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MECHANIZMY REGULACJI STANU REDOKS W ŻYWYCH KOMÓRKACH

Rozprawa doktorska napisana

pod kierunkiem

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ABSTRACT

Reactive oxygen species (ROS) are the basic element appearing in cells living in an oxygen environment. They are considered harmful metabolic products that can negatively affect the cells, causing ageing and death, but in many cases they can participate in cellular regulatory processes and positively affect cells. This work concerns the study of the mechanisms regulating the levels of some reactive oxygen species.

Using available databases, data available in the literature, as well as available experimental methods, the study examined whether the mechanisms regulating the cellular redox state act similarly in all cell types. The expression of genes related to oxidative stress as well as neutralization mechanisms was analyzed. The analyzes carried out for many different cell lines of different tissue origins suggest that various types of cells show differences in the expression of genes whose products are involved in, for example, H_2O_2 neutralization (genes: PRDX2, whose level is lower in kidney cell lines, TXNIP whose level is lower in skin and liver cells, and higher in breast, colon and upper digestive tract cell lines) and in the neutralization of $O_2^{\cdot -}$ (ATOX1 gene, the level of which is higher in skin cells). Sequence analysis of ROS-regulating genes shows the presence of sequences interacting with miRNAs for both genes encoding proteins involved in the production and neutralization of ROS, and thus the expression of enzymes related to ROS-regulating processes is controlled at the translation level by interactions with miRNAs.

Oxidative stress in cells can be caused by environmental factors such as ionizing or UV radiation. The study investigated whether cells respond in a similar way to environmental factors inducing oxidative stress by conducting detailed experimental studies for two cell lines Me45 and HCT116. Exposure of cells to UV radiation causes the induction of reactive oxygen species and changes in proliferation, depending on the dose of radiation used. Death is observed at higher doses of radiation, but of particular interest were the lower, cell line-specific doses that stimulated proliferation.

One of the main reactive oxygen species present in all cells is H_2O_2, which can function as a signaling molecule in extra- and intracellular signaling. In the work, a mathematical model describing the process of H_2O_2 neutralization in various types of cells was created and the efficiency of its neutralization systems was compared using computer simulations based on available data of the expression of genes that participate in this process. The simulations carried out confirm that cell lines of various and even the same tissue origin

neutralize H_2O_2 differently, leading to differences in the H_2O_2 levels. The simulation results suggest that the differences in the radiosensitivity among various types of cancer cells may be due to differences in the efficiency of H_2O_2 neutralization.

The presented experimental approach, combined with mathematical model simulations, gives an insight into new elements of issues related to the redox balance in cells. My research showing the impact of UV radiation on redox processes and cell proliferation is important because we are constantly exposed to UVA and ionizing radiation, and the results obtained regarding the neutralization of ROS may be useful for various types of therapies.