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Cytokines and Chemokines in Breast Cancer Progression: Immunological Insights and Therapeutic Targets

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Abstract: Breast cancer remains one of the most prevalent malignancies worldwide, characterized by complex interactions between tumor cells and the immune system. Increasing evidence underscores the pivotal role of cytokines and chemokines in orchestrating tumor initiation, progression, immune evasion, and metastasis. These soluble mediators function as key regulators of inflammation, cellular communication, and immune cell recruitment within the tumor microenvironment. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) promote tumor proliferation and survival, whereas immunosuppressive cytokines like transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10) facilitate immune escape. Chemokines, including CXCL12, CCL2, and CCL5, contribute to metastatic dissemination by directing tumor cell migration and shaping pre-metastatic niches. The dynamic interplay between cytokines, chemokines, and immune cells such as regulatory T cells and myeloid-derived suppressor cells further complicates therapeutic interventions. Recent advances in targeted therapies, including cytokine inhibitors and chemokine receptor antagonists, have opened new avenues for precision oncology. However, challenges such as signaling redundancy, systemic toxicity, and tumor heterogeneity limit clinical success. This review comprehensively examines the biological roles, signaling mechanisms, and therapeutic implications of cytokines and chemokines in breast cancer, highlighting emerging strategies to improve treatment outcomes.

Keywords: Breast cancer; Cytokines; Chemokines; Tumor microenvironment; Immunotherapy

1.0 Introduction – Inflammation and Cancer

The relationship between inflammation and cancer has evolved from a historical observation to a fundamental paradigm in oncology, wherein chronic inflammation is now recognized as a critical driver of tumorigenesis. Breast cancer exemplifies this intricate interplay, as inflammatory mediators significantly influence tumor initiation, progression, and metastasis. Cytokines and chemokines, as key components of the inflammatory network, regulate communication between cancer cells and immune cells, thereby shaping the tumor microenvironment (TME) [1].

Inflammation contributes to genomic instability, promotes angiogenesis, and facilitates immune evasion, all of which are hallmarks of cancer. In breast cancer, tumor-associated macrophages (TAMs), fibroblasts, and infiltrating immune cells secrete a diverse array of cytokines and chemokines that sustain a pro-tumorigenic milieu. This environment not only enhances tumor cell survival but also promotes resistance to therapy [2].

The dual nature of inflammation in cancer is particularly noteworthy. While acute inflammatory responses may facilitate tumor elimination, chronic inflammation often supports tumor growth. Cytokines such as IL-6 and TNF-α activate oncogenic signaling pathways, including STAT3 and NF-κB, thereby promoting

proliferation and inhibiting apoptosis [3]. Conversely, anti-inflammatory cytokines like IL-10 contribute to immune suppression, allowing tumor cells to evade immune surveillance.

Chemokines further amplify this complexity by regulating immune cell trafficking. They guide the migration of leukocytes into the tumor microenvironment, influencing both anti-tumor immunity and tumor progression. For instance, the CXCL12/CXCR4 axis plays a crucial role in directing metastatic breast cancer cells to distant organs such as the bone and lungs [4].

Understanding the role of cytokines and chemokines in breast cancer is essential for developing targeted therapeutic strategies. As research continues to uncover the molecular mechanisms underlying these signaling networks, new opportunities arise for modulating the immune landscape of tumors and improving clinical outcomes.

2.0 Cytokine Fundamentals – ILs, TNF, IFNs

Cytokines are small, secreted proteins that mediate intercellular communication within the immune system and play a central role in inflammation and cancer biology. They can be broadly classified into several families, including interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), growth factors, and chemokines. Each class exhibits distinct structural features and biological functions, yet they collectively regulate immune responses and cellular homeostasis [5].

