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Adipocyte: an assistant to breast cancer development and a potential treatment strategy for breast cancer

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Abstract

With obesity becoming an epidemic, adipocytes have attracted widespread attention. Growing studies have shown that the function of adipocytes is far more than storing energy. As endocrine organs, adipocytes play a pivotal role in the occurrence and prevention of many diseases. Especially it can secrete cytokines and mediate chronic inflammation, making it one of the assistants of tumor development. Breast cancer is the main cause of cancer death in women, and its development has experienced proliferation, invasion, migration, metastasis, and drug resistance. It reports that the mammary gland is rich in adipocytes. And adipocytes can communicate with breast cancer cells and play a pivotal role in breast cancer development. It displays that adipocytes promote the proliferation, metastasis, and drug resistance of breast cancer. This suggests that focusing on adipocytes may be helpful for tumor treatment. In this paper, we reviewed the regulation mechanism of adipocytes on the development of breast cancer and proposed strategies to treat breast cancer. And this may provide a research basis for the prevention and treatment of breast cancer.

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Declaration of Interest

The authors report no declarations of interest.

Author's contribution

Zhaodi Kong and Baoqi Ren: Writing-original draft. Fengjie Liu, Meng Lan, Lihong Li, and Tengteng Zou: Perfecting picture. Zhenjiang Yang, Tiange Cai, and Yu Cai: Conceptualization, Writing-review and editing. All authors read and approved the final manuscript.

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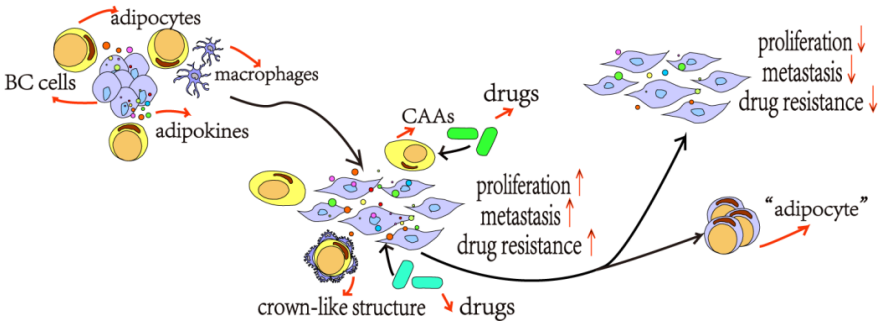
Highlights

- Adipocytes release cytokines to promote breast cancer development
- Adipocytes help tumor escape immune clearance by mediating immune remodeling
- Focusing on adipocytes can treat breast cancer

Abstract

With obesity becoming an epidemic, adipocytes have attracted widespread attention. Growing studies have shown that the function of adipocytes is far more than storing energy. As endocrine organs, adipocytes play a pivotal role in the occurrence and prevention of many diseases. Especially it can secrete cytokines and mediate chronic inflammation, making it one of the assistants of tumor development. Breast cancer is the main cause of cancer death in women, and its development has experienced proliferation, invasion, migration, metastasis, and drug resistance. It reports that the mammary gland is rich in adipocytes. And adipocytes can communicate with breast cancer cells and play a pivotal role in breast cancer development. It displays that adipocytes promote the proliferation, metastasis, and drug resistance of breast cancer. This suggests that focusing on adipocytes may be helpful for tumor treatment. In this paper, we reviewed the regulation mechanism of adipocytes on the development of breast cancer and proposed strategies to treat breast cancer. And this may provide a research basis for the prevention and treatment of breast cancer.

Graphical Abstract



Key words : Adipocytes, Cytokines, Inflammation, Breast cancer

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Contents

Abbreviations : IL-6: interleukin 6; CCL2: CC chemokine ligand-2; CXCL8: C-X-C-chemokine ligand-8; IFN-γ: interferon-γ· NK cells: natural killer cells; BC: breast cancer; EMT: epithelial-mesenchymal transition; PAT2: proton assistant amino acid transporter-2; P2RX5: purinergic receptor P2X, ligand-gated ion channel 5; UCP-1: uncoupling protein-1; CAAs: cancer-associated adipocytes; ERK: extracellular-regulated protein kinase; MAPK: mitogen-activated protein kinase; PPAR: peroxisome proliferation activated receptor; KLFs: krüppel-like factors; TGF-β: transforming growth factor; MCP-1: monocyte chemotactic protein-1; CD36: cluster of differentiation 36; $HER2^{+}$: human epidermal growth factor receptor 2 positive; VEGF: vascular endothelial growth factor; MVP: major vault protein; MMP1: Matrix metalloproteinase 1; IGF: insulin-like growth factor ; JAK: Janus-activated kinase; STAT3: signal transducer and activator of transcription 3; PI3K: phosphatidylinositol 3 kinase; ER^{+}: estrogen receptor positive; ABCB1: ATP-binding

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cassette subfamily B member 1; RDH5: retinol dehydrogenase 5; ITGB3: integrin beta 3; FAK: focal adhesion kinase; mTOR: mammalian rapamycin protein; NF-ϰB: nuclear factor ϰB; G-CSF: granulocyte colony stimulating factor; IGFBP-2: insulin-like growth factor binding protein-2; HIF1α: hypoxia inducible factor 1?; MDSCs: myeloid suppressor cells; CLS: crown-like structure

Introduction

For a long time, people innocently think that adipocytes are just energy storage cells, which store a lot of energy in the form of lipid droplets. Until 1994, Zhang et al. (Zhang, Yiying, Proenca & Ricardo, 1994) successfully cloned the mouse Ob gene, an open reading frame containing 167 amino acids, and predicted its protein-which was later called leptin. People realized that adipocytes are also endocrine organs. Over the past 20 years, it proved that adipocytes secrete hundreds of different cytokines, such as leptin, interleukin 6 (IL-6), CC chemokine ligand-2 (CCL2), CCL5, and C-X-C-chemokine ligand-8 (CXCL8) (Wu, Li, Li, Li, Sun & Sun, 2019; Zhao et al., 2020). In addition, researches also revealed that adipocytes are immune organs, which can affect the immune behavior of tumors, such as helping tumors escape immune clearance. For example, adipocytes and pre-adipocytes inhibit antibody-dependent cytotoxicity of breast cancer (BC) cells mediated by Trastuzumab by reducing the secretion of IFN-γ in natural killer cells (NK cells) (Duong et al., 2015).

The past decades have witnessed the rapid development of breast cancer (BC). As cancer with the highest incidence and the top five mortality rates in the world, BC is the main cause of cancer death among women in the world (2020). Obesity is an important factor in the pathogenesis of BC (Youn & Han, 2020), and obesity promotes the drug resistance and recurrence of BC by affecting immune homeostasis and immune escape (Gibson et al., 2020). Moreover, more and more evidence shows that adipocytes, as one of the important components in obese patients, can cross-talk with BC, and play an important role in proliferation, invasion, epithelial-mesenchymal transition (EMT), and drug resistance of BC (Gyamfi, Lee, Eom & Choi, 2018; Lehuédé et al., 2019).

However, the research on the regulation mechanism of adipocytes on the development of breast cancer is still in its infancy. There is no systematic regulation mechanism of adipocytes on the development of breast cancer. It is rare to focus on adipocytes to treat BC.

This article discusses how adipocytes help breast cancer develop from adipocyte factors and inflammation/immunity. In addition, the strategy of focusing on fat cells to achieve the treatment of breast cancer was discussed, which is promising to provide a treatment strategy for the treatment of breast cancer.

