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The key players of tumor microenvironment and their role in breast cancer

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Abstract

Background: Cancer studies were focused mainly on tumor cells. But not that much time passed since researchers began to focus not only on neoplastic cells, but also on significant alterations in the surrounding stroma or tumor microenvironment. These alterations are now recognized as a critical element for breast cancer development and progression, as well as potential therapeutic targets. Different elements of the breast cancer microenvironment (such as immune cells, soluble factors and modified extracellular matrix) act together to stop effective antitumor immunity and stimulate breast cancer progression and metastasis. Stromal cells in the breast cancer microenvironment are characterized by molecular alterations and aberrant signaling pathways, some of which are prognostic factors for clinical outcome.

Conclusions: Tissue microenvironment has profound effects on the progression of cancer cells by its paracrine signaling. Molecular characterization of various cell types from the normal breast tissue, ductal carcinoma *in situ* and invasive breast tumor revealed significant changes in gene profile in all cell types during breast tumor progression. Microenvironment changes influence tumor progression as well as the efficacy of various cancer therapies. There is compelling evidence that the elements of tumor microenvironment respond to different stimuli and release distinct mediators, some antitumorigenic, while others protumorigenic activity. Each of the known players of breast stroma involved in tumorigenesis and cancer progression can be influenced and directed towards an "anticancer" state.

Key words: breast cancer, tumor microenvironment, myoepithelial cell, fibroblast, macrophage, mast cell.

Introduction

Cancer studies were focused mainly on tumor cells. It was 1889 when Paget proposed the "seed and soil" theory which suggests that neoplastic cells (seed) may only initiate tumor formation when in the context of a hospitable and supportive microenvironment (soil) [1]. But not that much time passed since researchers began to focus not only on neoplastic cells, but also on significant alterations in the surrounding stroma or tumor microenvironment. These alterations are now recognized as a critical element for breast cancer development and progression, as well as potential therapeutic targets. Different elements of the breast cancer microenvironment, such as immune cells, soluble factors and modified extracellular matrix, act together to stop effective antitumor immunity and stimulate breast cancer progression and metastasis. Stromal cells in the breast cancer microenvironment are characterized by molecular alterations and aberrant signaling pathways, some of which are prognostic factors for clinical outcome. Several new therapies targeting stromal components are in development or undergoing clinical trials [2]. In this paper, there will be reviewed the key players of breast stroma and their role in tumorigenesis and cancer progression. However, a key question remains: which comes first, the dysfunction of epithelial cells or the dysfunction of their microenvironment? [3].

Myoepithelial cells

The human breast represents a branching ductal system composed of two epithelial cell types: an inner layer of polarized epithelial cells and an outer layer of myoepithelial cells, separated from the stroma by a laminin-rich basement membrane (BM) [4]. BM is also composed of heparan sulfate proteoglycans, glycosaminoglycans and entactin. Myoepithelial cells are attached to luminal cells by desmosomes and to the BM by hemidesmosomes [5]. The myoepithelial cells are a fascinating type of cell, because they belong to two completely different types of tissues, namely the epithelium and the mesenchyme, these having even a distinct embryonic origin. This two-sided nature is expressed not only by their position (on the one hand they are connected in typical manner with the secreting epithelium, whereas on the other hand they interact with the stroma and the basal membrane in the same way as smooth muscle cells), but also by their possession of potentialities of both tissues [6].

The branching ductal system ends with a terminal ductal-lobular unit (TDLU), this being the basic functional and histopathological unit of the breast. The myoepithelial cells lining the ducts are spindle-shaped cells oriented parallel to the long axis of ducts as a continuous layer. The myoepithelial cells in TDLUs are discontinuous, stellate-shaped, and form a basket-like network around acini, allowing some luminal epithelial cells to directly contact the BM. Both epi-

thelial and myoepithelial cells originate from the same precursor. This precursor cell niche is believed to hold the key to the definitive origin of both luminal epithelial and myoepithelial cells, as well as providing a possible cell population for the origin of breast cancer [4].