Interleukins represent a diverse group of cytokines that modulate immune cell differentiation, activation, and proliferation. In breast cancer, interleukins such as IL-6 and IL-10 are particularly significant due to their roles in tumor progression and immune suppression. IL-6 activates the JAK/STAT3 signaling pathway, leading to enhanced tumor cell survival, angiogenesis, and resistance to apoptosis. IL-10, on the other hand, suppresses anti-tumor immune responses by inhibiting antigen presentation and T-cell activation [6].

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine with both pro-inflammatory and anti-tumor properties. While TNF-α can induce apoptosis in cancer cells under certain conditions, chronic exposure often promotes tumor growth by activating NF-κB signaling, which enhances cell proliferation and survival. TNF-α also contributes to the remodeling of the tumor microenvironment by stimulating the production of other inflammatory mediators [7].

Interferons, particularly type I (IFN-α/β) and type II (IFN-γ), play crucial roles in immune surveillance and anti-tumor immunity. IFN-γ enhances antigen presentation and activates cytotoxic T lymphocytes, thereby facilitating tumor cell destruction. However, prolonged interferon signaling can lead to immune exhaustion and reduced therapeutic efficacy, highlighting the complexity of cytokine-mediated responses in cancer [8].

Cytokine signaling is mediated through specific receptors that activate intracellular pathways such as JAK/STAT, MAPK, and PI3K/AKT. These pathways regulate gene expression, cell survival, and immune responses. Dysregulation of cytokine signaling is a hallmark of breast cancer, contributing to tumor progression and resistance to therapy [9].

The pleiotropic and redundant nature of cytokines presents both opportunities and challenges for therapeutic targeting. While cytokines offer potential biomarkers and therapeutic targets, their overlapping functions and systemic effects complicate clinical applications.

3.0 Tumor Microenvironment – Inflammatory Signaling

The tumor microenvironment (TME) is a dynamic and heterogeneous ecosystem composed of cancer cells, stromal cells, immune cells, and extracellular matrix components. Cytokines and chemokines are central to the regulation of this microenvironment, orchestrating complex signaling networks that influence tumor behavior. In breast cancer, the TME plays a critical role in disease progression, therapeutic resistance, and metastasis [10].

Inflammatory signaling within the TME is primarily driven by cytokines such as IL-6, TNF-α, and TGF-β. These cytokines activate key transcription factors, including NF-κB and STAT3, which regulate the expression of genes involved in proliferation, survival, and angiogenesis. Persistent activation of these pathways leads to a chronic inflammatory state that supports tumor growth [11].

Tumor-associated macrophages (TAMs) are one of the प्रमुख cellular components of the TME. These cells can adopt either a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype. In breast cancer, TAMs predominantly exhibit the M2 phenotype, which promotes tumor progression by secreting immunosuppressive cytokines such as IL-10 and TGF-β. These cytokines inhibit cytotoxic T-cell activity and facilitate immune evasion [12].

Fibroblasts within the TME, often referred to as cancer-associated fibroblasts (CAFs), also contribute to inflammatory signaling. CAFs secrete cytokines and chemokines that enhance tumor cell proliferation and invasion. Additionally, they remodel the extracellular matrix, creating a supportive niche for tumor growth and metastasis [13].

Angiogenesis, the formation of new blood vessels, is another critical aspect of the TME regulated by cytokines. Vascular endothelial growth factor (VEGF), often induced by IL-6 and TNF-α, promotes the

development of blood vessels that supply nutrients and oxygen to the tumor. This process is essential for tumor expansion and metastatic dissemination [14].

The interplay between cytokines, chemokines, and cellular components of the TME underscores the complexity of breast cancer biology. Targeting inflammatory signaling within the TME represents a promising strategy for disrupting tumor progression and enhancing therapeutic efficacy.

4.0 Key Cytokines – IL-6, TNF-α, TGF-β, IL-10, IFNs

Among the vast array of cytokines involved in breast cancer, several key mediators have been extensively studied due to their significant roles in tumor progression and immune regulation. These include IL-6, TNF-α, TGF-β, IL-10, and interferons, each of which exerts distinct yet interconnected effects on tumor biology [15].

