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Advancements in Metastatic Cancer Treatment: Exploring Targeted Therapies and Immunotherapy Options

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Abstract:
One of the most difficult problems in oncology is metastatic cancer, defined as cancer that has spread from its starting point to other parts of the body. Although tumors in the early stages respond well to specific treatment techniques such as surgery, chemotherapy, and radiation therapy, metastatic disease often resists these strategies and requires a more complex and multidisciplinary approach. This summary examines the current state of metastatic cancer treatment, as well as advances in immunotherapy, targeted medicine, and personalized medicine, as well as difficulties in controlling metastasis. Several complex biological processes, such as invasion of surrounding tissues, blood flow or entry into the lymphatic system, survival in distant organs, growth in a new place, are responsible for metastasis. Genetic mutations, changes in the microenvironment of tumors, evasion of immune surveillance are the molecular basis of malignant disease. Developing treatments that can prevent or prevent metastasis requires an understanding of these pathways. Currently the primary treatment option for metastatic cancer is systemic therapy, which includes immunotherapy, targeted therapy, and chemotherapy. Chemotherapy is a biotherapeutic option for a number of metastatic diseases, despite its drawbacks, which require combination therapy or a combination of new drugs due to systemic toxicity and drug resistance. The treatment picture of some metastases has been completely replaced by immunotherapy, especially immunosuppressants. Immunotherapy can sometimes lead to long-term remission by improving the body's immunity, although not all patients benefit from this treatment. Developing ways to overcome immune resistance and finding biomarkers that identify which individuals may benefit from immunotherapy are key targets of ongoing research. A potential strategy for the treatment of metastatic cancer in recent years has been personalized or accurate medication. But even with these advances, the treatment of metastatic cancer still presents many difficulties. In addition, the appearance of secondary metastases in the liver, brain, and bones creates additional treatment difficulties and often calls for specialized methods to control the details of metastatic growth in these organs.

Keywords: Tissue-Specific Targeting, Cancer Immunotherapy, Therapeutic Resistance, Liver Metastasis, Cancer Survival.

تأثير الصحة العقلية في ظل الجائحة: معالجة الرفاهية المجتمعية في خضم جائحة كوفيد-19

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الملخص

يُعدّ السرطان النقيلي من أصعب المشاكل في علم الأورام، ويُعرّف بأنه السرطان الذي انتشر من بدايته إلى أجزاء أخرى من الجسم. على الرغم من أن الأورام في مراحلها المبكرة تستجيب جيدًا لتقنيات علاجية محددة كالجراحة والعلاج الكيميائي والعلاج الإشعاعي، إلا أن المرض النقيلي غالبًا ما يقاوم هذه الاستراتيجيات ويتطلب نهجًا أكثر تعقيدًا وتعددًا في التخصصات. يتناول هذا الملخص الوضع الراهن لعلاج السرطان النقيلي، بالإضافة إلى التطورات في العلاج المناعي والطب الموجه والطب الشخصي، بالإضافة إلى صعوبات السيطرة على النقائل. تُعدّ العديد من العمليات البيولوجية المعقدة، مثل غزو الأنسجة المحيطة، وتدفق الدم أو دخول الجهاز اللمفاوي، والبقاء في الأعضاء البعيدة، والنمو في مكان جديد، مسؤولة عن النقائل. تُعدّ الطفرات الجينية، والتغيرات في البيئة الدقيقة للأورام، والتهرب من المراقبة المناعية، الأساس الجزيئي للمرض الخبيث. يتطلب تطوير علاجات يمكنها منع النقائل أو الوقاية منها فهم هذه المسارات. يُعدّ العلاج الجهازي حاليًا الخيار العلاجي الرئيسي للسرطان النقيلي، والذي يشمل العلاج المناعي والعلاج الموجه والعلاج الكيميائي. يُعد العلاج الكيميائي خيارًا علاجيًا حيويًا لعدد من الأمراض النقيلية، على الرغم من عيوبه التي تتطلب علاجًا مركبًا أو مزيجًا من الأدوية الجديدة نظرًا لسميته الجهازية ومقاومته للأدوية. وقد استُبدل العلاج المناعي، وخاصةً مثبطات المناعة، بالعلاج التقليدي لبعض النقائل. ويمكن أن يؤدي العلاج المناعي أحيانًا إلى شفاء طويل الأمد من خلال تحسين مناعة الجسم، على الرغم من أن هذا العلاج لا يستفيد منه جميع المرضى. ويُعد تطوير طرق للتغلب على مقاومة المناعة وإيجاد مؤشرات حيوية تُحدد الأفراد الذين قد يستفيدون من العلاج المناعي أهدافًا رئيسية للأبحاث الجارية. وقد تمثلت إحدى الاستراتيجيات المحتملة لعلاج السرطان النقيلي في السنوات الأخيرة في إيجاد دواء مخصص أو دقيق. ولكن حتى مع هذه التطورات، لا يزال علاج السرطان النقيلي يُمثل العديد من الصعوبات. بالإضافة إلى ذلك، يُشكل ظهور النقائل الثانوية في الكبد والدماغ والعظام صعوبات علاجية إضافية، وغالبًا ما يتطلب أساليب متخصصة للتحكم في تفاصيل النمو النقيلي في هذه الأعضاء.