Overview

Adipocytes include White adipocytes, Brown adipocytes, Beige adipocytes, and Pink adipocytes. And they are different in morphology and function (Giordano et al., 2014; Ussar et al., 2014). Among them, white adipocytes-with underdeveloped mitochondria and single lipid droplets-are related to the storage and secretion of lipids, and their specific cell surface proteins are ASC-1 (Giordano et al., 2014; Ussar et al., 2014). While brown adipocytes, with numerous large mitochondria and many small lipid droplets, go hand in hand with lipid consumption and thermogenesis. Their specific cell surface proteins are proton assistant amino acid transporter-2 (PAT2) and purinergic receptor P2X, ligand-gated ion channel 5 (P2RX5) except uncoupling protein-1 (UCP-1). The general view is that beige adipocytes, similar to brown adipocytes' functions (such as thermogenesis), are the consequence of white adipocytes' browning. Pink adipocytes, also known as breast, are named after their pink color, the ability to store a large number of lipids, and only exist under the skin of women during pregnancy and lactation (Ussar et al., 2014). In recent years, it found that white and beige/brown adipocytes promote the development of BC. For example, white and beige adipocytes increased the migration of tumor cells. Among them, beige or brown adipocytes promote tumor formation faster (Gantov et al., 2021; Singh et al., 2016).

Adipocytes in the breast can be divided into pre-adipocytes, mature adipocytes, and cancer-associated adipocytes (CAAs) (Wu, Li, Li, Li, Sun & Sun, 2019). Pre-adipocytes have fibroblast-like morphology and

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can differentiate into mature adipocytes by many factors, including numerous signaling pathways (such as ERK/MAPK/ peroxisome proliferator-activated receptor (PPAR), Wnt signaling pathway), regulatory proteins (such as PPARγ, Krüppel-like factor (KLFs), transforming growth factor (TGF-β)) and long non-coding RNA (Zhang et al., 2020). Mature adipocytes in the breast are white adipocytes: with a single lipid droplet occupies 90% of the cytoplasm, while CAAs are adipocytes with fibroblast-like phenotype and small and scattered fat droplets, which are closer to brown adipocytes in morphology (Wu, Li, Li, Li, Sun & Sun, 2019; Zhao et al., 2020). Numerous studies showed that adipocytes could promote the proliferation, metastasis, and drug resistance of BC (Lehuédé et al., 2019; Hsieh, Wang & Huang, 2016).

Crosstalk between adipocytes and breast cancer

In the past few years, the research on the crosstalk between adipocytes and BC has risen. Various adipocytes promoted BC proliferation, metastasis, and drug resistance (Lehuédé et al., 2019; Hsieh, Wang & Huang, 2016).

Many studies have proved that adipocytes help the proliferation, metastasis, and drug resistance of BC (As shown in **Table 1**). For example, studies suggested that when used the secretion of 3T3-L1 or human mature adipocytes medium to culture BC cells , the conditioned medium up-regulated the expression of tumor IL-6, IL-1β, and monocyte chemotactic protein-1 (MCP-1) at mRNA level and promoted the proliferation and migration of tumor (Park et al., 2020). Besides, it illustrated that when used white or beige adipocytes secretion to culture BC cells, the migration of BC increased more apparent (Gantov et al., 2021). In addition, Studies have manifested that the proliferation, invasion, and migration of BC cells and the expression of differentiation cluster 36 (CD36) in BC increased when BC cells when cultured with adipocyte secretion medium, while CD36 was closely related to the drug resistance of human epidermal growth factor receptor-positive ($HER2^+$) BC cells to Lapatinib (Zaoui et al., 2019) (Feng et al., 2019).

These evidences show that the crosstalk between adipocytes and tumor cells helps tumor progress.

The mechanism of adipocytes promoting breast cancer progression

. Adipokines secreted by adipocytes affect the process of breast cancer

It is well-known that adipocytes can secrete hundreds of different types of cytokines, such as leptin, inflammatory cytokines (IL-6 and IL-1β), chemokines (CCL2 and CCL5), growth factors (VEGF and insulin-like growth factor (IGF)), and fatty acid-binding proteins (Wu, Li, Li, Li, Sun & Sun, 2019; Zhao et al., 2020; Kothari, Diorio & Durocher, 2020). These cytokines play a pivotal role in inflammation, tumor metastasis, and tumor EMT (Gyamfi, Lee, Eom & Choi, 2018; Kothari, Diorio & Durocher, 2020). This part focused on the action and mechanism of leptin, IL-6, and chemokines on BC to better understand the behavior of adipocytes on BC (As shown in **Figure 1**).

. Leptin and breast cancer

Secreting leptin is one of how adipocytes help BC to achieve rapid proliferation, metastasis, and drug resistance.

Leptin, mainly secreted by adipocytes, is a 167 amino acid peptide with a molecular weight of 16 kDa, which can reduce appetite, enhance the function of immune cells, increase energy expenditure, and inflammatory cytokine secretion (Zhang, Yiying, Proenca & Ricardo, 1994; Park & Ahima, 2015). Studies have reported that leptin can promote the growth, angiogenesis, invasion, and metastasis of colon cancer, gastric cancer, pancreatic cancer, BC, and thyroid cancer through various signal pathways (Ray & Cleary, 2017). Among this, it promoted tumorigenesis and bone metastasis of BC through Janus activator (JAK)/ signal transducer and activator of transcription 3(STAT3), MAPK, phosphatidylinositol 3 kinase (PI3K), ERK1/2 signal pathway, and estrogen pathway(Atoum, Alzoughool & Al-Hourani, 2020; Maroni, 2020).

Clinical studies have revealed that elevated serum leptin levels are usually correlated with malignant tumors of BC patients. For example, Bielawski et al. (Bielawski, Rhone, Bulsa & Ruszkowska-Ciastek, 2020) evaluated invasive BC women and found that high leptin levels, low adiponectin levels, and high plasma tissue factor

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activity are associated with increased recurrence risk and decreased survival rate in BC patients. Other studies have manifested that the leptin gene is over-expressed in obese estrogen receptor-positive (ER^+) BC tissues, and is positively correlated with the expression of aromatase, MAPK, and STAT3, suggesting that leptin contributes to the progress of BC through JAK/STAT3, ERK1/2, and estrogen pathway (Hosney, Sabet, El-Shinawi, Gaafar & Mohamed, 2017).

In vitro studies suggested that leptin levels in the supernatant of adipocytes and BC cells increased significantly in the co-culture system of BC and adipocytes (He et al., 2018), and leptin levels increased after pre-adipocytes were induced to differentiate into white and beige adipocytes (Gantov et al., 2021). The effect of leptin on BC proliferation and reversing tamoxifen anti-proliferation is relevant to increasing the expression of genes related to cell proliferation and drug resistance (such as adenosine triphosphate binding cassette subfamily B member 1(ABCB1), WNT4, retinol dehydrogenase 5(RDH5), integrin β3(ITGB3)) and binding to its receptor (Lipsey, Harbuzariu, Robey, Huff, Gottesman & Gonzalez-Perez, 2020; Linares, Benítez, Reynoso, Romero & Sandoval-Cabrera, 2019). Moreover, studies have displayed that autophagy caused leptin to promote the proliferation and migration of MCF-7 cells as well as the transformation of the mesenchymal phenotype and activation of the ERK1/2 pathway (García-Miranda et al., 2021). Besides, leptin activated the JAK2 signaling pathway after binding with its receptor, which increased colony formation of MCF-10A cells, suggesting that leptin promoted tumor formation (Boothby-Shoemaker, Benham, Paithankar, Shankar, Chen & Bernard, 2020). In addition, leptin activated focal adhesion kinase (FAK)/Src signaling pathway to increase the secretion of MMP2 and MMP9, and activated JAK/Akt/STAT3 and PI3K/Akt signaling pathway to promote tumor growth, metastasis and proliferation and inhibit apoptosis, which demonstrated that leptin contributed to the more invasive phenotype of BC (Juárez-Cruz et al., 2019; Olea-Flores et al., 2019; Kim, Hahm, Singh & Singh, 2020; Haque et al., 2018; Wei et al., 2016; Ding et al., 2016).

