors such as drugs, diseases and diet. Examination of metabolic profile of a given system allows for very early detection of changes taking place in it under the influence of, among others, toxic agents. It is suggested that measuring changes in concentrations of metabolites in the blood can allow for almost immediate detection of heart damage, long before application of standard tests (such as the measurement of cardiac troponin or creatine kinase) allows for that. Moreover, changes in metabolic profile depend on the type of heart damage: for example, during cardiac hypoxia lactate is detected in blood, the increased amount of lipids appears in infarcted areas of heart, and the impaired creatine metabolism indicate an energy failure occurring in the myocardium. Nature of the change can also depend on the type and mechanism of action of the toxic agent. Ionizing radiation also can affect the metabolome of heart cells, and this effect can be influenced by total dose, for which the heart is exposed.

The main objective of the proposed project is to assess whether and how low doses of radiation alter the metabolic profile of cardiac cells. Research will be conducted both on cell lines and in mouse heart muscle. Identification of the metabolites present in the samples will be performed using spectroscopic techniques - nuclear magnetic resonance (NMR) and mass spectrometry (MS). The results of these studies will enable to identify metabolites whose level changes as a result of heart exposure to low doses of radiation and to gain insight into the mechanisms by which ionizing radiation induce cardiotoxicity.

Early diagnosis of negative processes taking place in the heart could allow for inhibiting them and to take protective measures. One of the promising methods of protecting the cardiovascular system is the use of natural substances present in the human diet. These are substances found eg. in extracts from beet, garlic or grapes - their protective effect on the heart and vascular system is known, and more recently also analyzed scientifically. Promising results of such studies relate primarily to extract from the seeds and skins of grapes, which contains a mixture of many flavonoids and phenolic compounds, including resveratrol. Numerous studies on the use of resveratrol as a compound with protective action indicate that it is capable to reduce the damage to the heart caused by anthracyclines used in cancer chemotherapy and also bone marrow damage induced by ionizing radiation. Unfortunately, there are no reports concerning activity of resveratrol in the context of cardiotoxicity of ionizing radiation, especially its low doses. Because of its natural source, availability and low toxicity resveratrol would be the ideal compound for use in the prevention of cardiotoxicity. Therefore, another objective of the project is to assess whether resveratrol is able to prevent changes in cardiac cell metabolism induced by ionizing radiation. These studies will be based on the analysis of metabolic profile using the same spectroscopic techniques, as in the first part of the project.

Knowledge obtained during this project implementation could be used in the future to develop a rapid and non-invasive diagnostic methods for detecting the risk of heart damage as a result of exposure to ionizing radiation. In addition, we will obtain the evidence to determine whether the use of resveratrol may reduce the risk of cardiotoxicity associated with exposure to low doses of ionizing radiation.