IL-6 is a multifunctional cytokine that plays a central role in inflammation and cancer. It activates the JAK/STAT3 signaling pathway, promoting tumor cell proliferation, survival, and angiogenesis. Elevated levels of IL-6 have been associated with poor prognosis in breast cancer patients, highlighting its potential as both a biomarker and therapeutic target [16].

TNF-α, as previously discussed, exhibits dual roles in cancer. While it can induce apoptosis, its chronic expression in the TME often promotes tumor progression. TNF-α enhances the production of other pro-inflammatory cytokines and contributes to the activation of NF-κB signaling, which supports tumor growth and survival [17].

TGF-β is a potent immunosuppressive cytokine that plays a complex role in cancer. In early stages, it acts as a tumor suppressor by inhibiting cell proliferation. However, in advanced stages, TGF-β promotes epithelial-mesenchymal transition (EMT), a process that enhances tumor cell invasiveness and metastatic potential. It also suppresses immune responses by inhibiting T-cell activation [18].

IL-10 is primarily an anti-inflammatory cytokine that contributes to immune suppression in the TME. By inhibiting antigen presentation and reducing the activity of cytotoxic T cells, IL-10 facilitates tumor immune escape. High levels of IL-10 are often associated with poor clinical outcomes in breast cancer [19].

Interferons, particularly IFN-γ, play a crucial role in anti-tumor immunity. IFN-γ enhances the presentation of tumor antigens and activates immune effector cells. However, prolonged exposure to interferons can lead to immune exhaustion, reducing their therapeutic effectiveness [20].

The intricate balance between these cytokines determines the overall immune landscape of breast cancer. Therapeutic strategies aimed at modulating these cytokines must consider their dual roles and complex interactions within the TME.

5.0 Chemokines – CXCL12, CCL2, CCL5

Chemokines constitute a specialized subset of cytokines primarily involved in directing cell migration through chemotactic gradients. In breast cancer, chemokines play a decisive role in tumor progression, immune cell recruitment, and metastatic dissemination. Based on structural characteristics, chemokines are classified into four major families: CXC, CC, CX3C, and XC chemokines, with the CXC and CC families being most relevant in breast cancer biology [21].

Among these, the CXCL12/CXCR4 axis is one of the most extensively studied pathways. CXCL12, also known as stromal-derived factor-1 (SDF-1), binds to its receptor CXCR4, which is highly expressed on breast cancer cells. This interaction promotes tumor cell survival, proliferation, and directional migration toward organs rich in CXCL12, such as the lungs, liver, and bone marrow. This chemotactic mechanism is a critical determinant of organ-specific metastasis [22].

CCL2 (monocyte chemoattractant protein-1) plays a crucial role in recruiting monocytes and macrophages to the tumor microenvironment. Elevated levels of CCL2 are associated with increased infiltration of tumor-associated macrophages (TAMs), which predominantly exhibit an M2 phenotype and contribute to tumor progression and immune suppression. CCL2 also enhances angiogenesis and facilitates tumor growth [23].

CCL5 (RANTES) is another key chemokine implicated in breast cancer progression. It promotes tumor cell invasion and metastasis by enhancing epithelial-mesenchymal transition (EMT) and increasing the motility of cancer cells. Additionally, CCL5 recruits regulatory T cells (Tregs) to the tumor microenvironment, thereby contributing to immune evasion [24].

Chemokine signaling pathways often intersect with cytokine-mediated signaling, creating a complex network that regulates tumor behavior. Activation of chemokine receptors triggers downstream pathways such as PI3K/AKT, MAPK, and NF-κB, which are involved in cell survival, proliferation, and migration. This redundancy and cross-talk between pathways present significant challenges for targeted therapies [25].

The clinical relevance of chemokines in breast cancer lies in their potential as therapeutic targets and biomarkers. Inhibiting chemokine signaling may disrupt tumor progression and metastasis, offering new avenues for intervention.

