Am J Cancer Res 2020;10(2):383-392
www.ajcr.us /ISSN:2156-6976/ajcr0105973

Review Article

Yin-yang effect of tumour cells in breast cancer: from mechanism of crosstalk between tumour-associated macrophages and cancer-associated adipocytes

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Received December 5, 2019; Accepted January 2, 2020; Epub February 1, 2020; Published February 15, 2020

Abstract: Currently, adipocytes and macrophages are considered to be key cell types of breast cancer (BC) tissues. With the emergence of crown-like structures (CLS), cancer-associated adipocytes (CAAs) and tumour-associated macrophages (TAMs) are formed respectively in tumor microenvironment (TME). Both of them affect the progress of breast cancer, while forming crosstalk in the tumour tissue. CAAs play an important role, which produces hypoxia and inflammation environment and aggravates this environment. The formation and secretion of TAMs with M2 phenotypic characteristics, such as HIF-1α, and TNF-α, affect the progress of cancer cells by interfering with the secretion of MCP-1 by CAAs. Therefore, the interaction between CAAs and TAMs may be an effective therapeutic target for breast cancer. In this review, we focus on the biological effects of two types of cells in breast cancer, in order to better explain the crosstalk between them and provide new ideas for the future treatment of breast cancer.

Keywords: Breast cancer, crosstalk, tumour-associated macrophages, cancer-associated adipocytes

Introduction

Breast cancer (BC) is a highly heterogeneous malignant disease that gives rise to many cancer-related deaths worldwide [1]. Its development involves complex and contradictory biological processes, which are not only controlled by genetic abnormalities, but also by the interplay between cancer cells and the tumour microenvironment (TME) [2]. TME is a dynamic network, which includes immune cells, extracellular matrix and stromal tissue. Cancer-associated adipocytes (CAAs) and tumour-associated macrophages (TAMs) are important components of BC niche. They play important roles and have been extensively studied [3, 4].

Nevertheless, the interaction between cancer-related cells in BC microenvironment are less well understood. Recent studies have shown that CAAs are associated with BC cell transformation and reversible to some extent [5]. This provides a useful research direction for TAMs which are also involved in the BC cell transformation and affect CAAs. However, the exact role of CAAs and TAMs in the development of BC remains controversial.

As a dialectical way of thinking in China, the theory of yin-yang is quite different from the Western way of thinking in both literal and symbolic sense. However, the theory of yin-yang has been applied to the most influential academic journals, including science, nature and cell. At present, yin-yang theory is widely used in the biomedical field in the West; many authors also use yin-yang symbols to express their new discoveries [6, 7]. For example, yin-yang-1 factor, a transcription factor involved in tumour progression (in short, YY1 factor) [8]. In the immune system, tregs and suppressive cytokines are homeostatic with effective cells plus pro-inflam-

matory cytokines in healthy hosts which is defined as "Yang", and ADs are usually induced in case of disturbed homeostasis, which is defined as "Yin" [9].

Therefore, we discussed unique functional characteristics of CAAs and TAMs in BC microenvironment, and analysed the feasibility of crosstalk based on the relationship between yin-yang as a potential therapeutic direction.

Cancer-associated adipocytes (CAAs) and tumour-associated macrophages (TAMs) in breast cancer

CAAs

Adipose tissue is distributed throughout the human body. In the breast, adipocytes account for the largest proportion among the cells that comprise breast tissue [10]. There also exist adipocyte-precursor cells, preadipocytes in breast tissue which have fibroblast-like morphology and high proliferative activity.

The tumour genesis of breast tissue recapitulates glandular epithelial cell proliferation, adipocyte differentiation, extracellular matrix (ECM) remodeling, and reciprocal interactions between epithelial cell and adipocytes are also observed in the process of carcinogenesis in BC [4].

