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Research Progress of Breast Cancer Stem Cell Stemness and Breast Cancer Recurrence

Huifang Zeng[1], Guanming Lu[2*]

[1]Graduate School, Youjiang Medical University for Nationalities, Baise, China
[2]Department of Breast and Thyroid Surgery, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
Email: 1416850394qq.com, *luguanming@yeah.net

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Abstract

Currently, breast cancer is the most common malignant tumour in Chinese women with a high incidence rate, and recurrence and metastasis are the main reasons affecting survival. Breast Cancer Stem Cells (BCSCs) are stem cells capable of continuous regeneration in vivo with strong self-renewal ability and multidirectional differentiation potential, which are highly tumourigenic and insensitive to radiotherapy and chemotherapy, and are highly susceptible to breast cancer recurrence. Therefore, exploring the stemness of BCSCs and their mechanism associated with recurrence is important for developing new therapeutic strategies, improving therapeutic efficacy, and improving patient prognosis.

Keywords

Breast Cancer Stem Cells, Stemness, Recurrence, Tumour Microenvironment, Drug Resistance

1. Backgrounds

According to the latest cancer statistics for 2024, breast cancer accounts for 32% of all newly diagnosed malignant tumors in women, ranking first among new malignant tumors in women [1]. Its incidence is increasing year by year and it is a major threat of death from malignant tumors in women. The cause of breast cancer is still unclear. So far, scientists have not found the exact cause of breast cancer, but many high-risk factors related to breast cancer have been found. The breast is a target organ for various endocrine hormones, among which estrone and Estradiol are directly related to the incidence of breast cancer. Early menarche, late menopause, infertility, late age of first childbearing, short lactation time, estrogen replacement therapy after menopause, etc. can increase or pro-

long estrogen exposure in the body, which is closely related to the incidence of breast cancer. In addition, genetic factors are also high-risk factors for breast cancer [2] [3]. The spread of breast cancer screening and improved treatments in recent years have led to an increase in survival rates and a decrease in mortality. However, breast cancer recurrence remains a serious challenge with serious implications for patient health and survival [4].

Breast cancer stemness (Also known as the phenomenon of breast cancer stem cells) refers to the fact that some breast cancer cells exhibit characteristics similar to those of stem cells, including self-renewal, multidirectional differentiation, less susceptibility to death, and resistance to treatments such as chemotherapy and radiotherapy, and a subpopulation of tumor-initiating cells that have these stemness characteristics is called cancer stem cells (CSCs) [5]. This kind of cell can make the tumor easy to occur distant metastasis through its own movement, migration and other characteristics, in addition, it can also make the tumor cells no longer sensitive to a variety of therapeutic means through the characteristics of "dormancy", thus causing therapeutic resistance, and ultimately leading to tumor recurrence. BCSCs stemness is an important cause of treatment resistance, early recurrence and poor survival prognosis in breast cancer [6].

The progression of breast cancer is highly dependent on the interaction between tumor cells and tumor microenvironment (TME). TME is beneficial for enhancing the self-renewal ability and multi-directional differentiation potential of BCSCs. The role of BCSCs in the TME is significant and multifaceted. BCSCs interact with other cell populations within the TME, including immune cells, cancer-associated fibroblasts (CAFs), Mesenchymal stem cell cells (MSCs) and cancer cells. BCSCs affect the tumor immune microenvironment by interacting with immune cells and modulating immune responses. Furthermore, their interaction with CAFS and MSCS contributes to tumor progression and differentiation. BCSCS influences the behavior and characteristics of tumor cells, such as proliferation, migration, epithelial-mesenchymal transition (EMT) and dormancy, by establishing a communication network with tumor cells. The complex interactions between BCSCs and TME components highlight the need for further research [7].

This review summarizes the development of BCSCs and their characteristics, and describes the correlation between BCSCs stemness and breast cancer recurrence, providing new ideas and strategies for future breast cancer treatment.

2. The Development of CSCs and Their Characteristics

"The term "stem cells" was first coined in 1909 and has gradually come to the forefront of people's minds [8]. In 2003, using a nude mouse transplantation tumor model of breast cancer, AL-Hajj *et al.* [9] found that only 100 cells with a CD44+/CD24−/Lin-phenotype were required to form transplantation tumors in recipient mice, whereas 10,000 unspecific breast cancer cells failed to produce the same number of tumors in the same culture cycle over the same time period Tumors. Although such cells with the CD44+/CD24−/Lin-phenotype account

for only 2% of breast cancers, they are at least 50 times more tumorigenic than other tumor cells. Thus, AL-Hajj *et al.* demonstrated for the first time that breast cancer originates from CD44+/CD24−/Lin-cells (*i.e.*, BCSCs). In 2007, Ginestier *et al.* [10] found that a subpopulation of cells with high acetaldehyde dehydrogenase (ALDH) activity can initiate tumors *in vivo* and *in vitro*, and that ALDH+ is highly expressed in BCSCs.

Currently, there are two hypotheses about the origin of breast cancer stem cells [11], one is that breast cancer stem cells originate from adult stem cells and acquire malignant behaviors through genetic alterations, and the other is that breast cancer stem cells are transformed from early progenitor cells through self-renewal ability. These two hypotheses provide important clues for understanding breast carcinogenesis, and in recent years, more and more experimental data support the hypothesis of BCSCs and their characterization, and the field related to BCSCs has become one of the hotspots in breast cancer research.

3. Stemness Characterization of BCSCs

3.1. Self-Renewal Capacity and High Tumorigenicity of BCSCs

Self-renewal capacity is one of the key features of stemness of CSCs, which allows CSCs to persist in tumor tissues through continuous division and differentiation and can drive tumor growth and spread. The maintenance of stemness in CSCs is not a constant process, but a dynamically changing and relatively transient state. During continuous differentiation and passaging, CSCs gradually lose their stem cell properties, but under certain conditions can regain their stem cell properties of self-renewal capacity [12].