6.0 Metastasis – EMT and Pre-Metastatic Niche

Metastasis is the leading cause of mortality in breast cancer patients, involving a multistep process that includes local invasion, intravasation, circulation, extravasation, and colonization of distant organs. Cytokines and chemokines are central to each stage of this cascade, particularly through their roles in epithelial-mesenchymal transition (EMT) and the formation of pre-metastatic niches [26].

EMT is a biological process in which epithelial cells lose their polarity and adhesion properties, acquiring mesenchymal characteristics that enhance motility and invasiveness. Cytokines such as TGF-β, IL-6, and TNF-α are प्रमुख inducers of EMT in breast cancer. TGF-β activates SMAD-dependent signaling pathways, leading to the transcription of EMT-associated genes such as Snail, Slug, and Twist. IL-6 further amplifies this process through STAT3 activation [27].

Chemokines also play a critical role in EMT and metastasis. The CXCL12/CXCR4 axis enhances the migratory capacity of tumor cells, while CCL5 promotes cytoskeletal reorganization and cell motility. These chemokines create a directional gradient that guides tumor cells toward distant metastatic sites [28].

The concept of the pre-metastatic niche has gained significant attention in recent years. This niche is established before the arrival of tumor cells and is characterized by a supportive microenvironment that facilitates tumor colonization. Cytokines and chemokines released by primary tumors mobilize bone marrow-derived cells, which migrate to distant organs and prepare the niche for tumor cell seeding [29].

For example, CCL2 recruits monocytes to future metastatic sites, where they differentiate into macrophages that support tumor growth. Similarly, CXCL12 creates a favorable microenvironment for the survival and proliferation of disseminated tumor cells. These processes highlight the systemic effects of cytokines and chemokines in cancer progression [30].

Targeting EMT and pre-metastatic niche formation represents a promising strategy for preventing metastasis. However, the complexity and redundancy of signaling pathways pose significant challenges for therapeutic development.

7.0 Immune Suppression – Tregs, MDSCs

Immune suppression within the tumor microenvironment is a critical factor that enables breast cancer cells to evade immune surveillance and resist therapy. Cytokines and chemokines play a central role in orchestrating this immunosuppressive landscape by regulating the recruitment and function of immune suppressor cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [31].

Tregs are a subset of CD4+ T cells characterized by the expression of the transcription factor FOXP3. These cells suppress immune responses by inhibiting the activity of cytotoxic T lymphocytes and natural killer cells. Cytokines such as TGF-β and IL-10 are प्रमुख drivers of Treg differentiation and function. Elevated levels of Tregs in breast tumors are associated with poor prognosis and reduced response to immunotherapy [32].

MDSCs are a heterogeneous population of immature myeloid cells that accumulate in the tumor microenvironment and exert potent immunosuppressive effects. They inhibit T-cell activation through the production of reactive oxygen species, nitric oxide, and immunosuppressive cytokines. Chemokines such as CCL2 and CXCL5 are involved in the recruitment of MDSCs to the tumor site [33].

Cytokine signaling pathways further enhance immune suppression by promoting the expression of immune checkpoint molecules such as PD-L1. IL-6 and IFN-γ have been shown to upregulate PD-L1 expression on tumor cells, thereby inhibiting T-cell-mediated cytotoxicity. This interaction represents a key mechanism of immune evasion in breast cancer [34].

The interplay between Tregs, MDSCs, and cytokine signaling creates a highly suppressive microenvironment that limits the effectiveness of immunotherapies. Strategies aimed at targeting these cells or modulating cytokine signaling may enhance anti-tumor immunity and improve clinical outcomes.

8.0 Therapeutic Targeting – Cytokine Inhibitors and Biologics

The central role of cytokines and chemokines in breast cancer progression has made them attractive targets for therapeutic intervention. Various strategies have been developed to modulate these signaling pathways, including monoclonal antibodies, small molecule inhibitors, and receptor antagonists [35].

