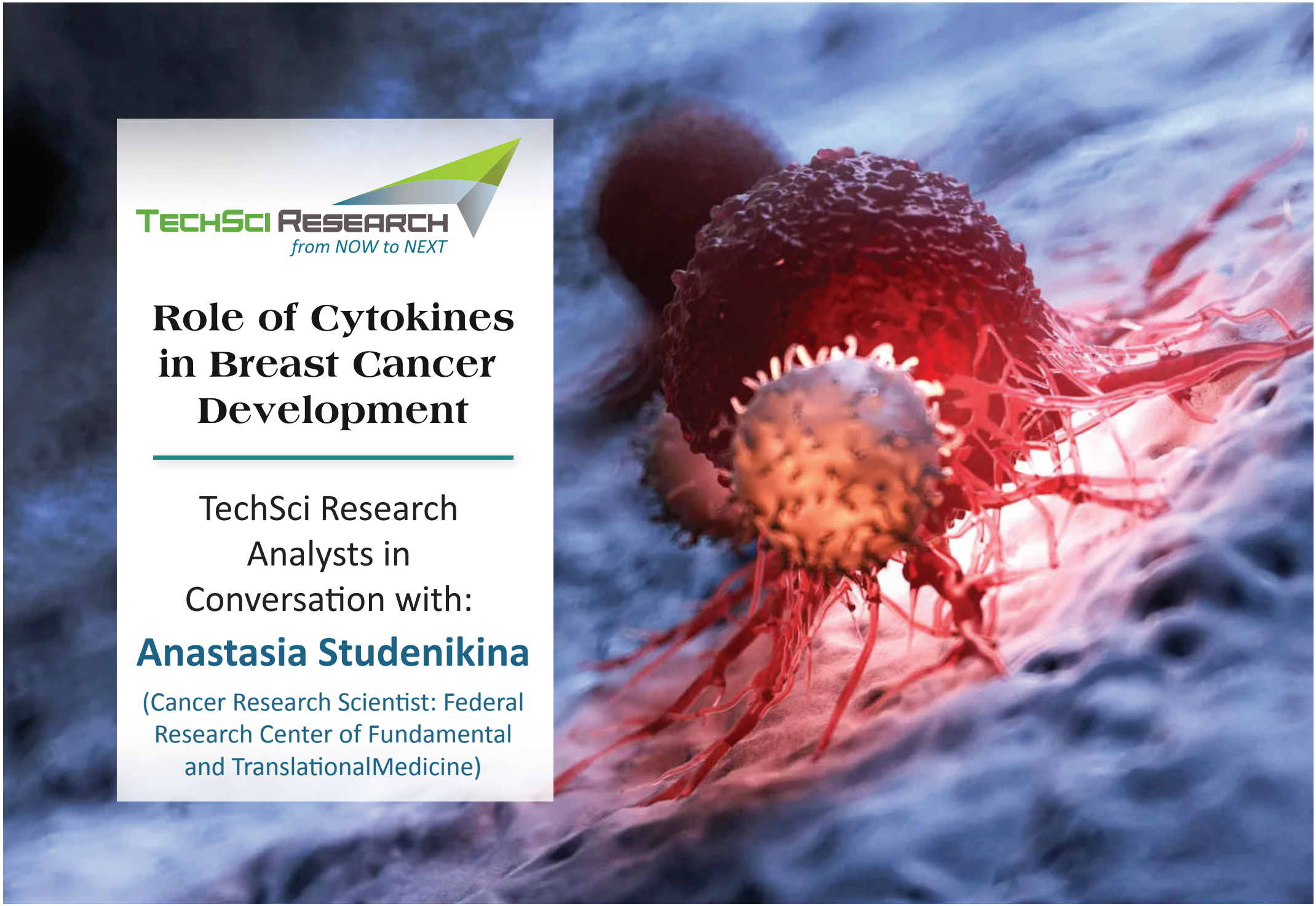

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Role of Cytokines in Breast Cancer Development

TechSci Research Analysts in Conversation with:

Anastasia Studenikina

(Cancer Research Scientist: Federal Research Center of Fundamental and TranslationalMedicine)

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In Conversation with Anastasia Studenikina

(Cancer Research Scientist: Federal Research Center of Fundamental and Translational Medicine)

How is your work/research related to breast cancer?

