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Interleukin-6 as a Biomarker for Breast Cancer Prognosis and Therapeutic Response

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ABSTRACT

The pleiotropic cytokine known as Interleukin-6 (IL-6) is a crucial component in the genesis and progression of breast cancer. It does this by acting on several signaling pathways at once, which has an impact on many different elements of tumor biology. The activation of signaling cascades that speed up cell cycle progression and prevent apoptosis is thought to be how IL-6 promotes tumor growth and proliferation. Furthermore, IL-6 promotes angiogenesis, which aids in the tumor's development of additional blood vessels microenvironment. The proliferation, survival, and therapeutic resistance of cancer cells are all made possible downstream signaling pathways including JAK/STAT as well as MAPK are activated. Additionally, this cytokine promotes the epithelial-mesenchymal transition (EMT), further supporting tumor metastasis and invasion. Furthermore, within controlling immune responses and encouraging an immunosuppressive environment, IL-6 has an impact on the tumor microenvironment.

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Introduction

Breast cancer is among the most prevalent types of cancer affecting women. It is caused by a variety of factors, can take years or decades to develop, and has a very different clinical course. There have been recent developments associated with the treatment of breast cancer, such as the introduction of novel therapeutic approaches. For instance, trastuzumab (HerceptinR), which is part of a class of medications known as "new generation" agents and is utilized in therapy with monoclonal antibodies to treat cancer, is one such example. Patients with breast cancer that overexpressed human epidermal growth factor receptor HER2 experienced a measurable reduction after receiving trastuzumab (Jiang et al., 2011) so an extended period of survival (Lin et al.,2015). However, the outcomes are still not satisfactory. The focus in recent years has been on cytokines' role as prognostic indicators.

Numerous researches have focused on the link between host as well as tumor cells immune system in recent years. It is believed that the immune system's innate and learnt components both play significant roles in the body's response to cancer (Moen et al., 2014; Chavey et al., 2007). Cytokines are vital biomolecules with diverse biological functions, playing crucial roles in infections, hematopoiesis, and homeostasis. They exhibit multifunctional properties that regulate responses to viral illnesses and even cancer, overseeing tissue regeneration, cellular maturation, and growth. Interleukins (ILs) stand out among these cytokines because they are secreted immunomodulatory proteins that are part of the cytokine superfamily and have many different roles in the immune system. The main role function of ILs is to help immune cells talk to each other. This includes important processes like cell movement, proliferation, maturation, and adhesion, which are all important parts of the inflammatory response (Moen et al., 2014). Interleukins play a crucial role in both immediate and prolonged inflammatory reactions.

These biomolecules act in response to the activation of cell surface receptors, initiating distinct signaling pathways on each occasion. Currently, science has identified approximately 38 different interleukins, each with distinct functions and contributions to immune regulation and inflammatory responses. Each of these

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interleukins has a unique origin, structure, and set of features. Several of these interleukins are thought to be present and to have a role in the development and spread of breast cancer. The regulation of the immune system involves a variety of factors, including interferons, cytokines like transforming growth factor-ß (TGF-ß) as well as tuomor necrosis factor-a (TNF-a), as well as different interleukins such as IL-1, IL-6, IL-10, as well as others. In short, lymphocytes and macrophages are the main cells that release cytokines. Cytokines change the role of target cells in a way that is either paracrine or autocrine (Fontanini et al., 1990). Multiple types of cancer have abnormal expression of IL-6, which is linked to a poor outcome and metastasis. It is common for breast cancer to trigger the IL-6 pathway, which can help breast cancer metastasis while also lowering the immune response against the tumor (Manore et al., 2022).

Interleukin 6

Interleukin-6 (IL-6) is a cytokine with a molecular weight of 26 kilodaltons. It is generated by different types of cells in the body, like as fibroblasts vascular endothelial cells, and mononuclear phagocytes. Its performances an important role in the immune response and inflammation regulation. In the context of cancer, IL-6 has been observed to be produced in bladder and cervical cancers, where its presence and activity may have implications for tumor progression and the tumor microenvironment. IL-6, IFN-2(interferon alpha-2), Hepatocyte-stimulating factor, which is also referred to as hybridoma/plasmacytoma growth factor, was the first factor to be discovered as being responsible for boosting the growth of hepatocytes like factor of a B cell stimulation in 1986. It helps effector B cells turn into antibody-producing cells by promoting their development (Scheller et al., 2011). It is released as a result of the activities generated by IL-1 and TNF, and it largely exerts its effects on B cells and hepatocytes. Indeed, Interleukin-6 (IL-6) performances a critical role as a primary agent in the inflammatory response, and its involvement extends to the pathology and angiogenesis of cancer. IL-6 is known to stimulate various cellular processes that contribute to tumor growth, survival, and invasion. IL-6 can speed up the growth of new blood vessels, a process called angiogenesis, which is needed for

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providing nutrients and oxygen to a growing tumor. IL-6 also changes the surroundings around a tumor, which makes it easier for cancer cells to grow and spread. As a result, inhibiting angiogenesis and stopping the growth of tumors can be achieved by targeting IL-6 and it signaling pathways (Hirano 2021). A large number of immune as well as non-immune cells, such as T cells, B cells, endothelial cells, mesangial cells, keratinocytes, fibroblasts, and monocytes release these substances. It's interesting to know that breast cancer cells and other tumor cells, lung cancer, colon cancer, prostate cancer, ovarian cancer, multiple myeloma, and pancreatic cancer (Miura et al., 2015), can produce this cytokine as well. Multiple immunological and physiological processes, including the production of IL-6 can change the way the body processes acute-phase proteins reactions to antigens, hematopoiesis, and cell metabolism (Hunter and Jones 2015). When IL-6 is present, it causes neoplastic cells to be able to invade the extracellular matrix and show a lot of drug tolerance. IL-6 could be expressed by cancer cells from the kidney, bladder, cervix, and breast cell types. The IL-6 receptor is then stated on the cell walls of the prostate, ovaries, kidneys, and breast. In many ways, IL-6 shows that it can do more than one thing. It is released by different tumors, and its growth is linked to a way that tumours grow called auto-paracrine activation. To find new ways to treat breast cancer, investigators are still looking into how IL-6 helps the surroundings around the tumor talk to the cells that are growing in the tumor (Manore et al., 2022).