CSCs are in the regulatory network of a series of signaling pathways, including Wnt/β-catenin, Notch, Hedgehog (Hh), and BMI1 pathways, and the activation of these molecular pathways tends to determine the active state of CSCs, which plays a central role in regulating and maintaining the process of CSCs self-renewal [13]. For example, under hypoxic conditions, a protein called integrin-linked kinase (ILK) interacts with integrin β1 (integrin) to form a key binding site. Through this combination, ILK is able to activate the ILK/PI3K/Akt signaling pathway, the activation of which promotes the continuous self-renewal of these stem cells in response to the hypoxic environment. This ability to self-replicate and renew is one of the key drivers of tumor growth and spread [14]. Transcription factors also play important roles in the self-renewal of CSCs. For example, SOX2 plays an important role in the development and maintenance of the stem cell state and is involved in the regulation of self-renewal, tumor growth, and therapeutic resistance of CSCs [15].

BCSCs are a very small subpopulation of breast cancer tissues with a core of self-renewing stem cells [16], meaning that they are able to continuously divide and differentiate, a property that makes BCSCs highly tumorigenic. In a variety of solid malignancies, CSCs are poorly differentiated, located at the top of the cell layer within multiple adult tissues, and are able to demonstrate extremely

strong tumorigenic capacity; they can not only form tumors independently, but also spread and metastasize by fusing with other normal cells to cause more extensive damage. BCSCs have the characteristics of CSCs described above, can be symmetrically divided into two CSCs or one CSC and a daughter cell for expansion [16], and can be maintained in this way to maintain their structures and functions. In contrast, progenitor or differentiated cells lack this ability for continuous growth and self-replication [17], suggesting that BCSCs can undergo multiple transformations through self-renewal to adapt to changing environmental demands. In addition, also unlike differentiated cells, in vivo xenografts with BCSCs can produce considerable tumors, *i.e.*, highly tumorigenic, in mice with severe combined immunodeficiency disease (SCID). Therefore, understanding and controlling the biology of self-renewal of BCSCs is crucial for the development of effective therapeutic approaches.

3.2. Multidirectional Differentiation Potential of BCSCs and Generation of Heterogeneous Tumors

Multidirectional differentiation is another important characteristic of the stemness of CSCs. CSCs are capable of directional differentiation both in vivo and ex vivo, not only being able to differentiate into a wide range of cell types in an in vitro culture environment, but also responding to the complex demands of the in vivo microenvironment, generating cancer cells with different biological properties by establishing a reversible or plastic hierarchy of differentiation, leading to the formation of a range of cell types within tumors, resulting in tumor cell heterogeneity, which in turn produces heterogeneous tumors. Where mutations in already differentiated cells can, in turn, acquire self-renewal capabilities and establish new hierarchies of CSCs differentiation, eventually differentiated cells can also be differentiated to acquire CSCs properties under specific conditions [18], thus increasing intra-tumor heterogeneity. This ability allows CSCs to adapt to and utilize a variety of surrounding signaling molecules and growth factors, and to exhibit different phenotypes and associated molecular signatures, thus demonstrating robust plasticity during tumor progression.

BCSCs can exhibit different phenotypes, not only in terms of marker heterogeneity, but also in terms of multiple different subtypes, with features such as plasticity of bidirectional transition from non-CSCs to CSCs states. For example, Chaffer *et al.* [19] demonstrated that upregulation of zinc finger E-box binding homology box 1 (ZEB1) protein expression induced by TGF-β induced the conversion of CD44− cell phenotypes (*i.e.*, non-BCSCs) to CD44+ cell phenotypes (*i.e.*, BCSCs) that lead to breast cancer formation. Treatment can alter intra-tumor heterogeneity by affecting phenotypic plasticity and thereby altering intra-tumor heterogeneity. For example, in the treatment of breast cancer, paclitaxel induces the transformation of differentiated cells to the state of BCSCs (CD44+CD24−), which allows for increased resistance to treatment [20].

The heterogeneity of BCSCs plays a role in the transition between a prolifera-

tive epithelioid-like state characterized by high acetaldehyde dehydrogenase activity (E-bCSCs) and a quiescent mesenchymal-like invasive state characterized by CD44+CD24− expression (M-bCSCs) [21], and this switching from the E state to the M state is very similar to epithelioid mesenchymal transition (EMT) programs, suggesting that the heterogeneity may be associated with metastatic dormancy in breast cancer cells. It has also been found that epigenetic alterations such as DNA methylation, histone modifications, and miRNAs play an important role in the acquisition of CSCs. For example, non-CSCs can be reprogrammed into CSCs through epigenetic changes that are associated with phenotypic heterogeneity of cancer cells [22]. EMT is to provide a direct link between epigenetics and CSCs by relying on various epigenetic modifications that affect the expression of the mesenchymal transcription factor ZEB1 [23].

The unique microenvironment of CSCs is an important factor in maintaining the "stemness" and "non-stemness" transformation of CSCs, leading to tumor heterogeneity. Recent studies [24] have shown that BCSCs have the ability to manipulate the immune microenvironment as a means of promoting their own survival and proliferation, and that while influencing the recruitment and polarization of immune cells, immune cells within the microenvironment are also influencing the behavior and properties of BCSCs. The multidirectional differentiation potential of BCSCs is at the root of the generation of tumor heterogeneity, and they can be resistant to radiotherapy, leading to treatment failure of breast cancer and consequently to recurrence.

