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Role of Oestrogen Receptors in Breast Cancer in Women

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Rola receptorów estrogenowych w raku piersi u kobiet

Review article/Artykuł poglądowy

Summary
In the study there was presented a review of current literature about the role ERs in breast cancer in women. There were discussed the problems concerning ERs expression, in particular cellular organella, the changes occuring in neoplasmatic transformation of cells and their influence on prognosis and sensivity on hormonal therapy in patients with breast cancer. There was also mentioned the influence of metabolic disorder on the development of breast cancer, where ERs can be an indirect mediator. The knowledge of the influence of ERs on risk, development, sensivity to treatment and prognosis can be useful in development of new diagnostic and therapeutic methods in this disease in the future.
Key words: oestrogen receptor, progesterone receptor, oestrogens, breast cancer, cell

Streszczenie
W pracy przedstawiono przegląd bieżącej literatury na temat roli receptorów estrogenowych w raku gruczołu piersiowego u kobiet. Omówiono zagadnienia dotyczące ekspresji ERs w poszczególnych organellach komórkowych, zmiany występujące w transformacji nowotworowej oraz ich wpływ na późniejsze rokowanie oraz wrażliwość na leczenie hormonalne u pacjentek z rakiem gruczołu piersiowego. Wspomniano również o wpływie zaburzeń metabolicznych na rozwój raka piersi, gdzie receptorem pośredniczącym w tym procesie może być ER. Znajomość wpływu ERs na ryzyko, rozwój, wrażliwość na leczenie oraz rokowanie w raku gruczołu piersiowego może przyczynić się do powstania nowych metod diagnostycznych i leczniczych w tej chorobie w przyszłości.
Słowa kluczowe: receptor estrogenowy, receptor progesteronowy, estrogeny, rak piersi, komórka

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INTRODUCTION

The aim of the study is a review of current literature about the role of oestrogen receptors (ERs) in genesis and development of breast cancer in women. ERs are present in cells in many human tissues (i.e. in uterus, ovary, vagina, mammary glands), they have different influence on the human organizm depending on the tissue and age of man. ER is a protein activated by binding of a ligand to the C-ending. The N-ending of ER is bound directly to DNA or other protein, which affects activating or supressing transcription of particular genes depending on ER. Modulation of those genes further affects biosinthesis of proteins coded by those genes. ER belongs to the group of receptors which are located inside the cell. According to present knowledge ERs are divided into two subtypes (ER alpha and ER beta), those subtypes have different ways of activation and different influence on the cell. The ER beta is further divided into five subtypes (ER beta 1-5). The knowledge about the influence of ERs on mammary gland cells can be very useful for cognition and better understanding of the process of neoplasmatic transformation of this gland and the mechanizm of tumour development.

THE EXPRESSION OF ERS IN THE CELL

In breast cancer cells there are detected different subtypes of ER whose function is still unclear, although the presence of particular subtypes can affect prognosis and the course of cancer, which is indicated by numerous scientific works [6,7,13,21,22,28]. Except for the profile of particular subtypes of ERs and their percentage share, it is very important where they are located. It is indicated that in proper mammary gland cells ERs are located in the nucleus of the cell, whereas in neoplasmatic transformation the receptors change location to the cytoplasm [18]. At present that fact is being intensively investigated, and particular location of ER and its subtypes in different organella of the cell is correlated with prognosis in breast cancer [28]. Patients, in whose cells ERs were detected only in the cytoplasm or in nucleus and cytoplasm had poor prognosis and survival rates. It is assumed that the relocation of ERs from the nucleus to the cytoplasm is one of the stages of changing phase of cellular cycle from G1 to S, and this process is caused among others by oestrogens [13]. There are already isolated first proteins responsible for those processes and there are made attempts of introducting inhibitors inactivating those proteins to the cell [13], which can indirectly result in inhibiting of neoplasmatic transformation in the future. In other studies it is proved that apart from the change of expression of ERs among the organella of the cell, also the profile of particular subtypes of ERs changes, where ER beta, which is normally detected in the nucleus, mitochondria and cellular membrane, is detected only in the nucleus in cancer cells [4,22]. Those data indicate a complete change of the ERs biology in neoplasmatic transformation in mammary gland cells.

THE INFLUENCE OF ERS ON THE PROGNOSIS IN BREAST CANCER

As it was mentioned, the analysis of particular subtypes of ER and cognition of the receptor profile in the cell affect prognosis in women with breast cancer. It turned out that the presence of fractions ER beta 2 and 5 in cancer cells gives much better response to hormonal treatment of breast cancer than i.e. presence of ER beta 1 in the cancer cell [28]. In the case of co-expression of ER beta 2, ER alpha and PGR in cancer cell the overall survival of patients is better and invasiveness of cancer is worse in comparison to other receptor configurations [28]. However, it is indicated in another study that in postmenopausal period only the presence of ER beta 1 gives better survival of patients, even without the expression of ER alpha, PGR and HER in the cancer cell [7]. Further studies using larger samples and focusing on the correlation of prognosis in breast cancer patients with immunologic profile (ER, HER), and also with histopathologic grade and cellular proliferation indicated the significance of immunologic profile in relation to prognosis only in the group of women with no expression of ER [6]. Nevertheless, among all so far known receptors ER is regarded as the most predictive in prognosis despite the fact that PGR and HER also play an important role but are less significant in prognosis in patients with breast cancer [21]. There is still conducted research on prediction of particular subtypes of ER, which will probably play more important role in prognosis in the future [6,21]. However, the current results and conclusions are still not clear at all, and in some cases seem to be contradictory. Perhaps, in the future the sole presence of ER or its lack in cancer cell will not say to a doctor anything about prognosis and will be useless for planning further therapeutic strategy, because the particular subtypes of this receptor can play different roles and exact knowledge about their expression will be necessary to make a decision about further treatment. Another problem is addressed by research on other markers causing resistance to hormonal therapy of breast cancer, which can result (or be enhanced by) from some processes that are not connected with the presence of ER, PGR or HER in cancer cells [8].