الكلمات المفتاحية: استهداف الأنسجة المحددة، العلاج المناعي للسرطان، المقاومة العلاجية، نقائل الكبد، البقاء على قيد الحياة من السرطان.

Introduction

Advances in clinical oncology and basic cancer sciences are essential to further improve the treatment of metastatic cancer. Clinical researchers and cancer biologists have collaborated in unprecedented ways over the past twenty years. The rapid accumulation of tumor genetic data made possible by technological advances sheds light on how medications work and how diseases grow. Clinical trials have become increasingly comprehensive after the emergence of treatment as well as drug resistance before and during treatment. The time taken to introduce the drug into clinical practice has been reduced. Creative experiences such as basket, umbrella and platform studies. Using these methods, scientists can quickly find indications of treatment response, confirm resistance mechanisms in in vivo models, and create future drugs. [1] Hypotheses about the underlying process of malignant disease are made through abundant datasets derived from this process, and then they can be tested in functional trials. As a result, preclinical and post clinical research contributes to improve our knowledge of metastatic biology and facilitate the creation of new treatments. Metastasis is increased in animal models and linked to replication in clinical practice, according to studies that combine gene expression data from acquired tumors. From experimental models of patient and disease. The cancer cells in the original tumor express some of these genes, exposing them to metastasis when they spread to certain organs. [2] Several genes promoting metastasis are currently undergoing clinical trials as potential targets for anti-metastatic therapies (revised in reference 18). Other research has used larger cancer genomic datasets to find pro-metastatic mutations. [3] Epigenetic changes may support good phenotypes in organ colonization and proliferation. Stem cells continuously produce different progeny and maintain tissue balance in the healthy epithelium. Symmetry epithelium regenerates after damage when silent ancestors give rise to proliferative daughter cells repairing the epithelial barrier. These maintenance mechanisms are allocated by a malignant tumor. As MICs, these cells are capable of entering, proliferating, and entering alternative resting sites for organ transplantation. Eventually the tumor is reconstructed. [4] These cells have the potential to produce different cancers that mimic the original organ growth pathways when given appropriate environmental stimuli. [5], organ regeneration and cancer. Nature Molecular Cell Biology Review. December 2010; 11 (12): 834-48. Metastatic cancer cells (CTCs), or cancer cells in the circulatory system, are the focus of most studies. Progenitor and EMT symptoms are revealed by CTC, and can be obtained from metastasis CTC studies. After removing the original tumor, CTCs mostly disappear because they have a short half-life in their bloodstream. Most counter-terrorism centres have been dismantled and never spread to other areas. After removing the primary tumor, some cancer cells may survive or recur, potentially indicating the presence of active metastases.

Metastatic cancer epidemiology

Metastatic cancer is one of the most difficult health problems worldwide. It is responsible for the majority of cancer-related deaths, accounting for more than 90% of all cancer-related deaths. Metastasis occurs when cancer

cells spread from their original location to other parts of the body, making treatment significantly more complex. The global burden of metastatic cancer is significant, and its prevalence varies based on geographic location, with some regions experiencing higher incidence rates due to factors such as genetics, lifestyle, and access to health care.

Globally, the most common cancers that are transmitted include breast, lung, colorectal and prostate cancers. For example, breast cancer alone was responsible for 2.3 million new cases and 685,000 deaths worldwide in 2020 [6][18][19], while lung cancer, which is closely related to cancer, saw more than 2 million new cases and 1.8 million deaths globally in the same year (20). Similarly, colorectal cancer causes about 1.9 million new cases annually, with 935,000 deaths globally [6]. These cancers often metastasize to common locations such as the liver, lungs, bones, and brain, each of which presents unique therapeutic challenges. For example, breast cancer spreads to the bones, liver, and lungs, while lung cancer often goes to the liver and brain.