For the past few years, my colleagues and I at the Central Research Laboratory of Novosibirsk State Medical University have been conducting research on the production of cytokines in patients with breast cancer. Our study participants are admitted to the oncology department of Novosibirsk City Clinical Hospital No. 1 for the removal of suspicious formations and subsequent treatment.

With the patients' written consent, we conduct blood sampling before surgery and collect small pieces of the tumor removed during the operation.When selecting patients for our research, it is crucial to consider several parameters.

Firstly, we only include patients who have not received any prior therapy before the removal of the tumor. Secondly, it is equally important to ensure that these patients do not have any active or chronic inflammatory diseases, as both of these factors can significantly affect the level of cytokines in the blood and tumor interstitial fluid, potentially distorting our results.

Can you elaborate the process by which breast cancer is initiated? What we know is everyone has different hypothesis regarding the initiation of breast cancer, some say it is inflammation. What do you think exactly contributes to the initiation of breast cancer?

This is a complex issue that is subject to much discussion. It is important to note that malignant transformation is a multi-stage process involving the functional restructuring of the genetic apparatus and can be induced by various factors.

Undoubtedly, the inflammatory process can contribute to the occurrence and development of breast cancer. However, other factors such as hormonal imbalance, somatic mutations induced by endogenous and exogenous substances, a predisposing genetic background, and features of the immune status also make significant contributions to the occurrence of breast cancer.

Returning to the role of inflammation, several mechanisms have been described by which the inflammatory process, particularly chronic inflammation in breast tissue, can lead to its malignant transformation. One such mechanism is the local increase in the concentration of reactive oxygen species produced by macrophages during inflammation, which can cause DNA damage and contribute to the emergence and growth of abnormal cells. Chronic inflammation is also accompanied by the excessive production of pro-inflammatory cytokines that promote hyperactivation of transcription factors, such as NF-kB and STAT3. These cytokines stimulate cell proliferation and reduce apoptotic death, leading to the survival and growth of mutated cells.

Additionally, cytokines and chemokines can attract immunosuppressive cells such as myeloid suppressor cells, regulatory T cells, and M2 macrophages, leading to the formation

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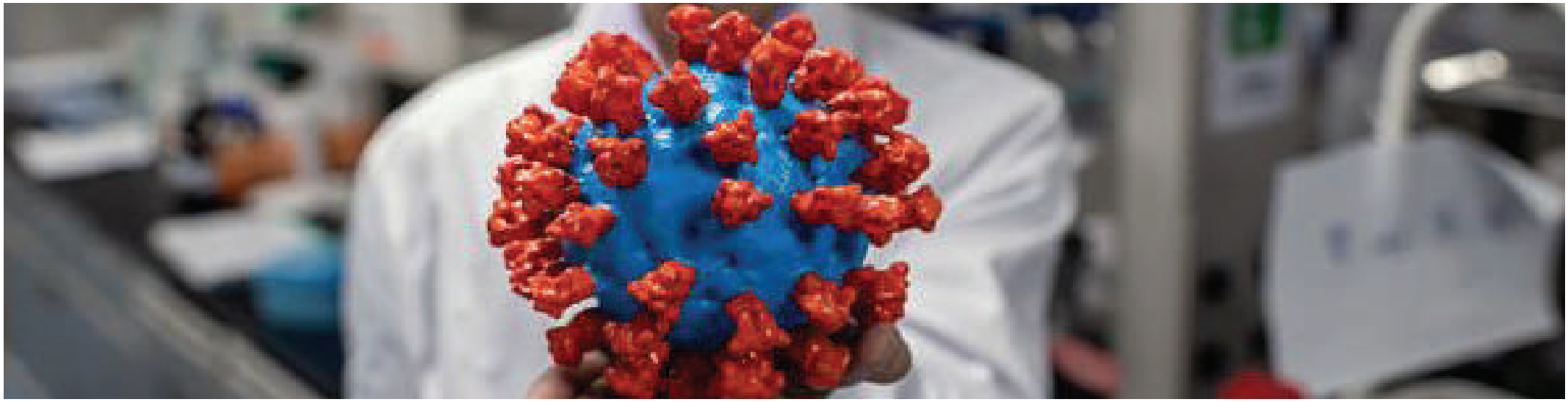