Myoepithelial cells contain a large amount of microfilaments and smooth muscle-specific proteins such as alpha-actin and myosin that are responsible for the contractile function mediated by oxytocin during lactation. Each myoepithelial cell has long cytoplasmic processes that wrap around a secretory unit and hence, contraction of the myoepithelial cell can eject secretory product from the secretory unit into its duct. Thus, contraction is the most obvious and important function. Normal myoepithelial cells are critical for correct polarity of luminal epithelial cells, most likely via production of laminin-1 [5]. Adriance *et al.* showed that human breast luminal cells, when grown in three-dimensional type I collagen as opposed to laminin-rich gels, form structures with altered integrins that have reversed polarity and lack central lumina; however, if these same cells are cocultured with myoepithelial cells in collagen I gels they exhibit correct apicobasal polarity [5]. On the other hand, Gudjonsson *et al.* showed that myoepithelial cells present in invasive breast carcinoma have many similar features with normal myoepithelial cells but they show either complete absence or reduced expression of laminin-1. This one is strongly expressed around normal breast epithelial structures and thus tumor myoepithelial cells are unable to induce the polarization of luminal epithelial cells [4, 5].

Because breast cancer arises mainly in the luminal epithelial compartment of the TDLU, until recently little attention has been paid to the surrounding myoepithelial cells [4]. However, progression to carcinoma involves alteration of the entire organized structure of the breast; depending on tumor grade, the changes can include the loss of polarity, collapse of the glandular structure, disappearance of normal myoepithelial cells, and disruption of the BM at the epithelial–stromal border [7]. Myoepithelial cells form a natural border which is a semi-continuous protective sheet separating the human breast epithelium and the surrounding stroma. They suppress stromal invasion of tumor cells not only physically, but also by the secretion of various anti-angiogenic and anti-invasive factors. Among these, maspin is one of the most important tumor suppressors that are secreted by myoepithelial cells. It is a member of the serpin family of serine proteases which inhibits tumorigenesis, tumor cell migration and metastasic spread thus it functions as a tumor suppressor. Maspin is secreted in large quantities by the normal cells whereas tumor cells do not secrete it [5].

Myoepithelial cells regulate the flow of fluid and control the entry and exit of nutrients, electrolytes and other growth factors. They also process signals of endocrine or paracrine nature and perhaps act as an intermediary in such signaling processes by passing information both inwards and outwards in a paracrine fashion. The disruption of this cell layer results in the release of the growth factors, angiogenic factors, reactive oxygen species that cause an alteration in the microenvironment and the loss of myoepithelial cells. BM is the distinctive key feature of invasive carcinoma, because most tumor epithelial cells have to first pass through the myoepithelial cell layer and then the BM in order to physically contact the stroma [5, 8]. It is also postulated and generally accepted that primary breast carcinomas show a dramatic increase in the ratio of luminal-to-myoepithelial cells, and that many invasive breast carcinomas essentially lack myoepithelial cells entirely [4]. It may be possible that the myoepithelial cells are degraded by the overproduction of the degradative enzymes or they are selectively eliminated by apoptosis [5, 8]. Myoepithelial cells rarely transform; however, when they do transform, they generally give rise to tumors of low malignancy [4].

We need to understand what prevents myoepithelial cells to exhibit the tumor suppressive properties. It is also possible that the tumor suppressive ability of myoepithelial cells depends on their complete differentiation and that changes in their expression pattern can lead to reversal of their function, i.e., that undifferentiated myoepithelial cells may actually promote tumor progression instead of suppressing it. These observations could open up the possibility of a future differentiation therapy where cancer cells are forced to differentiate along the myoepithelial pathway, thus manufacturing cells of lower malignancy or those that could suppress the aggressive behavior of their more malignant counterparts [4].

Confirmation of the myoepithelial cell layer on routine histology can be done with the help of alpha-smooth muscle actin (α-SMA) immunostaining; however, these cells can also be identified by S-100, calponin, h-caldesmon, smooth muscle heavy chain (SMMHC) antibodies and CD10 [5]. Because of epithelial origin, they also express cytokeratins (CK) characteristic for the basal layer of stratified epithelia, such as CK 5, CK 14, and CK 17 [4].