Therefore, leptin is one of the vital strategies for adipocytes to help the development of BC.

. IL-6 and breast cancer

Similar to leptin, IL-6 is another way for adipocytes to trigger the rapid development of BC.

IL-6, a member of the IL-6 cytokine family, can remodel bones and promote tumor development by combining with its ligand gp130 and IL-6R and mainly activate JAK/STAT, PI3K/AKT, and other signaling pathways to affect BC (Omokehinde & Johnson, 2020; Incio et al., 2018).

Incio et al. (Incio et al., 2018) observed that the plasma IL-6 level of obese BC patients increased, and in the tumor-bearing mouse model found that the increase of IL-6 in tumor tissue came from adipocytes and infiltrating $CD11b^+$ myeloid cells. Besides, elevated levels of IL-6 caused the anti-angiogenic agent Bevacizumab to weaken the tumor suppressor effect on patients and animals. It indicates that adipocytes secreted IL-6 to trigger tumor drug resistance.

Numerous researches demonstrated that when adipocytes were co-cultured with BC cells, adipocytes' IL-6 secretion increased (Omokehinde & Johnson, 2020; Liu et al., 2020a; Kim et al., 2018). Furthermore, studies have proved that the effect of adipocyte-derived IL-6 on promoting the proliferation, invasion, and migration of BC cells and promoting the growth of xenograft tumor was corresponding to activating of JAK/STAT3 and PI3K-AKT-mammalian rapamycin (mTOR) signaling pathways and increasing the expression of procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) (Gyamfi, Lee, Eom & Choi, 2018; Park et al., 2020; He et al., 2018; Kim et al., 2018; Nickel et al., 2018). In addition, when added the IL-6 to T47D and MCF-7 BC cells, the PIM1 gene (a proto-oncogene) in the STAT3 signaling pathway activated, and the PIM1 gene activated the cMYC gene. While the cMYC gene promoted the stemness and EMT of BC cells, illustrating that increasing the secretion of IL-6 is one of the effective ways that adipocytes promote the malignancy of BC (Gao et al., 2019).

. Chemokines and breast cancer

Chemokine, mainly divided into two categories: C-C-chemokines (such as CCL2, CCL5) and C-X-C-chemokines (such as CXCL8), are molecules with a molecular weight of 8–12 kDa, which can regulate

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immunity and induce bone remodeling (Brylka & Schinke, 2019).

. CCL2 and breast cancer

By releasing CCL2, adipocytes assisted the growth, proliferation, invasion, and drug resistance of BC.

CCL2, also known as MCP-1, is a cytokine that is secreted and released into the environment by tumor cells (osteosarcoma cells, mononuclear leukemia cells), embryonic fibroblasts, and peripheral blood mononuclear cells and can recruit monocytes to the inflammatory response area by binding to its receptor CCR2 (Yoshimura, 2018).

Researches displayed that when 3T3-L1 mature adipocytes co-cultured with 4T1 cells, adipocytes secreted elevated CCL2 (Liu et al., 2021). And binding to CCR2, CCL2 regulated the activity of the p42/44MAPK signaling pathway, the p42/44MAPK signaling pathway further increase the proliferation, invasion, and migration of BC and promote BC angiogenesis (Park et al., 2020; Han et al., 2018; Hu et al., 2019). Moreover, studies illustrated that adipocytes induced the increase of CCL12 expression in macrophages by producing CCL2, followed by the activation and recruitment of macrophages. In the meantime, this led to the angiogenesis, growth, and metastasis of BC increased (Park et al., 2020; Fang et al., 2016; Arendt et al., 2013). In addition, CCL2 activated PI3K/Akt/mTOR signaling pathway to inhibit apoptosis, promote BC proliferation and migration and induce drug resistance of BC to Tamoxifen (Li et al., 2020). All these studies demonstrated that adipocytes connected with BC and macrophages in the surrounding environment through CCL2/CCR2 axis, and promoted tumor cells to escape immune clearance.

. CCL5 and breast cancer

CCL5, also called RANTES, binding to its receptors CCR1 and CCR3-5 (especially combining with CCR5), can increase tumor growth, promote angiogenesis, recruit immune and stromal cells (Brylka & Schinke, 2019; Aldinucci, Borghese & Casagrande, 2020).

RANTES in 3T3-L1 or human mature adipocyte secretion was elevated, resulting in BC lymph node and distant metastasis (D'Esposito et al., 2012; D'Esposito et al., 2016). Furthermore, CCL5 could increase glycolysis, glucose uptake, and ATP production of BC cells by combine with CCR5. And then promote the proliferation of BC cells (Gao, Rahbar & Fish, 2016). Besides, CCL5 activated NF-ϰB signals to recruit macrophages to promote BC proliferation, invasion, and migration. CCL5 also led to collagen deposition, which caused the recurrence of BC (An, Wu, Huang, Feng & Zhao, 2019; Walens, DiMarco, Lupo, Kroger, Damrauer & Alvarez, 2019).

Thus, the CCL5/CCR5 axis is another way for adipocytes to trigger BC malignancy.

. CXCL8 and breast cancer

CXCL8, also known as IL-8, is expressed under the regulation of NF-κB, AP-1 (a transcription activator), EGFR pathways, and binds to its receptors (CXCR1 and CXCR2) to promote tumor proliferation, angiogenesis, and metastasis (Brylka & Schinke, 2019; Gales, Clark, Manne & Samuel, 2013).

Studies have indicated that 3T3-L1 or human mature adipocytes produced more IL-8 than pre-adipocytes (D'Esposito et al., 2012). Furthermore, it observed that the relapse-free survival time of patients with a low level of IL-8 in hormone-dependent early BC was significantly prolonged (Milovanovi, Todorovi-Rakovi & Vujasinovi?. . . , 2017). The elevated IL-8 binding to CXCR1 could activate the positive feedback loop of IL-6/NF-ϰB/Lin28B and STAT3 signaling pathway to activate BC stromal adipocytes. And then, IL-8 triggered the proliferation, migration, angiogenesis, and infiltration of BC (Al-Khalaf et al., 2019). In addition, IL-8 upregulated the expression of CTSB in BC cells, degraded collagen IV and promoted the invasion of BC through Src and ERK1/2 signals, and inhibited the secretion of IL-8 in triple-negative BC can reduce BC invasion by affecting Src, ERK1/2, MAPK, JAK-STAT, NF-ϰB and PI3K/Akt signal pathways (Aceto et al., 2012; Mohamed, El-Ghonaimy, El-Shinawi, Hosney & Mohamed, 2020; Messeha, Zarmouh, Mendonca, Cotton & Soliman, 2020). These studies suggested that CXCL8 plays a pivotal role in the process of adipocyte promoting BC development.

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. Other adipokines and breast cancer

Adipocytes can also secrete granulocyte colony-stimulating factor (G-CSF), IL-1β, secreted frizzled-related protein 5, visfatin, resistin, VEGF, IGF-1, insulin-like growth factor binding protein-2 (IGFBP-2), and exosomes to affect the process of BC (Liu et al., 2020a; Kolb et al., 2019; Zhou et al., 2020; Huang et al., 2019; Wang, Gao, Meng, Qiao & Wang, 2015). For instance, studies have found that adipocytes around metastatic BC made IGFBP-2 highly expressed, and advanced levels of IGFBP-2 accelerated MCF-7 cells metastasis and resistance to Doxorubicin (Wang, Gao, Meng, Qiao & Wang, 2015; Al Qahtani, Holly & Perks, 2017). In addition, polyploid adipose stem cells increased the expression of IGF-1 and reduced the expression of IGFBP-2 can activate the Akt pathway and promote the proliferation of BC cells (Fajka-Boja, Szebeni, Hunyadi-Gulyás, Puskás & Katona, 2020). The effects of other adipokines on BC are summarized in **Table 2** .