of a tumor-friendly microenvironment. In my opinion, breast cancer is most likely the result of a combination of genetic, hormonal, environmental, and lifestyle factors. To prevent its occurrence, it is essential to minimize the impact of potential risk factors, including smoking, alcohol consumption, excessive consumption of salty and fatty foods, and exposure to harmful chemicals and radiation. Additionally, regular screening measures and vigilance regarding changes in breast tissue are crucial for early detection and prompt treatment of breast cancer.

As stated by you, your studies are aimed at studying the production of cytokines in patients with breast cancer and with benign breast diseases. Can you let us know what benign breast diseases are being studied by you.

The patients included in our study with benign diseases are typically diagnosed with fibroadenoma, fibroadenomatosis, or fibrocystic mammary glands. It should be noted that although fibroadenomatosis is characterized by the proliferation of fibrous and glandular tissue, and fibrocystic cysts filled with fluid are formed in the breast tissue, medical professionals often use the general term "fibrocystic" to refer to benign pathology of the mammary glands. While patients with phyllodes tumors and other rare conditions are of particular interest, unfortunately, these conditions have not been included in our study at this time.

Can you comment on the production of cytokines in patients with breast cancer and how does it vary across different age groups, different stages of cancer progression, etc.

As far as I can tell, the production of cytokines in breast cancer can vary greatly depending on the stage of cancer, age, and many other individual characteristics of each patient. The functional state of the immune system and the hormonal status of patients have a great influence on cytokine concentrations, which may change with age.

In older patients, the phenomenon of immunosenescence may be observed, which is the physiological dysfunction of the immune system, including remodeling of lymphoid organs while reducing the functional activity and the number of different subpopulations of T cells, NK cells, dendritic cells, and macrophages, as well as reducing the expression of cytotoxic molecules such as gamma interferon (IFN-γ), granzyme B, and perforin. An important feature of immunosenescence is the degeneration of the thymus, which is accompanied by a decrease in the secretion of IL-7 and IL-15. One of the key signs of aging cells is the formation of a secretory phenotype (SASP), in which these cells secrete high levels of cytokines, growth factors, and proteases, the main ones being IL-1ß, IL-6, IL-8, IL-10, G-CSF, and GM-CSF. Another physiological process that affects the level of cytokines is the onset of the menopausal and postmenopausal period. It is

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believed that against the background of a decrease in ovarian function, there is an increase in the number of cytokines with proinflammatory effects, especially IL-1, IL-6, IL-8, TNF-α, and MCP-1.

However, the exact mechanisms by which estrogen influences the level of cytokines are still unknown; they may probably include the interaction of estrogen with other transcription factors and the modulation of nitric oxide activity. Cytokine production in breast cancer patients may also vary depending on the stage of cancer progression. This is largely due to the ability of tumors to form a unique microenvironment. In this regard, the concentrations of cytokines in the blood and tumor interstitial fluid undergo dynamic changes depending on the cellular composition and the rate of tumor growth, and probably can vary significantly depending on the size of the tumor focus (T), the degree of involvement of lymph nodes (N), and the molecular subtype of the tumor.