The regional distribution of metastatic cancer varies greatly. In developed countries such as the U.S. and Europe, cancer screening programs, early diagnosis methods, and innovative treatment options have helped improve survival rates. However, metastatic cancer is a major problem in these areas, especially for cancers such as lung, breast, and colorectal cancer, where end-stage diagnosis is still common. On the other hand, in low- and middle-income countries, metastatic cancer often appears in later stages due to limited access to diagnostic tools and early treatment, leading to increased mortality rates. In regions such as sub-Saharan Africa and Southeast Asia, where access to health care is often limited, the prevalence of metastatic disease increases due to challenges in early diagnosis, leading to a higher proportion of patients diagnosed with advanced cancer [7].

In addition, some cancers show different regional differences. For example, liver cancer is especially common in Asia, often due to high rates of hepatitis infection, which are major risk factors for circulating malignant liver. Meanwhile, East Asia, including China and Japan, shows a higher prevalence of stomach cancer, while in Western countries, colorectal cancer is diagnosed more commonly [8]. These regional differences are important when considering the global impact of metastatic cancer, as the burden is not evenly distributed and is shaped by local factors such as the availability of protective measures, genetic trends, and public health strategies.

Table 1 Regional prevalence of metastatic cancers by type and their associated mortality rates.

Region	Cancer Type	Prevalence	Associated Mortality Rate	Key Observations
North America	Breast Cancer	High (2.3 million new cases globally)	High (685,000 deaths globally)	Early detection programs have improved survival rates, though metastatic cases remain a challenge.
	Lung Cancer	High (2 million new cases globally)	Very High (1.8 million deaths globally)	Late-stage diagnosis leads to high mortality rates despite advances in treatment.
	Colorectal Cancer	High	Moderate (935,000 deaths globally)	Increased awareness and screening have improved early detection.
Europe	Prostate Cancer	Moderate	High (European mortality rates vary by country)	Significant regional variation due to differing access to healthcare.
	Melanoma	Moderate	Moderate	Rising incidence rates, especially in Northern Europe due to lifestyle changes.
Asia	Liver Cancer	High (especially East Asia)	Very High (700,000 deaths globally)	Hepatitis B and C infections are significant risk factors.
	Stomach Cancer	High (Eastern Asia)	High (830,000 deaths globally)	High rates in countries like Japan, China, and Korea. Early detection still a challenge.
Africa	Cervical Cancer	High	High	Limited access to screening and treatment options.
	Liver Cancer	High	Very High	Hepatitis infections and other regional factors contribute to high mortality rates.
Latin America	Colorectal Cancer	Moderate	High (Increased risk in urban areas)	Risk increases with urbanization and lifestyle changes.
	Stomach Cancer	Moderate	Moderate	Screening programs are improving, though late diagnosis remains common.

Health care systems around the world are significantly affected by metastatic cancer, especially in terms of treatment costs, resource allocation, and demand for specialized care. Managing metastatic cancer often requires a combination of treatments, including chemotherapy, immunotherapy, targeted therapy, and sometimes palliative care. These treatments can be expensive and often require long-term management, putting significant pressure on the health care system, especially in countries where the health care budget is limited. For example, in the United States, the cost of cancer care has reached approximately $174 billion annually, with metastatic cancer contributing significantly to these costs [9]. This financial burden is felt not only in developed countries but also in low-income areas, where the cost of cancer treatment can be very high, leading to unequal access to care.

In addition, the increased use of expensive treatments such as immunotherapy and targeted therapy has increased health care costs. While these treatments have revolutionized cancer treatment and improved survival rates for some patients, they have also put significant pressure on healthcare infrastructure. In countries with limited resources, the high cost of these treatments can limit access to state-of-the-art treatments, leading to disparities in survival outcomes. In many low-resource settings, the lack of modern imaging and molecular diagnostic tools means that patients often develop metastatic cancer at a stage where treatment options are limited, further complicating their care [6].

The social and psychological impact of metastatic cancer on patients and their families is another important issue. Patients diagnosed with metastatic cancer often experience poor prognosis, and many experience significant emotional distress while navigating complex treatment modalities. Side effects of treatments such as chemotherapy and immunotherapy can affect patients' quality of life, causing physical, emotional, and financial burdens. In addition, family members often play a role in caregiving, which can lead to emotional and financial stress. This makes metastatic cancer not only a clinical challenge but also a social and emotional challenge, highlighting the need for comprehensive care that includes traditional cancer treatment as well as psychological support and palliative care.