. *The inflammatory/immune environment of adipocytes promotes the development of breast cancer*

As energy storage and endocrine organs, the adipocytes around BC can mediate immune remodeling that is beneficial to the process of BC through a variety of ways (As shown in **Figure 2**). Take adipocytes and pre-adipocytes as an example. They reduced IFN-γ secretion in NK cells, resulting in inhibition of Trastuzumab-mediated antibody-dependent cytotoxicity of $HER2^+$ BC cells (Duong et al., 2015). Another example is adipocytes' secretions, such as CCL2 and CCL5, which could recruit macrophages to promote BC progression (Fang et al., 2016; Arendt et al., 2013; Li et al., 2020; An, Wu, Huang, Feng & Zhao, 2019; Walens, DiMarco, Lupo, Kroger, Damrauer & Alvarez, 2019). Furthermore, Liu et al. (Liu et al., 2021) observed that in the mouse model of BC in situ rich in adipocytes, there is a large amount of M2 macrophage infiltration and significantly reduced activated T cell infiltration in tumor tissues. This indicates that adipocytes help BC to form immunosuppression.

Adipocytes express PD-L1 to help breast cancer evade immune clearance

One mechanism of adipocytes to boost BC cells to evade immune clearance is inducing the expression of PD-L1.

PD-L1, a 40 KDa type 1 transmembrane protein, could shorten the interaction time of T cells and antigen-presenting cells, resulting in decreased T cell activation or T cell exhaustion, and can become a key target for the prediction and treatment of BC (Bastaki, Irandoust, Ahmadi, Hojjat-Farsangi & Jadidi-Niaragh, 2020).

Studies had proved that the expression of PD-L1 increased significantly when mature adipocytes produced lipid, which inhibited the anti-BC function of $CD8^+$ T cells. While inhibited adipogenesis by PPARγ inhibitor could selectively reduce the expression of PD-L1 in adipose tissue and improve the anti-PD-L1 antitumor efficacy. Besides, knocking out adipocytes' PD-L1 could also increase $CD8^+$ and $CD4^+$ T cell infiltration (Wu et al., 2018; Wu et al., 2020a). In addition, in the PD-L1 knockdown model mice, BC growth slowed down, and signaling pathways such as IFN-γ and TNF-α were significantly enhanced (Wu et al., 2020b).

Therefore, the expression of PD-L1 by adipocytes is one of its effective means to help tumors evade immunity.

Adipocytes secrete inflammatory cytokines to help breast cancer avoid immune clearance

Another mechanism of immune remodeling of BC by adipocytes is the secretion of inflammatory cytokines.

As mentioned earlier, co-cultured with BC cells, adipocytes can secrete numerous inflammatory cytokines (such as IL-6, IL-1β, and CCL2). These inflammatory cytokines promoted angiogenesis, proliferation, drug resistance, and recurrence of BC through various mechanisms.

It has been observed that adipocytes secrete a large amount of IL-6, which could activate the cMYC gene to increase the stemness of BC and promote BC EMT by activating the STAT3 signaling pathway (Kim et al., 2018; Nickel et al., 2018; Gao et al., 2019), while numerous studies have reported that by activating the STAT3 signaling pathway, IL-6 increased the expression of PD-L1 in myeloid cells, increased the

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myeloid-driven immunosuppression, and increased the accumulation of myeloid suppressor cells (MDSCs), thus promoting tumor growth (Smith et al., 2020; Lamano et al., 2019). Besides, IL-6 could also increase the accumulation of lactic acid around the tumor and then activate M2 macrophages, suggesting that high levels of IL-6 trigger the formation of tumor immune escape (Kesh et al., 2020). Another example is IL-1β, which promoted the expression of VEGFα of adipocytes and angiogenesis of BC (Liu et al., 2020a; Kolb et al., 2016). In addition, CCL2 could recruit macrophages, which led to the infiltration of M2 type macrophages in tumor tissues, and activated NF-ϰB and PI3K/Akt/mTOR signaling pathways to promote the drug resistance and recurrence of BC, and together with IL-1β recruited macrophages to promote angiogenesis of BC (Liu et al., 2021; Fang et al., 2016; Arendt et al., 2013).

Generally speaking, inflammatory cytokines secreted by adipocytes greatly promote BC to escape from host immunity.

Other ways that adipocytes help breast cancer escape immune clearance

The formation of the crown-like structure (CLS) is also a mechanism. CLS-a special tissue formed by infiltrating macrophages surrounding dead or dying adipocytes-could stimulate the growth of BC by secreting pro-inflammatory cytokines (such as IL-6, IL-1β) (Faria, Corrêa, Heyn, de Sant'Ana, Almeida & Magalhães, 2020). Studies have displayed that CLS and IL levels could be used as risk indicators for predicting the risk of malignant BC in African American women with benign breast disease (Shaik, Kiavash, Stark, Boerner & Cote, 2020). In addition, CLS enabled Trastuzumab-treated $HER2^+$ BC patients to develop distant metastases faster (Savva et al., 2021). Other studies have shown that CLS is related to adipocyte hypertrophy and a higher circulating level of C-reactive protein. And the more CLS, the higher the activity of aromatase. Aromatase's high expression is often related to the poor survival rate of ER+ BC patients. This evidence suggests that the formation of CLS is one of the ways that adipocyte help BC escapes immune surveillance (Iyengar et al., 2017; Friesenhengst, Pribitzer-Winner, Miedl, Pröstling & Schreiber, 2018; Mukhopadhyay et al., 2015).

In addition, adipocytes excrete lactic acid to form a weakly acidic microenvironment is another mechanism. Studies manifested that adipocytes increased lactic acid secretion when 3T3-L1 mature adipocytes co-cultured with BC (Wu et al., 2019). And lactic acid promoted macrophages polarization to M2 type by activating ERK/STAT3 signaling pathway (Kesh et al., 2020; Mu et al., 2018), while M2 type macrophages could promote angiogenesis, metastasis, drug resistance of BC and inhibit immune cell function of BC (Munir et al., 2021). These facts imply that by increasing lactic acid secretion, adipocytes helped BC achieve immune escape.

Focusing on adipocytes to treat breast cancer

Adipocytes, as one of the main components in the microenvironment of BC, promote the rapid development of BC by secreting cytokines and remolding the immunity of BC. And focusing on adipocytes may be a better treatment for BC (As shown in **Figure 3**).

Reducing cytokines secreted by adipocytes or inhibiting the expression of their receptors to treat breast cancer

As mentioned earlier, adipocytes promote BC to achieve rapid growth, proliferation, metastasis, and drug resistance by secreting numerous cytokines. We can't help but wonder whether breast cancer can treat by inhibiting the secretion of these cytokines or inhibiting the expression of these cytokine receptors?

Inhibition of IL-6/IL6R and breast cancer treatment

Considering that the secretion of IL-6 by adipocytes accelerated the progression of BC, we propose that reducing IL-6 secretion or inhibiting IL-6R expression may delay the progression of breast cancer, and studies have proved this.

Currently, IL-6 inhibitors are divided into two categories: one is drugs targeting IL-6, such as Sirukumab, Olokizumab, Clazakizumab, and Siltuximab. The other is drugs targeting IL-6R, such as Tocilizumab, Sari-

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lumab, and Vobarilizumab. Clinically, it is mainly used in inflammatory diseases such as rheumatoid arthritis and is rarely used in tumor treatment (Kang, Tanaka, Narazaki & Kishimoto, 2019).