IL-6 can make any anti-apoptotic proteins work better or cause proangiogenic cytokines to work together. Also, IL-6 makes cell lines make a protein called vascular endothelial growth factor. Thrombocytopenia is a common side effect of treatment for people with cancer. In these cases, IL6 is a strong molecule that helps make blood cells. IL-6 controls how much VEGF (Vascular endothelial growth factor) is regulated in the human have mega - karyoblastic leukaemia cell line such as MEG-01. IL-6 is believed to act as an angiogenic factor by controlling VEGF levels in platelets and stimulating the growth of endothelial cells, potentially facilitating the formation of new blood vessels. The levels of IL-6 in the blood show that the process of neoplastic growth is still going on. It is likely that serum IL-6 is linked to a worse survival rate.

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When IL-6 was responsible for keeping used to grow cell line MCF-7 in human breast cancer, also found that IL-6 was a soluble receptor (Jiang et al., 2011).

Moreover, using IL-6 as a focused therapy for breast cancer has demonstrated potential in suppressing the growth of estrogen receptor (ER) positive cells. Nevertheless, in the context of breast cancer, IL-6 is primarily employed as a prognostic marker. Various studies, such as the one conducted by Lin et al., have demonstrated that increased blood levels of IL-6 are related to a worse prognosis in breast cancer patients. This emphasizes the significance of IL-6 as a potential biomarker for observing patient results and following the progress of the disease in breast cancer cases (Lin et al. in 2015).

IL-6 in breast cancer

Multiple cancer forms, include breast cancer, have been shown to overexpress IL-6 either locally and systemically (Chien et al., 2010). Patients who have breast cancer high amounts of IL-6 in their blood tend to have a bad prognosis and a low survival rate (Purohit et al., 2002) (Fig. 1). Over 50% of breast cancers have active STAT3, because of this, many studies have looked into new small-molecule drugs that stop STAT3 from activating in breast cancer, and Interleukin-6 (IL-6) is the main trigger for its activation. This relationship highlights the significance of targeting IL-6 as well as STAT3 signaling pathways hold promise as potential targets for therapeutic interventions strategies for uses breast cancer treatment (Kozłowski et al., 2003). It is believed that cancer cells, tumor-associated macrophages (TAMs), fibroblasts, helper T (Th) cells, as well as myeloid-derived suppressor cells (MDSCs) are the primary generators of IL-6 in the tumor microenvironment. These diverse cell types collectively play a role in producing IL-6 in the proximity of the tumor (Barbieri et al., 2010; Oh et al., 2013). So, it looks like we can think of a new way for these cells to make tumors grow, in addition to the ways that have already been outlined (Jiang et al., 2011). In most cases, cancer cells utilize the growth factor IL-6 in an autocrine manner, meaning they produce and respond to IL-6 themselves. On the other hand, the survival and development of the illness are significantly less affected by the paracrine secretion of IL-6 by nearby cells. It indicates that IL-6 is a possible target for

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therapeutic therapies as it may be vital for increasing the advance and survival of cancer cells by stimulating them to stimulate themselves (Fisher et al., 2014). However, IL-6 can alter the growth of tumors by IL6 trans-signaling in a variation of ways, containing autocrine and paracrine release (Lederle et al., 2011).

The occurrence as well as activity of ER and PR (estrogen and progesterone receptors) in breast cancer cells directly influences their responsiveness to interleukin-6 (IL-6). Hormone-sensitive cells, which express ER and PR, exhibit a stronger reaction to IL-6 compared to hormone-insensitive cells. This is because hormone-sensitive cells tend to produce higher levels of IL-6 themselves. As a result, the presence of ER and PR enhances breast cancer cells' ability to react to IL-6 signaling, potentially affecting their growth and behavior in response to this cytokine (Chavey et al., 2007). Breast cancer cells lacking the ER mostly express the mIL-6R, in contrast to the sIL-6R that is predominantly secreted by ER cells. It has also been demonstrated that, under normal conditions, IL-6 performs in an autocrine method to quit the growth of ER-negative cells. While sIL-6R doesn't have the cytoplasmic and transmembrane domains, it does have the important domains needed to bind to IL-6, which allow it to ligate with IL-6 with the same level of affinity as mIL-6R (Selander et al., 2004).

IL-6 turns on enzymes that make estrogen, such as aromatase, estrone sulfatase, and 17 beta-hydroxysteroid dehydrogenases, which results in an increase in the amount of estrogen in circulation as well as at the location of the tumor. Since estrogen sulfate is more likely to be found in circulation after a period of time than estrogen, one can think of it as a reservoir for estrogen. On the other side, it has been proven that malignant breast tissues have an increased amount of estrone sulfatase expression. As a result, interleukin-6 is an essential factor in determining whether or not MCF-7 ER-positive cells convert estrone to estradiol (Purohit et al., 2002), which may show to there is a lot of estrogen in cancerous breast tissue. In the process of metastasis, Cancer cells invade neighboring tissues and take on a mesenchymal phenotype for propagation reaching distant organs, an important component in breast cancer death. Epithelial mesenchyml transition (EMT) as well as mesenchymal epithelial transtion (MET) are the two primary processes involved in this transformation. It is well known that inflammation contributes significantly to the promotion of EMT, a

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crucial step of the both cancer cells' migration and the spread of metastatic disease (Lamouille et al., 2014; Ricciardi et al., 2015).