4. Correlation between BCSCs Stemness and Breast Cancer Recurrence

4.1. ATP-Binding Cassette Transporter Proteins (ABC Transporter Proteins) and Resistance in BCSCs

ATP-binding cassette transporter proteins are a class of ATP-driven pumps consisting of two transmembrane structures flanked by ATP-binding domains. The human genome is composed of 49 basic ABC genes arranged in seven subfamilies called ABCA-G [25]. Overexpression and preferential activation of ABC transporter proteins are thought to be the main cause of chemoresistance in CSCs [26]. ABC transporter protein transports and excretes a variety of substances, including metabolites, drugs, toxic substances, source lipids, peptides, peptides and steroids, and is regarded as a detoxification pump, which affects pharmacokinetics and therapeutic efficacy due to its ability to facilitate the excretion of chemotherapeutic agents through multiple pathways, greatly reducing the effectiveness of chemotherapeutic agents that originally had significant inhibitory or cancer cell-killing activity in the killing of CSCs. ABC transporter proteins protect CSCs from the killing effects of drugs, which leads to the phenomenon of primary multidrug resistance (MDR) of tumor cells to chemotherapeutic drugs [27].

Among the ABC transporter proteins, P-glycoprotein (MDR1/ABCB1), mul-

tidrug resistance-associated proteins 1 and 2 (MRP1 or ABCC1 and MRP2 or ABCC2), and mammary resistance protein (BCRP/ABCG2) are the key molecules of the MDR, and also associated with the pathophysiology of BCSCs [28]. It was shown that three ABC superfamily multidrug efflux pumps, ABCB1/MDR1, ABCC1/MRP1 and ABCG2/BCRP, were associated with drug resistance in cancer cells [29]. For example, ABCB1/MDR1, whose physiological role is to excrete toxic metabolites in normal tissue epithelium, is expressed in various solid cancers and can lead to chemotherapy failure [30]. In addition to ABCB1/MDR1, ABCC1/MRP1 is an important class of oncogenes, which is highly expressed in many tumor cells and is resistant to many anticancer drugs, such as anthracyclines, Vinca alkaloids, and camptothecin [31]. ABCG2/BCRP is at the center of a complex set of biological processes and was first identified from chemotherapeutic drug-resistant breast cancer cells, where this protein is essential for cancer cell adaptation and evasion of drug attack, and is a key determinant of drug uptake, distribution, and elimination. For example, the down-regulation of ABCG2 enhances the chemosensitivity of BCSCs [32]. In addition, Sun *et al.* [33] found that BCSCs exhibited higher chemosensitivity when siRNAs blocking the expression of ABC transporter proteins were added to the BCSCs culture medium together with drugs.

4.2. Resistance to and Repair of DNA Damage

DNA damage is a biological process that poses a serious risk to human health, and DNA damage in eukaryotic cells is caused by either endogenous factors (e.g., oxidative damage, base mismatches) or exogenous factors (e.g., ionizing radiation, ultraviolet light, and chemical mutagens) [34]. Among them, DNA Double Strand Break (DSB) is an extremely serious form of DNA damage, which, if not repaired in time, will lead to serious consequences such as cell cancer or death. In vertebrates, non-homologous end-joining (NHEJ) as well as homologous recombination (HR) are used as two conserved repair pathways to deal with these toxic DNA break ends. After DNA damage in tumors, CSCs can be repaired through the DNA damage response (DDR) pathway, allowing cancer cells to survive after treatment [35], which leads to tumor recurrence after treatment [36].

The ability of CSCs to resist and repair DNA damage is most evident in ionizing radiation. Radiation-induced DNA damage ultimately affects cell proliferation and alters the cell cycle, leading to apoptosis or other programmed cell death [37], and it can also lead to DNA damage through the production of highly reactive free radicals. CSCs, however, can survive DNA damage by activating a complex set of responses, which leads to cancer recurrence after DNA damage. Signaling pathways and transcription factors associated with CSCs are involved in DNA damage repair, for example, activation of the Wnt/β-catenin signaling pathway not only enhances DNA damage repair in CSCs, but also promotes EMT, which induces radioresistance. Transforming growth factor β (TGF-β)

regulates radiation resistance, cell cycle distribution, and inhibition of ROS in BCSCs by inducing EMT [38], which improves resistance to and repair of DNA damage in BCSCs.

In breast cancer, BCSCs exhibit radiation resistance through high expression of relevant stemness genes and activation of anti-apoptotic and antioxidant signaling pathways [39], which may render radiation-induced DNA damage resistant and lead to radiation nullification. It has been found that radiation resistance of ALDH1+ BCSCs in S phase may be associated with enhanced DSB repair and HR-induced replication fork protection [40]. In addition, BCSCs enable faster DNA damage repair by enhancing NHEJ activity [41]. Survival of BCSCs after radiation induction was also associated with low levels of endogenous reactive oxygen species (ROS) expression in the free radical scavenging system, which was significantly reduced and compared with non-tumorigenic cells (NTCs). Low levels of ROS in BCSCs resulted in little DNA damage, and enhanced anti-ROS in BCSCs contributed to reduced levels of post-irradiation DNA damage [42].

4.3. Stationary of BCSCs

Tumor dormancy is a clinically undetectable cancer state in which disseminated tumor cells remain in a nonproliferative quiescent state for an extended period of time, and the awakening of these dormant cells leads to MDR, minimal residual disease (MRD), tumor growth, cancer recurrence, and metastasis. CSCs can then mediate treatment resistance through quiescence, leading to tumor recurrence and metastasis [35]. This is because most chemotherapeutic agents, including mitotic inhibitors, antimetabolites, and topoisomerase inhibitors, may exhibit tumor cytotoxicity only to proliferating cells. CSCs are resistant to a variety of harsh environmental conditions such as chemotherapy, radiotherapy and hypoxia when they remain in a quiescent state and resume growth after cessation of treatment, leading to recurrence [43].

