

Streszczenie w języku angielskim

Cellular stress, caused by the disruption of the balance between oxidative and antioxidant factors, often accompanies the progression of cancer and arises as a result of anti-cancer therapy. Cancer cells have mechanisms that allow them to survive such danger. The activation of the transcription factor NRF2 plays a crucial role in survival as it controls the expression of various cellular antioxidant systems. Key mechanisms of NRF2 activation include activating mutations and inactivation of the negative regulator of NRF2, known as the KEAP1 protein. Activating mutations in the NRF2 gene *NFE2L2* and inactivating mutations in the *KEAP1* gene have been described in various types of cancer, including non-small cell lung cancer (NSCLC), although the exact frequency of their occurrence has not been precisely determined.

The aim of this doctoral dissertation was to assess the mutational status of the *NFE2L2* and *KEAP1* genes in patients with operable non-small cell lung cancer from the northeastern region of Poland. A total of 88 non-small cell lung cancers were examined, collected during radical tumor resection in patients with stage I-IIIa of cancer. Exons 2 of the *NFE2L2* gene and 1-5 of the *KEAP1* gene were subjected to mutational analysis. Mutations were detected using the conventional chain termination sequencing (Sanger method) and the BLAST bioinformatics program. The phenotypic effect of the detected sequence variants was assessed based on data from the COSMIC database.

Nine mutations with confirmed pathological significance and involvement in cancer progression were detected in the *NFE2L2* and *KEAP1* genes. The frequency of activating NRF2 mutations in the operable non-small cell lung tumors of the examined patients was 10.2%. The majority of mutations (7 out of 9) were identified in the *KEAP1* gene, while only 2 mutations were found in the *NFE2L2* gene. Based on the COSMIC database, it was determined that these mutations prevented the interaction of the KEAP1 protein with the NRF2 transcription factor and the proper negative regulation of NRF2 activity.

The activation of molecular mechanisms that allow cancer cells to survive oxidative stress likely occurs during the development of non-small cell lung cancer. In some cancers, this activation occurs through mutations in the *KEAP1* and *NFE2L2* genes, disrupting their interaction and proper negative regulation of NRF2 activity. In this work, the relatively low percentage of tumors with confirmed alterations (10.2%) may be due to the early stages of cancer in the examined patients.