Recent studies have shown that the graft of adipose tissue could potentially promote or accelerate the development of a subclinical tumour or support its locoregional recurrence, which prompted the microenvironment surrounding breast cancer cells and may stimulate growth and promote progression of residual cancer cells when surgery is performed on the main tumour mass [11].

The association of adipocytes and BC cells have been demonstrated in vivo and in vitro evidence that, (i) invasive cancer cells dramatically impact surrounding adipocytes; (ii) peritumoral adipocytes exhibit a modified phenotype and specific biological features sufficient to be named CAAs; and (iii) CAAs modify the cancer cell characteristics/phenotype leading to a more aggressive behavior.

These results strongly support the innovative concept that adipocytes participate in a highly complex vicious cycle orchestrated by cancer cells to promote tumour progression [12]. Experiments with adipocytes and tissues have shown their correlation. Therefore, they are considered to be a critical cell type and are associated with the TME of BC.

TAMs

As an important subset of tumour infiltrating immune cells, TAMs participate in the whole process of tumour progression.

There are two main sources of TAMs: Monocyte-Derived Macrophages (MDMs) derived from bone marrow, and Tissue-Resident Macrophage (TRMs) derived from the yolk sac and colonized in specific tissues. In most cases, TAMs are derived primarily from circulating monocytes and aggregated around tumour tissue via the chemokine CCL2 [13].

Changes in surface markers usually occur when circulating monocytes accumulate in tumour tissue. $Ly6C^+$ monocytes enter into inflammation tissue, cell morphological changes, volume increase, mononuclear cells continuously replace the yolk sac in macrophages, become an MHC II^+ macrophage, this process is also a mature mononuclear cell differentiation process, called the "waterfall effect" (**Figure 1**) [14]. This phenomenon originated from the study of intestinal monocytes and may extend to tumour tissues, providing a basic model for describing the terminal differentiation of monocytes in tumour tissues. In tumour tissue, however, the distribution of different mature stage TAMs is affected by tumour location, type, stage and the influence of size. The different stages of maturity TAMs play a certain role in the process of tumour development, such as MCH II^+ TAMs presenting antigen, initiating an immune response, effectively killing the tumour cells.

Although TAMs can inhibit tumour cells, it is believed that TAMs can promote tumor growth in other studies. This seemingly contradictory result is related to the phenotype of TAMs. TAMs are considerably plastic and assume opposing phenotypes and functions that can be either tumour-supportive (M2 macrophages) or tumouricidal (M1 macrophages). In most tumours, the tumour-supportive M2 phenotype prevails [15].

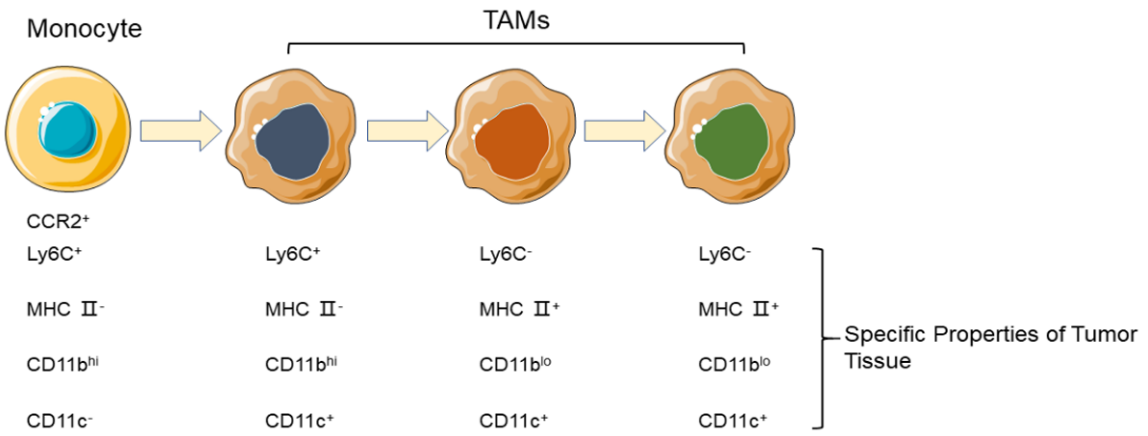

Figure 1. Differentiation phenotype of TAMs in different stages.