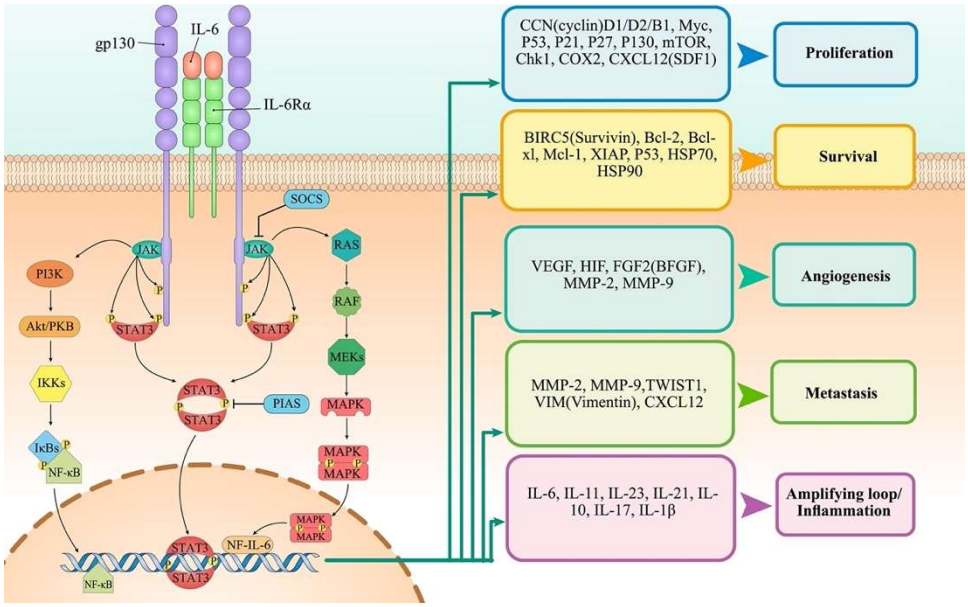

Fig. 1 Role of IL-6 in Cancer Progress. When IL-6 binds to its receptor on cancer cells, it turns on a number of signaling pathways, like as JAK/STAT3, PI3K/AKT, and Ras/MAPK, which all help tumors grow. By using these routes, IL-6 causes the release of different molecules that help cancer cells stay alive, spread, make more cells, and make new blood vessels (Masjedi et al., 2018).

So, it has been revealed that IL-6 is involved in EMT and makes it easier for mesenchymal stem cells (MSC) to enhance human breast cancer cells (Madden et al., 2011; Korkaya et al., 2012). By upregulating CXCR4 (an alpha-chemokine receptor specific for stromal-derived-factor-1) through STAT3 and c-Jun, IL-6 helps many cancers spread to the bone (Tawara et al., 2011). The fact that MCF-7 cells release IL-6 on their own makes it easier for them to enter the extracellular matrix (Sansone et al., 2007). In the EMT process, one of the most important things that happens is that E-cadherin, a chemical that helps cells stick together, stops working. This makes fixed

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tumor cells move around. When IL-6 was added to MCF-7 cells, the EMT trait happened because molecules like N-cadherin, Vimentin, Snail, as well as Twist were turned up and E-cadherin was turned down (Sullivan et al., 2009).

IL-6 and metastasis

Metastasis, not the growth of the original tumor, is the most common reason for passing away as a result of breast cancer. Several cell culture studies have linked IL-6 to spread. IL-6 promotes tumor development through various mechanisms, comprising promoting cell invasion as well as migration, initiating the epithelial-to-mesenchymal transition (EMT), and enlisting mesenchymal stem cells (MSC) (Korkaya et al., 2012). During embryogenesis, a process known as EMT transforms immobile epithelial-like cells into moving mesenchymal-like cells. EMT is induced by IL-6 of human breast cancer cells, promoting their invasive and migratory properties and contributing to metastasis. Targeting IL-6 could be a potential strategy to prevent cancer spread (Sullivan et al., 2015). EMT is brought on by developmental signaling pathways (Notch, Hedgehog, TGF-b and Wnt) and their downstream transcription factors. These pathways transform cells that have a phenotype alike to epithelial tissue into cells that have a phenotype similar to aggressive mesenchymal tissue. Additionally, it has been demonstrated that cells called MCF-7 that have received IL-6 adopt an EMT pattern. These cells do this by upregulating the production of the proteins Vimentin, Twist, Snail, as well as N-cadherin while simultaneously downregulating the indication of the E- Cadherin (Sullivan et al., 2015; Leslie et al., 2010). In addition, TGFβ raises the expression of Jagged 1 in metastatic breast cancer cells. Jagged 1 then activates NOTCH1 in osteoblasts, which raises IL-6 expression to help metastatic breast cancer cells stay alive and causes the formation of osteoclasts (Sullivan et al., 2015).

The lack of function of the protein E-cadherin, which helps cells stick to each other, one of the most important phases in EMT, causes fixed tumor cells to become itinerant. Conversely, the presence of IL-6 did not affect cell-to-cell adhesion or the expression of E-cadherin in main cultures of human normal breast epithelium, according to the results. MSC are stromal cells that haven't been changed, and tumors

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can use them to help the tumor grow and spread to other areas. The relationship between mesenchymal stem cells (MSCs) or cancer stem cells (CSCs) is mediated by IL-6, which is essential. It promotes CSC growth by acting as a signaling molecule released by MSCs, creating a supportive microenvironment for CSCs. Targeting IL-6 could offer a potential approach to disrupt this communication and hinder CSC-mediated tumor progression (Liu et al., 2011). Under low amounts of oxygen, IL-6, which is released in large quantities by breast cancer cells, which not only stimulates but also attracts MSCs. By inhibiting IL-6 signaling, it is possible to reduce the rate at which MSCs are recruited. Breast cancer cells exposed to media made from MSCs performed better in comparison for breast cancer cells cultivated with MSC-conditioned media alone and treated with IL-6 antibodies displayed a significant decrease in migration (De Luca et al., 2012).