For example, the level of pro-inflammatory cytokines such as IL-6 and TNF-α is often elevated in patients with late-stage breast cancer compared to patients with early-stage disease. In our studies, IL-8 concentrations were lower in patients with the luminal A subtype compared to other molecular subtypes.

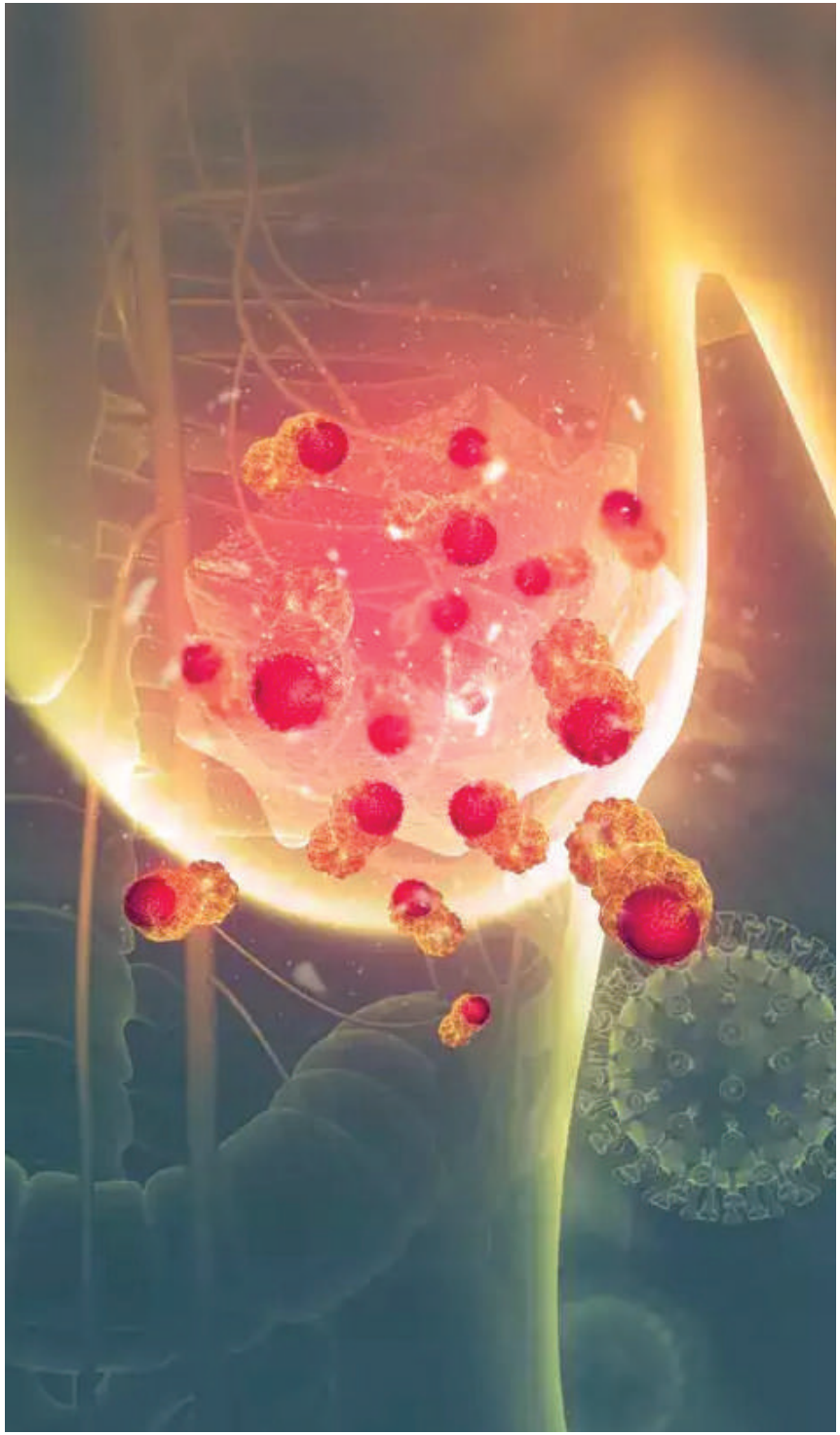
At the same time, patients with triple-negative molecular subtype, on the contrary, were distinguished by high concentrations of cytokines, especially IL-6, IL-8, IL-17A, IL-18, TNF-α, GM-CSF, and VEGF compared to other subtypes. However, it should be remembered that the relationship between cytokine production and breast cancer is complex and has not been fully studied.

