SIGNIFICANCE OF MICRORNA AND MUTATION WITHIN *GT198* GENE IN DIAGNOSIS AND TREATMENT OF PATIENTS WITH BREAST CANCER

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S u m m a r y. Breast cancer is one of the most frequently diagnosed malignant tumors among women. Most of the patients die due to late diagnosis of the disease since cancer is most commonly diagnosed in advanced stage. At the time of diagnosis the patients have already developed lymph nodes metastasis as well as micro-metastasis to other distant organs. Dynamic development of modern diagnostics gives a chance for early detection of ongoing neoplastic process, and thus created a chance of curing patients completely.
K e y w o r d s: breast cancer, microRNA, GT198

INTRODUCTION

Malignant tumors are the second most common cause of death in Poland as a result of which about 96,000 Poles die each year. Among cancers diagnosed in 2015 in Poland, breast cancer was the most common type diagnosed among Polish women; approximately 17,000 new cases were recorded. It is estimated that by 2025 there will have been an increase in the incidence of breast cancer, and the number of detected cases will have amounted to about 21,000 [4, 25, 29]. This phenomenon is associated with continuously growing number of women with many risk factors for developing cancer.

Breast cancer is characterized by a long preclinical phase, and the occurrence of symptoms after the latent period, and as a result the treatment depends on the stage of development [31]. The causes of breast cancer are not fully understood. The risk factors increasing the probability of its occurrence include age (the risk of breast cancer increases with age, starting from the fourth decade of life), exposure to ionizing radiation, older age at first delivery (after the age of 30 years), family predisposition, small number of pregnancies, history of breast diseases such as atypical ductal or lobular hyperplasia, early age at menarche, and genetic factors (e.g. mutations of tumor suppression genes *BRCA1* and *BRCA2*) [3, 35, 41]. Other genes the mutation of which may increase the risk of developing breast cancer include *PTEN, MDM2* and *TP53* [20, 41]. Using estrogen replacement therapy, obesity after menopause, high-fat diet, excessive alcohol consumption, smoking and lack of physical activity also contribute to the observed increase in the incidence of breast cancer [3, 13].

Currently, one of the most important tasks of oncology diagnostics is to detect cancer at an early stage, which allows better results of treatment administered. Therefore, research is carried out aimed at developing new methods and discovering tumor markers or mutations that allow for early manifestations of neoplastic process, and thus can reduce the mortality rate of patients with breast cancer [2, 26]. Recent scientific reports indicate the important role of microRNA and mutations in *GT198* gene at the early stages of diagnostic process in patients with suspected breast cancer.

GT198 gene

GT198 gene is located on chromosome 17q21, encodes GT198 protein (other names: TBPIP or Hop2), and is responsible for the stimulation of RAD51 involved in the DNA repair mechanism by homologous recombination [6, 7, 23]. Moreover, *GT198* gene is involved in the production of a steroid receptor co-activator, and its activity is regulated by estrogens [16, 27].

A team of researchers from the medical faculty of Georgia in Augusta and Georgia Cancer Center in Australia indicated the importance of *GT198* gene mutation in the early diagnosis and therapy of patients with breast cancer. They examined 254 samples obtained from women diagnosed with breast cancer at the pre- and post-menopausal age. In the study group, pathological changes of unknown etiology were observed within the normal breast cells, i.e. fibroblasts, fatty cells, pericytes (poorly differentiated cells that regulate blood pressure and can be embedded into a network of small blood vessels in order to strengthen them), and myoepithelial cells [17, 36]. The researchers found the presence of somatic mutation in *GT198* gene in the breast tumor stromal cells, and concluded that it could explain the aforementioned abnormalities. *GT198* mutation was observed both in the blood and in tumor tissues. It was shown that the presence of a single mutation located in the stem cells contributed to abnormalities in all tissues which originate from those cells. The researchers concluded that the mutation of *GT198* gene induced tumor growth. Abnormal protein produced by mutated *GT198* gene activated the vascular endothelial growth factor (VEGF) in cell cultures, which was responsible for the formation of capillaries and adipogenesis [21, 36]. Moreover, Dr Lan Ko, observed *GT198* gene mutations among patients with ovarian cancer [22].

The research results can help develop new targeted therapy based on the regulation of mutated stem cell activity in patients with breast cancer which can destroy cells that feed the tumor. It can be more beneficial than currently used treatment methods targeting mainly the cancer cells which are the final result of the progenitor cell division [36].