THE INFLUENCE OF ER ACTIVATION ON THE DEVELOPMENT OF BREAST CANCER

The latest studies on activation of ERs and their influence on the cell show that this receptor has a few different ways of activation, which are not always dependent on oestrogens [30]. The subtype of ER responsible for that kind of activation is mainly ER alpha [15,17], which means that the level of overall ER is insufficient to evaluate breast cancer risk and the grade of activation of ERs and their influence on the cell. The cross-talk mechanisms (‘interreceptor’ activations), described also in other studies [32] cause that ERs can be activated by the influence of other hormones (i.e. gestagens), or some

processes initiated in the cell by substances which are not hormones [27,32], i.e. HER2 activation. Interesting is also the fact that many studies revealed that administration of small doses of oestrogens has a positive effect on tissues depending on those hormones and makes the cancer cells containing no ERs sensitive to the effect of antyoestrogen drugs [14,20,27,29]. It seems that this 'interreceptor' communication can be significant in neoplasmatic transformation and tumor development, and the drugs blocking those processes on the level of kinases (or other intracellular molecular processes) can be very useful and give substantial therapeutic effects [27].

The results of research on the influence of androgens on breast cancer show that the level of those hormones is not useless either, and especially important role is played here by progesterone-testosteron and testosterone-estron ratios [9]. The significant role can also be played by the metabolits of estrogens such as their less known derivatives, i.e. 17-beta estradiol, which is regarded as a neoplasmatic transformation stimulator [25]. To sum up, the most frequent mentioned subtype of ER, which seems to be the most probably responsible for neoplasmatic transformation of the cells of mammary gland (the most common in literature) and which also can be activated independently of oestrogens, is ER alpha [1,15,16,17,31]. The genes discovered in breast cancer cells are usually connected with this subtype of ER and code the proteins binding to it. Those proteins are not detected by antyER immunoglobulins, and the presence of those proteins is correlated with poor prognosis in women with breast cancer [31].

The conception of receptor genesis of breast cancer can be also confirmed by the protective influence of pregnancy on neoplasmatic transformation [1,10,23,24], which as it is widely known, causes changes in receptor profile in cells of tissues dependent on sexual hormones (changes in amount of particular receptors and percentage share of particular subtypes of ERs and PGRs in cells) [33]. Further studies of the influence of pregnancy on neoplasmatic transformation indicate that alphafetoprotein is the most significant protective substance, whose production is caused by the effect of other hormones, whose level in blood serum significantly increases in pregnancy (estradiol, estriol, progesterone, hCG) [10]. Nevertheless, many processes in cells taking place in neoplasmatic transformation and their causes have not been explained so far, and also many of them still remain unknown, but it is generally regarded that oestrogens alone have carcinogenic effect and affect genesis and development of breast cancer [5,34].

Last but not least, apart from the receptor profile of cell, genetic genesis of neoplasmatic transformation is also very important. It turned out that the breast cancer cells in women have different genomic profile to proper cells [2]. The presence of BRCA is also connected with larger instability of genom of cell in comparison to the cells without BRCA. It can be concluded that larger genomic instability is connected with higher probability of neoplasmatic transformation in mammary gland cell [19]. In another study, there were described genes responsible for resistance of cell to tamoxifen [12], which indicates that in all described above processes genetic factor plays an important role. However, this aspect is so extensive that it can be a subject of another study.

THE INFLUENCE OF METABOLIC DISTURBANCES ON ERS

The influence of metabolic disturbances on cancer risk is frequently mentioned in literature. This influence on breast cancer is also mentioned, it is discussed i.e. in studies on the influence of diet on this disease [3] as well as on women's intake of large amount of carbohydrates, which apart from obesity increases breast cancer risk [11]. The connection of those disturbances with genesis of cancer has to be also localized on the level of cell, and the described correlations indicate that there is a connection between those disturbances and receptor profile of cell. Obese women in postmenopausal period, who eat large amounts of carbohydrates have more prognosticly unfavourable receptor profile of mammary gland cell (ER-) [11].Those studies obviously require further confirmation, but some authors even already describe common markers of obesity and breast cancer [26]. They include: basic fibroblast growth factor (bFGF), prostate-specific antigen (PSA), human kallikrein 2 (hK2), urinary plasminogen activator (uPA). All those markers were common in pre- and postmenopausal breast cancer, although obesity is only connected with postmenopausal breast cancer. The most specific marker was PSA, which was inversely proportional to BMI of women who did not fall in breast cancer [26]. The discovery of markers connecting some chronic diseases or substances with breast cancer risk can be very useful in prophylaxis and diagnosis of this diease.

CONCLUSIONS

ERs play an important role in genesis and development of breast cancer and prognosis in women with this disease. Many processes connected with expression, activation and influence of those receptors on transformation of cell still remain unclear. However, undoubtedly in the future, the presence and profile of ER subtypes will be very significant because of their different ways and effects of activation as well as prognosis for patient. Perhaps ERs will be the common point of some metabolic disturbances and breast cancer risk in women. A better cognition of processes taking place in the cell in molecular level, and the influence of expression of particular genes on those processes or introducing of the markers of breast cancer risk will result in more effective prophylaxis, diagnostics and treatment of breast cancer in women.

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