M1 macrophages is regulated by cytokines secreted by Th1, such as interferon-γ (INF-γ), lipopolysaccharide (LPS) and toll-like receptor (TLR), and is characterized by the secretion of pro-inflammatory cytokines including IL-6, IL-12, IL-23 and tumour necrosis factor-α (TNF-α). In addition, the tumour specific antigen presented needs by M1 macrophages high expression of major histocompatibility complex (major histocompatibility complex) I classes and II molecules. Therefore, M1 macrophages are considered to be cells that kill bacteria and tumour cells and secrete a variety of pro-inflammatory cytokines [16].

M2 macrophages have the opposite function of M1 macrophages, which are recognized as anti-inflammatory and carcinogenic cells.

The generic use of M2 to define macrophage activation other than M1 is justified based on the sharing of selected functional properties (e.g. low IL-12) and their general involvement in type II responses, immunoregulation and tissue remodeling. We propose to refer to the three well defined forms of M2 as: M2a (where a also stands for alternative), induced by IL-4 or IL-13; M2b, induced by exposure to the IC and agonists of Toll-like receptors (TLRs) or IL-1R; and M2c, induced by IL-10 and glucocorticoid hormones [17].

Recent studies have suggested that teams tend to contribute to the environment of tumour formation and development, not only because macrophages can constitute up to 50% of tumour masses [18], but also because of the occurrence of tumour cells vascular endosmosis and immunosuppression mediated by macrophages.

Crosstalk of CAA with TAM in breast cancer

Crown-like structures at the beginning of the crosstalk

Crown-like structures (CLS), composed of macrophages surrounding dead or dying adipocytes, are found in breast tissue regardless of the presence of breast cancer [19], and are a histologic hallmark of the proinflammatory process which adipose tissue contributes to the increased risk and worse prognosis of breast cancer in obese, postmenopausal patients [20]. The formation of CLS can be seen as a sign of the beginning of crosstalk (**Figure 2**).

Firstly, the latest studies have shown that CLS formation is associated with breast cancer [21, 22]. Secondly, the number and density of CLS increased in proportion to the size and number of adipocytes and the abundance of macrophages in the parasitoid adipose tissue of breast cancer. Then, CLS formation, as a potential mutagenic agent, triggers a series of vicious cycles in the breast cancer tumour microenvironment. Macrophages in CLS engulf cell debris and lipid droplets, release fatty acids and triglycerides [23]. Fatty acids and triglycerides are two of the most common metabolites of tumour-associated fat cells. Studies have confirmed that fatty acids can participate in the glucose uptake process of various tumour cells, such as prostate cancer cells, and promote the growth of malignant tumours by promoting the release of inflammatory factors in malignant