Interleukin-6 systemic levels and breast cancer risk and prognosis

Taking non-steroidal anti-inflammatory drugs (NSAIDs) has been linked to a lower chance of getting breast cancer. This finding suggests that circulating pro-inflammatory chemicals in the body may have a role in the emergence of cancer. NSAIDs function by lowering inflammation, and their capacity to lower the rate of breast cancer raises the possibility that there is a connection between inflammation and the emergence of cancer. Two prospective trials have looked into the link between increased risk of breast cancer so circulating levels of IL-6 (Yu et al.,2010). However, none of these researches found a link between the two. The investigations had limited prediction power and few cancer incidences because they were conducted on older people. Despite the lack of a correlation, significant research has been done to determine IL-6 polymorphism importance in connection to breast cancer risk (Taudorf et al., 2008). It is likely that systemic levels of IL-6 over an extended period of time contributed to the physiology the breast cancer. There is no evidence that having high amounts of IL-6 in the blood makes you more likely to develop breast cancer. Elevated the levels of IL-6 in the breast cancer patients might suggest a poor prognosis because of things like slower metabolism, weight gain brought on by the medication, and inactivity (Knüpfer and Preiß 2007). Considering

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these factors alongside IL-6 levels is vital for improving treatment outcomes and patient prognosis,in addition to the overall inflammation brought about by a large number of tumors (Dethlefsen et al., 2013).

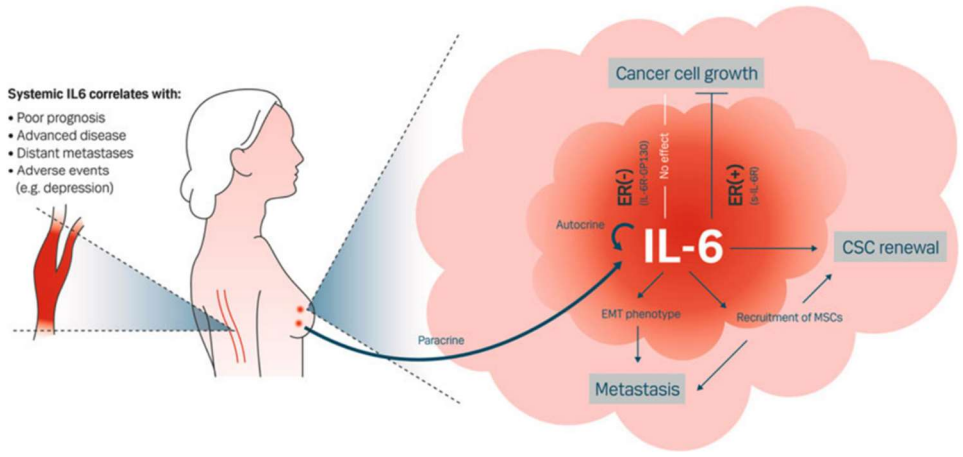

Fig.2 Poor prognosis is associated with elevated levels of IL-6 in patients have breast cancer, an advanced state of the disease, and metastases. On the other hand, both paracrine and autocrine IL-6 signals are used to control breast cancer (Dethlefsen et al., 2013).

IL-6 signaling pathways

In more than 50% of breast cancer patients, STAT3 is quite active (Masjedi et al., 2018; Barbieri et al., 2010), STAT3 is a critical signaling orchestrator for cancer-promoting actions induced not only by IL-6 but also by other interleukins like IL-11, LIF, and OSM. The related signal transducer STAT1 can have the opposite effect of OSM when it is active as part of the JAK/STAT pathway. Targeting STAT3 is essential to disrupt these cancer-promoting effects as well as stop the growth of tumors and metastasis (Johnson et al., 2018). There is mounting indication to suggest that STAT3 facilitates increased cross-talk between the JAK/STAT pathway and the various activities that

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rely on gp130 and IL6ST. This is one of the factors which leads to the actions of the PI3K/AKT with MAPK/MEK/ERK signaling pathways, which promote the development of cancer. These consequences include epithelial-mesenchymal transition (EMT) as well as chemo-resistance (Leslie et al., 2010; Liang et al., 2019). Many studies examined at how IL6 affects growth in vitro (Omokehinde and Johnson 2020). Indeed, recombinant IL-6's impact on ER-positive (ER+) cells line models in breast cancer have been a subject of research interest, but different studies have reported varying results (Martínez-Pérez et al., 2021).One of the many roles that IL6 plays in breast cancer is the influence that it has on the development of cells. Studies have shown that IL6 can influence genes linked to EMT, a mechanism vital to the spreading process, and hence exert a pro-metastatic cause (Lin et al., 2017). The decreased activity of E-cadherin, which ultimately results in a lack of adhesion, is another factor that contributes to the transition from a stable for a moving phenotype (Lin et al., 2017; Sullivan et al., 2009). IL6 can also cause pro-angiogenic effects by making tumor-associated vascular cells make more VEGF. This happens through STAT3 and MAPK (Yang et al., 2009), Despite the fact that the IL6 inflammatory loop is capable of activating pathways linked to drug resistance (Conze et al., 2001; Korkaya et al., 2012).

There are several different IL-6 signaling mechanisms (Fig.3. Janus kinase (JAK) tyrosine kinases are triggered whenever interleukin-6 collaborates to its receptor, IL-6R. The phosphorylation of STAT3 that results from interleukins like IL-6 binding to cell receptors leads to the creation of homodimers. These turned-on STAT3 homodimers move into the nucleus and function like transcriptional regulators that control the expression of genes essential for cell growth and survival. Targeting STAT3 activity is a possible therapy for the treatment of cancer (Heinrich ET AL., 2003). When the IL-6 or JAK or STAT3 pathway is activated in cancer cells, several genes essential for cell growth, survival, as well as behavior exhibit altered gene expression. This promotes the growth, dissemination, and development of treatment-resistant cancer. Targeting this pathway might be an attractive cancer treatment plan. certainly, chemicals like protein inhibitors of activated STAT (PIAS) as well as suppressors of cytokine signaling (SOCS) regulate the STAT3 pathway. When STAT3 is activated, the expression of these inhibitors is normally enhanced under

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physiologically normal conditions. The interleukin-6 (IL-6) protein also activates the phosphoinositide 3-kinase (PI3K)-protein kinase B (PkB)/Akt signaling pathway. Phosphorylation of PIP2 (phosphatidylinositol-4,5-bisphosphate) through cytokine activation results in the production of PIP3 (phosphatidylinositol-3,4,5-trisphosphate) via PI3K. PIP3 then activates PkB/Akt through phosphorylation. Akt regulates genes crucial for cell survival and growth, making this pathway essential in various cellular processes, including cancer (Chien et al., 2010).

