Alterations in DNA methylation may cause disturbances in regulation of gene expression, including drug metabolism and distribution. Moreover, many cancers, including breast cancer, are characterized by DNA hypomethylation and a decreased 5-hydroxymethylcytosine level. The abnormal cell growth found in breast carcinoma might be the result of impaired up-regulation of breast cancer receptors. Receptors’ expression in breast cancer determines clinical outcome, and it is possible that they lead to different DNA methylation patterns. Excessive steroid exposure can affect DNA methylation by promoting demethylation of CpG islands in promoter regions of genes, and hence may have an impact on promotion and progression of breast cancer cells. Tamoxifen, as a leading drug in breast cancer hormone therapy, has an ability to act like estrogen or antiestrogen depending on the type and localization of the breast cancer receptor. Further studies are needed to determine whether tamoxifen, similarly to steroids, may evoke changes in methylation pattern.

Key words: breast cancer receptors, epigenetics, DNA demethylation, tamoxifen.
The potential influence of breast cancer estrogen receptors’ distribution on active DNA demethylation

Breast cancer subtypes

Breast cancer is the most frequent malignancy amongst women worldwide. It affects over 2.1 million women per year globally and it is the cause of death for almost 600 thousand of them [29]. This type of cancer, similarly to others, displays global hypomethylation as a result of genome instability. Furthermore, it was conclusively demonstrated that alterations in DNA methylation of pivotal genes (BRCA, p53, ERα) are involved in cancer progression [30]. Changes in DNA methylation are associated with molecular subtypes of breast cancer, which may suggest an important role of impaired DNA methylation in carcinogenesis [31].

Breast cancer is classified into five biological subtypes based on expression of ER, PR, human epidermal growth factor 2 (HER2) receptors, and nuclear antigen Ki-67 (Table 1). According to the 5th St Gallen International Breast Cancer Conference, expression of steroid hormones and
Two genes, \(\beta\) and \(\alpha\). Isoforms of ER (ER\(\beta\) and ER\(\alpha\)) are under the control of DNA and have an impact on regulation of gene expression. After ligand activation, ERs undergo conformational changes, and as a result, ligand-activated transcription factors are able to stimulate each other: G protein-coupled estrogen receptor can trigger HER2 signaling, while tyrosine kinases cascade preceded by HER2 activation may phosphorylate and initiate the activation of ER and its proteins [42]. HER2 (+) occurs only in 15% of breast cancer patients; however, 10% of them also expressed ER(+) [43].

It is becoming increasingly clear that there is a high probability that abnormal cell growth found in breast carcinoma might be the result of impaired up-regulation of ER, GPER and HER2. The potential signaling pathways are able to stimulate each other: G protein-coupled estrogen receptor can trigger HER2 signaling, while tyrosine kinases cascade preceded by HER2 activation may phosphorylate and initiate the activation of ER and its proteins [44, 45]. Receptors’ expression in breast cancer determines the clinical outcome. Hence, it could be possible that the DNA methylation pattern varies between human breast cancer cells with diversified expression of receptors.

Estrogens as natural ER ligands are implicated in growth and proliferation of cells, e.g. in mammary gland. Nevertheless, excessive estrogen exposure may have an impact on promotion and progression of breast cancer in humans [46]. Inhibited proliferation of cancer cells after high concentrations of \(\beta\)-estradiol (E2) was also observed in human cancer cell lines [47]. Moreover, E2 may act as a gene expression regulator though its ability to bind ER. Based on literature data, it was suggested that E2 can affect DNA methylation by promoting demethylation of CpG islands in promoter regions of genes [48, 49]. Furthermore, a recent study revealed that E2 supplementation of cultured cells resulted in almost entire removal of 5-mC in the SVEP1 gene promoter, and thus increased the unmethylated DNA level [50].

**Breast cancer receptors’ significance**

ERs are members of the nuclear receptor superfamily of ligand-activated transcription factors. After ligand activation, ERs undergo conformational changes, and as a result they could bind to estrogen response elements (ERE) in DNA and have an impact on regulation of gene expression [34]. Isoforms of ER (ER\(\alpha\) and ER\(\beta\)) are under the control of two genes, ESR1 and ESR2. Contrary to ER, isoforms of progesterone receptor (PRA and PRB) are coded by one gene, POR [35]. The expression and activity of PR are regulated by ER: PR is expressed as a result of ER activation [36].

