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STEM CELLS IN BREAST CANCER: THE ROLE OF GENDER STEROID RECEPTORS

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СТВОЛОВЫЕ КЛЕТКИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: РОЛЬ ПОЛОВЫХ СТЕРОИДНЫХ РЕЦЕПТОРОВ

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SUMMARY

Breast cancer (BC) is the most common cancer among women, and current treatments available often have high success rates. However, BC can acquire drug resistance and sometimes relapse. Current knowledge about the most aggressive forms of BC indicates the role of specific cells with stem properties located in BC, the so-called "BCSCs" (Breast cancer stem cells). The role of BCSCs in cancer formation, growth, invasiveness, therapy resistance, and tumor recurrence is becoming increasingly evident. The growth and metastatic properties of BCSCs are regulated in a variety of ways that are only partially known. Sex steroid receptors (SSRs), which are involved in the etiology and progression of BC, promote the proliferation, dedifferentiation and migration of BCSCs. However, the literature contains incomplete information about their roles. In particular, there are conflicting findings regarding the expression and role of classic BC hormone biomarkers such as estrogen receptor alpha (ER α), together with scanty, albeit promising, information on the properties of ER-beta (ER β) and androgen receptor (AR) that control pathways of transduction in BCSC. In this review, we will discuss the role that SRs expressed in BCSCs play in BC progression and relapse, and how these findings have opened up new therapeutic options.

These cells are predictors of BC and promising new therapies are being developed to target these cells and improve BC recurrence.

РЕЗЮМЕ

Рак молочной железы (PMЖ_(рус), BC_(англ)) является наиболее распространенным раком среди женщин, и современные доступные методы лечения часто имеют высокие показатели успеха. Тем не менее, BC может приобрести лекарственную устойчивость, а иногда и рецидив. Современные знания о наиболее агрессивных формах BC указывают на роль специфических клеток со стволовыми свойствами, расположенных в BC, так называемых «стволовых клеток PMЖ» (BCSCs -Breast cancer stem cells). Роль BCSC в формировании рака, росте, инвазивности, резистентности к терапии и рецидиве опухоли

становится все более очевидной. Рост и метастатические свойства BCSCs регулируются различными путями, которые известны только частично. Половые стероидные рецепторы (SSR_(англ)), которые участвуют в этиологии и прогрессировании ВС, способствуют пролиферации, дедифференцировке и миграции BCSC. Однако в литературе есть неполная информация об их ролях. В частности, существуют противоречивые выводы относительно экспрессии и роли классических гормональных биомаркеров ВС, таких как альфа-рецептор эстрогена (ER α), вместе со скудной, хотя и многообещающей информацией о свойствах ER-бета (ER β) и андрогенного рецептора (AR), которые контролируют пути трансдукции в BCSC. В этом обзоре мы обсудим роль, которую SR, экспрессируемые в BCSC, играют для прогрессирования и рецидива ВС, и как эти результаты открыли новые терапевтические возможности.

Эти клетки являются прогностическими факторами ВС на их основе разрабатываются новые перспективные методы лечения, нацеленные на эти клетки и улучшающие рецидив ВС.

Key words: breast cancer; Steroids; Sex steroid receptors; Cancer stem cells; Therapeutic implications

Ключевые слова: рак молочной железы; Стероиды; Половые стероидные рецепторы; Раковые стволовые клетки; Терапевтические последствия

INTRODUCTION

Breast cancer (BC) is the most common cancer in women worldwide and the second most common cancer overall [1]. Although it is considered postmenopausal, genetic predisposition, aging, gender, menarca age, zero ratio, late menopause, and a family history of breast cancer are still major risk factors for breast cancer [2].

Breast stem / progenitor cell transformation has been implicated in breast carcinogenesis [3], and many studies have reported the presence of cancer stem cells (CSCs) in malignant BC [4-6]. CSCs can positively influence tumor survival, spread of metastases and escape of therapy [7]. In particular, the secretion of interleukins 6 and 8 (IL-6 and IL-8) by tumor-associated fibroblasts, mesenchymal stem cells, and macrophages promotes self-renewal of CSCs in BC, which additionally indicates the role of the tumor microenvironment in cancer progression [7]. Estradiol also affects the breast cancer stem cell (BCSC) population in a paracrine manner, as well as other factors, including metalloproteases (MMP), insulin growth factor (IGF), platelet growth factor (PDGF), secreted by the surrounding cancer cells, which may affect on proliferation, invasiveness and metastatic spread of BC cells [8,9].