Fortunately, the antitumor effect of inhibiting IL-6 has achieved initial success in cell and animal models. Take silencing IL-6 as an example. Silencing IL-6 inhibited the migration of 4T1 BC cells and reduced tumor volume and angiogenesis (Masjedi et al., 2020). Furthermore, Nagasaki et al. (Nagasaki, Hara, Nakanishi, Takahashi, Sato & Takeyama, 2014) observed that in a xenotransplantation mouse model. The mouse anti-IL-6R antibody significantly reduced the tumor volume and inhibited tumor angiogenesis, displaying that targeting the cells around the tumor instead of targeting cancer itself can treat cancer more effectively. In addition, Kesh et al. (Kesh et al., 2020) discovered that after using anti-IL-6R antibody, the tumor volume and weight decreased, while M2 macrophages in tumor tissue decreased and $CD8^+$ T cell infiltration increased.

All these evidences manifest that inhibiting IL-6/IL6R is an effective strategy against BC.

Inhibition of CCL2/CCR2 and breast cancer treatment

Owning to CCL2 played a significant role in recruiting monocytes to produce inflammation to help tumors escape immune surveillance; drugs that inhibit CCL2/CCR2 have been researched to treat tumors.

The anti-CCL2/CCR2 drugs have demonstrated therapeutic effects on tumors in vivo and in vitro. For instance, using a CCL2 antagonist in a tumor-bearing model could effectively reduce MDSC cell recruitment and delay tumor progression. Besides, CCL2 antagonist combined with anti-PD1 antibody significantly increased $CD4^+$ and $CD8^+$ T cell infiltration and IFN-γ production than they used alone, suggesting that CCL2 antagonist partially reversed tumor immune escape (Wang, Zhang, Yang, Xue & Hu, 2018). Similarly, the use of nanoparticles containing CCL2 trap significantly inhibited the growth of breast tumors, with the down-regulation of M2 macrophages and MDSC cells, as well as the infiltration of $CD3^+$ T cells and the up-regulation of IFN-γ (Liu et al., 2021). In addition, it was observed that the CCL2 neutralizing antibody can inhibit tumor growth and up-regulate IFN-γ (Teng et al., 2017), while the CCL2 inhibitor Propagermanium inhibited metastasis of tumor-bearing mice (Yumimoto et al., 2015).

Judging from the antitumor effect of animal models, inhibiting CCL2/CCR2 is a promising treatment for BC.

On the one hand, the promotion effect of these cytokines is weakened by inhibiting adipokines or their receptors. On the other hand, this strategy improved the immunity of the tumor and alleviated immunosuppression. Inhibiting adipokines or their receptors are promising to treat BC.

Combining nanotechnology to deliver drugs to adipocytes to treat breast cancer

Current researches illustrate that inhibiting cytokines or cytokine receptors seems to be a promising treatment strategy for BC. However, this method has some limitations. For example, it reported that the use of CCL2 neutralizing antibodies significantly inhibited lung metastasis of breast tumors. However, it would accelerate lung metastasis and lead to the death of tumor-bearing mice after drug withdrawal (Bonapace et al., 2014). In addition, in the long-term treatment (lasting for 275 days), it is discovered that the lack of CCL2 led to an increased risk of metastasis (Li, Knight, Snyder, Smyth & Stewart, 2013). These unexpected results may be related to the failure to remodeling the environment around the tumor. How to overcome these unsatisfactory results is an urgent problem.

With the development of a targeted drug delivery system, the Nano-drug delivery system has shown unique advantages in the precise treatment of tumors, including enhancing the efficacy of antitumor drugs, eliminating immunosuppression, and improving hypoxia. It found that the pH-sensitive nanoparticles significantly inhibited the growth and lung metastasis of BC in situ by increasing the level of mitochondrial reactive oxygen species and up-regulating apoptosis-related proteins, and the systemic toxicity study showed that it was less toxic (Tao et al., 2021). Furthermore, compared with free CCL2 monoclonal antibody, CCL2 traps lipid nanoparticles modified by a specific sigma receptor ligand-aminoethyl anisamide-significantly in-

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hibited the growth of breast tumors. Meanwhile, CCL2 trap lipid nanoparticles restored CAAs to normal adipocytes and remodeled the immunity of the BC (M2 macrophages and MDSC cells decreased, and T cell infiltration increased). In addition, compared with the CCL2 monomer, there was no rebound effect and accelerated tumor progression after stopping using CCL2 trap lipid nanoparticles for two weeks (Liu et al., 2021). Electrostatically-stabilized polyplex nanoparticles prolonged the presentation time of MHC-I, increased the reactivity of $CD8^+$ T cells, and inhibited tumor growth and lung metastasis (Qiu et al., 2018). These studies displayed that the drugs prepared by nanotechnology reduced the side effects of therapies and enhanced their efficacy.

However, just as Nagasaki et al. (Nagasaki, Hara, Nakanishi, Takahashi, Sato & Takeyama, 2014) observed, inhibiting the cells around the tumor seemed to inhibit the tumor volume. We can't help but wonder: Is there a way to deliver drugs to adipocytes around tumors to break the crosstalk between adipocytes and BC?

The continuous efforts of predecessors made it possible to deliver drugs to adipocytes: in 2001, Tatjana et al. (ALBREKTSEN, RICHTER, CLAUSEN & FLECKNER, 2001) discovered a specific membrane surface protein in adipocytes—APMAP. Subsequently, Liu et al. (Liu et al., 2012) screened its specific aptamer—adipo8 by cell-SELEX technology. Two years later, Chen et al. (Chen, Liu, Tong, Liu, Wang & Liu, 2015) further chemically modified adipo8: introducing thiosulfate group and coupling it with polyethylene glycol. The modified adipo8 has higher stability, can recognize white adipocytes, and inhibit adipocyte differentiation. The modified adipo8 provided the possibility to connect adipo8 with good stability in drug delivery systems to achieve targeted adipocytes. A few years later, Yu et al. (Yu et al., 2020) used 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (EDC) /N-hydroxysuccinimide (NHS) technology to couple adipo8 with emodin-loaded nanoparticles to prepare emodin nanoparticles. And cell experiments demonstrated that it significantly increased the targeting of emodin nanoparticles and released emodin slowly. In addition, it had no cytotoxicity to cells other than adipocytes In addition; it has no cytotoxicity to cells other than adipocytes. It illustrates that using adipo8 can improve drug precision treatment and reduce the toxicity of drugs, and targeting adipocytes to treat BC is a promising strategy in the future.

Other strategies focusing on adipocytes in the treatment of breast cancer

Expect delaying the development of BC by reducing the secretion of cytokines and targeting adipocytes. It's a promising strategy for treating BC with drug-loaded adipocytes or converting BC cells into adipocytes

Using adipocytes to carry drugs to treat breast cancer

Studies have displayed that BC tends to recruit adipocytes from the host or microenvironment. Meanwhile, lipid droplets in adipocytes are ideal solvents for water-insoluble drugs. Therefore, it's a new trend to use drug-loaded adipocytes to treat BC in the future (Singh et al., 2016).

There are two methods for drug-loaded adipocytes' preparation. One way is adding the drug directly to the adipocyte culture medium. Another way is adding drugs-encapsulated with specific materials (such as nanoparticles, viruses)-to the adipocyte culture medium (Masuda et al., 2020; Aoki, Kakimoto, Goto & Higuchi, 2019; Wen et al., 2019).