The quiescence of CSCs is controlled by intrinsic regulatory mechanisms and extrinsic signals from the microenvironment. For example, the oncogene p53, retinoblastoma protein (RB), and the cell cycle protein-dependent protein kinase inhibitors p21, p27, p57 are involved in the regulation of CSCs quiescence [35]. Multiple signaling pathways, including TGF-β/SMAD [44], BMP [45], and YAP/TAZ [46] are associated with CSCs quiescence, as well as PTEN, a negative regulator of the PI3K-AKT pathway, also regulates CSCs quiescence [47]. It was shown that metabolic regulation and epigenetic modifications are also involved in the maintenance of quiescence in CSCs [48]. In xenograft tumor models, protein 4 of the SET structural domain (SETD4) induces quiescence of BCSCs, leading to resistance to radiotherapy, and SETD4 is catalytically promoted to promote heterochromatin formation via H4K20me3, which epigenetically controls quiescence of BCSCs [49].

Pilar *et al.* [50] by analyzing infiltrating cells inside and outside the ecological

niche of quiescent cancer cells (QCCs) in triple-negative breast cancer (TNBC), found that clusters of QCCs appeared to be populated with more depleted T cells, tumor-protective fibroblasts, and dysfunctional dendritic cells. It is shown that QCCs constitute immunotherapy resistance by orchestrating an immunosuppressive environment of local hypoxia and preventing T cell function. Thus, elimination of quiescent cancer cells (QCCs) holds promise for reducing immunotherapy resistance and preventing TNBC recurrence. Similarly, quiescent BCSCs can be coordinated with the tumor microenvironment, leading to drug resistance and recurrence of breast cancer [51]. When BCSCs are in a quiescent state, they are unable to enter the normal cell proliferation cycle, which makes them resistant to attack from the immune system as well as to interference from multiple anticancer therapies. Moreover, this quiescent state is reversible and BCSCs can be activated and re-enter the cell cycle under favorable conditions, leading to tumor recurrence and metastasis [35].

4.4. BCSCs and Tumor Microenvironment (TME)

The tumor microenvironment (TME) is a complex environment composed of cancer cells, CSCs, cancer-associated fibroblasts (CAF), extracellular matrix (ECM), immune cells, blood vessels and differentiated cells [52]. TME has three distinctive features: hypoxia, chronic inflammation and immunosuppression, which constitute a complex regulatory network and play a key role in tumorigenesis and progression. It has been found that rapid proliferation of tumor cells induces hypoxia, which enhances the stemness of CSCs and maintains their plasticity, resulting in resistance to radiotherapy, leading to recurrence and metastasis [53]. The effects of hypoxia on CSCs are controlled by a series of hypoxia-inducible factors (HIFs), which play a key role in tumorigenesis and progression as the main regulators of CSCs' adaptation to hypoxia and nutrient deficiency. HIF not only promotes angiogenesis in tumors, but also enhances the "stemness" of tumor cells and inhibits apoptosis [54].

BCSCs are a dynamic population of tumor-initiating cells in the tumor environment and are an important cause of recurrence within the TME [55]. Interactions between BCSCs and other components within the TME play a major role in microenvironment-mediated dry enrichment [56]. On the one hand, immune cells in TME can regulate the stemness of BCSCs; on the other hand, BCSCs in TME can also escape the body's immune surveillance by interacting with cells such as tumor-associated macrophages (TAMs), T regulatory (Treg) cells, tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, and dendritic cells (DCs) [57].

TAM promotes the stemness of CSCs by secreting a variety of inflammatory factors, thereby evading the body's immune surveillance and promoting tumor progression [58]. For example, IL-8 produced by TAM promotes the amplification of BCSCs and prevents their programmed death [59]. In addition, TAM produces pro-inflammatory cytokines IL-6, IL-10 and activates the STAT3 sig-

naling cascade response to promote self-renewal of BCSCs, leading to resistance of BCSCs to chemotherapeutic agents [60]. TIL is a class of immune cells composed of CD8+ cytotoxic T cells, CD4+ helper T cells, and CD4+ regulatory T (Tregs) cells [61]. In TME, T cells are the predominant immune-responsive cells during early tumorigenesis and development but are transformed into Treg cells after prolonged stimulation and interaction with tumor cells, thereby blocking anti-tumor responses and promoting cancer progression [62]. CSCs can recruit Treg cells as part of their immune escape mechanism and are better adapted to TME [63], leading to treatment failure and relapse. NK cells may interact with tumor cells or other components of the TME to regulate tumor growth within the TME [64]. In TME of breast cancer, ALDH+ BCSCs exhibit significant resistance to NK cytotoxicity, a resistance mechanism that allows tumor cells to circumvent the surveillance of the immune system, thereby increasing the risk of tumor recurrence [65].

In TME, ECM is a class of non-cellular components consisting of collagen, proteoglycans, laminin and reticulin that provide biochemical components and basic structural support. ECM enhances breast cancer invasion and metastasis by providing proliferative signaling, resisting apoptosis, inducing neovascularization, and maintaining stemness of BCSCs [52] [55]. In addition, other components of TME, such as tumor-associated fibroblasts (CAFs), tumor-associated neutrophils (TANCells), endothelial cells, adipocytes, etc., can also contribute to breast cancer recurrence by acquiring and maintaining BCSCs stemness and treatment resistance [66].