The presence and frequency of CSC, however, is associated with type BC, and many results have shown a strong correlation between CSC and BC aggressiveness. Meta-analyzes from twelve published studies have shown that BCSCs are significantly associated with high histological grade, positivity of human epidermal receptor-2 (Her-2), estrogen receptor (ER) and progesterone receptor (PR), and lack of any correlation with tumor size or nodal status [10]. In addition, BCSCs are resistant to classical therapy. By enriching the BCSC population, anti-cancer treatments often fail. The chemical or radio resistance of BCSCs has been attributed to various factors. As in SCs, they are constantly dormant (phase G0) while cancer cells replicate rapidly. Therefore, standard therapies that only target rapidly dividing cells are ineffective against BCSC [11]. Again, BCSCs have an increased expression of ATP binding cassette (ABC) and aldehyde dehydrogenase (ALDH) transporters, which are capable of decreasing drug concentration within cells [12]. Finally, BCSCs show an altered response to DNA damage that protects them from apoptosis [11].

All these properties make them resistant to the currently available anticancer therapy.

The role of sex steroids (estrogens, progestins and androgens) as well as SSR in BC is widely recognized [13]. It is now also believed that sex steroids support the stem cell population in normal and malignant mammary glands. An increase in the stem cell population can lead to cancer susceptibility in normal mammary glands, while an increase in BCSCs affects both drug resistance and tumor recurrence [14,15]. Taken together, these data suggest that CSCs represent a very promising predictor of BC, although more research is needed to confirm their importance in clinical practice.

In this review, we present the latest evidence on the role of sex steroid receptors (SSRs) in BCSC. The therapeutic implications of these studies will also be debated as BCSC-targeted therapies appear to be very promising in the clinical management of BC patients.

BCSCs

The morphology of the mammary gland is constantly changing throughout life. At birth, the epithelium of the human mammary gland consists of a network of ducts. During puberty, the milk ducts form lateral branches and also form numerous lobuloacinar structures containing milk-secreting alveolar cells during pregnancy and lactation.

By activating massive apoptosis and tissue remodeling, the mammary gland then shrinks at the end of lactation [16]. For this, a group of cells with a high proliferative potential and the ability to differentiate must be localized in the cells of the mammary gland. Despite various studies demonstrating the presence of SCs in breast tissue, these cells have not yet been identified and isolated [3]. SC mammary glands (Ma) are undifferentiated and their cell division can be symmetrical, resulting in the formation of two self-renewing or asymmetric cells. Thus, various pluripotent differentiated cells, including luminal and basal SC, as well as pluripotent progenitors, can differentiate into ductal, alveolar, and myoepithelial cells. Consistent with CSC theory, both MaSCs and progenitor cells can induce BCSCs during these cell divisions, thereby promoting carcinogenesis [17]. Another theory states that BCSCs are derived from undifferentiated cancer cells caused by changes in the tumor microenvironment, chemotherapy, or other targeted treatments. As a result of genetic or epigenetic

modifications, transformed cells can acquire a stem-like phenotype [17-20].

BCSCs are more resistant than MaSC and are characterized by the expression of specific cell surface markers such as high levels of differentiation cluster 44 (CD44) and low levels of differentiation cluster 24 (CD24). In particular, high expression of CD44 maintains multipotency of BCSCs, while low levels of CD24 support cell stemality [21]. More recently, additional markers have been identified, including ALDH1, which oxidizes retinol to retinoic acid, thereby playing a role in the first stage of BCSC differentiation. Increased expression of ALDH1 identifies BCSCs and correlates with poor prognosis in receptor negative BCs [22,23]. Again, other cell surface markers such as cluster of differentiation 133 (CD133), 49f (CD49f) and 90 (CD90) have been identified as markers for CSC and are associated with drug resistance, poor prognosis, and decreased BC survival [24].