In addition to age and stage of cancer, the production of cytokines in breast cancer patients may be influenced by concomitant diseases (such as obesity, diabetes) and genetic factors.

Studies suggest that cytokines play a key role in both induction and protection of breast cancer. What are your views on this?

You know, the effect of cytokines on breast cancer is ambiguous, and the exact role they play may depend on many factors and on each specific cytokine in question. The pleiotropy of cytokines further complicates the understanding of their role in the tumor. Depending on the concentration and cellular environment, cytokines can contribute to the development and progression of cancer, or they can have a protective effect, enhancing or suppressing the local immune response.

Pro-inflammatory cytokines, such as IL-6 and TNF-α, can promote the growth and survival of breast cancer cells, as well as the formation of blood vessels that support tumor growth. Their high concentrations are noted in the later stages of cancer. At the same time, anti-inflammatory cytokines (IL-10 and TGF-β) can have an overwhelming effect on the immune system and promote the growth of cancer cells. An important parameter that I mentioned earlier is the ability of cytokines to form a unique microenvironment that promotes tumor



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growth and development. For example, some cytokines, such as IL-8 and MCP-1, can promote the recruitment of immune cells and direct the proliferation of macrophages to M2 and neutrophils to N2 phenotypes, which can suppress the immune system and contribute to the formation of an anti-tumor environment. At the same time, there are several cytokines that have a protective effect against breast cancer. For example, IFN-γ and IL-12 have an antitumor effect by activating cytotoxic immune cells. I would like to emphasize that further research is needed to better understand the interactions between cytokines and breast cancer, as well as to identify potential therapeutic targets.

Can you comment on the role of different cytokines such as TGF-β, IL-6, TNF-α in breast cancer.

As I have already mentioned, the interaction between cytokines and breast cancer is a complex issue that many scientists are working to clarify. Additionally, there are numerous cytokines to consider when describing their potential roles in breast cancer. Let's focus on the three cytokines you have proposed: TGF-β, IL-6, and TNF-α.

Transforming growth factor-beta (TGF-β) is a cytokine that can have both suppressive and tumor-stimulating effects. It is mainly produced by T cells and macrophages and is sometimes considered a prognostic marker of breast cancer. In the early stages of breast cancer, TGF-β can inhibit tumor growth by inducing cell cycle arrest and activating the apoptosis program. However, in the late stages of cancer, TGF-β can promote tumor growth and metastasis by stimulating a process called epithelial-mesenchymal transition (EMT). During EMT, cancer cells acquire mesenchymal traits that endow them with a more invasive phenotype that facilitates metastasis. Breast cancer patients with high levels of TGF-β have significantly worse overall and relapse-free survival rates. Blocking TGF-β signaling in mouse models of breast cancer was effective in reducing tumor growth and metastasis.

IL-6 is a central cytokine that links chronic inflammation with the development of cancer. It promotes the emergence of malignant cells and mediates their proliferative activity, survival, and migration. IL-6 can also induce EMT and promote the recruitment of immune cells that suppress antitumor immune responses. In addition, IL-6 is an inducer of angiogenesis, the process of forming new blood vessels, by increasing the production of vascular endothelial growth factor (VEGF), and may mediate the development of drug resistance in patients with breast cancer. Despite all of the above, IL-6 is also able to stimulate antitumor immunity by attracting effector CD8+ T cells, which leads to increased apoptosis and delayed growth of neoplastic cells. Tumor necrosis factor-alpha (TNF-α) can have both antitumor and pro-tumor effects.