Targeting IL-6 signaling has shown promise in preclinical and clinical studies. Monoclonal antibodies such as tocilizumab, which block the IL-6 receptor, have demonstrated potential in reducing tumor growth and overcoming resistance to chemotherapy. Similarly, inhibitors of the JAK/STAT3 pathway are being explored as therapeutic options [36].

TNF-α inhibitors, widely used in inflammatory diseases, have also been investigated in cancer therapy. While these agents can reduce inflammation, their role in cancer treatment remains controversial due to the dual nature of TNF-α signaling [37].

TGF-β inhibitors represent another promising class of therapeutics. By blocking TGF-β signaling, these agents can inhibit EMT, reduce metastasis, and enhance immune responses. However, the pleiotropic effects of TGF-β necessitate careful consideration of potential side effects [38].

Chemokine receptor antagonists, particularly those targeting CXCR4, have shown significant potential in preventing metastasis. Agents such as plerixa for disrupt the CXCL12/CXCR4 axis, thereby inhibiting tumor cell migration and colonization of distant organs [39].

Combination therapies that integrate cytokine and chemokine targeting with conventional treatments such as chemotherapy, radiotherapy, and immune checkpoint inhibitors are emerging as effective strategies. These approaches aim to overcome resistance and enhance therapeutic efficacy.

9.0 Biomarkers – Cytokine Profiling

Cytokines and chemokines have significant potential as biomarkers for breast cancer diagnosis, prognosis, and therapeutic response. Advances in high-throughput technologies have enabled comprehensive profiling of cytokine expression, providing insights into tumor biology and patient outcomes [40].

Elevated levels of IL-6, TNF-α, and CCL2 have been associated with poor prognosis and increased tumor aggressiveness. Conversely, higher levels of IFN-γ may indicate a robust anti-tumor immune response and better clinical outcomes. These biomarkers can aid in patient stratification and treatment selection [41].

Multiplex assays and proteomic analyses have facilitated the simultaneous measurement of multiple cytokines and chemokines, allowing for the identification of complex biomarker signatures. These signatures may provide more accurate predictions of disease progression and therapeutic response compared to single markers [42].

The integration of cytokine profiling with genomic and transcriptomic data further enhances its utility in precision oncology. However, variability in assay methods and the dynamic nature of cytokine expression present challenges for clinical implementation.

10.0 Challenges – Redundancy and Toxicity

Despite the promising potential of targeting cytokines and chemokines, several challenges limit their clinical application. One of the प्रमुख issues is the redundancy of signaling pathways. Multiple cytokines can activate the same downstream pathways, making it difficult to achieve effective inhibition with single-target therapies [43].

Systemic toxicity is another significant concern. Cytokines are involved in essential physiological processes, and their inhibition can lead to adverse effects such as immunosuppression, increased susceptibility to infections, and organ toxicity. Balancing therapeutic efficacy with safety remains a critical challenge [44].

Tumor heterogeneity further complicates treatment strategies. Different breast cancer subtypes exhibit distinct cytokine and chemokine profiles, necessitating personalized approaches to therapy. Additionally, the dynamic nature of the tumor microenvironment can lead to adaptive resistance mechanisms.

11.0 Future Perspectives

Future research in this field is likely to focus on the development of more selective and targeted therapies that minimize toxicity while maximizing efficacy. Advances in nanotechnology, gene editing, and immunotherapy are expected to play a significant role in this regard.

Personalized medicine approaches that integrate cytokine profiling with molecular and clinical data may enable more precise treatment strategies. Furthermore, the identification of novel cytokines and chemokines involved in breast cancer progression may uncover new therapeutic targets.