These results, summarized in Table 1, allowed the development and synthesis of specific antibodies to target these BCSC markers and provide a more effective therapy for aggressive BC. To make this terrain more challenging, many of the pathways activated in MaSC are not regulated in the BCSC. These include the Notch, Wnt, Hedgehog, and Hippo pathways, which, in addition to cross-reacting with each other, intersect with major signaling pathways (PI3-K / Akt; MEK-dependent pathway) in BCSC. Thus, their successful targeting is very ambitious, since inhibition of one circuit often causes activation and / or hyperactivation of other pathways [24]. Unfortunately, less is known about the classical and nonclassical pathways normally activated by SSR in BC cells. In subsequent sections of this review, we discuss the scant data in the literature that consolidate and improve our knowledge of this topic.

ER in BCSCs

Two isoforms of ER, ER α and ER β , are expressed in BC [25-28], with ER α being the most important hormonal biomarker in this cancer. ER α is expressed in

almost 75% of BC, and its presence correlates positively with the response to endocrine therapy [29]. In some studies, ER β has also been associated with improved survival in patients treated with tamoxifen [30,31]. The two ER subtypes are encoded by genes on different chromosomes and differently activate common elements of estrogen response (ERE) in gene reporter assays [32,33]. In target cells, both ER isoforms act through transcriptional and non-transcriptional mechanisms, thereby controlling cell cycle progression, invasiveness, and metastatic phenotypes [34-36]. Recently, a new 36 kDa-truncated ER α variant (ER α 36) has been identified that is expressed in both ER α -positive and negative BC cells. ER α 36 lacks both ER transactivating domains, localizes on the plasma membrane as well as in the cytoplasm and responds to estrogens and antiestrogens. It also regulates BC cell proliferation and promotes BC aggressiveness [37].

However, the expression and role of each ER isoform in BCSCs is still a matter of debate. Most studies indicate the absence of ER α in BCSCs [38]. It has been continuously reported that CD44 + / CD24- / ALDH + CSC lack ER or express it at very low levels [15,39]. Although ER α -negative, both BCSCs and MaSCs can be increased by estradiol stimulation [38], probably because other receptors (eg, G-protein-coupled receptor 30, ER α 36 or ER β) can mediate estrogen in these cells. These findings will be discussed in detail below.

Additional studies also claim that BCSCs do not contain ER, and that the receptor rather arises from the original BC. As a result, ER α will be expressed in BCSCs derived from ER α -positive BC, while it will be absent in BCSCs derived from ER α -negative BC [40]. Since this occurs in prostate CSCs [41,42], these rather different results may be related to experimental differences such as ER assays, cell culture conditions, and BC cell populations.

However, it is now generally accepted that estrogens act on BCSCs through non-genomic biomarkers of breast cancer stem cells.

Table 1

Breast cancer stem cell biomarkers

Biomarker	Expression	Role	Source .
CD44	Positive / High	Maintaining multipotency of breast cancer stem cells, cell proliferation and cell migration	Schabath <i>et al</i> [21], 2006
CD24	Negative / Low	Cell migration and metastases	Jaggupilli <i>et al</i> [82], 2012
ALDH1	Positive / High	Stem formation , cell migration, invasion and tumor metastases	Ma <i>et al</i> [28], 2017
CD133	Positive	Cell differentiation	Sin <i>et al</i> [83], 2017
CD49f	Positive	Tumor initiation and metastasis	Sin <i>et al</i> [83], 2017
CD90	Positive	Drug resistance and poor prognosis	Schabath <i>et al</i> [21], 2006

CD44: cluster of differentiation 44; CD24: cluster of differentiation 24; ALDH1: aldehyde dehydrogenase 1; CD133: cluster of differentiation 133; CD49f: cluster

of differentiation 49f; CD90: cluster of differentiation 90.

