



Mesenchymal Stem Cells; the Knife Cuts on Both Sides of Breast Cancer

Alaa Alshareeda T*

Department of Stem Cells and Regenerative Medicine, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia

Abstract

The development and progression of any tumour is not only determined by the corresponding cancer cells but also by the microenvironment of the tumour. This includes an orchestrated network of interacting cell types such as Mesenchymal Stem Cells (MSCs), immune cells, and endothelial cells, through the extracellular matrix and different soluble factors. Breast Cancer (BC) is a leading cause of death in women around the world. BC is not a single disease, but it is a collection of diseases that have different histopathological features, genetic and genomic variability, and the significant prognostic factors varied by diagnosis. MSCs derived from adipose tissue, bone marrow, placenta and other tissue, are multipotent adult cells with potential to treat human diseases such as cancer. A major development has been introduced in defining cellular hierarchy and the niche of stem cell in the human mammary gland. For decades autologous fat grafting has been suggested to be used after mastectomy for reconstructive purposes (restore form and anatomy). Additionally, adipose fat has the inherent advantage of being autologous tissue. It is considered to be the best natural-appearing filler; nevertheless given its unpredictable engraftment and rates of retention, it lacks reliability. Presently, stem cells have become the targets of BC therapy, although the investigations are mostly on a basic stage level. In this review we discuss the double-edged sword of MSC in BC.

Keywords: Breast cancer; Mesenchymal stem cells; MSCs receptors; Adipose fat; Breast construction

Abbreviations

BC: Breast Cancer; MSCs: Mesenchymal Stem Cells; M: Macrophages; ER: Estrogen Receptor; HER-2: Human Epidermal Growth factor receptor 2 positive; PgR: Progesterone Receptor; CK: Cytokeratin; EGFR: Epidermal Growth Factor Receptor; PARP: Poly ADP Ribose Polymerase; iPSC: induced Pluripotent Stem Cell; ECM: Extracellular Matrix; CMSC: Chorionic MSC; DMSC: Decidua Basalis MSC; DPMSC: Decidua Parietalis MSC; AMSC: Amniotic Mesenchyme MSC; WJMSC: Wharton's Jelly MSC; ALDH: Aldehyde Dehydrogenase; HUMSCs: Human Umbilical Cord Mesenchymal Stem Cells; EMT: Epithelial-To-Mesenchymal Transition; IFN- β : Interferons-Beta; MMP-9: Metalloproteinase-9; TLRs: Toll-Like Receptors; HMGB1: High Mobility Group Box 1 Protein

Background

Breast cancer epidemiology

BC is a leading cause of death in women around the world. The rate varies; it is up to five times more prevalent in some countries than others. In 2010, BC was the 9th leading cause of death for women in Saudi Arabia additionally, it is estimated that the incidence of BC in Saudi Arabia will increase over the coming years because of the population's growth and aging [1].

Pathogenesis and etiology of BC

Initially, it was thought that BCs mostly originate in the mammary epithelium, through a distinct sequence of histological changes including hyperplasia, atypical hyperplasia, in-situ carcinoma, and invasive, malignant disease [2]. However, at each histological change, there is a significant genetic/epigenetic development that will give rise to new cell feature. This model has been proven by many molecular studies. Generally, these studies only focused on epithelium tumor cells and therefore the potential association of other epithelial and myoepithelial cells with the development of the tumor has not been explained in details. However, the normal rate of mutation is limited to the genetic alterations that are usually essential for tumor growth. Therefore, it is proposed that mutations

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*Correspondence:

Alaa Alshareeda T, Department of Stem Cells and Regenerative Medicine, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia, Tel: (+966) 011-4294317; E-mail: al-shareedaal@ngha.med.sa

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in different genes associated with cellular functions including DNA repair and chromosomal segregation would cause instability of the genome and this appears as the starting event in the induction of tumorigenesis [3]. BC is broadly classified into two groups: Estrogen Receptor positive (ER+) and Estrogen Receptor negative (ER-). Each group is divided into more biologically and clinically relevant subgroups. ER+ tumor subgroups or luminal group express genes that encode proteins of luminal epithelial cells such as CK8/18, whereas, ER- tumors are subdivided into Human Epidermal Growth Factor Receptor 2 positive (HER-2⁺), and Basal Like Breast Cancer (BLBC). BLBC is characterized by negative expression of ER, Progesterone Receptor (PgR) and HER-2. In addition, it expresses basal epithelial cell markers such as Cytokeratins (CK); CK5, CK14 and CK17 and Epidermal Growth Factor Receptor (EGFR). The gene expression variation of these subtypes influences overall outcome and response to treatment. Generally, HER-2 positive and BLBCs have the poorest prognosis, whereas, ER⁺ tumors usually show favorable outcome [4].