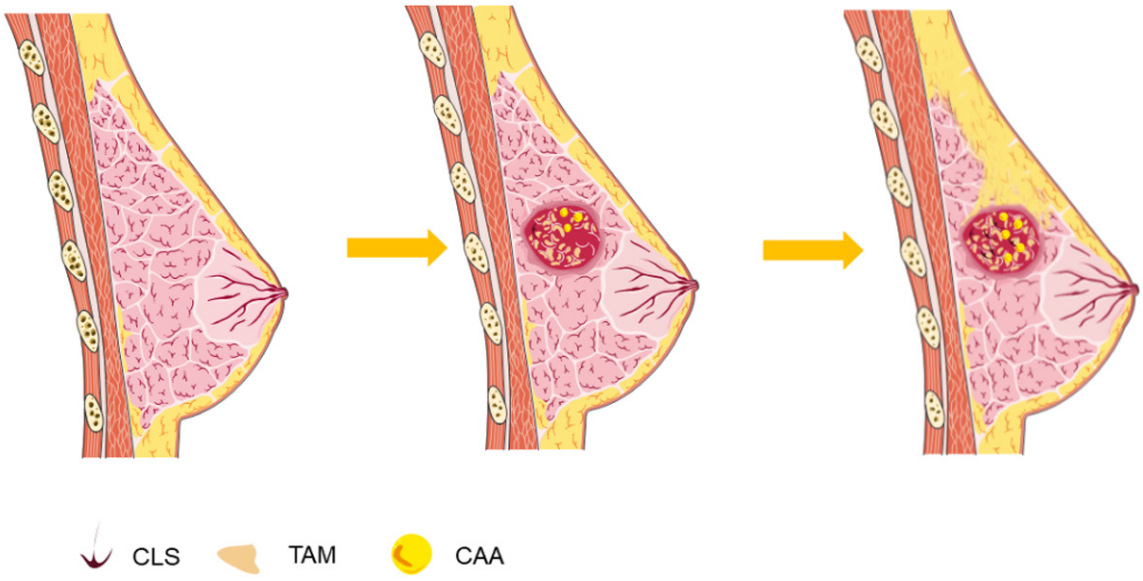

Figure 2. Crown like structure (CLS) in adipose tissue nearby breast cancer.

tumours and mediating the recruitment of macrophages and lymphocytes to malignant tumour cells. Other studies have confirmed that triglycerides can reduce the apoptosis of malignant tumour cells by inhibiting the release of ceramide in human body [23, 24].

The tumour microenvironment as a venue for crosstalk

The so-called TME is being considered as a key factor in the occurrence, progression and treatment of cancer lesions. In addition to genetic mutation, the presence of malignant microenvironments forms the basis of a new perspective in cancer biology, in which system-level linkages are the basis. From this point of view, all aspects of interaction between CAAs and TAMs can be considered from a unified perspective, thus forming a new research field and clinical breakthrough point.

Hypoxia: Hypoxia in TME is particularly prominent. The vascular system is highly disordered and constantly changing due to the increase and decrease of blood vessels. The result of this change is the fluctuation of oxygen and glucose levels, which leads to the coexistence of hypoxia, anaerobic and aerobic glycolysis. In this process, proliferating cells and dead cells coexist in the hypoxic and acidic environments and produce a large number of harmful cytokines. With the participation of CAAs, vascular abnormalities and special metabolic characteristics of tumours are caused. At the same time, tumour microenvironment recruits and changes the phenotype of TAMs, regulates the immune response, including TAMs, and leads to immune escape or tolerance.

Healthy cells rely on mitochondria to oxidize sugar molecules to release ATP, while the high concentration of lactic acid in TME produces a special Warburg effect: infinitely increased energy metabolism of cancer cell changes, even in an aerobic environment, glycolysis is used to replace the aerobic cycle (aerobic glycolysis). There is evidence that there is a large amount of TAMs aggregation in the hypoxic region of progressive tumours. Casazza et al. [25] confirmed that the recruitment of TAMs depends on the activation of the signal pathway of semaphores 3A/neuropilin-1 (Sema3A/Nrp1). Sema3A can chemotactic macrophages by binding with homologous receptor complex Nrp1/plexinA1 (pA1)/plexinA4 (pA4). Meanwhile, Sema3A can promote the migration of TAMs to hypoxic areas. When TAMs tend to hypoxic regions, hypoxia can alter macrophage phenotypes and make them develop intotumourigenic phenotypes. Hypoxia-inducible factor 1α (HIF-1α) is a key transcription factor in the phenotypic change of macrophages. The expression of chemokine receptor 4 (C-X-C motif) receptor 4, CXCR4-dependent HIF-1α in

macrophages and the increase of its specific ligand CXCL12 also lead to the increase of chemokine response in macrophages [26]. Increased expression of macrophage chemokines further led to more TAMs recruited into hypoxic regions and become M2. M2 macrophages are highly localized in hypoxic tumours and exhibit good angiogenic activity in vivo, and the number of M2 macrophages increases with the progression of tumours