Some studies using adipocytes to carry drugs have shown an antitumor effect. For example, Masuda et al. (Masuda et al., 2020) introduced lentivirus, which contained anti-HER2 antibody cDNA, into human proliferative adipocytes. Meanwhile, they evaluated drug-loaded adipocytes' antitumor ability and observed that it significantly inhibited the proliferation of BC cells and reduced the tumor volume in animal models. Besides, it also reported that pancreatic cancer cells have recruited adipose-derived stem cells loaded with PLGA nanoparticles containing Pirarubicin. The engineered adipocytes inhibited tumor growth. In the meantime, it induced apoptosis of tumor cells in the center of the tumor and vascular cells around cancer, indicating that loading drugs in adipocytes may minimize the side effects of anticancer drugs (Aoki, Kakimoto, Goto & Higuchi, 2019). In addition, rumenic acid and Doxorubicin were introduced into lipid droplets of adipocytes to evaluate their antitumor effects. It was displayed that adipocytes mediated tumor

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apoptosis, down-regulated the expression of tumor PD-L1, and increased the infiltration of $CD4^+$ and $CD8^+$ T cells (Wen et al., 2019).

In short, the use of adipocytes to carry drugs is a new way to target breast tumors.

Transforming tumor cells into adipocytes to treat breast cancer

Metastasis is one of the staple causes of death in BC patients, and overcoming BC metastasis is a significant way to improve the survival rate of BC patients.

Metastasis includes tumor cells breaking through the basement membrane, entering the vascular system, overcoming blood mechanical shear force and surviving, transferring to secondary tissue, planting and growing in secondary tissue, during which the tumor cells underwent the transition from EMT to MET. EMT promotes both tumor metastasis and tumor resistance to chemotherapy and immunotherapy (Massagué & Obenauf, 2016; Lu & Kang, 2019). Using the plasticity of EMT and MET transformation of the tumor, Ishay-Ronen et al. (Ishay-Ronen et al., 2019; Ishay-Ronen & Christofori, 2019) found that anti-diabetes drug Rosiglitazone combined with BMP2, which transformed BC cells into adipocytes in vitro. While, in vivo experiment, the combination of Rosiglitazone and MEK inhibitor Trametinib succeeded transforming metastatic BC into adipocytes. Meanwhile, the invasion and metastasis of BC inhibited, suggesting that transforming tumor cells into adipocytes without differentiation ability is a new strategy for BC treatment.

In brief, transforming BC cells into adipocytes may be an effective strategy to improve the survival rate of BC patients.

Conclusions

In summary, numerous researches showed that the communication between adipocytes and BC is an important factor that promotes the progress of BC. Adipocytes are one of the bridges linking the immune microenvironment with the inflammatory microenvironment. In addition, adipocytes changed the proliferation, invasion, and migration of BC by secreting cytokines (such as leptin, IL-6.), mediating inflammation and affecting immunity.

Besides, inhibit adipokines secretion and target adipocytes are beneficial for BC treatment. And use drug-loaded adipocytes or transform BC into adipocytes are new ideas to delay BC.

However, as mentioned earlier: many cytokines are not only secreted by adipocytes, such as tumor cells and macrophages also secrete CCL2 (Yoshimura, 2018). The current researches mainly use adipocytes (mouse-derived) co-cultured with breast cancer cells (human-derived). And then by detecting cytokines (mouse-derived) changes to confirm that cytokines are adipocytes' secretion. Future research should try to differentiate the same cytokine secreted from different cells. And this may better understand the impact of fat cells (or other cells in the tumor microenvironment) on breast cancer progression.

Nevertheless, the strategy of focusing on adipocytes to treat BC is still in its infancy. The current research has only reported drugs that break the communication between adipocytes and tumors. Take aspirin, an anti-inflammatory therapy, as an example. It inhibited the proliferation and migration of 4T1 cells by reducing pro-inflammatory factors (such as IL-6 and CCL2) and pro-angiogenic factors (VEGF). Besides, it inhibited adipocyte differentiation and lipid accumulation (Hsieh & Huang, 2016; Hsieh, Chiu, Wang & Kuo, 2020). And few scholars have focused on targeting adipocytes to fight tumors. Simply inhibiting adipokines may lead to post-withdrawal reactions (Bonapace et al., 2014; Li, Knight, Snyder, Smyth & Stewart, 2013). So we should make adipokines inhibitors specific deliver to tumor tissues. Besides, in the future, adipo8 can be bound to the surface of drug-encapsulated nanoparticles to target adipocytes. And evaluate its ability to break the crosstalk between adipocytes and BC and reduce the side effects of drugs. Besides, researchers should examine whether all BC cells can convert into adipocytes. If the transformation is incomplete, will BC cells convert into adipocytes accelerate the development of BC? If the conversion is complete, will these new adipocytes cause obesity-related metabolic diseases? And how to treat the diseases caused by these new

adipocytes? It is vital to solving the above problems, which may be a new strategy to delay the progress of BC and improve the survival rate of BC patients.

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Table 1 Crosstalk between adipocytes and breast cancer (BC)

Different kinds of adipocytes cross-talk with breast cancer, leading to increased secretion of cytokines in adipocytes and increased proliferation, invasion, and metastasis of breast cancer cells.

Adipocytes type	BC cells type	Changes of adipocytes
3T3-L1 mature adipocytes	MCF-7 /MDA-MB-231 cell	showed beige/brown cell phenotype (CAAs)
3T3-L1 mature adipocytes	4T1 cells	MCP-1、vascular endothelial growth factor (VEGF) and PA
3T3-L1 mature adipocytes	4T1 cells	transformed into CAAs
human mature adipocytes	MDA-MB-231 cells	Changed into CAAs and increased IL-6, IL-1β and G-SF sec
beige/brown adipocytes	$HMLE^{HRASV12}$	
3T3-F442A adipocytes	MDA-MB436 /E0771 cells	
normal human pre-adipocytes	DCIS.com	upregulated FSP1 and α-SMC expression, increased PAI-1、
human mature adipocytes	MCF-7、MDA-MB-468 cells	increased IL-6 secretion
3T3-L1 mature adipocytes	MDA-MB-231 cells	increased IL-6 secretion

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Table 2 The roles of other adipokines on breast cancer (BC)

Adipocytes secrete different cytokines, and these cytokines help breast cancer proliferation, invasion, migration, metastasis, and drug resistance by activating signal pathways.

Adipokines	Effected on breast cancer	Mechan
G-CSF	Promoted invasion and metastasis	Activat
IL-1β	Promoted angiogenesis	Stimula
	Promoted proliferation and metastasis	Activat
secreted frizzled-related protein 5	Inhibited migration and invasion , and associated with good clinical prognosis	Down-r
Visfatin	Promoted proliferation and invasion	Up-reg
	Mediated migration, invasion and tumor growth	Up-reg
Resistin	Mediated the invasion and metastasis	Activat
	Inhibited doxorubicin induced apoptosis	Throug
VEGF	Promoted proliferation	Interac
	Promoted oxidative stress resistance and tumor growth	Regula
TNF-α	Promoted EMT and invasion	Activat
	Promoted proliferation	Activat
	Increased the stemness	Activat
IGF-1	Promoted proliferation	Bound
	Promoted angiogenesis	Combi
IGFBP-2	Promoted lymphatic metastasis	Increas
Exosomes	Promoted proliferation and metastasis	Activat