The impact of metastatic cancer on health care systems and patients highlights the importance of improving access to early diagnosis, expanding treatment options and strengthening care infrastructure, especially in low- and middle-income countries. Joint international efforts, improved health care policies, and innovations in cancer care are essential to address the growing burden of metastatic cancer worldwide.

The spread of cancer from its original location to distant organs, called metastases, is one of the most complex and deadly features of cancer. Understanding the molecular mechanisms underlying metastasis is critical to developing targeted therapies for the prevention or treatment of metastatic diseases. The process of metastasis involves a series of complex steps, including the migration and invasion of cancer cells, complex molecular signaling pathways, and epithelial migration to mesenchymal (EMT). These mechanisms are necessary to increase the ability of cancer cells to spread and produce new tumors in distant organs.

Migration and invasion of cancer cells

The migration and invasion of cancer cells is an important process in a malignant tumor. These processes allow cancer cells to leave the primary tumor, invade surrounding tissues, enter the bloodstream or lymphatic system, and establish new growths in distant organs. The ability to invade and migrate cancer cells is often the result of changes in the structure and function of the extracellular matrix (ECM) and cytoskeleton.

One of the key factors involved in the migration of cancer cells is the activation of matrix mineral proteins (MMPs), enzymes that break down ECM components, allowing cancer cells to migrate through tissues. MMPs facilitate basement membrane dysfunction, which is an important barrier separating the tumor from the surrounding tissue. This process is tightly regulated, and an imbalance in MMP activity, due to over-expression or lack of inhibition, can contribute to the invasive ability of cancer cells.

In addition, cancer cells show changes in adhesion molecules, such as integrin and cadherin, which are involved in cell-cell-cell and cell-ECM interactions. Changes in these adhesion molecules allow cancer cells to separate from the primary tumor and gain mobility. For example, loss of E-cadherin, a key molecule responsible for maintaining cellular cell dysfunction, is often seen in cancer cells and is associated with increased migration and invasion.

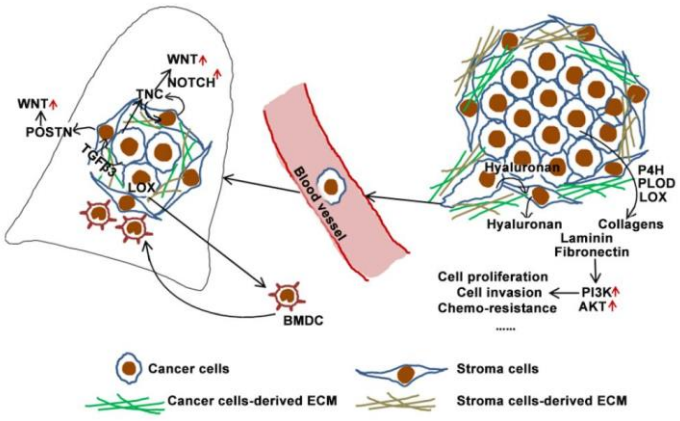

Figure 1 the process of cancer cell migration and invasion through the extracellular matrix

Molecular Signaling Pathways

A variety of molecular signaling pathways drive metastatic cancer cell migration, invasion, and survival. These signaling pathways include growth factors, cytokines, and external signals that regulate processes such as cell survival, growth, and movement. Some of the most studied pathways in metastasis include:

- **PI3K/AKT pathway**: This pathway plays an important role in promoting cell survival, growth and migration. It is often active in cancer cells, especially those that metastasize. Activation of PI3K/AKT signaling promotes the survival of cancer cells by inhibiting apoptosis (apoptosis) and promoting cell movement, which is important for invasion.
- **RAS/RAF/MEK/ERK pathway**: Another important signaling pathway involved in cancer metastasis is the RAS/RAF/MEK/ERK pathway. This pathway is involved in the regulation of cell growth, differentiation, and migration. Changes in the head or other components of this pathway are commonly found in cancer, and these changes often lead to an increase in the ability of cancer cells to invade and migrate.
- **TGF-β pathway**: Beta growth factor conversion (TGF-β) is a multifunctional cytokine involved in various cellular processes, including immunosuppression and cell migration. In the early stages of cancer, TGF-β acts as a tumor inhibitor, but as the disease progresses, it promotes metastasis by stimulating the EMT process and aiding in immune evasion.
- **Wnt/β-catenin pathway**: This pathway is another important player in metastasis, in which β-catenin acts as a transcription agent involved in regulating cell chatter, cell migration and invasion. An imbalance of the regulation of this pathway has been linked to the development of metastasis in different types of cancer.