In hypoxic mammary adipose tissue, the proliferation of oxygen decreases with the increase of cell volume, and the growth of blood vessels is impaired. Mitochondrial production of excessive free fatty acids leads to an increase in reactive oxygen species (ROS), which leads to oxidative stress [27]. Therefore, adipokines secreted by adipose tissue (i.e. cell signalling proteins secreted by adipose tissue) is defective, leading to angiogenesis and inflammation [28]. This chain reaction forms a malignant environment in the breast cancer region to promote the development of breast cancer cells.

Inflammation: Chronic inflammation is considered a precursor to cancer development. Breast cancer patients are often accompanied by chronic low-grade inflammation, and the degree of pathological changes increases with the accumulation of fat and inflammation of fat. At the same time, there is increasing evidence that adipose tissue inflammation is a key driver of oestrogen production in obese postmenopausal women, which plays an important role in ER^+ breast cancer. Chronic inflammation produces malignant lesions by producing harmful ROS and decays surrounding adipose tissue to form CAAs. With the release of CAAs pro-inflammatory adipokines such as leptin, activating transcription factors are activated, such as nuclear factor κB (NF-κB), transcription activator 3 (STAT3), HIF-1α, and various inflammatory mediators such as cytokines, chemokines and prostaglandins are produced in large quantities. Various inflammatory cells such as TAM, MDSC, mast cells and neutrophils are recruited and further promoted. This process by influencing the proliferation and survival of cells, promoting angiogenesis, inhibiting the anti-tumour immune response, promoting the infiltration and metastasis of tumour cells, finally, mediates the occurrence and development of tumours.

Chronic low-grade inflammation persists in tumour microenvironment, which is another inducing condition for malignant transformation of TAMs. Under the induction of STAT3, macrophages in the stroma of tumours tend to differentiate into TAMs with M2 characteristics. In addition, the high lactic acid state produced by glycolysis inhibited the migration ability of mononuclear macrophages and reduced the release of TNF and IL-6. At the same time, under the action of lactic acid, macrophage phenotype transforms to M2 type, which inhibits its antigen presenting function, thus promoting the occurrence of immune escape.

Tumour factors act as crosstalk products

When abnormal energy metabolism occurs in malignant tumour cells and malignant tumour microenvironment, the lipolysis of tumour-related adipocytes becomes very active, which secretes tumour-related adipokines and inflammatory factors, including leptin, adiponectin, Visfatin, IL-6 and IL-8, and produces fatty acids and other metabolites.

Leptin, spherical adiponectin, Resistin, insulin-like growth factor binding protein-2 (IGFBP-2), chemokine ligand 5 (CCL5) and other cytokines derived from adipocytes in tumour microenvironment can act as paracrine signals in breast cancer cells and up-regulate the expression of invasive related proteins or proteases, such as calcium binding protein S100A7, matrix metalloprotein-9 (MMP-9) and urokinase-type plasminogen activator (UPA), or activate PI3K/AKT signalling pathways, or media EMT to enhance the movement, migration or invasion of breast cancer cells [29-31]. On the other hand, recent studies have confirmed that cancer cells can promote the release of FFA from adipocytes, and on the contrary, enhance the invasiveness of tumours by inducing metabolic remodeling [32].