MicroRNA

MicroRNAs are single-stranded sequences of non-coding ribonucleic acid, responsible for the regulation of gene expression at the post-transcriptional level. They affect mRNA degradation and participate in the processes of apoptosis, aging and cell proliferation [8]. Most microRNA molecules are found intracellularly, but some of them also occur in the extracellular space (saliva, tears, plasma) [9, 34]. Changes observed in the concentration and composition of the extracellular microRNAs are most frequently connected with an ongoing pathological processes (including cancer). That enables the application of different types of microRNAs as potential biomarkers, significant in the diagnostic and therapeutic processes, as well as monitoring the progress of treatment [5, 9].

Jeremy TG Chang et al. used data on breast cancer genome collected in The Cancer Genome Atlas (TCGA), and applied various bioinformatic tools to examine 309 mature miRNAs samples whose expression value was >90%. The results showed that a relatively high level of miR-320a, miR-361-5p, miR-103a-3P and miR-21-5p was significantly associated with a longer time of survival in the patients with breast cancer [1]. Literature data indicate the important role of miR-320a in inhibiting breast cancer metastases and sensitizing cancer cells for chemotherapy [11, 18, 32, 39]. The results of many studies classified miR-21-5p and miR-103 as oncomiR, and increased expression was correlated with metastases, recurrence and poor prognosis [10, 14, 15, 19, 28, 30, 40]. That was contradictory to the results obtained by J. Chang. However, the researchers explained that prolonged survival time is the combined effect of disease progression and response to treatment, and indicated that their hypothesis needed re-evaluation since the data contained in TCGA was incomplete. Another research showed that miR-103 inhibited cancer stem cell formation in triple negative breast cancer [24]. Further research experiments aiming to determine the role of miR-320a, miR-361-5p, miR-21-5p and miR-103a-3P may explain the mechanisms underlying the development of breast cancer, metastasis, and the length of patients' life.

Le-ChihYeh et al. observed higher expression of miR-151-3p in cancer cells of patients with breast cancer in comparison to the cells and tissues unaffected by cancer. They found that miR-151-3p directly modulated the expression of *TWIST1* and thereby suppressed the migration and invasion of breast cancer cells by increasing the expression of E-cadherin, it did not affect the growth of these cells, though [37].

A report published in 'Oncology Letters' presented the results of an investigation in the group of 21 patients diagnosed with breast cancer using RT-qPCR method. The results indicated a significant increase in the expression of miR-520e in cancer cells

compared with adjacent healthy breast tissues. It was also found that overexpression of miR-520e might inhibit breast cancer cell apoptosis and promote proliferation of these cells in vitro. This suggested that miR-520e could act as a new oncomiR in breast cancer, and might be a potential therapeutic target [38].

The team led by Hong Yeting showed higher expression of miR-96 in breast cancer cells compared to normal cells. They also found that miR-96 activated the proliferation and migration of breast cancer cells in vitro and influenced tumor cells growth in vivo. The examination of molecular mechanism of miR-96 involvement in developing breast cancer found that the level of miR-96 expression in cancer tissues inversely correlated with the PTPN9 protein concentration. The analysis of results and literature data let conclude that miR-96 inhibited PTPN9 gene expression, thus contributed to the development of breast cancer [12].

A signi□cant role in the pathogenesis of breast cancer is also played by miR-124-3p. It was found that miR-124-3p contributed to the inhibition of proliferation and invasion of cancer cells and CBL expression in breast cancer. Scienti□c studies showed that CBL inhibited the transforming growth factor β, and thus stimulated the development of tumor. Thus, the inhibition of CBL expression by miR-124-3p could inhibit the growth of breast cancer [33].

CONCLUSIONS

In the future, modern therapy designed for patients with breast cancer may be based on the induction or inhibition of different types of microRNAs expression. Recent advances in molecular biology and oncology associated with microRNA pro□ling and understanding the effects of that molecule on the pathophysiological processes characteristic of breast cancer will help better understand the pathogenesis of that cancer, and to understand why an applied treatment failed. It will increase the chances of diagnosing breast cancer at an early stage and offer better prognosis and implementation of therapy, which, most likely, will be reflected in the reduced mortality rate among cancer patients.

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