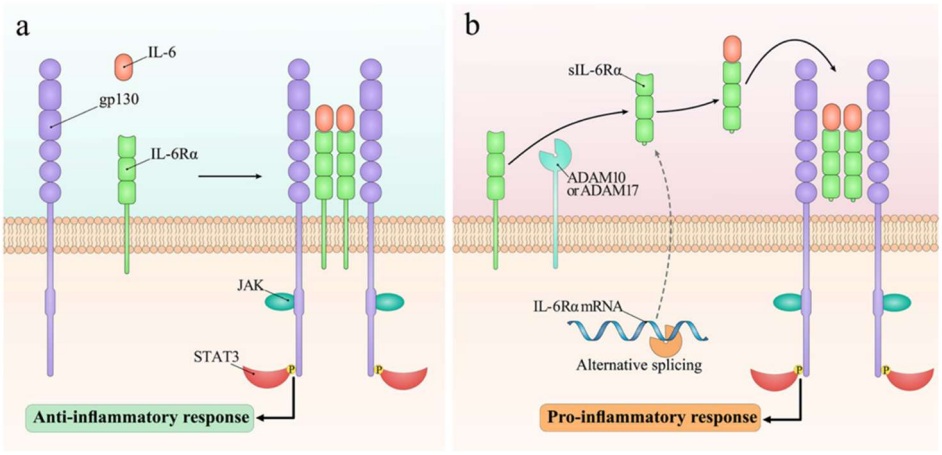

Fig. 3. IL-6 stimulates different stimulated pathways. (a) Classic signaling, which happens mostly in white blood cells and liver cells, begins when IL-6 binds to the mIL-6R and joins gp130 in a complex. b) In contrast, IL6 has the ability to activate trans-signaling in all cells that produce gp130. Inducing transsignaling makes pro-inflammatory responses happen, while stimulating classic signaling makes anti-inflammatory responses happen (Masjedi et al., 2018).

IL-6 is a potential target for treating cancer

These activities are carried out by IL-6 in conjunction with a number of other components; nevertheless, STAT3 stands out as the most significant participant among them (Bromberg and Wang 2009). Targeting the IL-6/JAK/STAT3 pathway has produced in several kinds of cancer, which suggests that it could be a good way to

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treat cancer. Blocking this pathway seems like a promising way to treat cancers with high amounts of IL-6, such breast cancer. A number of treatments, such as monoclonal antibodies (mAb) against IL-6/IL-6R or sIL-6R, have been designed to do this (Guo et al., 2012; Wolf et al., 2014; Jones et al., 2011), inhibitors that only block IL-6 signaling factors further down the chain, such STAT3 or kinase inhibitors (e.g. JAK inhibitor) (Kontzias et al., 2012).

Chemoprevention aims to stop cancer from starting, spreading, or getting worse. Products that come from food are involved in every step of the process that leads to cancer (Steward and Brown 2013). When vitamin E (-tocopherol) is administered to a model mouse of non-Hodgkin's inside T-cell lymphoma, its production of the IL-6 gene as well as protein goes down researchers found that (Sharma and Vinayak 2011). In a similar way, UDN glycoprotein, which comes from plants, lowers the amount of IL-6 in mice that have been given 1,2-dimethylhydrazine. This suggests that UDN glycoprotein may be a good way to avoid colon cancer. In colon cancer chemoprevention, Balsalazide, a 5-ASA prodrug, and VSL3, a probiotic agent, can both inhibit the IL-6/STAT3 pathway (Do et al., 2016). Apigenin and luteolin, which come from food, block the IL-6/STAT3 pathway to stop human vascular cells from making new blood vessels (Lamy et al., 2012). Chemoprevention and treatment of glioblastoma have been mentioned to use quercetin, a chemical that can be found in many plant foods because it blocks IL-6 (Michaud-Levesque et al., 2012). Evista (Raloxifene HCl), an estrogen receptor modulator, has been found to have an additional effect on disrupting the interaction between IL-6 and the GP130 protein. This property makes Evista a potential chemopreventive agent for There are many classes of cancer, such as breast, liver, stomach, as well as multiple myeloma cancer. By getting in the way of the IL-6 signaling system, Evista may be a good way to stop or slow down the growth of these cancers (Shi et al., 2018; Wang et al., 2017).

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The level of IL-6 in the blood serum of breast cancer individuals

Increasingly, research papers talk about how IL-6 levels rise in the blood of people with breast cancer. These articles show that a raised level of IL-6 in the blood is a bad sign for people with mammary carcinoma. Table 1 shows the published research that looked at the IL-6 levels in the blood of breast cancer patients. Numerous studies have investigated the level of IL-6 in individuals both with as well as without breast cancer. Additionally, these studies have compared IL-6 levels between early and late stages of the disease (Kozłowski et al., 2003).Researchers looked at the levels of IL-6, IL-8, and IL10 in the blood serum of women with breast cancer to see if they were linked to the development of the disease. They found that the serum amounts of Interluekin-6, IL-8, as well as IL-10 were statistically advanced in women who have breast cancer than in women not the disease. This had to do with the state of the cancer as well (Yokoe et al., 2000), In a study, researchers found that women with breast cancer had higher amounts of IL-6 in their blood were significantly higher (ranging from 38.3 to 138.7 pg/ml) compared to healthy women (ranging from 0.7 to 2.5 pg/ml). But in this study, they didn't look at the link between serum IL-6 concentration as well as disease-free survival or total survival to see if there was a link between IL-6 levels and how patients did. Still, these results support what found (Yokoe et al., 2000), Researchers looked at what role IL-6 plays in higher or recurring breast cancer, as well as the link among interleukin 6 level as well as clinical results and the effect of medroxyprogesterone acetate (MPA), which is thought to stop the production of IL-6. The outcomes of a multivariate study exhibited that high blood IL-6 levels could be used on their own to predict the future. They came to the conclusion that the presence of IL-6 in the blood is linked to a lower chance of life for people via metastatic breast cancer.