The key point is that adipocytes can secrete leptin and IL-6 and activate the transcription factor Egr-1 in macrophages, thus up-regulate the expression of vascular endothelial growth factor-A (VEGF-A) in macrophages at the transcriptional level and mediate the metastasis of breast cancer cells. In the microenvironment of tumours, Visfatin secreted by CAAs can promote the growth of malignant tumour cells

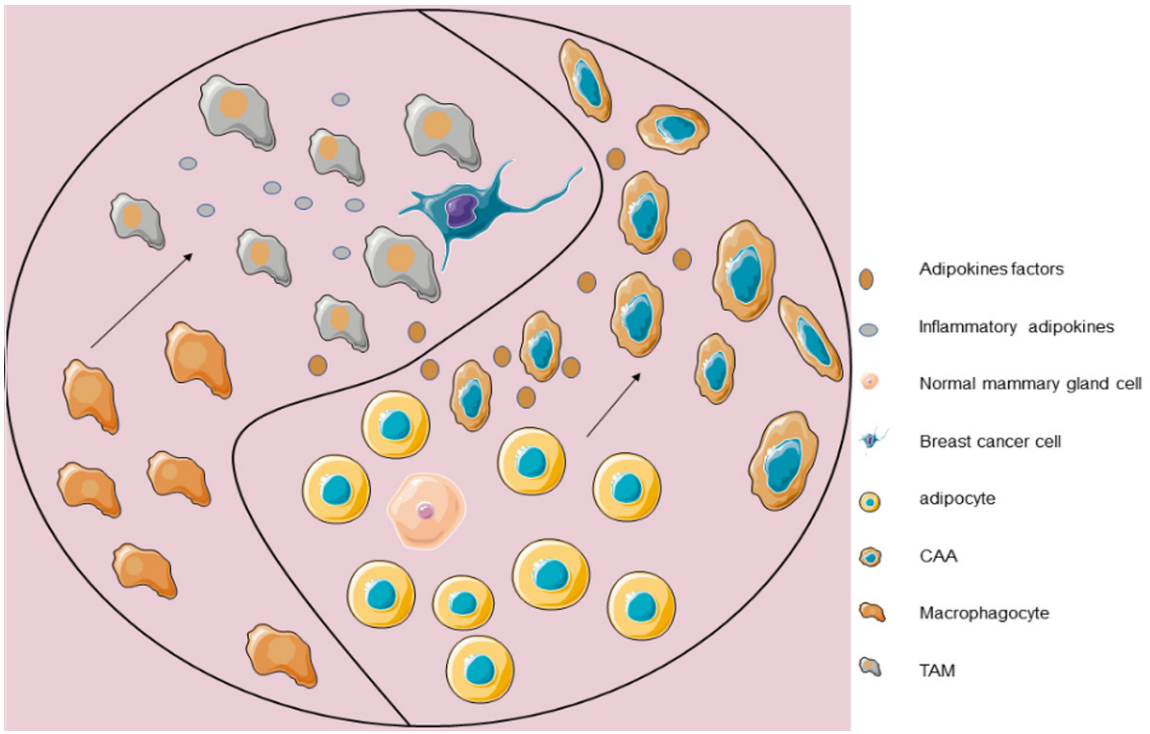

Figure 3. With the development of breast cancer, TAMs and CAAs play the role of yin-yang: in tumour microenvironment, CAAs are derived from adipocytes and CAAs secreted adipokines to interfere with macrophages evolution in tumour microenvironment. TAMs and CAAs secrete cytokines to interfere with the progress of cancer cells. At the same time, they influence each other to form crosstalk through their own specific tumour factors.

by accelerating the glycolysis process of malignant tumour cells, which can produce high lactic acid to induce polarization of M2 macrophages and promote the expression of oncogene VEGF and Arg1 in macrophages [33]. VEGF expression in cancer tissues is usually regulated by HIF-1α, a tissue inducible factor that can play a stable role even in hypoxic environments. It has also been reported that the deletion of Arg1 in bone marrow cells can significantly reduce the growth rate of subcutaneous transplanted tumours. It is speculated that the expression of Arg1 in TAMs can promote the growth of tumours. Similarly, cell metabolites of tumour-related adipocytes, such as fatty acids, can participate in the glucose uptake process of breast cancer cells and other cancer cells, and promote the growth of malignant tumours by promoting the release of inflammatory factors in malignant tumours and mediating the recruitment of macrophages.