In the early stages of breast cancer, TNF-α, together with IFN-γ and IL-2, can inhibit tumor growth by inducing apoptosis and activating the immune system. TNF-α also has an antiangiogenic effect by inhibiting VEGF production and triggering endothelial cell apoptosis. However, in the late stages of breast cancer, TNF-α can promote tumor growth and metastasis by activating signaling pathways and stimulating the production of factors that promote angiogenesis and

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EMT.

Additionally, TNF-α can suppress the immune system, allowing cancer cells to evade immune surveillance. In breast cancer, TNF-α contributes to the development of multidrug resistance and is directly related to the conversion of estrogen-dependent malignant cells into estrogen-independent ones.

Studies suggest that cytokines are responsible for causing discomfort to women suffering from breast cancer. What are your views on this?

It is difficult for me to make a definitive judgment on this topic, as I do not have direct contact with patients and cannot conduct observations myself. However, the topic seems quite interesting.

It seems logical that elevated levels of proinflammatory cytokines may be associated with locally occurring inflammatory processes, such as those resulting from surgical removal of a tumor, and may cause discomfort. I came across an interesting study that reported elevated levels of IL-6 and TNF-α in women with breast cancer, which correlated with weight loss and a decrease in red blood cell production, leading to anemia.

Furthermore, these cytokines can contribute to fatigue, pain, and other symptoms, and also lead to an increase in body temperature and a disturbance in its regulation (feeling cold). Another study highlighted that high levels of IL-6 were associated with greater fatigue in women undergoing chemotherapy for breast cancer.

Additionally, a study reported that elevated TNF-α levels were associated with greater pain in women with breast cancer. Despite these examples, in my opinion, it still remains unclear whether cytokines directly cause discomfort or if they are simply a marker of the severity of the disease. Therefore, before creating cytokine-targeted approaches to alleviate discomfort in breast cancer patients, it is important to consider that these signaling molecules are involved in many physiological processes occurring in the body, such as promoting wound healing and fighting infection.

There are few studies who have established the ability of cytokine-secreting cancers to function as cellular vaccines that augment systemic immunity against wild-type cancers. Also, there are cytokines which are used for cancer therapy. Can you please comment and elaborate.

The possibility of using cytokine-secreting cancer cells as cellular vaccines is insanely interesting. In this case, tumor cells are used to deliver cytokines to the immune system, serving as a bait for the immune system by stimulating an immune response targeted at cancer cells throughout the body. One example of this approach is the use of genetically modified cancer cells that secrete IL-2, which promotes the proliferation of tumor-specific T-cell clones and enhances the body's immune response against cancer.

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In addition to using cytokine-secreting cancer cells as vaccines, cytokines themselves appear to be very promising therapeutic agents. Such therapy is aimed at stimulating the body's own immune system to attack cancer cells, and encouraging results have already been achieved. For example, work is underway on the use of IL-2, which can stimulate the proliferation, differentiation, and survival of immune cells (T, NK, and B cells), as an immunotherapy for certain types of cancer, including melanoma, kidney cancer, colorectal, and non-small cell lung cancer. Another promising cytokine is IL-12, which is able to activate and strengthen immune cells.

Preclinical studies have shown that the use of this cytokine leads to the inhibition of certain cancers, such as melanoma and breast cancer, and the safety and efficacy of IL-12 as an anticancer agent are currently being evaluated. Interferon-alpha (IFN-α) is another cytokine with antitumor and immunostimulating effects, which has been used to treat several types of cancer, including melanoma and chronic myeloid leukemia. Other cytokines, such as IL-4, IL-15, IL-21, IL-24, TNF-α, and TGF-β, are also being studied as antitumor therapeutic agents.