These pathways not only facilitate the ability of cancer cells to invade and migrate, but also enhance their survival in distant organs, which is an important aspect of metastasis. Understanding these molecular signals is essential for the development of therapies that aim to inhibit these processes and prevent metastatic spread.

Mesomal epithelial migration (EMT)

Mastural epithelial translocation (EMT) is a basic biological process by which epithelial cells acquire mesenchymal properties, such as increased motility and invasion, which are essential for metastasis. EMT is an important event in the early stages of metastasis, causing cancer cells to separate from the primary tumor and migrate to distant locations. During EMT, cancer cells undergo drastic changes in their morphology, behavior, and gene expression, facilitating their ability to invade surrounding tissues and enter the bloodstream.

EMT is characterized by the loss of epithelial markers such as E-cadherin and the acquisition of intermediate wift markers such as N-cadherin, wymantin, and fibronectin. This transition results in a decrease in cellular cell chatter, making the cells more energetic and aggressive. In addition to facilitating invasion, EMT also enhances stem-like properties in cancer cells, which are associated with treatment resistance and tumor recurrence.

The EMT process is regulated by a number of transcription factors, such as snails, slugs, toast, and ZEB1, which are activated by various signal pathways, including TGF-β, Wnt/β-catenin, and Notch signals. These transcription agents suppress the expression of epithelial markers while stimulating the expression of mesenchymal markers, thereby enhancing the EMT process.

EMT is not only an important mechanism of metastasis but also contributes to cancer progression and treatment resistance. Cancer cells undergoing environmental medication treatment are more likely to survive chemotherapy and immunotherapy, leading to poor outcomes for patients. Understanding EMT regulation and identifying ways to inhibit this process is critical to developing effective treatments against metastatic cancer.

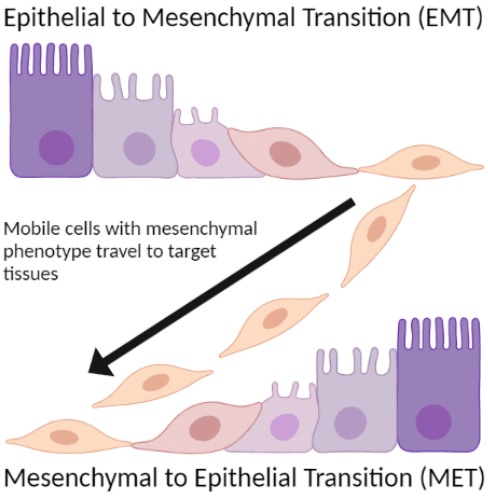

Figure 2 Epithelial-mesenchymal transition (EMT) process [10]

Role of the Tumor Microenvironment in Metastasis

The tumor microenvironment (TME) plays an important role in advancing metastasis, spreading cancer cells from the primary tumor to distant organs. It consists of a complex network of components, including immune cells, blood vessels, fibroblasts, extracellular matrix (ECM) and signaling molecules, which interact with cancer cells to promote tumor growth, invasion, and secondary tumor formation. These reactions within the TME facilitate the early stages of metastasis and affect the survival of metastatic cancer cells in distant locations.

Immune cells within the TME can either promote or inhibit cancer growth depending on the type of immune cells and its interaction with the tumor. In the early stages of tumor development, immune cells such as T lymphocytes, natural killer (NK) cells, and dendritic cells are recruited to target and eliminate cancer cells. However, as the tumor grows, it often manipulates the immune system to promote its survival and support malignant tumors. Tumors recruit tumor-associated macrophages (TAMs) that secrete cytokines, growth factors, and proteases, helping to attack tumors, suppress immunity, and promote metastatic spread. These TAMs support angiogenesis (formation of new blood vessels), which provide the tumor with oxygen and nutrients as well as extracellular matrix degeneration (ECM), allowing cancer cells to migrate to surrounding tissues and enter the blood vessels, which is an important step in metastasis. The presence of regulatory T cells (Tregs), which suppress the immune response, contributes to immune evasion by reducing the activity of cytotoxic T lymphocytes and natural killer cells. The balance between pro-tumor immune cells, such as TAM and Tregs, and antitumor immune cells, such as CTLs, determines the metastatic potential of the tumor. Tumors that may weaken this balance in favor of immune systems are more likely to spread to other organs.