Signaling by activating GPR30, a seven-name transmembrane receptor expressed in both ER-positive and ER-negative breast cancer [43]. This has been reported to interfere with the Behemoth's pathway through taphazzin activation (TAZ). In the BCSC, TAZ activation is responsible for the metastatic properties of BC [44]. Again, elevated TAZ levels, coupled with its increased activation, can be found in poorly differentiated BCs, where it confers the self-renewal capacity of non-CSCs [45]. Other reports indicate that estrogens act by activating ER α or a variant thereof, ER α 36. In ER α -positive tumor spheres derived from MCF-7 harvested on day 21 (tertiary tumor spheres), when they have high levels of stem markers and the ability to self-renew, estrogen stimulation increases levels of PI-9, a granzyme B inhibitor. The effect weakens immune surveillance and increases both the number and size of tumor spheres [46]. ER α 36, which has no transcriptional activity and acts exclusively through non-genomic action, could mediate these responses, since estrogen treatment of tertiary tumor areas increases ER α 36 levels and decreases full-length ER α [46]. Although ER α 36 is predominantly a plasma membrane-based receptor and lacks the transactivating domains of both AF-1 and AF-2 ER α 66 (ER α wt), it also acts as a negative regulator of genomic estrogen signaling mediated by both ER α wt and ER β [47]. A small amount of ER α 36 is found in the nucleus, where it competes with two receptors for DNA binding sites (ERE, [47]).

Again, after estrogen stimulation, ER α 36 rapidly activates the MAPKs / ERK pathway, thus triggering cell proliferation [47]. The MAPK / ERK pathway is activated not only by estrogens, but also by the antiestrogenic tamoxifen in a stronger and more prolonged manner [47]. These results may explain the major role of ER α 36 in BC antiestrogen resistance

The expression of ER β and stem cell markers has recently been studied in mammospheres obtained from fresh primary BC and BC cells. In about 50% of cases, ER β was elevated in BCSCs. More importantly, it was co-expressed with CD44 and ALDH1 in the absence of ER α . Again, ER β was responsible for mammosphere growth and glycolysis activation. Thus, ER β can actually be considered as a stealth marker in BC cells [28]. This study offers new clues for a better understanding of ER β function in BC and, in contrast to the concept that BCSCs respond to estradiol through paracrine signaling, it suggests that estrogens directly induce BCSCs through ER β activation. Finally, the identification of ER β -rich BCSCs offers new therapeutic options based on the use of ER β antagonists in combination with classical drugs (antiestrogens or aromatase inhibitors) commonly used in the clinical management of BC.

In general, the data discussed to date indicate that ER α and ER β can both be found in BCSCs. Depending

on the specific context, they may be aimed at limiting the proliferative and invasive frequency of BCSCs. Although these cells are generally resistant to classical ER-targeted therapies, the data presented supports the idea that ER acts unconventionally in BCSCs, paving the way for the study of new GPR30 [48] or ER β [28] inhibitors or drugs / peptides that specifically inhibit non-genomic action induced by ERs in BC [25,35]. Some of the main pathways operating in BCSC are shown in Figure 1.

PR in BCSCs (Progesterone in breast cancer)

Progesterone and its receptor play a key role in the lateral branching of the mammary gland, which occurs during puberty, as well as in the development of lobular-alveolar development during pregnancy. PR exists in two isoforms, PR-A (PR-A, 94 kDa) and PR-B (PR-B, 114 kDa). The same gene encodes two PR isoforms, but PR-A lacks the first 164 amino acids of PR-B and can act as a trans-repressor for the transcriptional activity of PR-B, although it can even transpress ER activity, androgen receptor (AR) and glucocorticoid and mineral-corticoid receptors [49]. The two isoforms are co-expressed at the same levels in normal breast cells, but this balance is altered in cancer cells, where one of the two isoforms, PR-A, is usually overexpressed [50].

By enhancing the proliferation of SC and increasing the number of progenitor cells, progesterone affects the growth of the mammary gland [50] and induces the formation of a breast tumor [38]. As for ER and AR, ligand-activated PR works in BC cells through genomic and non-genomic mechanisms, thus controlling transcriptional mechanisms, epigenetic modifications, and rapid signaling pathways depending on Src or PI3-K activation [51]. This is, however, a simple picture of the action of progesterone in target cells. Now we understand that the rapid activation of signaling cascades by ligand-bound PR promotes chromatin remodeling and gene transcription, on the one hand [52]. On the other hand, a progestin-activated transcriptional mechanism can regulate cytoplasmic events, which affects the activation of signaling [53].