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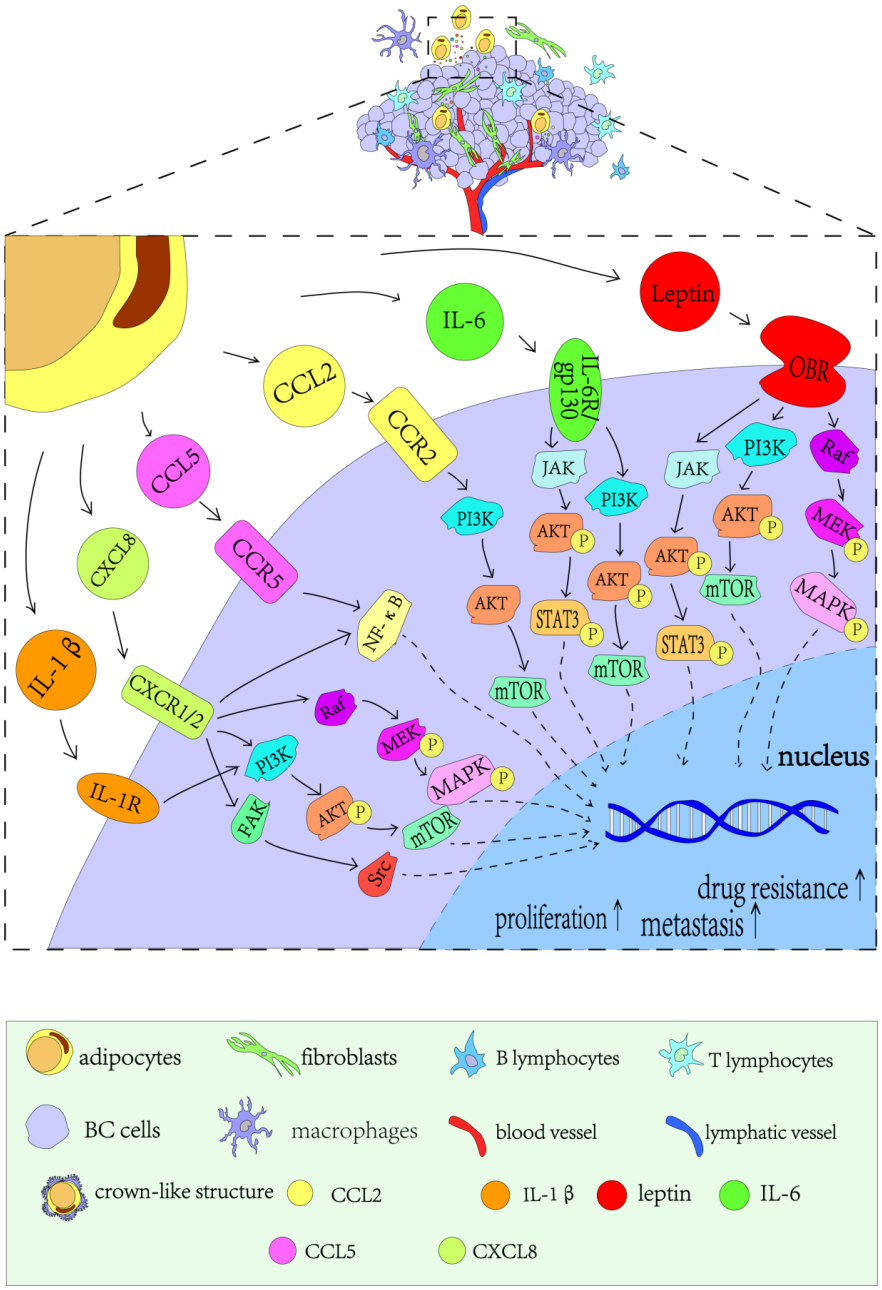

Figure 1 Mechanism of rapid development of breast cancer (BC) induced by cytokines secreted by adipocytes.

Adipocytes secrete numerous cytokines, such as leptin, IL-6, CCL2 and CCL5, which promote the proliferation, migration and drug resistance of BC by activating various signaling pathways.

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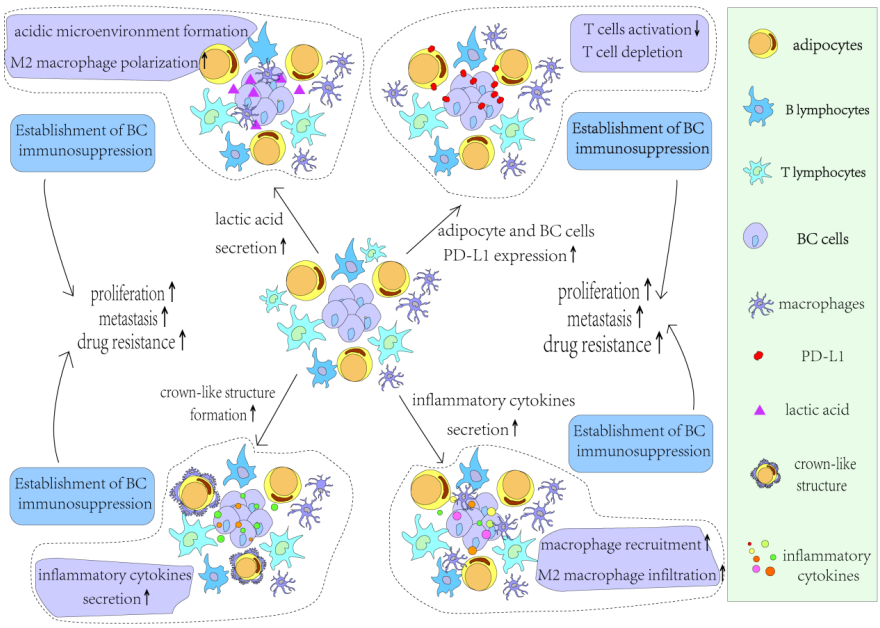

Figure 2 Mechanism of adipocytes helping breast cancer (BC) escape immune surveillance.

Adipocytes help BC escape immune clearance by expressing PD-L1, secreting inflammatory cytokines, forming crown-like structure and secreting lactic acid.

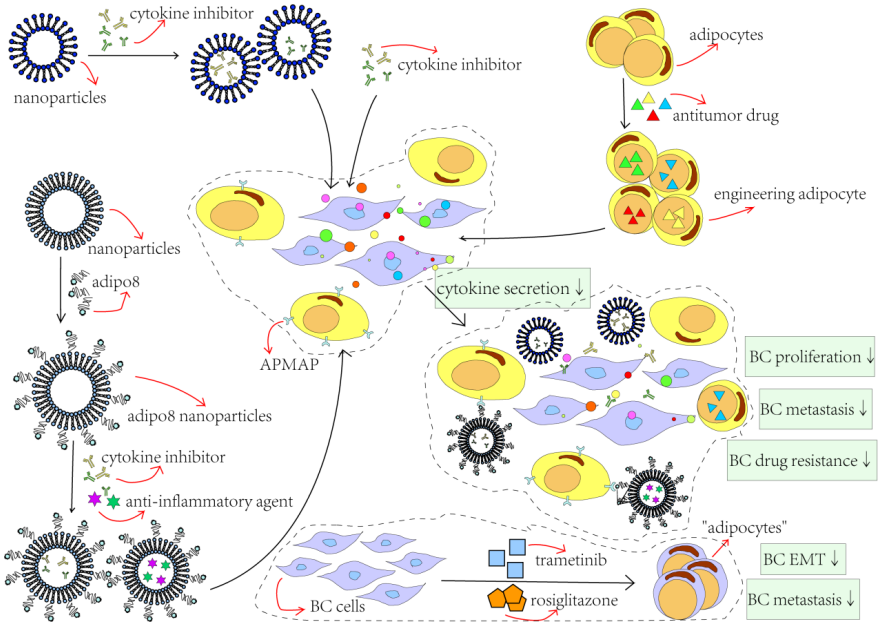

Figure 3 Potential strategies for breast cancer (BC) treatment.