When TAMs are recruited and activated, they can directly release IL-10 or indirectly up-regulate Treg activity by releasing IL-23, thus inhibite the immune response of anti-tumor immune cells and mediate the immune escape of tumours. TNF-α and IL-1 secreted by TAMs cells can promote the secretion of vascular endothelial growth factor, while the expression of Arg-1, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are significantly increased, promoting the proliferation and differentiation of tumour cells [14]. TAMs also secrete MMP, which can promote the metastasis of cancer cells by degrading extracellular matrix components. The cytokines secreted by TAMs also affect adipocytes.

Aspirin can inhibit the differentiation and lipid accumulation of adipocytes 3T3-L1, and inhibit the secretion of MCP-1. This effect is more obvious when adipocytes are stimulated by TNF-α from macrophages to produce inflammation.

TAMs and CAAs secrete cytokines to interfere with the progress of cancer cells. At the same time, they influence each other to form crosstalk through their own specific tumour factors (**Figure 3**). This characteristic can be used as a potential therapeutic target in the future, and it

is also a difficult point to solve the progress of cancer.

Treatment based on crosstalk in breast cancer

Intervene TAMs

There is growing evidence that TAMs are associated with poor prognosis. Tumour therapy targeting of TAMs may become a hot pot in the future. At present, the main strategies of cancer therapy targeting TAMs are: inhibiting the recruitment of macrophages, transforming tumourigenic M2 into anti-tumor M1, and inhibiting the survival of TAMs.

Chemokine (CK) derived from tumours and stroma promotes the recruitment of macrophages into tumours. Therefore, inhibition of macrophage recruitment by regulating CK may be an effective cancer therapy.

Current studies have shown that the pharmacological inhibition of CCL2 by Bindarit can significantly reduce macrophage recruitment and inhibit tumour growth [34]. The selective inhibition of vascular endothelial growth factor receptor (VEGFR) 2 can effectively reduce the infiltration of macrophages and tumour growth together with specific antibodies [35]. Meanwhile, the therapy targeting the colony stimulating factor (CSF) 1 receptor may be another new strategy for regulating the number of macrophages in tumours. Studies showed that in patients with diffuse giant cell tumours, human monoclonal antibody RG7155 could effectively inhibit the formation of CSF1-R dimer, and then significantly reduce the infiltration of $CSF\text{-}1R^{+}CD163^{+}$ macrophage subsets in tumours [36]. PLX3397, a tyrosine kinase inhibitor of CSF1-R, can improve the effect of tumour immunotherapy by reducing macrophage accumulation and promoting lymphocyte infiltration in tumour tissues [37].

It has been found that activation of some TLRs can transform M2 macrophages into M1 macrophages, which kill tumour cells [38]. In tumour-bearing mice, activated TLR3/Toll-IL-1 rapidly induced the production of pro-inflammatory cytokines by activating Poly (I:C) and then accelerated the production of M1 macrophages. Zoledronic acid is a clinical drug for cancer. It has been found that zoledronic acid can inhibit the occurrence of spontaneous breast cancer by reducing macrophages from M2 phenotype to M1 phenotype [39]. In addition, macrophage transformation can effectively inhibit the growth of breast tumours and inhibit the angiogenesis of tumours. For example, histidine-rich_glycoprotein (HRG) can down-regulate the expression of placental growth factor (PIGF), induce macrophages to transform into anti-cancer phenotype and vascular remodeling [40]. These results suggest that the activation of TAMs is reversible, and a new therapeutic strategy for the redifferentiation of TAMs is proposed.