Fibroblasts

Tumors are known as wounds that do not heal. This implies that cells that are involved in angiogenesis and the response to injury, such as endothelial cells and fibroblasts, have a prominent role in the progression, growth and spread of cancers [8]. Fibroblasts are cells that form the basic cellular component of connective tissue and contribute to its structural integrity. They play important roles in wound healing, regulation of epithelial differentiation and inflammation. In healthy organs, fibroblasts have a low proliferation index and minimum metabolic capacity. By contrast, during wound healing and in cancers, fibroblasts become activated, start to proliferate, secrete higher amounts of extracellular matrix (ECM) components, and acquire contractile features. Fibroblasts from tumors are known as reactive fibroblasts, peri-tumoral fibroblasts, myofibroblasts, tumor-associated or cancer-associated fibroblasts (CAFs) [3]. Characteristic feature of CAFs is expression of α-SMA and its expression is higher in fibroblasts derived from cancer tissues than in those derived from normal tissues [9].

Fibroblasts are associated with cancer cells at all stages of cancer progression, and their structural and functional

contributions to this process are beginning to emerge. Their production of growth factors, chemokines and ECM facilitates the angiogenic recruitment of endothelial cells and pericytes. Cancer cells tumoriginity was dramatically increased when inoculated with fibroblasts. Fibroblasts are therefore considered a key determinant in the malignant progression of cancer and represent an important target for cancer therapies [3, 10]. Normal fibroblasts maintain the extracellular environment through the production and remodeling of the ECM. CAFs have distinct characteristics and substantial data to support a role for CAFs in promoting tumor progression through morphological and phenotypic changes in various breast cancer subtype cells by production of TGF-β [8, 9]. In human breast tumors, the abundance of stromal CAFs is associated with aggressive adenocarcinomas and predicts human disease recurrence. In addition, CAFs have been shown to contribute to drug resistance and to reduce anti-tumor immunity [11].

The origin of CAFs has been actively investigated and multiple hypotheses have been proposed. One possibility is that they are derived from native interstitial fibroblasts whose phenotype has been modified by persistent aberrant signaling from neighboring tumor epithelial cells. Alternatively, they can be differentiated from bone marrow-derived mesenchymal stem cells that are recruited to the tumor site via endocrine stimulation by tumor-derived factors [8].

CAFs often express α-SMA. These cells are also positive for vimentin and desmin, but do not express CKs, CD31 and smooth muscle myosin [3].

Leucocytes

Immune cells are one of the most dynamic cell populations present within tumors and healing wounds and during the remodeling of breast tissue in pregnancy and involution. The smoldering inflammation was proposed as the seventh hallmark of cancer [1, 8]. High numbers of infiltrating leukocytes are present in ductal carcinoma *in situ* (DCIS) with focal myoepithelial cell layer disruptions, suggesting that they might play a role in invasive progression [8].

Among leucocytes, tumor associated macrophages (TAMs) represent the vast majority, sometimes more than 50%. Their importance should not be underestimated because they are able to control the immune response, cellular mobility and to stimulate/inhibit angiogenesis and lymphangiogenesis [12]. During chemically induced neoplastic transformation macrophages induce DNA damage through the release of reactive oxygen and nitrogen intermediates. Such macrophages have the potential to promote the survival of transformed cells and establish a state of chronic inflammation via secretion of the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β [1]. Moreover, macrophages can modulate the drug resistance and stimulate tumor regrowth by various substances secreted into the microenvironment. For example, irradiation causes tumor necrosis, vascular damage, and hypoxia, which together or separately can induce the upregulation of several myeloid cells/monocytes chemoattractants, like vascular endothelial growth factor (VEGF) in the tumor microenvironment. *De novo* recruitment of myeloid cells drives tumor regrowth via their effects on the tumor blood vessels and, possibly, the cancer cells [12, 13].