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Table 1 Several studies have looked at blood IL-6 with patients of breast cancer.

Objective of the study	Clinical significance	Results	References
Compares the amounts of IL-6 in individuals as well those with breast cancer	25 vs 45 36 vs 111	3.3 vs 31.7(median) ,0.7 ± 2.5 vs 38.3 ± 138.7 (In both cases, breast cancer cases had much greater serum IL-6 levels than controls).	Kozłowski et al., 2003 Jiang et al., 2000
Compares the levels of IL-6 in different tumor stages (median)	6,23,12,4	Stage IIA had an IL-6 level of 18.7, Stage IIB had 19.3, Stage IIIA had 40.9, and Stage IIIB had 44.1 (indicating higher IL-6 levels with advanced disease stages).	Jiang et al., 2000
Studies at the link between IL-6 levels and clinical outcomes	43	Patients via metastatic breast cancer who had high amounts of IL-6 in their blood (median cutoff: >5 pg/ml) lived less time before their cancer got worse and less time ultimately.	Kozłowski et al., 2003
The study compared the IL-6 levels in breast cancer cases who experienced non-recurrence with those who had cancer recurrence.	17,65	Non-recurrent: 1.96 ± 1.38 Recurrent: 6.50 ± 7.48 IL-6 (when compared to non-recurrent instances, levels were considerably greater in recurrent cases).	Jiang et al., 2000

IL-6/JAK/STAT3 in Therapeutic Resistance

Since IL-6/JAK/STAT3 signaling makes breast cancer stem cells (CSCs) work better, and CSCs are known to help cancer grow and become resistant to treatment, it's not surprising that IL-6 is involved in chemoresistance. When this is activated pathway can promote the survival and growth of CSCs, making them less responsive to chemotherapy treatments, which ultimately leads to challenges in overcoming chemoresistance in breast cancer. When compared to the matching parental lines, therapeutically resistant breast cancer cells release along with express considerably more IL-6. Additionally, injection of recombinant IL-6 caused upregulating the

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medication-resistance gene mdr1 will make breast cancer cells more susceptible to therapy (Conze et al., 2001). In vivo, giving leptin made breast cancers more sensitive to chemotherapy. It was found that STAT3 controls the renewal of breast CSCs and their tolerance to chemotherapy by causing fatty acid b-oxidation (Wang et al., 2018). HER2+ breast cancer cells become resistant to transtuzumab when the IL-6 inflammatory pathway is turned on. This shows that IL-6's proinflammatory activity adds to breast cancer treatment resistance (Barre et al., 2009). Researchers have explored combining Inhibition of IL-6 or JAK or STAT3 signaling through standard-of-care therapies (Table 2). The drug sabutoclax, which blocks Bcl-2 and IL-6/STAT3 signals, has shown promise in enhancing the effectiveness of chemotherapy in breast cancer cells that are unresponsive to conventional therapies. This approach offers a potential solution to overcome chemoresistance and improve breast cancer treatment outcomes (Hu et al., 2018). A defiant ER+ patient-derived xenograft (PDX) rat model was used in the investigation, researchers discovered that ruxolitinib, a STAT3 inhibitor, significantly delayed tumor growth compared to fulvestrant alone, which is a standard-of-care treatment for ER+ breast cancer (Siersbæk et al., 2020). Clinical evidence indicates that cytoplasmic spotting of IL-6R is significantly correlated with tamoxifen resistance in patients with ER+ breast cancer. This observation underscores the importance of IL-6/JAK/STAT3 signaling as a potential therapeutic target to enhance the sensitivity of tumor cells to current standard-of-care (SOC) treatments. To overcome treatment resistance and enhance the results of ER+ breast cancer individuals receiving tamoxifen therapy, targeting this route may present a potential technique (Tsoi et al., 2021).

Table 2 Investigating the inhibition of IL-6, JAK, and STAT3 signaling in preclinical models of breast cancer.

Compound	Target	Models Used	Ref
Siltuximab	IL-6	The study involved treating six orthotopically transplanted patient-derived xenograft (PDX) lines in vivo. In the xenograft mouse model, human marrow stromal cells were conditioned and engrafted with	Di Cosimo et al., 2016; Casneuf et al., 2016