The strategy of improving the therapeutic effect of tumours by inhibiting the activity of TAMs has been recognized and applied clinically. For example, trabectidine (ET-743), a DNA damage drug for soft tissue sarcoma and recurrent platinum-sensitive ovarian cancer, can kill TAMs and exert anti-cancer effects [41]. It specifically inhibits TAM by activating exogenous apoptotic pathways through tumour necrosis factor-related apoptosis inducing ligand (TRAIL) receptors. In mice model of drug-resistant transplanted tumours, trabectidine can significantly inhibit the growth of tumours, and the density of TAMs in tumour microenvironment is significantly reduced. In addition, docetaxel can also eliminate immunosuppressive TAMs and exert anti-proliferation effect on myeloid-derived suppressor cells [42].

Intervene CAAs

CAAs are heterogeneous and closely related to the types, stages and grades of tumours. They are thus “inhibited” and “educated” by tumours to varying degrees, which poses a challenge for targeting CAAs. Transforming CAAs into normal adipocytes and inhibiting related biologically active molecules are currently available means. Metformin has long been reported to have anti-tumor effects. It can not only directly target cancer cells, but also reverse dysfunctional adipocytes and normalize them. Studies have shown that metformin not only regulates the expression of leptin, PAI-1 and other cytokines in adipocytes, but also participates in the regulation of sugar uptake and lipid metabolism. In addition, metformin also regulates insulin signalling pathway [43].

In addition, PPAR γ agonists can not only reverse the disorder of bioactive molecules, such as up-regulation of adiponectin, but also inhibit tumours. Factor, down-regulation of

leptin, IL-6, TNF-α and other tumour factors can also promote adipogenic differentiation and reduce the source of oestrogen. At present, TZDs such as rosiglitazone and pioglitazone have been used in the clinic [44, 45]. Similarly, a large number of studies have found that a variety of target genes specifically promote or inhibit adipogenic differentiation of microRNAs, such as microRNA143, microRNA21 and so on, while microRNAs-27a/b and microRNAs-130 have inhibitory effects [46].

The feasibility of research and clinical application of bioactive molecules secreted by CAAs as targets has been reported. It has been reported that polypeptide analogues located at the binding site of leptin and leptin receptor (ObR) can inhibit the development and metastasis of breast cancer by selectively inhibiting the interaction between leptin and leptin receptor [47].

Promoting the benign transformation of tumour cells

In the theory of yin-yang of Chinese philosophy, yin-yang is mutually rooted and interdependent. In simple terms, yin-yang is homologous and transformative. Interestingly, the occurrence and development of breast cancer accord with the characteristics of yin-yang. Tumour cell plasticity and EMT are dynamic and can occur during different steps of cancer metastasis.

Ronen et al. showed that the cellular plasticity of cancer cells undergoing EMT can be exploited to force transdifferentiation of breast cancer cells into post-mitotic and functional adipocytes, leading to the repression of primary tumour invasion and metastasis formation [5].

Notably, adipogenic differentiation therapy with a combination of Rosiglitazone and a MEK inhibitor efficiently inhibits cancer cell invasion, dissemination, and metastasis formation in various preclinical mouse models of breast cancer. The results underscore the pivotal role of cancer cell plasticity in malignant tumour progression and reveal the therapeutic potential that lies in the targeting of cellular plasticity, for example by forcing post-mitotic adipogenesis.

Conclusions

Although remarkable progress has been made in understanding the respective mechanisms and functions of CAAs and TAMs, there are still many areas to be found. In the past, CAAs and TAMs may be a treatment barrier because they participate in the mechanism of resistance to various breast cancer therapies. Recent studies have proved that they interact in the TME, and pointed out the possibility of targeting therapy through intervention of interactive products. In addition, the reversible transformation of tumour cells into adipocytes has been confirmed. However, whether cancer cells can reverse to macrophages and whether CAAs and TAMs can be inhibited to form or transform into cell phenotypes with benign anti-cancer effects need to be further clarified.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (Grant No. 81873311, No. 81573983 and No. 81674028). Zhu Zhongbo thanks to the help provided by School of Pharmacy, Health Science Center, Xi'an Jiaotong University.

Disclosure of conflict of interest

None.

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