Macrophages are highly heterogenic members of the mononuclear phagocyte system. They are distributed throughout every organ of the body and can ingest microbes and present antigens to T lymphocytes, therefore constituting a first line of defense against invading pathogens [1, 12]. In inflamed and remodeling tissues, elevated macrophage turnover is indefinitely supplied largely from hematopoietic progenitor cells (HPCs), which proliferate and differentiate into promonocytes in the bone marrow before they exit into the circulation as monocytes. This proliferation program is orchestrated through colony stimulating factor 1 (CSF1), a key growth factor regulating macrophage proliferation and survival, produced by the local tissue stroma. Monocytes then undergo final differentiation into macrophages as they strain in the target tissues. Once resident in tissues, macrophages acquire a distinct, tissue-specific phenotype in response to signals present within individual microenvironments. Depending on the microenvironmental signal type, macrophages can be polarized into "classical" (or M1) and "alternative" (or M2) phenotypes [1, 12, 14, 15].

During M1 activation, IFN-γ and other molecules are involved to bring a Th1 response, thus type I inflammation, intracellular pathogen killing and antitumor immunity. M2 activation is known to accelerate tissue repair and tissue growth. These suggest that the increase of M1 macrophages in cancer is associated with less tumor aggressiveness, while M2 macrophages stimulate tumor growth and lead to poor prognosis [14, 16].

Various mouse studies have shown that monocytes are recruited into tumors in large numbers by chemokines secreted by both malignant and stromal cells. Upon monocyte differentiation into TAMs, these cells support the proliferation, survival, and motility of the cancer cells as well as angiogenesis; suppress antitumor immunity; support progression of cancer cells at the primary tumor site and extravasation/growth at distant metastatic sites. Previously, activated macrophages were believed to exhibit antitumor activity by directly attacking tumor cells in the tumor microenvironment. However, many recent studies have indicated the protumoral functions of TAMs, and thus, TAMs are believed to be predominantly polarized in the tumor microenvironment toward an M2-like phenotype and that this underlies their ability to promote the growth and vascularization of tumors. This is supported by expression of CD163 and CD204, a characteristic feature of M2 macrophages [12, 16]. Another typical markers of M2 macrophages are MRC1, TGM2, CD23, CCl22; M1 express CD64 and CXCL10 markers [14].

TAMs are responsible for immune alterations in breast cancer. The first way is inhibition of antitumor T-cell responses by secreting anti-inflammatory cytokines, like IL-10. Other mechanisms are the recruitment of immunosuppressive leucocytes and the inhibition of tumoricidal function by decreasing of MHC class II expression.

The main function of MHC class II molecules is to present processed antigens, which are derived primarily from exogenous sources, to CD4+ T-lymphocytes. MHC class II molecules thereby are critical for the initiation of the antigen-specific immune response [14, 17]. They are doing this to limit tissue damage due to deleterious inflammation. The continually activated macrophages undergo apoptosis or functionally 'stand-down', adopting an anti-inflammatory phenotype defined by the ability to suppress persistent immunity and facilitate wound healing [1].

Anatomically, macrophages are present at high numbers at the margins of mammary tumors with decreasing frequency throughout the stroma moving in within the tumor. Within the tumor mass, macrophages, either individually or in clusters, are commonly found in association with blood vessels and orchestrate the migration of tumor cells [1].

Macrophages have emerged as an important key player in breast cancer progression and represent an attractive target for breast cancer therapy. Current interventions have focused on three strategies: blocking macrophage precursor recruitment, depletion of TAMs and their progenitors, and reprograming macrophage function within tumors [1].

Mast cells

Mast cells are granulated immune cells characterized by their cargo of inflammatory mediators, comprised of a wide array of preformed bioactive molecules stored in cytoplasmic granules, which are released upon encountering the appropriate stimuli and have beneficial roles in immunological responses against pathogens, including intestinal helminths, bacteria, and viruses. Mast cell-derived mediators also participate in tissue physiological processes, such as wound healing and tissue repair, and in some pathological conditions, such as immediate allergic reactions [18]. Human mast cells derive from $CD34^+$, $CD117^+$ pluripotent hematopoietic stem cells, which arise in the bone marrow. Mast cell progenitors enter the circulation and subsequently complete their maturation in tissues [19].