In women with preexisting BC, progestins are responsible for the reactivation of ER / PR cancer stem cells [54]. Progesterone stimulation of differentiated cancer cells (ER+, PR+, CK5-) increases the number of stem cells (ER-, PR-, CD44+, CK5+) in the tumor. Ligand activation of PR does not alter the number of cells, but rather dedifferentiates the more abundant ER+ / PR+ / CK5- cells into ER- / PR- / CK5+ cells with stem-like properties [54]. In particular, the activated PR binds two putative progesterone response elements located in the CK5 promoter. This transcriptional regulation ultimately leads to an increase in CK5 expression and is more efficient in small, almost undetectable BCs, allowing them to recur.

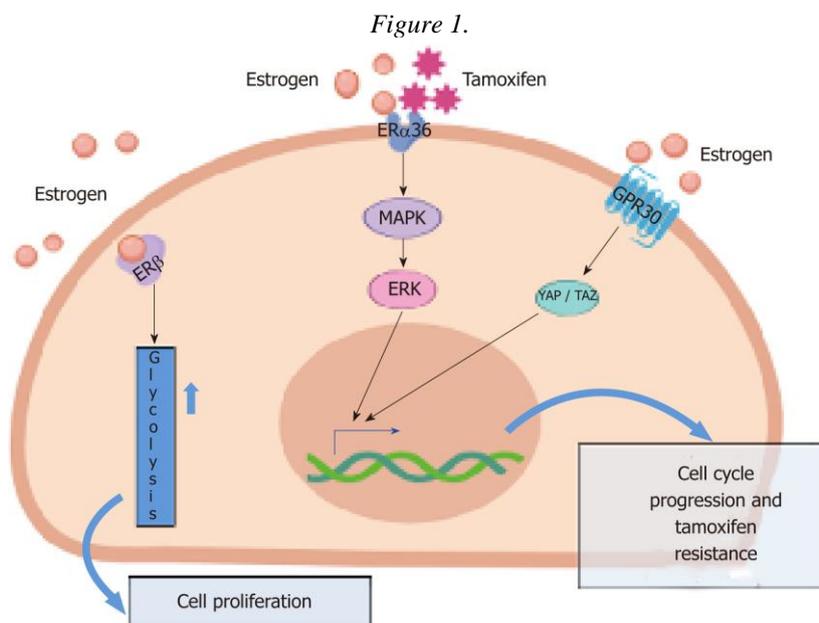


Figure 1. Main pathways activated by different estrogen receptor isoforms in breast cancer stem cells responsible for cell proliferation and tamoxifen resistance. GPER: G protein coupled receptor; ERα36: estrogen receptor alpha 36; ERβ: beta estrogen receptor; MEK: mitogen activated protein kinase; ERK: extracellular signaling regulated kinase; YAP: YES-associated protein; TAZ: Tafazzin.

PR is usually considered as an indicator of the transcriptionally intact ER axis [55]. In BC-derived T47D cells, which express two PR isoforms under basal conditions, PR-A is the main driver of CSC expansion, while PR-B regulates anchoring-independent growth. In particular, the expansion and biochemical features of CSC (ALDH1, CD44 + / CD24-, CD49f + / CD24-) are associated with the phosphorylation of PR-A at the Ser 294 residue. Therefore, the PR-A + tumor spheres are small, but express enriched basal a similar CSC phenotype (CD49f + / CD24-), indicating an increased malignant and metastatic potential. On the other hand, PR-B + tumor spheres are larger than PR-A + spheres and have a CD49f + / CD24 + phenotype. Cells expressing the PR-A mutant, which cannot be phosphorylated at the Ser 294 residue, exhibit a weakened CSC phenotype associated with enhanced anchorage-dependent growth [55].

Taken together, the data presented to date highlight the role of the progestin / PR axis in maintaining BCSC survival and growth and highlight the role of each PR isoform in these processes. A better understanding of the role of each PR isoform in BCSCs could open up new perspectives in the therapeutic approach to this type of cancer, especially in its recurrent forms.