5. Conclusion

The relationship between breast cancer stem cells and recurrence is a research field that has attracted much attention. With the in-depth study of the stemness characteristics of BCSCs, such as self-renewal, multidirectional differentiation, heterogeneity, high tumorigenicity, drug resistance, etc., Breast cancer stem cells were found to be resistant to drugs through the action of ABC transporters, Resistance and repair ability to DNA damage, remain quiescent and interact with tumor microenvironment, which lead to treatment failure and breast cancer recurrence. It has been clarified that the stemness of BCSCs is an important cause of breast cancer recurrence, and it has opened up a new way of thinking for the treatment of breast cancer. Overall, BCSCs play an important role in the recurrence of breast cancer, further studies will help to gain a deeper understanding of the biological properties of BCSCs and provide important guidance for the prevention and treatment of breast cancer, which is expected to solve the thorny problem of breast cancer recurrence, thus reducing the poor prognosis of breast cancer and lowering the mortality rate.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Siegel, R.L., Giaquinto, A.N. and Jemal, A. (2024) Cancer Statistics, 2024. *CA*: *A Cancer Journal for Clinicians*, **74**, 12-49. https://doi.org/10.3322/caac.21820

[2] Wang, X. and Wei. W. (2022) HR Positive/HER2 Negative Breast Cancer CDK4/6 Inhibitor Combined with Endocrine Therapy—Interpretation of the Chinese Society of Clinical Oncology (CSCO) Guidelines for Diagnosis and Treatment of Breast Cancer (2022 Edition). *Zhejiang Medical*, **44**, 2595-2599.

[3] Sun, Y., Zhao, Z., Yang, Z., Xu, F., Lu, H., Zhu, Z., *et al.* (2017) Risk Factors and Preventions of Breast Cancer. *International Journal of Biological Sciences*, **13**, 1387-1397. https://doi.org/10.7150/ijbs.21635

[4] Rajput, S., Sharma, P.K. and Malviya, R. (2023) Biomarkers and Treatment Strategies for Breast Cancer Recurrence. *Current Drug Targets*, **24**, 1209-1220. https://doi.org/10.2174/0113894501258059231103072025

[5] Bahmad, H.F., Chamaa, F., Assi, S., Chalhoub, R.M., Abou-Antoun, T. and Abou-Kheir, W. (2019) Cancer Stem Cells in Neuroblastoma: Expanding the Therapeutic Frontier. *Frontiers in Molecular Neuroscience*, **12**, Article 131. https://doi.org/10.3389/fnmol.2019.00131

[6] Zheng, Q., Zhang, M., Zhou, F., Zhang, L. and Meng, X. (2021) The Breast Cancer Stem Cells Traits and Drug Resistance. *Frontiers in Pharmacology*, **11**, Article 599965. https://doi.org/10.3389/fphar.2020.599965

[7] Zhang, L. (2023) The Role of Mesenchymal Stem Cells in Modulating the Breast Cancer Microenvironment. *Cell Transplantation*, **32**. https://doi.org/10.1177/09636897231220073

[8] Jansen, J., Thompson, J.M., Dugan, M.J., Nolan, P., Wiemann, M.C., Birhiray, R., *et al.* (2002) Peripheral Blood Progenitor Cell Transplantation. *Therapeutic Apheresis*, **6**, 5-14. https://doi.org/10.1046/j.1526-0968.2002.00392.x

[9] Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J. and Clarke, M.F. (2003) Prospective Identification of Tumorigenic Breast Cancer Cells. *Proceedings of the National Academy of Sciences*, **100**, 3983-3988. https://doi.org/10.1073/pnas.0530291100

[10] Ginestier, C., Hur, M.H., Charafe-Jauffret, E., Monville, F., Dutcher, J., Brown, M., *et al.* (2007) ALDH1 Is a Marker of Normal and Malignant Human Mammary Stem Cells and a Predictor of Poor Clinical Outcome. *Cell Stem Cell*, **1**, 555-567. https://doi.org/10.1016/j.stem.2007.08.014

[11] Liu, X. and Bo, L. (2023) Research Progress of Stem Cell Immunotherapy Targeting Breast Cancer. *Chinese Cancer*, **32**, 550-556.

[12] Lytle, N.K., Barber, A.G. and Reya, T. (2018) Stem Cell Fate in Cancer Growth, Progression and Therapy Resistance. *Nature Reviews Cancer*, **18**, 669-680. https://doi.org/10.1038/s41568-018-0056-x

[13] Borah, A., Raveendran, S., Rochani, A., Maekawa, T. and Kumar, D.S. (2015) Targeting Self-Renewal Pathways in Cancer Stem Cells: Clinical Implications for Cancer Therapy. *Oncogenesis*, **4**, e177. https://doi.org/10.1038/oncsis.2015.35

[14] Pang, M., Siedlik, M.J., Han, S., Stallings-Mann, M., Radisky, D.C. and Nelson, C.M.

(2016) Tissue Stiffness and Hypoxia Modulate the Integrin-Linked Kinase ILK to Control Breast Cancer Stem-Like Cells. *Cancer Research*, **76**, 5277-5287. https://doi.org/10.1158/0008-5472.can-16-0579

[15] Hüser, L., Novak, D., Umansky, V., Altevogt, P. and Utikal, J. (2018) Targeting SOX2 in Anticancer Therapy. *Expert Opinion on Therapeutic Targets*, **22**, 983-991. https://doi.org/10.1080/14728222.2018.1538359

[16] Batlle, E. and Clevers, H. (2017) Cancer Stem Cells Revisited. *Nature Medicine*, **23**, 1124-1134. https://doi.org/10.1038/nm.4409

[17] Lathia, J.D., Mack, S.C., Mulkearns-Hubert, E.E., Valentim, C.L.L. and Rich, J.N. (2015) Cancer Stem Cells in Glioblastoma. *Genes & Development*, **29**, 1203-1217. https://doi.org/10.1101/gad.261982.115