Table 1: Cytokines and Their Roles in Breast Cancer

Cytokine	Source	Signaling Pathway	Role in Breast Cancer
IL-6	Tumor cells, macrophages	JAK/STAT3	Proliferation, survival, angiogenesis
TNF-α	Macrophages, T cells	NF-κB	Inflammation, tumor growth
TGF-β	Tumor cells, Tregs	SMAD	EMT, immune suppression
IL-10	Tregs, macrophages	JAK/STAT	Immune suppression
IFN-γ	T cells, NK cells	JAK/STAT1	Anti-tumor immunity

Table 2: Chemokine Pathways and Therapeutic Targets

Chemokine	Receptor	Function	Therapeutic Target
CXCL12	CXCR4	Migration, metastasis	CXCR4 inhibitors (plerixafor)
CCL2	CCR2	Monocyte recruitment	CCR2 antagonists
CCL5	CCR5	EMT, invasion	CCR5 inhibitors

12.0 Conclusion

Cytokines and chemokines represent central immunological regulators of breast cancer progression, linking chronic inflammation, tumor microenvironment remodeling, immune escape, angiogenesis, epithelial-mesenchymal transition, and metastatic organ tropism. Mediators such as IL-6, TNF-α, TGF-β, IL-10, and IFNs exert context-dependent effects that may either enhance anti-tumor immunity or support tumor survival and immune suppression. Similarly, chemokine axes such as CXCL12/CXCR4, CCL2/CCR2, and CCL5/CCR5 regulate immune-cell recruitment, macrophage polarization, tumor-cell migration, and pre-metastatic niche formation. Their clinical significance extends beyond mechanistic biology because cytokine and chemokine signatures may support prognosis, treatment stratification, and therapeutic monitoring.

Targeting these pathways offers promising opportunities, particularly when combined with chemotherapy, endocrine therapy, radiotherapy, immune checkpoint blockade, or nanomedicine-based delivery. However, therapeutic translation remains challenging because cytokine networks are redundant, pleiotropic, dynamic, and deeply integrated with normal immune physiology. Future progress will depend on precision approaches that identify dominant inflammatory circuits in individual patients, minimize systemic toxicity, and integrate cytokine or chemokine modulation into rational combination regimens. Overall, cytokine and chemokine biology provides a powerful framework for understanding breast cancer progression and developing next-generation immunotherapeutic strategies.

References

1. Esquivel-Velázquez M, Ostoa-Saloma P, Palacios-Arreola MI, Nava-Castro KE, Castro JI, Morales-Montor J. The role of cytokines in breast cancer development and progression. **J Interferon Cytokine Res.** 2015; 35(1):1–16.
2. Ben-Baruch A. Inflammatory cells, cytokines and chemokines in breast cancer progression. **Breast Cancer Res.** 2003; 5(1):31–36.
3. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. **Cell.** 2010; 140(6):883–899.
4. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. **Nature.** 2008; 454:436–444.
5. Manore SG, Doheny DL, *Wong* GL, Lo HW. IL-6/JAK/STAT3 signaling in breast cancer metastasis. **Cancers (Basel).** 2022; 14:1050.
6. Gyamfi J, Eom M, Koo JS, Choi J. IL-6/STAT3 signaling regulates EMT in breast cancer. **Sci Rep.** 2018; 8:8859.
7. Aggarwal BB. Signalling pathways of TNF-α in cancer. **Nat Rev Cancer.** 2003; 3(10):745–756.
8. Taylor MA, Lee YH, Schiemann WP. Role of TGF-β in breast cancer progression. **Gene Expr.** 2011; 15(3):117–132.
9. Yang Y, Kang X, Zhang X, Li X. TGF-β signaling in metastatic breast cancer. **Oncoimmunology.** 2019; 8:e1624123.
10. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells in cancer. **J Immunol.** 2009; 182(8):4499–4506.
11. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. **Cell.** 2008; 133(5):775–787.
12. Zielińska KA, Katanaev VL. CXCL12/CXCR4 signaling in breast cancer. **Cancers (Basel).** 2020; 12:3071.
13. Balkwill F. The chemokine system and cancer. **J Pathol.** 2012; 226(2):148–157.
14. Singh R, Lillard JW Jr, Singh S. Chemokines in cancer metastasis. **Front Biosci.** 2011; 3:1569–1582.
15. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression. **Cell.** 2010; 141(1):39–51.
16. Kitamura T, Qian BZ, Pollard JW. Immune cell promotion of metastasis. **Nat Rev Immunol.** 2015; 15:73–86.
17. Liu H, Yang Z, Lu W. Chemokine receptors as cancer therapeutic targets. **Cancer Med.** 2020; 9:3786–3799.
18. Yi M, Niu M, Wu Y. Targeting cytokine signaling pathways in cancer therapy. **Signal Transduct Target Ther.** 2024; 9:176.