Angiogenesis is an important process for tumor and malignant growth because tumors require a constant supply of oxygen and nutrients to maintain rapid cell division. As tumors grow, they often exceed the blood supply, resulting in a low-oxygen (low-oxygen) environment. Hypoxia, in turn, activates the secretion of pro-vascular factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hypoxia trigger factor (HIF). These factors stimulate the growth of new blood vessels, allowing the tumor to obtain oxygen and nutrients to continue to expand. However, the blood vessels formed in tumors are often poorly organized and leaky, leading to increased interstitial pressure and ineffective nutrient exchange. Despite these abnormalities, abnormal blood vessels provide a way for cancer cells to enter the bloodstream or lymphatic system, promoting the spread of cancer to distant organs. In addition, hypoxia plays a role in immune evasion, as cancer cells in low-oxygen conditions often express high levels of immune checkpoint proteins, such as PD-L1, which suppress the function of immune cells such as cytotoxic T cells, helping the tumor evade immune recognition and enhance its metastatic potential.

The extracellular matrix (ECM) is an important component of TME that affects metastasis by providing structural support to tissues. In the context of cancer, the ECM is often reconstituted in a way that supports tumor migration and invasion. Cancer cells secrete matrix mineral proteins (MMPs), which are enzymes that break down various components of the ECM, including collagen and laminin. ECM degradation facilitates the migration of cancer cells by impairing the structural integrity of surrounding tissues. In addition, ECM remodeling alters the mechanical properties of the tumor's microenvironment, making it easier for cancer cells to invade and penetrate blood vessels, which is an essential step for metastasis. Other enzymes, such as plasminogen stimulation and cathepsin, also contribute to ECM reconstitution by breaking down ECM components, which promotes the migration of cancer cells. Interactions between cancer cells and ECM also include cancer-associated fibroblasts (CAFs), which secrete additional ECM proteins and growth factors that support tumor growth and metastasis.

Together, ECM remodeling and the changing interactions between cancer cells and their environment play a key role in promoting the invasion of cancer cells to distant organs.
The microenvironment of the tumor is a dynamic and multifaceted system that significantly affects the process of metastasis. Immune cell infiltration, angiogenesis and hypoxia, and ECM remodeling contribute to the metastatic cascade by promoting the survival, migration, and invasion of cancer cells. By altering these processes, TME not only facilitates the spread of cancer, but also helps the metastatic cells survive in distant organs. Targeting TME components represents a promising strategy for developing new therapies for the prevention or treatment of metastatic cancer that allow tumors to grow, invade, and spread to other parts of the body.
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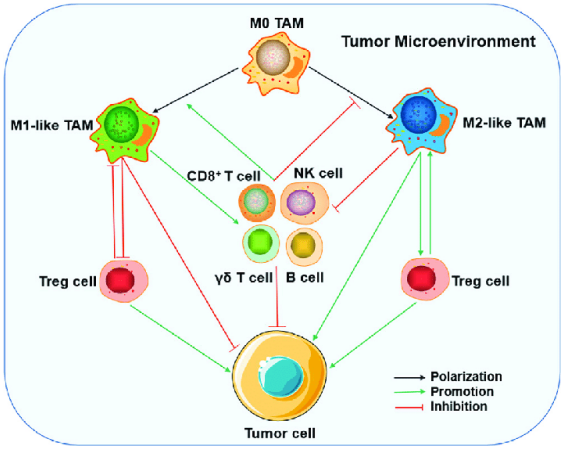

Figure 3 Immune cell infiltration in the tumor microenvironment, including immune suppressive cells like TAMs and Tregs from [11]

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Table 2 List of key angiogenic factors involved in metastasis and their roles in promoting tumor growth and invasion.

Angiogenic Factor	Role in Tumor Growth	Role in Metastasis
VEGF (Vascular Endothelial Growth Factor)	Stimulates the formation of new blood vessels (angiogenesis).	Facilitates cancer cell invasion by enhancing vascular permeability and promoting tumor spread to distant organs.
FGF (Fibroblast Growth Factor)	Promotes the development of blood vessels and supports tumor cell survival.	Stimulates ECM degradation and facilitates cancer cell migration, contributing to metastasis.
HIF (Hypoxia-Inducible Factor)	Regulates cellular response to low oxygen conditions, enhancing angiogenesis.	Promotes tumor adaptation to hypoxic conditions, driving metastasis by upregulating angiogenesis and invasion mechanisms.
Angiopoietins (Ang-1, Ang-2)	Regulate blood vessel maturation and integrity, enhancing tumor vascularization.	Ang-2 promotes vessel destabilization and increased vascular leakage, which facilitates tumor cell dissemination [20][21].
TGF-β (Transforming Growth Factor Beta)	Regulates cellular growth and differentiation, promotes ECM remodeling.	Induces epithelial-mesenchymal transition (EMT) and promotes immune evasion, aiding metastasis.
IL-8 (Interleukin 8)	Enhances endothelial cell proliferation and angiogenesis.	Induces endothelial cell migration, which promotes tumor cell adhesion and invasion into surrounding tissues.