[18] Meacham, C.E. and Morrison, S.J. (2013) Tumour Heterogeneity and Cancer Cell Plasticity. *Nature*, **501**, 328-337. https://doi.org/10.1038/nature12624

[19] Chaffer, C.L., Marjanovic, N.D., Lee, T., Bell, G., Kleer, C.G., Reinhardt, F., *et al.* (2013) Poised Chromatin at the ZEB1 Promoter Enables Breast Cancer Cell Plasticity and Enhances Tumorigenicity. *Cell*, **154**, 61-74. https://doi.org/10.1016/j.cell.2013.06.005

[20] Goldman, A., Majumder, B., Dhawan, A., Ravi, S., Goldman, D., Kohandel, M., *et al.* (2015) Temporally Sequenced Anticancer Drugs Overcome Adaptive Resistance by Targeting a Vulnerable Chemotherapy-Induced Phenotypic Transition. *Nature Communications*, **6**, Article No. 6139. https://doi.org/10.1038/ncomms7139

[21] Liu, S., Cong, Y., Wang, D., Sun, Y., Deng, L., Liu, Y., *et al.* (2014) Breast Cancer Stem Cells Transition between Epithelial and Mesenchymal States Reflective of Their Normal Counterparts. *Stem Cell Reports*, **2**, 78-91. https://doi.org/10.1016/j.stemcr.2013.11.009

[22] Takahashi, R., Miyazaki, H. and Ochiya, T. (2014) The Role of Micrornas in the Regulation of Cancer Stem Cells. *Frontiers in Genetics*, **4**, Article 295. https://doi.org/10.3389/fgene.2013.00295

[23] van den Beucken, T., Koch, E., Chu, K., Rupaimoole, R., Prickaerts, P., Adriaens, M., *et al.* (2014) Hypoxia Promotes Stem Cell Phenotypes and Poor Prognosis through Epigenetic Regulation of Dicer. *Nature Communications*, **5**, Article No. 5203. https://doi.org/10.1038/ncomms6203

[24] Zeng, X., Liu, C., Yao, J., Wan, H., Wan, G., Li, Y., *et al.* (2021) Breast Cancer Stem Cells, Heterogeneity, Targeting Therapies and Therapeutic Implications. *Pharmacological Research*, **163**, Article 105320. https://doi.org/10.1016/j.phrs.2020.105320

[25] Yu, J., Chen, H., Xu, J. and Zhou, P. (2022) Research Advances in the Role and Pharmaceuticals of ATP-Binding Cassette Transporters in Autoimmune Diseases. *Molecular and Cellular Biochemistry*, **477**, 1075-1091. https://doi.org/10.1007/s11010-022-04354-y

[26] Tan, K.W., Li, Y., Paxton, J.W., Birch, N.P. and Scheepens, A. (2013) Identification of Novel Dietary Phytochemicals Inhibiting the Efflux Transporter Breast Cancer Resistance Protein (BCRP/ABCG2). *Food Chemistry*, **138**, 2267-2274. https://doi.org/10.1016/j.foodchem.2012.12.021

[27] McIntosh, K., Balch, C. and Tiwari, A.K. (2016) Tackling Multidrug Resistance Mediated by Efflux Transporters in Tumor-Initiating Cells. *Expert Opinion on Drug Metabolism & Toxicology*, **12**, 633-644. https://doi.org/10.1080/17425255.2016.1179280

[28] Di, C. and Zhao, Y. (2014) Multiple Drug Resistance Due to Resistance to Stem

Cells and Stem Cell Treatment Progress in Cancer (Review). *Experimental and Therapeutic Medicine*, **9**, 289-293. https://doi.org/10.3892/etm.2014.2141

[29] Dean, M., Moitra, K. and Allikmets, R. (2022) The Human ATP-Binding Cassette (ABC) Transporter Superfamily. *Human Mutation*, **43**, 1162-1182. https://doi.org/10.1002/humu.24418

[30] Zhu, Y., Liu, C., Nadiminty, N., Lou, W., Tummala, R., Evans, C.P., *et al.* (2013) Inhibition of ABCB1 Expression Overcomes Acquired Docetaxel Resistance in Prostate Cancer. *Molecular Cancer Therapeutics*, **12**, 1829-1836. https://doi.org/10.1158/1535-7163.mct-13-0208

[31] Vulsteke, C., Lambrechts, D., Dieudonné, A., Hatse, S., Brouwers, B., van Brussel, T., *et al.* (2013) Genetic Variability in the Multidrug Resistance Associated Protein-1 (ABCC1/MRP1) Predicts Hematological Toxicity in Breast Cancer Patients Receiving (neo-)Adjuvant Chemotherapy with 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC). *Annals of Oncology*, **24**, 1513-1525. https://doi.org/10.1093/annonc/mdt008

[32] Das, S., Mukherjee, P., Chatterjee, R., Jamal, Z. and Chatterji, U. (2019) Enhancing Chemosensitivity of Breast Cancer Stem Cells by Downregulating SOX2 and ABCG2 Using Wedelolactone-Encapsulated Nanoparticles. *Molecular Cancer Therapeutics*, **18**, 680-692. https://doi.org/10.1158/1535-7163.mct-18-0409

[33] Sun, M., Yang, C., Zheng, J., Wang, M., Chen, M., Le, D.Q.S., *et al.* (2015) Enhanced Efficacy of Chemotherapy for Breast Cancer Stem Cells by Simultaneous Suppression of Multidrug Resistance and Antiapoptotic Cellular Defense. *Acta Biomaterialia*, **28**, 171-182. https://doi.org/10.1016/j.actbio.2015.09.029

