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Modelowanie i analiza wybranych mechanizmów regulacji procesów wewnątrzkomórkowych

Autor: Daria Kałużyńska

Promotor: prof. dr hab. inż. Jarosław Śmieja

Promotor pomocniczy: dr inż. Anna Lalik

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Intracellular processes are maintained in homeostasis, in part, through conservatively acting signal pathways that govern the proper progression and pace of reactions, molecule transport, and the control of molecule synthesis and degradation. One of the commonly studied signaling pathways involves apoptosis. Apoptosis is a natural process of programmed cell death that occurs when a cell is irreparably damaged and cannot return to its original state. One of the most well-known and extensively studied proteins in this pathway is p53, also known as the guardian of the genome. This protein is responsible for halting the cell cycle to repair DNA and, if necessary, making the decision to initiate signaling cascades leading to cell death.

The series of processes leading to the creation of an active protein actively involved in regulating signaling pathways is called gene expression. One of the final stages of this process is translation, in which the mRNA generated in the preceding transcription phase is translated by ribosomes into a chain of amino acids. Subsequently, through appropriate post-translational modifications, this chain is shaped into an active protein.

Translation is a highly regulated process influenced by numerous factors, both intracellular and extracellular. One of the most intensively studied factors regulating translation is microRNA (miRNA). MiRNAs are short (approximately 21-25 nucleotides long) non-coding RNA molecules primarily involved in the repression of translation of target proteins. Due to the complexity of regulatory mechanisms and various effects leading to expression inhibition (such as initiation inhibition or mRNA degradation) resulting from this regulation, the precise workings of miRNAs have not been fully elucidated.

This doctoral thesis focuses on analyzing selected mechanisms that regulate the translation process. A mathematical model based on state machines has been proposed to describe the translation process, taking into account the polysomal profile (structures where more than one ribosome is present on a single mRNA strand, allowing for the parallel production of more than one amino acid chain from one mRNA molecule). Additionally, a factor regulating translation, in the form of miRNA, and ionizing radiation (X-rays), have been introduced into the model. Simulations were conducted based on original biological results in which the levels of selected proteins, transcripts, and miRNAs were determined in human colon cancer cells (HCT116) under control conditions and at 4 and 12 hours post-irradiation. Furthermore, polysomal profiles (ribosome distribution) within specific transcripts and miRNAs were determined in the study. All experiments were based on proteins involved in the apoptosis signaling pathway (p53 and PTEN), which are well-described in the literature as proteins actively participating in DNA repair processes (e.g., following radiation-induced damage). MiRNAs were selected based on literature reports that clearly indicated their direct interaction with specific proteins and their role in inhibiting their expression.

The proposed model aimed to investigate whether miRNA-mediated translation regulation is a dominant mechanism among the selected translation regulation mechanisms and whether this mechanism may change following cell irradiation. Due to technical limitations and the costs of experiments studying miRNA activity, this model may prove valuable in experiment planning.