Although the latter two are associated with stimulating tumor growth, as mentioned above, they can also have an antitumor effect in certain conditions. Despite the fact that cytokine-based therapy looks promising, there are several significant limitations to its use. For example, it can cause significant side effects, including fever, chills, and flu-like symptoms.

Additionally, the effectiveness of cytokine therapy may vary depending on the type and stage of cancer. Furthermore, systemic administration of cytokines is limited by their instability and low efficiency.

In this regard, researchers are actively conducting studies to create optimal systems and to increase the local concentration of cytokines in the tumor micro-environment, in addition to searching and testing immuno-therapeutic molecules.

How do you foresee the role of cytokines in terms of emerging as a cancer therapeutic rather than one responsible for metastasis?

Of course, cytokines, given their huge range of actions in oncological diseases and breast cancer, in particular, seem to be very promising therapeutic agents. However, before using cytokines as an anticancer agent, it is necessary to fully understand the mechanisms of their action and potential side effects. In conclusion, cytokines can potentially become valuable tools in the fight against cancer. By using cytokine-secreting cancer cells as vaccines and developing cytokine-based cancer treatments, researchers are exploring new ways to stimulate the immune system and enhance the body's ability to fight cancer. This approach to therapy can offer new treatment options for patients with tumors and become an important part of the arsenal in the fight against cancer.

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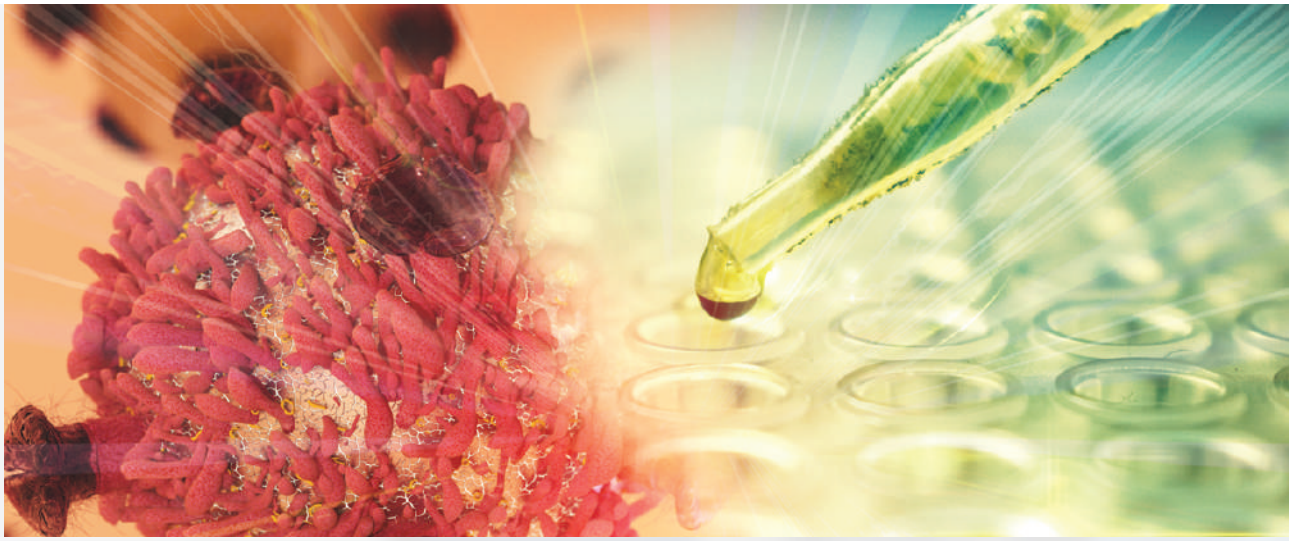

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AUTHORS

Karan Chechi

Research Director

Himanshu Saxena

Assistant Manager

Shaurya Singh

Senior Research Analyst

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