[34] Bhattacharya, S., Srinivasan, K., Abdisalaam, S., Su, F., Raj, P., Dozmorov, I., *et al.* (2017) RAD51 Interconnects between DNA Replication, DNA Repair and Immunity. *Nucleic Acids Research*, **45**, 4590-4605. https://doi.org/10.1093/nar/gkx126

[35] Chen, W., Dong, J., Haiech, J., Kilhoffer, M. and Zeniou, M. (2016) Cancer Stem Cell Quiescence and Plasticity as Major Challenges in Cancer Therapy. *Stem Cells International*, **2016**, Article 1740936. https://doi.org/10.1155/2016/1740936

[36] Sharma, N.K., Ansari, U., Churchill, G., Patel, K. and Feigenberg, S. (2018) Assessment of Accelerated Partial Breast Irradiation as Monotherapy Following Breast Conserving Surgery in the Treatment of Favorable Risk Breast Cancer. *Advances in Breast Cancer Research*, **7**, 33-64. https://doi.org/10.4236/abcr.2018.71004

[37] Wang, J., Wang, H. and Qian, H. (2018) Biological Effects of Radiation on Cancer Cells. *Military Medical Research*, **5**, Article No. 20. https://doi.org/10.1186/s40779-018-0167-4

[38] Konge, J., Leteurtre, F., Goislard, M., Biard, D., Morel-Altmeyer, S., Vaurijoux, A., *et al.* (2018) Breast Cancer Stem Cell-Like Cells Generated during TGFβ-Induced EMT Are Radioresistant. *Oncotarget*, **9**, 23519-23531. https://doi.org/10.18632/oncotarget.25240

[39] Liu, Y., Zheng, C., Huang, Y., He, M., Xu, W.W. and Li, B. (2021) Molecular Mechanisms of Chemo- and Radiotherapy Resistance and the Potential Implications for Cancer Treatment. *MedComm*, **2**, 315-340. https://doi.org/10.1002/mco2.55

[40] Meyer, F., Engel, A.M., Krause, A.K., Wagner, T., Poole, L., Dubrovska, A., *et al.* (2022) Efficient DNA Repair Mitigates Replication Stress Resulting in Less Immunogenic Cytosolic DNA in Radioresistant Breast Cancer Stem Cells. *Frontiers in Immunology*, **13**, Article 765284. https://doi.org/10.3389/fimmu.2022.765284

[41] Chang, C., Zhang, M., Rajapakshe, K., Coarfa, C., Edwards, D., Huang, S., *et al.* (2015) Mammary Stem Cells and Tumor-Initiating Cells Are More Resistant to Apoptosis and Exhibit Increased DNA Repair Activity in Response to DNA Damage. *Stem Cell Reports*, **5**, 378-391. https://doi.org/10.1016/j.stemcr.2015.07.009

[42] Oshi, M., Gandhi, S., Yan, L., Tokumaru, Y., Wu, R., Yamada, A., *et al.* (2022) Abundance of Reactive Oxygen Species (ROS) Is Associated with Tumor Aggressiveness, Immune Response, and Worse Survival in Breast Cancer. *Breast Cancer Research and Treatment*, **194**, 231-241. https://doi.org/10.1007/s10549-022-06633-0

[43] Wells, A., Griffith, L., Wells, J.Z. and Taylor, D.P. (2013) The Dormancy Dilemma: Quiescence versus Balanced Proliferation. *Cancer Research*, **73**, 3811-3816. https://doi.org/10.1158/0008-5472.can-13-0356

[44] Brown, J.A., Yonekubo, Y., Hanson, N., Sastre-Perona, A., Basin, A., Rytlewski, J.A., *et al.* (2017) TGF-β-Induced Quiescence Mediates Chemoresistance of Tumor-Propagating Cells in Squamous Cell Carcinoma. *Cell Stem Cell*, **21**, 650-664.E8. https://doi.org/10.1016/j.stem.2017.10.001

[45] Sachdeva, R., Wu, M., Johnson, K., Kim, H., Celebre, A., Shahzad, U., *et al.* (2019) BMP Signaling Mediates Glioma Stem Cell Quiescence and Confers Treatment Resistance in Glioblastoma. *Scientific Reports*, **9**, Article No. 14569. https://doi.org/10.1038/s41598-019-51270-1

[46] Corvaisier, M., Bauzone, M., Corfiotti, F., Renaud, F., Amrani, M.E., Monté, D., *et al.* (2016) Regulation of Cellular Quiescence by YAP/TAZ and Cyclin E1 in Colon Cancer Cells: Implication in Chemoresistance and Cancer Relapse. *Oncotarget*, **7**, 56699-56712. https://doi.org/10.18632/oncotarget.11057

[47] Yue, F., Bi, P., Wang, C., Shan, T., Nie, Y., Ratliff, T.L., *et al.* (2017) *Pten* Is Necessary for the Quiescence and Maintenance of Adult Muscle Stem Cells. *Nature Communications*, **8**, Article No. 14328. https://doi.org/10.1038/ncomms14328

[48] Ren, R., Ocampo, A., Liu, G. and Izpisua Belmonte, J.C. (2017) Regulation of Stem Cell Aging by Metabolism and Epigenetics. *Cell Metabolism*, **26**, 460-474. https://doi.org/10.1016/j.cmet.2017.07.019

[49] Ye, S., Ding, Y., Jia, W., Liu, X., Feng, J., Zhu, Q., *et al.* (2019) SET Domain-Containing Protein 4 Epigenetically Controls Breast Cancer Stem Cell Quiescence. *Cancer Research*, **79**, 4729-4743. https://doi.org/10.1158/0008-5472.can-19-1084