Suppressing the secretion of cytokines, targeting drugs to adipocytes combined with nanotechnology, using adipocytes to carry drugs and transforming BC into adipocytes are beneficial to delay the process of BC.

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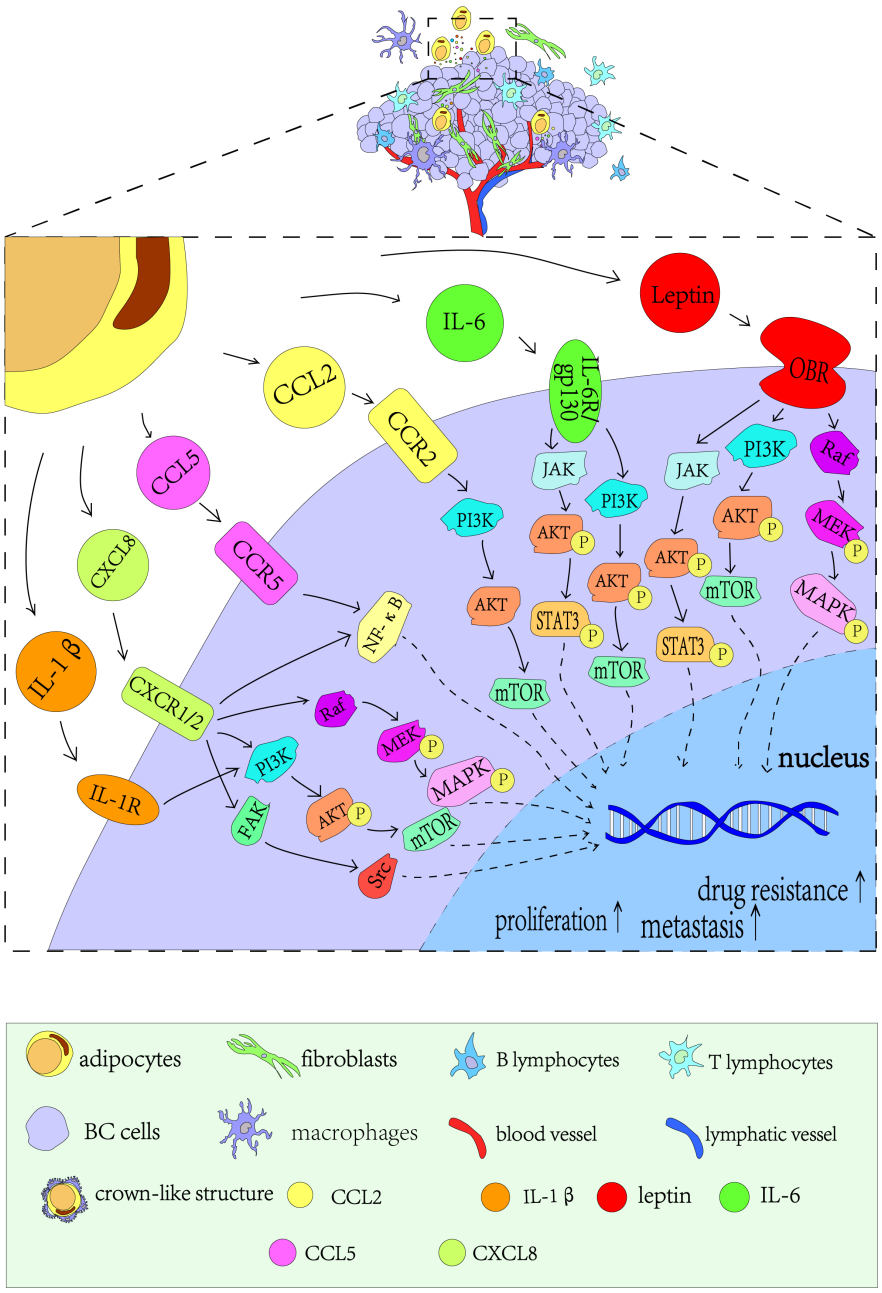

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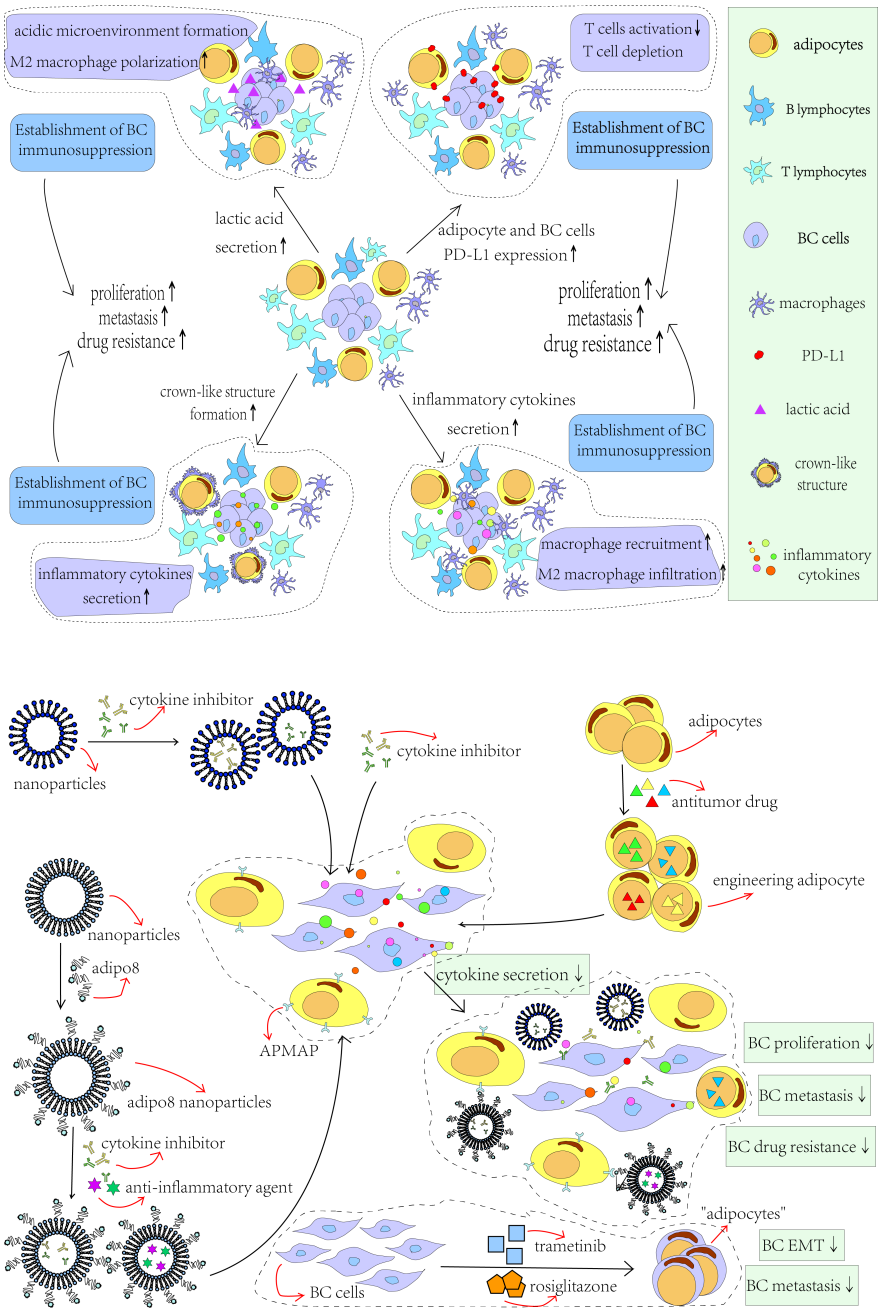

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