19. Siersbæk R, Scabia V, Nagarajan S. IL-6/STAT3 drives breast cancer metastasis. **Cancer Cell.** 2020; 38:412–423.
20. Dunn GP, Bruce AT, Ikeda H. Cancer immunoediting. **Nat Immunol.** 2002; 3:991–998.
21. Whiteside TL. Immune suppression in tumor microenvironment. **J Clin Invest.** 2010; 120(6):1875–1878.
22. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. **Cell.** 2011; 144(5):646–674.
23. Joyce JA, Pollard JW. Microenvironment regulation of metastasis. **Nat Rev Cancer.** 2009; 9:239–252.
24. Massagué J, Obenauf AC. Metastatic colonization. **Nature.** 2016; 529:298–306.
25. Balkwill FR, Capasso M, Hagemann T. Tumor microenvironment and cytokines. **J Cell Sci.** 2012; 125:5591–5596.
26. Thiery JP, Acloque H, Huang RYJ. EMT in cancer progression. **Cell.** 2009; 139(5):871–890.
27. Lamouille S, Xu J, Derynck R. Molecular mechanisms of EMT. **Nat Rev Mol Cell Biol.** 2014; 15:178–196.
28. Müller A, Homey B, Soto H. CXCR4 directs metastasis of breast cancer cells. **Nature.** 2001; 410:50–56.
29. Kaplan RN, Riba RD, Zacharoulis S. VEGFR1+ bone marrow progenitors in metastasis. **Nature.** 2005; 438:820–827.
30. Sceneay J, Smyth MJ, Möller A. The pre-metastatic niche. **Cancer Metastasis Rev.** 2013; 32:449–464.
31. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators. **Nat Rev Immunol.** 2009; 9:162–174.
32. Facciabene A, Motz GT, Coukos G. T-regulatory cells in cancer. **Nat Rev Cancer.** 2012; 12:298–306.
33. Veglia F, Perego M, Gabrilovich D. MDSCs in cancer progression. **Nat Immunol.** 2018; 19:108–119.
34. Chen DS, Mellman I. Cancer immunity cycle. **Immunity.** 2013; 39:1–10.
35. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation and cancer. **Cold Spring Harb Perspect Biol.** 2014; 6:a016295.
36. Kang S, Tanaka T, Narazaki M. Targeting IL-6 signaling. **Nat Rev Rheumatol.** 2019; 15:249–264.
37. Balkwill F. TNF-α in cancer therapy revisited. **Nat Rev Cancer.** 2009; 9:361–371.
38. Herbertz S, Sawyer JS, Stauber AJ. TGF-β inhibition in cancer therapy. **Clin Cancer Res.** 2015; 21:2781–2789.
39. De Clercq E. CXCR4 antagonists in cancer therapy. **Nat Rev Drug Discov.** 2003; 2:581–587.
40. Schwarzenbach H, Hoon DSB, Pantel K. Circulating biomarkers in cancer. **Nat Rev Cancer.** 2011; 11:426–437.
41. Bachelot T, Ray-Coquard I, Menetrier-Caux C. Prognostic value of cytokines in breast cancer. **Clin Cancer Res.** 2003; 9:153–158.
42. Tan W, Zhang W, Strasner A. Tumor-infiltrating immune cells and cytokines. **Cancer Res.** 2011; 71:5441–5446.
43. Hoos A. Development of immunotherapy combinations. **Nat Rev Drug Discov.** 2016; 15:235–247.
44. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. **Science.** 2018; 359:1350–1355.