Stem cells as a potential cancer cell!

Would it not seem to make more sense for organisms if each cell simply is able to proliferate when required to stream substitutes for its damaged neighbours? But that leads to make each single cell in the body a potential cancer cell.

Stem cells, including Mesenchymal Stem Cell (MSC), possess two fundamental properties; self-renewal, which is the ability to undergo many cycles of cell division while maintaining the undifferentiated state, and the capacity to differentiate into multiple specialised cell types. A hallmark of cancers, too, is the heterogeneity of cell types MSCs contain, as though the cancers were a very unsystematic form of a whole organ. Hematopoietic stem cells migrate to distant parts of the body through the Extracellular Matrix (ECM) in response to injury signals, proliferation and differentiation [5,6], as have cancer cells. MSC reside in almost all adult tissues where they are responsible for tissue maintenance and repair throughout the lifetime of the organism. The potential for MSC to repair a wide range of damaged or degenerating tissues, and their rarity, prompted studies to find alternative sources of large numbers of MSC required for clinical trials. Highly available, non-controversial and non-invasive sources of MSC were found in the placenta and its associated tissues such as human umbilical cord tissue [7].

MSC can promote/inhibit breast tumor growth

MSCs are present in the tumor environment; as a result they contribute to tumorigenesis in a complicated and not completely understood manner. The tumor stroma is complex and includes myofibroblasts, endothelial cells, inflammatory cells, and most important to this work, MSC [8]. These various cell types secrete a variety of factors that mediate cell-cell communication which culminates in changes to the extracellular matrix and the behavior of nearby tumor cells. The milieu of cells and factors in the tumor microenvironment is thought to be important for promoting and maintaining tumor growth, angiogenesis and metastasis. Nevertheless, animal model studies where tumor cells and MSCs are co-injected, show both promotion and inhibition effects on metastasis (Table 1). Besides numerous sources and heterogeneous populations, MSCs share common features ranging from the expression of different surface markers (CD73, CD90, CD105) to the differentiation into other lineages such as adipogenic, chondrogenic and osteogenic [9]. This leads to an extremely variation in their functions in addition to tissue-specific origins and the microenvironment surrounding the

MSCs. Accordingly, for *in vitro* culture, MSCs from different sources can develop different morphologies and properties by continuing stemness and can be maintained for up to 10 passages without loss their ability to proliferate, telomerase activity or capacity of differentiation [10,11]. Despite the enormous therapeutic potential of stem cells to treat many serious diseases one of the main concerns on the usage of patho-tropic stem cells for the treatment of breast cancer is their ability to release signaling molecules that may possibly alter the microenvironment of the tumour and then participate in tumour invasiveness, growth, and angiogenesis. MSCs show tissue repair functions and oppositely stimulate breast tumour growth [12,13]. The interaction between stem cells and cancer cells can be achieved directly or indirectly. Therefore, the MSCs migration towards the site of inflammation develops a cellular interaction that arises both directly through a gap junction, membrane receptors and nano-tubes and however, indirectly communication proceeds via, soluble structures and factors such as cytokines and growth factors. The action of secreting endocrine and paracrine signals can trigger MSCs to stimulate nearby cells with pro-and/or anti-cancer activities. Sequentially, cancer cells can stimulate MSCs in order to develop abnormal tumour-associated phenotypes [14]. However, MSC conditioned medium contains a very complex mixture of soluble proteins, growth factors but their concentration is considered to be too low to account for therapeutic effects. Thus other components of MSC conditioned medium were investigated to identify the mediator of the paracrine effects observed.