[50] Baldominos, P., Barbera-Mourelle, A., Barreiro, O., Huang, Y., Wight, A., Cho, J., *et al.* (2022) Quiescent Cancer Cells Resist T Cell Attack by Forming an Immunosuppressive Niche. *Cell*, **185**, 1694-1708.E19. https://doi.org/10.1016/j.cell.2022.03.033

[51] Li, C., Qiu, S., Liu, X., Guo, F., Zhai, J., Li, Z., *et al.* (2023) Extracellular Matrix-Derived Mechanical Force Governs Breast Cancer Cell Stemness and Quiescence Transition through Integrin-DDR Signaling. *Signal Transduction and Targeted Therapy*, **8**, Article No. 247. https://doi.org/10.1038/s41392-023-01453-0

[52] Hinshaw, D.C. and Shevde, L.A. (2019) The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Research*, **79**, 4557-4566. https://doi.org/10.1158/0008-5472.can-18-3962

[53] Deepak, K.G.K., Vempati, R., Nagaraju, G.P., Dasari, V.R., Nagini, S., Rao, D.N., *et al.* (2020) Tumor Microenvironment: Challenges and Opportunities in Targeting Metastasis of Triple Negative Breast Cancer. *Pharmacological Research*, **153**, Article 104683. https://doi.org/10.1016/j.phrs.2020.104683

[54] Yang, L., Shi, P., Zhao, G., Xu, J., Peng, W., Zhang, J., *et al.* (2020) Targeting Cancer Stem Cell Pathways for Cancer Therapy. *Signal Transduction and Targeted Therapy*, **5**, Article No. 8. https://doi.org/10.1038/s41392-020-0110-5

[55] He, J., Lee, H., Saha, S., Ruan, D., Guo, H. and Chan, C. (2019) Inhibition of USP2 Eliminates Cancer Stem Cells and Enhances TNBC Responsiveness to Chemotherapy. *Cell Death & Disease*, **10**, Article No. 285. https://doi.org/10.1038/s41419-019-1512-6

[56] Aponte, P.M. and Caicedo, A. (2017) Stemness in Cancer: Stem Cells, Cancer Stem Cells, and Their Microenvironment. *Stem Cells International*, **2017**, Article 5619472. https://doi.org/10.1155/2017/5619472

[57] Guha, A., Goswami, K.K., Sultana, J., Ganguly, N., Choudhury, P.R., Chakravarti, M., *et al.* (2023) Cancer Stem Cell-Immune Cell Crosstalk in Breast Tumor Microenvironment: A Determinant of Therapeutic Facet. *Frontiers in Immunology*, **14**, Article 1245421. https://doi.org/10.3389/fimmu.2023.1245421

[58] Ge, Z. and Ding, S. (2020) The Crosstalk between Tumor-Associated Macrophages (TAMs) and Tumor Cells and the Corresponding Targeted Therapy. *Frontiers in Oncology*, **10**, Article 590941. https://doi.org/10.3389/fonc.2020.590941

[59] Wan, S., Zhao, E., Kryczek, I., Vatan, L., Sadovskaya, A., Ludema, G., *et al.* (2014) Tumor-Associated Macrophages Produce Interleukin 6 and Signal via STAT3 to Promote Expansion of Human Hepatocellular Carcinoma Stem Cells. *Gastroenterology*, **147**, 1393-1404. https://doi.org/10.1053/j.gastro.2014.08.039

[60] Bonavita, E., Galdiero, M.R., Jaillon, S. and Mantovani, A. (2015) Phagocytes as Corrupted Policemen in Cancer-Related Inflammation. *Advances in Cancer Research*, **128**, 141-171. https://doi.org/10.1016/bs.acr.2015.04.013

[61] Yu, T. and Di, G. (2017) Role of Tumor Microenvironment in Triple-Negative Breast Cancer and Its Prognostic Significance. *Chinese Journal of Cancer Research*, **29**, 237-252. https://doi.org/10.21147/j.issn.1000-9604.2017.03.10

[62] Adams, S., Gray, R.J., Demaria, S., Goldstein, L., Perez, E.A., Shulman, L.N., *et al.* (2014) Prognostic Value of Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancers from Two Phase III Randomized Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199. *Journal of Clinical Oncology*, **32**, 2959-2966. https://doi.org/10.1200/jco.2013.55.0491

[63] Miyan, M., Schmidt-Mende, J., Kiessling, R., Poschke, I. and de Boniface, J. (2016) Differential Tumor Infiltration by T-Cells Characterizes Intrinsic Molecular Subtypes in Breast Cancer. *Journal of Translational Medicine*, **14**, Article No. 227. https://doi.org/10.1186/s12967-016-0983-9

[64] Melaiu, O., Lucarini, V., Cifaldi, L. and Fruci, D. (2020) Influence of the Tumor Microenvironment on NK Cell Function in Solid Tumors. *Frontiers in Immunology*, **10**, Article 3038. https://doi.org/10.3389/fimmu.2019.03038

[65] Wang, B., Wang, Q., Wang, Z., Jiang, J., Yu, S., Ping, Y., *et al.* (2014) Metastatic Consequences of Immune Escape from NK Cell Cytotoxicity by Human Breast Cancer Stem Cells. *Cancer Research*, **74**, 5746-5757. https://doi.org/10.1158/0008-5472.can-13-2563

[66] Nallasamy, P., Nimmakayala, R.K., Parte, S., Are, A.C., Batra, S.K. and Ponnusamy, M.P. (2022) Tumor Microenvironment Enriches the Stemness Features: The Architectural Event of Therapy Resistance and Metastasis. *Molecular Cancer*, **21**, Article No. 225. https://doi.org/10.1186/s12943-022-01682-x