The extracellular matrix (ECM) is an important component of TME that affects metastasis by providing structural support to tissues. In the context of cancer, the ECM is often reconstituted in a way that supports tumor migration and invasion. Cancer cells secrete matrix mineral proteins (MMPs), which are enzymes that break down various components of the ECM, including collagen and laminin. ECM degradation facilitates the migration of cancer cells by impairing the structural integrity of surrounding tissues. In addition, ECM remodeling alters the mechanical properties of the tumor's microenvironment, making it easier for cancer cells to invade and penetrate blood vessels, which is an essential step for metastasis. Other enzymes, such as plasminogen stimulation and cathepsin, also contribute to ECM reconstitution by breaking down ECM components, which promotes the migration of cancer cells. Interactions between cancer cells and ECM also include cancer-associated fibroblasts (CAFs), which secrete additional ECM proteins and growth factors that support tumor growth and metastasis. Together, ECM remodeling and the changing interactions between cancer cells and their environment play a key role in promoting the invasion of cancer cells to distant organs.

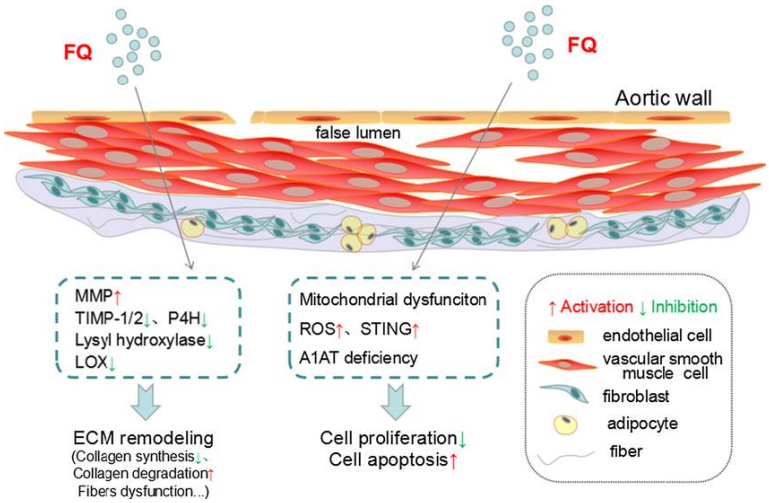

Figure 4 ECM remodeling, including the degradation of ECM components by MMPs and the involvement of TIMPs in regulating this process from [12].

The microenvironment of the tumor is a dynamic and multifaceted system that significantly affects the process of metastasis. Immune cell infiltration, angiogenesis and hypoxia, and ECM remodeling contribute to the metastatic cascade by promoting the survival, migration, and invasion of cancer cells. By altering these processes, TME not only facilitates the spread of cancer, but also helps the metastatic cells survive in distant organs. Targeting TME

components represents a promising strategy for developing new therapies for the prevention or treatment of metastatic cancer that allow tumors to grow, invade, and spread to other parts of the body.

Advances in the treatment of metastatic cancer

Advances in the treatment of metastatic cancer have significantly improved prognosis for patients, providing more effective options than conventional chemotherapy. Immunotherapy has emerged as a transformative approach in the treatment of metastatic cancer, harnessing the power of the body's immune system to recognize and attack cancer cells. One of the most promising advances in immunotherapy is the use of immune checkpoint inhibitors, such as PD-1/PD-L1 inhibitors and CTLA-4 inhibitors, which inhibit immune checkpoint proteins that cancer cells use to evade immune recognition. These inhibitors have shown remarkable success in treating cancers such as skin cancer, non-small cell lung cancer (NSCLC) and kidney cancer. By exposing the tumor to the immune system, these treatments can lead to long-term remission and, in some cases, a complete response. However, not all patients respond to immunotherapy, and resistance may develop, making it important to identify biomarkers that predict which patients will benefit the most from these treatments.