Placental Decidua MSC (DMSC) showed an increase in the migration ability toward BC site. Additionally, these DMSCs demonstrated an inhibitory effect on the growth of primary tumours and in the development of new tumours in a preclinical model of mammary tumours (breast) [15]. The absence of DMSC-homogenate interaction proposes that the migration mechanism of the DMSCs is possibly controlled by soluble factors exists in the tumour homogenate that cross the trans-well membrane. However, the mechanism of MSCs migration involved in BC remains to be elucidated. It has been suggested that MSCs can inhibit tumorigenesis growth of BC through a paracrine mechanism, when Chemokine ligand 1 (CXCL), CXCL2 or CXCL12 accelerated tumorigenesis in a comprehensive range of BC models through their respective receptors CXCR2 and CXCR4 on the cells [16,17]. Karnoub et al. [13] have showed that co-injection of bone-marrow-derived human MSCs with metastatic human BC cells (MCF-7, MDA-MB-231, HMLR, and MDA-MB-435), accelerated the metastatic potency of the cancer cells as well as developed a tumour xenograft in mice. This finding was explained by a paracrine manner since the secretion of the Chemokine Ligand 5 (CCL5) by the MSCs activated the G-protein coupled receptor GPR75 in cancer cells [13]. Signaling of CCL5 among further stimuli led to increase the migration, invasive and metastasis of these cancer cells [13].

In vitro, umbilical cord Wharton Jelly derived MSC-conditioned medium inhibited breast adenocarcinoma, ovarian carcinoma, and osteosarcoma cell migration by inducing apoptosis and suppressed angiogenesis [18]. Chao et al. [19] have investigated the effect of Human Umbilical Cord MSCs (HUMSCs) on tumorigenesis of ER⁻ BC in mice model and *in vitro* [20]. For *in vitro* test, the cancer cells directly underwent apoptosis. Additionally, the injection of HUMSC into the developed BCs mouse model was effective in both BC types; *in situ* or metastatic BC. The level of anti-cancer activity of HUMSC has been documented to be associated with different genes

that have roles in 1) migration (e.g. *CTNNA1*, *MALAT1*, *SEMA3C*), 2) filopodia formation (e.g. *MyO10*, *SH3PXD2A*), 3) apoptosis (e.g. *IL6ST*), 4) death of cancer cells (e.g. *TCF25*), and 5) vesicle secretion (e.g. *SCAMP1*, *MYO6*) [20]. Similarly, Zhou et al. have co-cultured MDA-MB-231 and bone marrow-derived MSCs and reported an inhibition of growth of these cancer cells [21]. In a recent study Lacerda et al. [22] have showed that the co-injection of human bone marrow MSCs with the triple negative inflammatory BC cell line, led to the inhibition of primary tumour growth but increase invasion and metastasis in mice [22]. These findings show the role of MSCs at the site of the tumour in the metastasis promotion probably through the Epithelial-To-Mesenchymal Transition (EMT) induction in the primary tumour cells.

IIIouz et al. [23] have studied the effect of another source of stem cells; Adipose Stem Cells (ADSCs) on recovering cellular potential and delaying/treating BC in animals model of human BC [23]. The injection of ADSCs peripheral to the tumour leads to decrease tumour growth and tumour withdrawal after 3 to 8 weeks finally a total recovery within 6 months was reported. Ruy et al. [24] have cultured ADSCs at high density and resulted in suppression of growth of the human ER-positive BC cell line (MCF-7) via the mechanism of (Interferons-Beta) IFN- β -dependent. Despite the therapeutic potential of ADSCs, Rowan et al. [25] have reported that ADSCs promoted progression and metastasis of local BC in murine model. In their study, human ADSCs cells from abdominal lipoaspirates were shown to underlie metastasis of MDA-MB-231 BC xenografts to many organs. Table 1 summarizes the applications of stem cell in the treatment of breast cancer. To conclude, before developing any stem cell based therapy for BC, the pro-neoplastic features of normal stem cells within a deregulated tumour microenvironment must be considered. Likewise, the administration route and cell concentration must be identified for the best therapeutic outcome [26,27].