The elevated estrogen activity in cancer cells is connected with increase of ER\(\alpha\) quantity; thus ERs is used as a target of hormonal therapy of breast cancer. Moreover, the grade of malignancy and stage of differentiation are associated with ERs expression. In contrast to ER\(\alpha\), ER\(\beta\) is expressed mainly in healthy mammary gland [37]. Moreover, ER\(\beta\) could exert an antagonistic effect on ER\(\alpha\) action in certain tissues, which in turn may lead to decrease of cellular proliferation. Reduced ER\(\beta\) expression in cancer suggests that this isoform has suppressor activity in hormone-dependent tissue, e.g. in mammary gland [38].

In 2000 Filardo et al. observed that the rapid response to 17\(\beta\)-estradiol is a consequence of extracellular regulated kinase (ERK) activation, which was not connected with ER\(\alpha\) or ER\(\beta\), but with a G-protein-coupled receptor named GPR30/GPER [39]. Later, it was conclusively demonstrated that GPER also binds estradiol with high affinity and is connected with rapid non-genomic signaling of estradiol [40]. GPERs are classified as membrane receptors, although they may also occur in cytoplasm and nucleus [41].

The HER family is arranged in regulation of growth and development in breast cancer cells. HERs, in contrast to ER and PR, are epidermal growth factor receptors (EGFR) expressed in the cell membrane. Due to the fact that HER2 acts without a known ligand, it constitutively occurs in active conformation, and undertakes dimer formation with another EGFR. Hetero- or homodimerization leads to tyrosine kinase phosphorylation, and activation of the signaling pathway [42]. HER2 (+) occurs only in 15% of breast cancer patients; however, 10% of them also expressed ER(+) [43].

It is becoming increasingly clear that there is a high probability that abnormal cell growth found in breast carcinoma might be the result of impaired up-regulation of ER, GPER and HER2. The potential signaling pathways are able to stimulate each other: G protein-coupled estrogen receptor can trigger HER2 signaling, while tyrosine kinases cascade preceded by HER2 activation may phosphorylate and initiate the activation of ER and its proteins [44, 45]. Receptors’ expression in breast cancer determines the clinical outcome. Hence, it could be possible that the DNA methylation pattern varies between human breast cancer cells with diversified expression of receptors.

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**Biochemistry of tamoxifen**

There are three possible treatment strategies of hormone-dependent breast cancer: arresting of estrogen synthesis via aromatase inhibitors, competitive binding to estrogen receptors and modulating their activity by antiestrogens, and prevention of ER signaling by causing degradation of ER by selective estrogen degraders (SERDs) [51]. The second group, represented widely as selective estrogen receptor modulators (SERMs), has been in clinical use for nearly 40 years [52]. The best known representative of SERMs is tamoxifen, which is currently used in all stages of ER(+) breast cancer in pre- and postmenopausal women, and in ductal carcinoma in situ [53]. Moreover, tamoxifen is used for prevention of breast cancer for women at very high risk of developing the disease [54].

| Breast cancer subtype       | Estrogen receptor | Progesterone receptor | HER2 receptor | Ki-67 |
|-----------------------------|-------------------|-----------------------|--------------|------|
| Luminal A-like              | Positive          | Positive              | Negative     | Low (< 20%) |
| Luminal B-like (HER2 negative) | Positive          | Negative or low       | Negative     | High (> 20%) |
| Luminal B-like (HER2 positive) | Positive          | Any                   | Positive     | Any  |
| HER2 positive (HER2 enriched) | Negative          | Negative              | Positive     | Any  |
| Triple negative (basal like) | Negative          | Negative              | Negative     | Any  |
Additionally, longer tamoxifen treatment, up to 10 years, results in a 50% decrease in breast cancer mortality in the course of the second decade after diagnosis [55]. Based on pharmacological research, tamoxifen is transformed into three active metabolites in the human organism: 4-hydroxytamoxifen, N-desmethyltamoxifen, and 4-hydroxy-N-desmethyltamoxifen (endoxifen) [56]. Conversion of tamoxifen implicates hepatic CYP2D6 and CYP3A4/3A5 cytochromes, which metabolize tamoxifen to its metabolites in two different manners: to N-desmethyltamoxifen (CYP3A4/3A5), and further to 4-hydroxy-N-desmethyltamoxifen (CYP2D6), or to 4-hydroxytamoxifen (CYP2D6) and then to 4-hydroxy-N-desmethyltamoxifen (CYP3A4/3A5) [57]. It has been established by pharmacological profiling that tamoxifen is a prodrug, hence its therapeutic action results from its active metabolites: 4-hydroxytamoxifen and endoxifen [58]. The affinity of 4-hydroxytamoxifen and endoxifen to ERα and ERβ is considerably similar, much the same as the other antiestrogens associated with regulation of estrogen-dependent gene expression [59]. However, given that the plasma level of endoxifen is 5–10 fold higher compared to 4-hydroxytamoxifen, it is suggested that this metabolite is presumably a key tamoxifen derivative accountable for pharmacological activity of tamoxifen in the human organism [60].