At least two major populations of mature mast cells have been described in humans based on their protease content. Mast cells containing only tryptase are termed MC_T, while those containing tryptase, chymase, carboxypeptidase A, and cathepsin G are named MC_{TC}. These mast cell subsets differ in their tissue localization; for instance, the MC_{TC} is the predominant type found in normal skin and small bowel submucosa, whereas the MC_T is almost the exclusive type found in small bowel mucosa and in bronchial/bronchiolar areas [18].

Back in 1992, Judah Folkman suggested that TAMs and mast cells play an important role in angio- and lymphangiogenesis [20]. Researchers have demonstrated that mast cells produce several proangiogenic (VEGF-A, VEGF-B, and FGF-2) and lymphangiogenic factors (VEGF-C and -D). In addition, it was shown that VEGFs are chemotactic for mast cells, indicating that mast cells are a target, in addition to be a source, for VEGF. Human mast cells produce different matrix metalloproteinases (e.g., MMP-9) and proteases (tryptase and chymase), which regulate the digestion of ECM favoring the migration of cancer cells [19].

The role of mast cells in cancer is dual and uncertain. Some scholars highlight the anticancer function of mast cells. Human mast cells contain different proinflammatory mediators, but are unique in their ability to pre-store and release potentially beneficial anticancer mediators. For example, human mast cells have pre-stored and released TNF-α within their granules. Furthermore, human mast cells release granulocyte-macrophage colony-stimulating factor (GM-CSF). Both TNF-α and GM-CSF have been used as anti-cancer agents. In this way, antitumor agents from mast cells could be used as a potential "Trojan Horse" of cancer cellular immunotherapy [21].

Xie et al. suggests that mast cells can induce prostate cancer chemotherapy and radiotherapy resistance by modulation of p38/p53/p21 [19, 22]. Mast cells have a protumor action in human bladder cancer through stimulating estrogen receptor β (ERβ). In a murine model of bladder cancer, authors showed that a selective ERβ antagonist inhibited mast cell-promoted tumor growth [19, 23].

Some groups have concluded that the prognosis is worse with a higher density of mast cells in the breast cancer tissue [24]. Xiang et al. have observed more numerous peritumoral MCs in G3 breast cancers, increased tryptase being associated with higher tumor grade and more lymph node metastasis compared to lower grades. They have also noted that tryptase promotes the invasion and migration of breast cancer cells along with the activation of matrix metalloproteinase-2, and have concluded that tryptase promotes breast cancer migration and invasion [25]. Raica et al. revealed strong positive correlations between populations of MCs and lymphatic vessels in some molecular subtypes of breast cancer, thus supporting the idea of MCs involvement in metastasis by lymphangiogenesis [26]. Ribatti et al. have pointed out that angiogenesis increased in parallel with the number of tryptase-positive MCs particularly inside lymph nodes associated with micrometastases compared to non-metastatic lymph nodes [27]. It has also been demonstrated that during breast cancer progression MCs may contribute to stromal remodeling and differentiation of myofibroblasts, through tryptase released in the stromal microenvironment [28]. All these mean that targeting MCs could be involved in the inhibition of angiogenesis, lymphangiogenesis and many other negative effects of MCs' activation. Our research showed that mast cells dynamics is strongly influenced by hormone receptors and HER2 status. Mast cells from intratumoral stroma increased in aggressive tumor types and is a worse prognostic factor [29].

Tissue microenvironment has profound effects on the progression of cancer cells by its paracrine signaling. Molecular characterization of various cell types from the normal breast tissue, DCIS and invasive breast tumor revealed significant changes in gene profile in all cell types during breast tumor progression. Microenvironment changes influence tumor progression as well as the efficacy of various cancer therapies [5]. There is compelling evidence that the

elements of tumor microenvironment respond to different stimuli and release distinct mediators, some antitumorigenic, while others protumorigenic activity [19].

Conclusions

In further researches it is necessary to unravel the factors determining the failure of breast stroma elements to exert anticancer functions. Even if a lot of things are known about breast cancer, the mortality is still high. Our findings suggest that cancer therapy should be an individual one, approved after complex diagnosis of the patient. Each of the known players of breast stroma involved in tumorigenesis and cancer progression can be influenced and directed towards an "anticancer" state. This could be the therapy of future.

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