MSCs receptors and breast cancer

One major obstacle in the treatment of BC is cancer relapse after a prolonged disease-free interval, referred to as dormancy of the tumour. It has been stated that 1 in 5 clinically disease-free patients after surgical removal of primary tumour developed cancer after 5 to 25 years [28]. The recruitment of normal stem cells for the eradication of tumour cells has been used as a therapy for BC. Several studies have revealed that MSCs show the inherent ability to migrate toward inflammation sites, injury, ischemia and, most significantly, tumour niches. The migratory mechanisms of MSCs toward sites of cancer are not yet unravelled, although signalling of cytokine (such as stromal cell-derived factor 1, hepatocyte growth factor, Vascular Endothelial Growth Factor (VEGF), platelet-derived growth factor, and monocyte chemo attractant protein 1) have been known as a key regulator of this behaviour [29]. Interestingly, not only engineered but also unmodified MSCs show antitumor activity in several cancer models (mice), as they secrete tumoricidal factors [30]. In addition, one of the main concerns on the use of stem cells for cancer treatment is their capability to secrete signaling molecules that could alter the microenvironment of the tumour and take part in the invasiveness/growth and angiogenesis of tumour [31].

Toll-Like Receptors (TLRs) are a class of pattern recognition receptors that play a key role in bridging innate and adaptive immune system in cancer [32]. It has been revealed that MSCs express many Toll-Like Receptor (TLR)- 1, 2, 3, 4, 5 and 6 and TLR-agonist interaction stimulated migration and immunomodulatory factor

secretion of MSCs [32]. In addition the polarisation of MSCs has been proposed to depend on the signaling of TLR, and there was a functional difference between human bone marrow derived MSCs stimulated by either TLR4 or 3. Interestingly, the stimulated MSCs by TLR4 showed an anti-tumour effect. Mehmeti et al. [33] have showed that TLR4 was functionally expressed in ER/PR-negative BC [33]. Lapteva et al. [34] have developed a tumour vaccine with the ability to elicit antitumor immunity [34]. The vaccine was reported to inhibit the growth of primary breast tumour and block metastasis in a TLR4 dependent manner. Therefore, investigations regarding therapies of TLR4-antagonist should be focusing on BC. The effectiveness of chemotherapy is defined by their ability to disturb the tumour cells division in addition to the inclusion of an adjuvant such as High Mobility Group Box 1 protein (HMGB1). HMGB1 has been shown to activate TLR4 on dendritic cells and been used successfully in BC treatment [35].

Autologous fat adipose-derived mesenchymal stem cells and breast reconstruction

For breast construction, fat grafting into the breast has been used by plastic surgeons, but with some difficulties and a fluctuating success rate. In spite of some premature advertising that has encouraged the potential benefits of stem cell-enriched fat transfers; they are still being under investigation for their safety and efficiency and thus remain experimental.

It must be recognized that, fat is not an inactive filler similar to a silicone breast implant. In contrast, it is a biologically active tissue, secreting an abundance of active and signaling molecules such as hormones, cytokines and growth factors [36]. Likewise, the believe that ADSCs act mainly in the controlling scenario of adipose tissue cell turn-over needs more attention for the potential interaction between local, grafted ADSCs and residual BC cells or adjacent *in situ* lesions. This result tempted attention and delivered some concerns about using fat grafting with ADSCs enrichment in construction of the breast post mastectomy [37].

Adipose tissue is composed mostly of lipid-storing adipocytes and critical for supplying energy, protection and mechanical cushion. Adipocytes are supported by fine connective tissue dispersed with many cells including endothelial cells, macrophages as well as stromal cells. Traditionally, the stromal cells were referred to as 'pre-adipocytes' but are now called adipose stem cells. The majority of studies investigating the role of fat in mammary carcinogenesis are focusing on hormone-dependent mechanisms because adipose tissue is the main extra-gonadal source of estrogen and the majority of BC (~60%) expresses Estrogen Receptors (ER) [38].

Abdominal fat is considered the most common source for ADSCs [39], in addition to breast tissue, either after reduction mammoplasty [40] or post-surgery of BC [41]. According to Hanson et al. study, [42] ADSCs from breast and abdominal are express similar surface marker phenotypes (positive for CD29, CD73, CD90, and CD105 and lack for hematopoietic and endothelial markers such as CD14, CD31, CD34, and CD45). ADSCs are physiologically found in the breast and potentially near any occurring BC. Furthermore, additional ADSCs may possibly be inoculated through re-constructive cell-assisted lipografting nearly the cancer bed [43].

The main potential concern is paradoxically the one in which fat transfer acts to show the most exciting possibilities, specifically underlining defects resulting from wide local excision and adjuvant

Table 1: The applications of stem cell in the treatment of breast cancer.

