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WYDZIAŁ FARMACEUTYCZNY

ROZPRAWA DOKTORSKA

EKSPRESJA I POLIMORFIZMY GENÓW *RUNX1*, *RUNX3* I *CEBPA* W OSTREJ BIAŁACZCE LIMFOBLASTYCZNEJ

Dagmara Szmajda-Krygier

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Kierownik Pracowni oraz Promotor pracy:
prof. dr hab. n. farm. Ewa Balcerczak

Promotor pomocniczy:
dr n. farm. Marta Żebrowska-Nawrocka

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Summary

Acute lymphoblastic leukemia represents a group of lymphoid neoplasms at the precursor stage of the B or T line, resulting from genetic changes that block lymphoid differentiation and lead to abnormal cell proliferation and survival. However, the exact pathomechanisms behind this disease remain unknown. Most likely, the process of leukemogenesis can be triggered by a small change in the expression or function of some transcription factors. Such factors are the proteins encoded by the *RUNX* family genes and the *CEBPA* gene.

The main assumption of the doctoral dissertation was the assessment of selected genes encoding transcription factors involved in hematopoiesis, apoptosis and proliferation. Using the PCR-RFLP technique, polymorphisms of the *RUNX1* rs2268277 and *RUNX3* rs6672420 genes were evaluated. Relative expression levels of the *RUNX1*, *RUNX3* and *CEBPA* genes were examined using RT-qPCR. The presence of *RUNX1/RUNX1T1* fusion gene expression was assessed using a TaqMan probe. The study included 60 patients diagnosed with acute lymphoblastic leukemia, treated at the Institute of Hematology and Transfusion Medicine in Warsaw. Investigated material comprised peripheral blood collected on EDTA, from which DNA and RNA were isolated, respectively. In addition, 60 samples of DNA collected from healthy people were used as a reference group for the tested polymorphisms.

Conducted analysis allowed to define final conclusions. The rs2268277 and rs6672420 polymorphisms evaluated in the study are not related to the observed levels of expression and the course of the disease process among patients with ALL. When assessing transcript levels, the performed experiments seem to confirm the previous hypotheses of researchers that both the reduction and increase of mRNA levels of the *RUNX* family genes may be involved in the pathogenesis of acute leukemias. The *RUNX1* gene in ALL cases exhibits oncogene traits, while the *RUNX3* gene appears to play a suppressor role. The lack of correlation between expression levels and patient demographic characteristics, such as gender and age, suggests that assessment of *RUNX1* and *RUNX3* genes can be used as potential targets in targeted therapy. However, to confirm this hypothesis, further studies are required with larger investigated groups. The *RUNX1/RUNX1T1* fusion gene is not associated with an increased incidence of ALL since its presence was not found in any of the

studied patients. The level of *CEBPA* gene expression is probably not related to the development and progression of acute lymphoblastic leukemia.

Characteristics and understanding of the *RUNX* and *CEBPA* genes function in the group of patients with acute lymphoblastic leukemia may translate into new therapeutic strategies and their individualization. Which in the future may help patients with ALL, especially adults and the elderly, obtain a greater chance of complete disease remission and reduce the risk of recurrence.