Mechanisms of SERM action in breast cancer cells

SERMs may act as antagonists or agonists of ERs depending on type of receptor: nuclear or G protein-coupled. The antagonistic action of SERMs is associated with nuclear ERs and connected to breast cancer treatment. After binding to ER, tamoxifen evokes the receptor’s conformational changes, but distinct from the ER-estrogen complex. The tamoxifen-ER bond dimerizes and translocates to the nucleus, where it prevents transcription of estrogen-dependent genes by attaching to estrogen response elements (ERE) in DNA [61]. This successively results in inhibition of estrogen activity, which is connected with growth and proliferation of cells [62, 63]. As estrogen receptor agonists, SERMs affect GPERs, which has been identified as a main factor in rapid responses to estrogens [64]. Tamoxifen activation of GPER results in modification of the estrogen receptor or its co-activators by phosphorylation, which can cause independent ligand activation or an impaired response to other ER regulators [27] (Fig. 2). This type of interaction occurs mainly in bones and liver [3]. However, it is possible that estrogens and SERMs affect impaired cell growth and proliferation though activation of GPERs, and it may be the predominant pathway in transformation of breast cancer cells into cells resistant to hormone therapy. Hence, it could conceivably be suggested that the role of tamoxifen is not only limited to involvement in regulation of estrogen-induced genes.

Tamoxifen as an antiestrogen may inhibit breast cancer cell growth and proliferation. However, acquired resistance to SERMs therapy still remains a problematical issue as adjuvant therapy is extended. The proposed mechanism of antiestrogen resistance is associated with GPER activation. It was suggested that GPERs may precede stimulatory estrogen signaling for proliferation and migration, regardless of ER expression [65]. Moreover, abnormal activity of CREB – cAMP response element binding protein, cAMP – cyclic adenosine monophosphate, ER – estrogen receptor, ERE – estrogen response elements, ERK – extracellular regulated kinase, GPER – G-protein-coupled receptor, HER2 – human epidermal growth factor 2 receptor, HB-EGF – heparin-binding EGF-like growth factor, MAPK – mitogen activated protein kinases, MMP – matrix metalloproteinase, PKA – phosphoinositide 3-kinase, SERM – selective estrogen receptor modulator

Fig. 2. Mechanisms of possible tamoxifen signaling
ER caused by antiestrogens may be linked with changes in gene expression as a result of epigenetic modifications [8]. It was conclusively demonstrated that estrogen receptor signaling and DNA methylation are implicated in regulation of the cell cycle by modulating antiproliferative and proliferative genes [66, 67]. Although there are some data concerning partially overlapping gene regulation by estrogen signaling and DNA methylation, its detailed molecular mechanism and common target genes have remained enigmatic [8, 68]. It may be possible that SERMs can potentially interrupt estrogen receptor function and thus similarly affect the DNA methylation pattern. Moreover, several studies have proved that sustained SERM therapy can manifest distinct global gene expression and DNA methylation of promoters in breast cancer cells [69, 70].

Conclusions

The treatment of choice of ER/PR(+) breast cancer patients is based on the selective estrogen receptor modulator tamoxifen, which in long-term therapy serves as a considerably reliable drug. Of note, tamoxifen therapy leads to recovery in hundreds of thousands of ER/PR(+) breast cancer cases [71]. Since the discovery of tamoxifen, the use of the drug has evolved by embracing its ability to act like estrogen or antiestrogen depending on the receptor type and its localization around the body. Such ability created new possibilities in drug development and therapeutic use, i.e. tamoxifen acts like estrogen in osteoporosis treatment by preventing bone density loss, and like antiestrogen in breast cancer therapy by inhibition of estrogen action [72]. Hence, it is becoming increasingly clear that the action of SERMs at different target sites is more complex than just switching estrogen activity. It may be dependent on other factors and processes taking place in target cells. Further studies are needed to determine whether tamoxifen, similarly to steroids, may evoke changes in the methylation pattern. Such research may provide new information, which may pave the way for new diagnostic and therapeutic methods as well as innovations in personalized medicine approaches.

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