Cell source	Tumor development/type	Effect	Reference
Umbilical cord- derived human MSC	MDA-MB-231 <i>in vitro</i>	Positive	[18]
Umbilical cord-derived human MSCs	<i>In vivo</i> (mice) using MDA-MB-231	Positive	[20]
Human ADSCs	In animal models of human breast cancer <i>in vivo</i>	Positive	[23]
Human ADSCs	MCF-7 <i>in vitro</i>	Positive	[24]
Bone marrow-derived human MSCs	MDA-MB-231 <i>in vitro</i>	Positive	[21]
Bone marrow-derived human MSCs	MDA-MB-231, HMLR, MDA-MB-435and MCF-7, <i>in vivo</i> (mice) and <i>in vitro</i>	Negative	[13]
Bone marrow-derived human MSCs	SUM149 <i>in vivo</i> (mice)	Positive &	[22]
		Negative	
Bone marrow-derived human MSCs	MDA-MB-231 and T47D <i>in vitro</i>	Positive	[26]
Human ADSCs	MDA-MB-231 <i>in vivo</i> (mice)	Negative	[25]
Human ADSCs	ZR75-1 <i>in vivo</i> (mice) and <i>in vitro</i>	Negative	[27]
Umbilical cord-derived human MSCs	<i>In vivo</i> (mice) using MDA-MB-231	Positive	[19]
placenta-derived human MSCs (Decidua)	N-nitroso-N-methylurea	Positive	[15]

Positive effect, means reduce or suppress tumour growth unlike Negative

Table 2: The main explored issues in the safety of adipose fat in breast cancer reconstruction.

The amount of stem cells in adipose tissue	1 in 100 adipose tissue cells is an MSC, compared with 1 in 100,000 bone marrow cells. [56-58]
Are ADSCs capable of differentiation to other lineages?	Yes, ADSCs can differentiate into osteogenic, adipogenic, myogenic, and chondrogenic lineages and can gain mature endothelial phenotype under appropriate conditions [59,60]
Involvement of ADSC in mammary carcinogenesis?	Potentially, ADSC directly alter the breast microenvironment supporting the transition from pre-malignancy to malignancy [38,61].
What are the main complication after autologous fat grafting?	Interference with the early detection of BC through mammography. Not perfused fat tissue can die and form necrotic cysts. Because autologous fat grafting are usually accompanied by a high ratio of graft resorption and fat necrosis. Fat necrosis is usually associated with the micro calcifications formation in the long-term [62] which may lead to misdiagnosis of BC. However, There is no scientific evidence that fat grafting interferes with the detection of BC [63,64].

radiotherapy in the treatment of BC [44]. The main concern here is what is the contribution of fat adipose engraftment in BC progression? Adipose tissue (transferred fat) is considered a high source of MSCs, and as discussed above, MSCs can differentiate into a range of cell types and release VEGF [45,46] (promote tumour invasion and metastasis in many cancers) [47,48] as well as home to injured tissues. There are controversial evidences regarding the ability of the transplanted ADSCs to engraft and Trans-differentiate into epithelial cells at risk of malignant changes. Manabe et al. [49] have co-cultured rat mature adipocytes with ER receptor positive and negative BC cell lines, and revealed an increase in the growth rate of the cancer cells [49]. Another *in vitro* study, Gehmert et al. [50] has found ADSCs migrate towards conditioned medium of highly metastatic human and mice cancer cells. The connection between obesity and increased lifetime risk of BC progression has been established [51,52]. This has been related to the high level of aromatases in white human ADSCs and estrogen. Furthermore, surplus adipose tissue has been linked to worsen the prognosis at onset of BC disease and can contribute to drug resistance [53,54]. Zhang et al. [55] revealed that the direct injection of ADSCs and endothelial cells into systemic circulation of a transgenic mouse (breast adenocarcinoma (MDA-231)), leads to their homing to and engraftment into stroma and vasculature, respectively. In addition, the recruitment of ADSCs by tumours is sufficient to accelerate tumour progression. Finally, they have revealed that migration of stromal and vascular progenitor cells from white adipose tissue grafts to breast tumours is related to acceleration of cancer growth. These findings deliver a biological vision for the association between obesity and BC. Implant-based reconstructions include some complications, such as rupture, deformation/distortion,

rippling, and migration. Table 2 highlights concerns in the safety of adipose fat in BC reconstruction.