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		MCF-7 cells either as a single medication or in combination through fulvestrant.	
MEDI5117	IL-6	Treatment with taxanes or gefitinib in combination, as well as treatment with a single medication in the MCF-7 xenograft, was compared to treatment using a mouse model of a trastuzumab-resistant breast tumor (BT474-PTEN-LTT).	Zhong et al., 2016
Diacerein	IL-6Ra	The use of a mouse xenograft model involving MDA-MB-231 cells	Bharti et al., 2016; Bharti et al., 2017
Manuka Honey	IL-6Ra	Findings obtained in vitro utilizing MDA-MB-231 cells	Aryappalli et al., 2019
Tubulosine	IL-6Ra/ gp130	The MDA-MB-468, Hs578T, MCF10A, MDA-MB-231, as well as MCF-7 cells were used in the in vitro tests.	Kim et al., 2019
Raloxifene	gp130	The study included in vitro experiments using SUM-159 cells and separate in vitro findings using MDA-MB-231 cells.	Li et al., 2014; Shi et al., 2017
Glyceryl Trinitrate	JAK2	The in vivo findings were obtained by implanting 4T1 cells into the right flank of a syngeneic mouse strain	Bouaouiche et al., 2021
Withaferin A	JAK2	Observations obtained in vitro with MDA-MB-231 and MCF-7 cells	Liu et al., 2018
Stattic	STAT3	Stattic's identification and the results of in vitro experiments using MDA-MB-435S and MDA-MB-456 cells; Investigations carried out in vitro reveal that stattic therapy lowers the survival rate of MCF7-HER2 cells; We looked at the outcomes of treating ZR-75-1 breast cancer cells by doxorubicin in vitro.	Chung et al., 2014; Schust et al., 2006; Ghorbani et al., 2019
Naringenin	STAT3	Findings obtained in vitro utilizing MDA-MB-231 cells	Noori et al., 2020
Catechol	STAT3	Results obtained in vitro with MCF-7 as well as MDA-MB-231 cells	Choi et al., 2018

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Nifuroxazide	STAT3	In vitro, tests with MDA-MB-231,4T1 and MCF-7 cells were part of the investigation. For an in vivo study of lung tumors, 4T1 mice were used as models, and the drug Nifuroxazide was used to test the mice. Also, MCF-7, 4T1 and MDA-MB-231, cells were used in different experiments done in a lab dish.	Yang et al., 2015
Flubendazole	STAT3	The study involved in vitro experiments using MDA-MB-231, Hs578T, 4T1 and BT-549 cells. Additionally, in vivo metastasis models were developed using 4T1 stem cells.	Oh et al., 2018
Carfilzomib	STAT3	Findings from MDA-MB-231 cell in vitro studies	Vyas et al., 2017
CDDO-Me	STAT3	The effects of CDDO-Me on the microenvironment of breast tumors in vitro using MDA-MB-468 cells in vivo	Payton et al., 2017; Demaria et al., 2005

IL-6 Inhibitors

IL-6/JAK/STAT3 pathway inhibitors for the treatment of breast cancer are still pending FDA approval. However, preclinical studies are ongoing, focusing on the Small molecule inhibitors (SCI) and the monoclonal antibodies (mAb). The FDA has already approved the chimeric IL-6 mAb multicentric Castleman disease therapy with siltuximab in 2014 (Deisseroth et al., 2015). After testing the effectiveness of siltuximab in a number of PDX models, Morancho and colleagues found that just two of six lines were responsive to treatment. Not all PDX cultures showed a substantial decrease in pSTAT3 after IL-6 inhibition, contradicting earlier findings and highlighting the importance of identifying IL-6-dependent cancers are necessary for the efficacy of anti-IL-6 therapy (Di Cosimo et al., 2016). Serum IL-6 concentrations may be utilized as a sample or as a potential biomarker for IL-6-mediated therapy. In breast cancer individuals who tested positive for ERa, researchers discovered a connection between serum IL-6 concentrations and intratumoral pSTAT3 protein expression.

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IL-6Ra Inhibitors

Multiple IL-6, IL-6Ra, and JAKs-targeting anti-rheumatic medicines have been approved by the FDA and have dramatically improved the prognosis of autoimmune and inflammatory disease treatments. Because tocilizumab can be used for a variety of cancers, including breast cancer, it has been the subject of a lot of study. Tocilizumab's direct IL-6Ra suppression renders tamoxifen more effective in vitro and in vivo by re-sensitizing refractory ER+ cells (Tsoi et al., 2021). When tocilizumab or ruxolitinib, which is a JAK1/2 inhibitor, is given to HER2+ cells, increased cell death as well as decreased pSTAT3 protein levels. Additionally, tocilizumab therapy decreased tumor growth, HER2+ orthotopic xenograft tumors' production of the pSTAT3 protein as well as the growth of their cells. These results show the potential efficacy of JAK1/2 inhibition and tocilizumab as treatment strategies for HER2+ breast cancer (Masjedi et al., 2018).

gp130 Inhibitors

In order to block further IL-6 signaling, the gp130 receptor has become a desirable therapeutic target. The inhibition of gp130 activity by small compounds has been discovered, and these chemicals include those that have already been approved by the FDA for various medicinal uses. Since gp130 is the part of cytokines in the IL-6 family that sends signals, there aren't many gp130 inhibitors that can block only IL-6. Linked with conjugated estrogens, The FDA has approved bazedoxifene, a selective estrogen receptor modulator (SERM). It was already known that it inhibited the production of ERa and cyclin D1 and slowed the growth of breast cancer cells, but it wasn't clear how it worked against tumors until recently (Tian et al., 2019). Bazedoxifene was found by using a process called multiple-ligand simultaneous docking as well as drug repositioning to find a small molecule that could directly bond to "hot-spot" residues on gp130 to stop IL-6 and gp130 from interacting with each other as proteins. Bazedoxifene stops STAT3 from making transcriptions, which stops breast cancer colonies from growing, moving, and spreading. Bazedoxifene also lowers the size of TNBC tumors, which suggests that the compound could be used as an IL-6/JAK/STAT3 inhibitor.TNBC is desperately asking for treatment plans that work.

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More and more evidence show that glycoprotein 130 kDa (GP130), a key player in the interleukin 6 (IL-6) and signal transducer and activator of transcription 3 (STAT3) signaling pathways, is highly linked to the growth of tumors. GP130 could then become a new target for treating TNBC (Sandborn et al., 2017).

JAK Inhibitors

By directly stopping one or more enzymes in the JAK family, the IL-6/JAK/STAT3 signaling pathway can also be targeted. Ruxolitinib, tofacitinib, upadacitinib and baricitinib, are all JAK inhibitors that have received FDA approval to treat diseases other than breast cancer. These conditions include juvenile idiopathic arthritis as well as rheumatoid arthritis with a polyarticular course, psoriatic arthritis, severe ulcerative colitis, and myelofibrosis (Wollenhaupt et al., 2019; Bouaouiche et al., 2021). Also, more JAK inhibitors have been studied before they are used in people and have been shown to work in vivo. Through s-nitrosylation, glyceryl trinitrate blocks JAK2 to stop TNBC cells from moving and spreading when IL-6 is present. Also, a TNBC syngeneic mouse model shows that glyceryl trinitrate injection reduces lung metastatic lesions (Bouaouiche et al., 2021).