AR at BCSC

AR expression is closely associated with a group of hormone-related diseases, including cancers of the prostate, breast, ovary, pancreas, liver, and lungs. It is also associated with a variety of diseases, which include muscle wasting, osteoporosis, diabetes, and neurodegenerative disorders [56-58].

AR is expressed in both ER-positive and ER-negative BC [59]. In ER-positive BC, AR is correlated with a more favorable prognosis, while it is generally thought to control progression and drug resistance in

triple negative BC [2,60]. It is believed that AR activation by androgens regulates important changes in gene transcription or signaling pathway activation (i.e. Src / Ras / MAPKs, PI3K / Akt, filaminA / Rac). These actions control various processes, including proliferation, migration, and invasiveness of normal and cancer cells [25, 58, 61, 62].

The role of androgens and ARs in BCSC has not been adequately studied, and few data are published in the literature. After examining the US National Library of Medicine (<https://www.ncbi.nlm.nih.gov/pubmed/>), we found only 43 results that matched our analysis. In a recent study [63], AR expression was correlated with stem markers (ie CD44, CD24, and ALDH1) in 166 BC patients. A significant correlation between AR and CD24 was observed in stages I-III of invasive BC. This phenotype correlates with favorable clinical and pathological features and identifies a subgroup of patients with better disease-free survival [63]. However, AR expression in CSCs may contribute to BC invasiveness. Forced suspension culture ARpositive MDA-MB453 with SUM195pt cells induces an increase in the BCSC-like population and protects cells from anoikis. These effects depend on AR, as shown by experiments with the antiandrogenic enzalutamide [64].

Again, dihydrotestosterone treatment increases the CK5 + population in MCF-7, but not in T47D cells. It is noteworthy that CK5 + cells are resistant to therapy, have an increased potential for tumor growth, and express the SC marker CD44 [65]. The finding that androgens have different effects in the two cell types derived from BC may be related to different intersections of AR with other SSRs occurring at the level of transcription or non-transcription in cells derived from breast and prostate cancer [41,42,66]. In addition, AR maintains the BCSC population in AR-

positive TNBCs, since its knockdown or treatment with enzalutamide reduces the number of ALDH1+ cells, as well as the formation of the mammosphere [67]. It should be noted that synthetic progestins activate AR [68]. Therefore, progestin-induced BCSC enrichment may be associated with AR activation [69]. In addition to reinforcing the concept that SRs are substituted for each other in mediating important biological effects [25,70,71], such a mechanism may take place in BCs expressing high AR levels in combination with low or undetectable PR levels. In accordance with this hypothesis, it can also be argued that progestins have a double impact, affecting both AR and PR. Overall, these considerations account for the clinical correlation between progestin-treated women with an increased risk of BC, and highlight the complexity of the role of AR in BC pathogenesis. The contribution of the androgens / AR axis to BCSC regulation, however, is still uncertain.

STEROID RECEPTOR-REGULATED MYRNS IN BCSC

In BCSCs, steroid receptors are also able to control miRNA levels. ER α regulates the expression of microRNA (miRNA), thereby controlling the ability of BCSCs to influence proliferation, death, adhesion, and intercellular communication [72]. In BCSCs, activated ER α binds to a specific ERE flanking the miRNA-140 promoter region, thereby suppressing miRNA-140 transcription and enhancing the expression of SOX2, a stem marker that maintains SCs [73].

PR regulates different microRNAs in BC. Among them, the miR-29 and mi-R 200 families are involved in the formation of BCSC. The miR-29 family includes three members, miR-29 a, b, and c, which are all suppressed by progestins in BC. This suppression is associated with an increase in the transcription factor KLF4, as well as CD44 and CK5, followed by cell dedifferentiation [74]. It has also been shown that a progestin-induced increase in GATA3 leads to downregulation of miR-29b and a subsequent increase in the BCSC population [75]. Again, the miR-200 family includes miR-141, which is suppressed by PR. miR-141 increases the population of CD44+ and CK5+ cells while simultaneously decreasing the levels of PR and Stat-5, two important transcription factors involved in controlling the fate of breast cells [76].

There is no research on the regulation of miRNA by AR in BCSCs. Few data obtained have shown that AR is responsible for the suppression of microRNA [77]. In cells, ER- / PR- / AR + AR enhances the differentiation of miRNA let7a, which, in turn, inhibits cell proliferation by suppressing c-MYC and K-Ras [78].