Discussion and Conclusion

Throughout the last decade, evidence that stem cells could be converted into malignant and that only certain cancer cells have in common a range of traits with stem cells supported the idea that the driving force implicit in tumour growth might be a subpopulation of stem like cancer cells. The theory has an extensive history; nevertheless in the past the needed technology to prove it was missing.

MSCs are a heterogeneous population of cells showing differing differentiation capacities and MSCs derived from the bone marrow, adipose tissue and dental pulp are not functionally identical, as a result the studies using MSCs derived from other sources may possibly not be replicated using bone marrow derived MSCs [7]. MSCs have a suppressive or promotive impact on the development of the tumour (Table 1). The use of different tissue sources, variability of individual donor, and MSCs injection time in each experiment may have an effect on this discrepancy [56-64]. It is apparent that there is some discrepancies between studies in the isolation techniques used for MSCs, where only a few used gradient centrifugation to separate a MSC's population [65,66]. Likewise, each study lists a set of different markers to characterise the isolated population [22]. Consequently, there is the overall consistency are missing in molecular or phenotypic characterisation of MSCs used in each study. Changes in the techniques used for isolation of MSCs and growth conditions can help assured subpopulations and future investigation in this area and should place emphasis on the isolation and characterisation methods to improve explaining on the population of stem cells

used experimentally. Therefore, the lack of common standards and a precise definition of preparations of the MSC remains the main obstacle in MSC research and application.

There is a lot of interest to study the association between inflammation and cancer. TLR family plays an important role in inflammation mediated cancers in addition to cancer related inflammation. It is clear that targeting TLRs for cancer treatment is complex and its benefits may possibly be reliant on the specific MSCs polarisation and immune cells in the microenvironment of tumour, as well as to the expression patterns of TLR within the tumour epithelia in each individual patient [67]. The TLR expression is variable at different time points during the treatment, which may possibly influence the MSCs effects on the progression of tumour. Whether MSCs support or suppress the progression of tumour, it is apparent that systemically administered MSCs can be enrolled by, and migrates toward, tumours. These outcomes are important as they can be utilised as a source for future investigations to explore the application of engineered MSCs as novel carriers for anti-tumour agent's delivery to cancer site, directing the development of tumour targeted therapies. Receptors for the main factors expressed on MSCs, can be potentially modified genetically via transfection, which may expand the MSC's efficacy in clinical settings and decrease the MSC's migration to non-targeted sites. The use of MSCs as carriers for anticancer drugs is extremely selective and can overcome the obstacle of limited drug half-life as MSCs can be genetically modified to continually secrete the drug of choice; however, even un-engineered MSCs show anticancer activity as discussed above [30]. Documenting the massive body of initial investigational evidence, emerging clinical evidence also proposes that the use of MSC as therapy in BC may possibly be a game changing approach of the therapy. Future studies investigating the MSCs roles in tumorigenesis of the breast and formation of metastasis are required, considering the potential of MSCs for the treatment of BC.

Currently, treatment of BC is puzzling because of chemotherapy resistance, particularly in some subtypes such as ER negative cancers as well as in advanced (metastatic) stages. MSCs bear a high potential in the therapy of BC, as they constitute a good vehicle for specific carriage of anticancer therapeutics to the sites of the tumour in addition have high abilities to repair tissue. One of the main concerns on the use of stem cells for cancer treatment is their capability to secrete signaling molecules that could alter the microenvironment of the tumour and take part in the invasiveness/growth and angiogenesis of tumour [31]. Due to the above limitation, clinical trials examining the effect of stem cell-mediated therapy for the specific treatment of BC are rather lacking. In spite of current impediments, the improvement in stem cell-based therapy, in combination with conventional chemotherapy, still remains a significant approach for scientists of BC and holds a positive future in BC's treatment. Recent progresses in the field of BC research, as the *ex vivo* culture of BC circulating tumour cell, antibiotics use, Nanomedicine, and the employment of normal stem cells for the elimination of BC circulating tumour cell, have endorsed the establishment of new individualized treatment systems and are paving the way toward a further approach of patient-friendly therapy [31].

Up to now, the MSCs involvement in breast carcinogenesis, irrespective of their primary site, has exclusively focused on their effects on fully malignant breast epithelial cells. Now, considering the early stages of BC is necessary, in order to design stromally-based

targeted therapies to control and prevent the increasing cases of early diagnosed lesions without the toxicities related to standard chemo- and radio-therapeutic regimens [38].

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