STAT3 Inhibitors

In the last few years, STAT3 has drawn a lot of attention as a potential therapy target for cancer treatment; however, there are no STAT3-targeted cancer treatments that have been authorized by the FDA as of yet. As a result of this, a number of researches have been conducted to examine potential small-molecule drugs that inhibit breast cancer and STAT3 activation (Huang et al., 2020). The ability of increasing dosages of stattic to inhibit STAT3 dimerization and nuclear translocation was demonstrated, which finally resulted in a decrease in pSTAT3 that was produced by IL-6. Apoptosis is caused in TNBC cells by the drug stattic. Since that time, numerous researchers have found that stattic is effective against by preventing the production of STAT3-associated stemness genes, breast cancer stem cells are prevented from growing. such as Oct-4, Sox-2, and Slug. It's interesting to note that a variety of naturally occurring compounds have been shown to have anti-cancer effects and a decreased

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STAT3 activity. For instance, when tested in vitro, When CDDO-Me, a kind of triterpenoid, was present, it was discovered that ovarian and breast cancer cells had lower levels CDDO-Me also displays anti-inflammatory properties as a result of nuclear translocation, STAT3 anti-apoptotic gene expression, that elevated STAT3 protein expression (Morancho et al., 2016).

Conclusion

Breast cancer gives interleukin-6 (IL-6) a key role, and it has great potential as a therapeutic target. It affects many facets of breast cancer progression, such as tumour development, metastasis, angiogenesis, and immunological regulation. Increased IL-6 levels have been associated with aggressive tumor behavior and a poor prognosis in people with breast cancer. Targeting IL-6 signaling pathways with monoclonal antibodies or as small molecule inhibitors is likely to be used as a therapeutic strategy. The goal of these treatments is to inhibit the interactions between IL-6 stop the signaling cascades that follow, and stop IL-6 from making tumors grow. Combination therapies, which combine IL-6-targeted drugs with traditional chemotherapy, targeted therapies, or immunotherapies, may offer synergistic effects by targeting multiple pathways involved in the growth the breast cancer. But further research is required to completely comprehend the mechanisms IL-6 causes its effects and to find the most effective way to use IL-6-targeted therapies to treat breast cancer.

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پوختە:

سایتاکینی پلێیۆتڕۆپیک کە بە ئینتەرلوکین-٦ (IL-6) ناسراوە هۆکارێکی گرنگە بۆ سەرهەڵدان و پێشکەوتنی شێرپەنجەی مەمک. ئەمەش بە کارکردن لەسەر چەندین ڕێڕەوی ئاماژەدان بە یەکجار ئەنجام دەدات، ئەمەش کاریگەری لەسەر زۆر توخمە جیاوازەکانی بایۆلۆجی وەرەم هەیە. چالاککردنی پەستانی ئاماژەدان کە پێشکەوتنی خولی خانەکان خێراتر دەکەن و ڕێگری لە ئەپۆپتۆزی دەکەن، وا بیردەکرێتەوە کە چۆن IL-6 گەشەکردن و بڵاوبوونەوەی وەرەم بەرەوپێش دەبات. جگە لەوەش، IL-6 یارمەتی دروستبوونی خوێنبەرەکان دەدات، کە یارمەتیدەرە لە گەشەکردنی خوێنبەرە نوێیەکان لە ژینگەی بچووکی وەرەمدا. ئەم سایتاکینە سەرەڕای ئەوەش هانی گواستنەوەی پۆششی-مێزانشیم (EMT) دەدات، کە یارمەتیدەرە لە داگیرکردنی وەرەم و گوازرانەوە. بڵاوبوونەوە، مانەوە و بەرگری لە چارەسەرکردنی خانە شێرپەنجەییەکان بەهۆی چالاککردنی ڕێڕەوی ئاماژەدانی خوارەوە وەک JAK/STAT و MAPK ئاسان دەکرێت. سەرەڕای ئەوە، لە ڕێگەی کۆنترۆڵکردنی وەڵامەکانی بەرگری و هاندانی ژینگەیەکی سەرکوتکەری بەرگری، IL-6 کاریگەری لەسەر ژینگەی بچووکی وەرەم هەیە.

الملخص:

يعتبر السيتوكين متعدد الاتجاهات المعروف باسم إنترلوكين 6 (IL-6) عاملاً مهمًا في نشأة سرطان الثدي وتطوره. يقوم بذلك من خلال العمل على العديد من مسارات الإشارات في وقت واحد ، مما يؤثر على العديد من العناصر المختلفة في بيولوجيا الورم. يُعتقد أن تنشيط سلاسل الإشارات التي تسرع من تقدم دورة الخلية وتمنع موت الخلايا المبرمج هو الطريقة التي يعزز بها IL-6 نمو الورم وانتشاره. علاوة على ذلك ، يعزز IL-6 تكوين الأوعية الدموية ، مما يساعد في نمو أوعية دموية جديدة في البيئة الدقيقة للورم. يشجع هذا السيتوكين أيضًا الانتقال الظهاري واللحمة المتوسطة (EMT) ، مما يساعد في غزو الورم والورم الخبيث. يتم تسهيل تكاثر الخلايا السرطانية وبقائها ومقاومتها للعلاج من خلال تنشيط مسارات إشارات المصب مثل JAK / STAT و MAPK. علاوة على ذلك ، من خلال التحكم في الاستجابات المناعية وتشجيع البيئة المثبطة للمناعة ، يؤثر IL-6 على البيئة الدقيقة للورم.