Overall, the data obtained here indicate that ER and PR increase miRNA levels involved in CSC formation and differentiation. As such, they represent excellent targets for attenuating CSC formation and probably BC recurrence.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

An increasing number of studies are trying to elucidate the role of BCSCs in the pathogenesis and progression of BC. Although interest in the study of

BCSCs is currently high, it is not yet known how these cells work in cancer, and what are the features of the pathways involved.

Based on the stem cell hypothesis, cancer can arise from a cell population with a self-renewing stem cell. Such property may already be owned by the cells or may be acquired. Thus, malignant tumors originating from these cells are organized in a hierarchical manner, in which SC or stem cells control the malignant process and generate a population of non-renewable cells that regulate the volume of cancer [79, 82].

Less is known about the role of SSR in SC. Although some reports claim that ERs are not expressed in BCSCs, many studies have been published regarding the expression and role of this receptor, with very conflicting data. The classical ER α isoform acts, for example, through a genomic pathway that regulates miRNA expression and the SC phenotype, while the ER α variant, ER α 36, or GPR30, may act through non-genomic pathways, thereby promoting cell dedifferentiation, tumor metastases and resistance therapy. Surprisingly, ER β is generally considered a stem marker in BCSC. Its targeting of specific antagonists can be considered mono- or combinatorial therapy in the clinical management of BC.

Both PR isoforms appear to play a key role in BCSC expansion and proliferation and are closely related to the metastatic and malignant properties of BC. Thus, in-depth knowledge of the PR controlled mechanism in BCSCs could be a big step forward in predicting BC recurrence and inhibiting the growth of BC refractory to current treatments. The role of AR remains uncertain and data on its behavior in BCSC are very scarce. Therefore, it is very difficult to draw any conclusions regarding the role of this receptor in BCSC.

In conclusion, the data discussed indicate that PR isoforms and ER β are more compelling targets for the reduction of the BCSC population in human BC. Hence, a better and fuller understanding of other SSRs is required to develop new treatments for BC and control the drug resistance that often entails BCSC.

Preclinical and clinical data indicate that BCSCs control progression, invasion, metastasis, and drug and radiation resistance. Consequently, the elimination of the BC is strictly dependent on the elimination of the BCSC. New molecules such as GDC0449 or eribulin have been clinically tested for their anti-tumor stem cell activity [80,81]. Further preclinical and clinical studies are needed to elucidate the significance of CSC signaling in BC recurrence and therapy resistance.

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PROSPECTS FOR USE OF TARGET DRUGS IN NEOADJUVANT CHEMOTHERAPY OF COLORECTAL CANCER METASTASIS IN THE LIVER (REVIEW)

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SUMMARY

To increase the effectiveness of chemotherapy (CT) of metastases of colorectal cancer (CRC) in the liver therapy, targeted drugs are used, usually in combination with standard CT. However, at present, there is not enough clinical research data confirming the effectiveness of a combination of various chemotherapy regimens with drugs-inhibitors of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) in conditions of neoadjuvant chemotherapy in this category of patients, which indicates the need for similar studies.

Key words: colorectal cancer, liver metastases, preoperative chemotherapy, targeted drugs.

Colon cancer is one of the most common malignant tumors, annually in the world from 800 thousand to 1.2 million patients with colorectal cancer and about 600 thousand deaths from these diseases are registered (approximately 56% of all cases). In 20% of patients with colorectal cancer (CRC) at the time of diagnosis, distant metastases are detected, primarily in the liver, and in 50% of patients metastases develop during the course of the disease, which becomes the cause of their death [1,3,11-15].

To date, surgery has been the only treatment to achieve long-term survival in patients with liver metastases of CRC. However, only a small group of patients (15-20%) can count on a potentially radical treatment, including removal of the primary tumor of the colon and liver resection. At the same time, traditional liver resection in operable patients allows achieving a 5-year survival rate of 21-37%. Recent advances in chemotherapy (CT) for metastatic colorectal cancer have significantly expanded the indications for treatment of patients at all stages of the