With immunotherapy, targeted therapies have revolutionized the treatment of metastatic cancer by focusing on specific genetic mutations or molecular changes that drive cancer development. Targeted therapies, such as EGFR inhibitors for non-small cell lung cancer and HER2 inhibitors for breast cancer, work by blocking the signals that tumors use to grow and spread. These treatments may be more effective and less toxic than conventional chemotherapy, as they specifically target molecular drivers of cancer. However, resistance to targeted therapies can also occur, often by acquiring additional mutations in the tumor, which makes it necessary to combine these therapies with other treatment strategies to overcome resistance.

Chemotherapy, despite its limitations, is an important treatment for many metastatic cancers. It works by killing fast-dividing cancer cells, but it also affects normal cells, causing significant side effects such as fatigue, nausea, and immune suppression. However, combining other treatments with chemotherapy, such as immunotherapy or targeted therapy, improved outcomes for many patients. For example, the combination of chemotherapy and PD-1 inhibitors in NSCLC metastatic showed a better survival rate than chemotherapy alone. Synergy between chemotherapy and immunotherapy or targeted therapy is one of the most interesting advances in the treatment of metastatic cancer, as it can increase the effectiveness of each treatment while reducing the likelihood of resistance.

Advances in early identification of metastases

Advances in early diagnosis of metastasis have significantly improved the ability to diagnose and treat cancer in the early stages, providing a better chance of successful intervention and improving patient outcomes. The most interesting development in early diagnosis is the use of liquid biopsy, which involves analyzing blood samples to detect gene mutations associated with cancer, metastatic cancer cells (CTCs) and tumor-derived DNA or RNA. Liquid biopsy offers many advantages over conventional tissue biopsies, including being able to detect cancer at least invasive, rapid and early stages or relapse before clinical symptoms appear. By identifying genetic mutations or the presence of cancer cells, liquid biopsy can provide important information about the type of metastasis and the most effective treatment options. Furthermore, the ability to track tumor growth through liquid biopsy over time allows real-time monitoring of early detection of treatment effectiveness and resistance, helping to develop treatments for individual patients.

In addition to liquid biopsy, advances in biomarker discovery have also contributed to the early detection of metastases. Biomarkers are molecules or genes that indicate the presence of cancer or the possibility of malignant tumors. The identification of cancer-associated specific biomarkers, such as rolling tumor DNA (ctDNA), rolling tumor RNA (ctRNA) and other tumor-related markers, allow for more accurate prediction of metastatic potential. These biomarkers can be detected using modern molecular techniques and used in conjunction with imaging methods to monitor the spread of cancer in real time. Combining biomarkers, liquid biopsies and imaging can allow doctors to detect metastases at an earlier stage than ever before, improving the chances of effective treatment.

Imaging techniques, such as computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), are also necessary for early identification of metastases. CT scans provide detailed images of the body's internal structures, allowing doctors to determine the location and size of the tumor and determine any possible spread to lymph nodes or other organs. MRI is particularly useful for detecting metastases in soft tissues and organs such as the brain and liver, as it can provide high-resolution images of tumors and surrounding tissues. Positron emission tomography scans, often combined with computerized tomography (PET-CT), provide functional imaging that can characterize areas of high metabolic activity, indicating the presence of cancer cells. Positron emission tomography scans are particularly effective in identifying metastases in areas that may not be visible on CT or MRI alone. Combining these imaging techniques allows doctors to detect malignant tumors in early stages, allowing for more targeted and timely treatment.

Early intervention strategies are key to improving prognosis for patients with metastatic cancer. One of the most promising methods is the use of new adjuvant therapies, which are treatments given prior to initial treatment (such

as surgery) to shrink or control malignant tumors. New adjuvant treatments may include chemotherapy, immunotherapy, targeted therapy, or radiation therapy. By using these early treatments, doctors can reduce tumor burden and make surgery or other interventions more effective. In addition, personalized medicine — personalizing treatment based on the genetic and molecular characteristics of cancer — allows for earlier and more effective interventions. Targeted therapies combined with modern diagnostic methods enable doctors to treat certain changes that play a role in metastasis, improving treatment outcomes.

Targeting special tissues

Due to their protein-deficient flexibility, scalability, lack of immune response, and choice of conductivity, peptide-based systems are an attractive strategy for developing gene therapies. Technologies and process peptide-based delivery systems, which can properly distribute CRISPR components into different types of cells for therapeutic and research reasons, are the main focus of our study, which looks at the latest efforts toward modern non-viral delivery systems. There is currently no cure for neurodegenerative diseases, but there is currently no cure for neurodegenerative diseases. Some promising methods have been identified. Another notable method that restores motor performance in mice is the use of CAS13 to convert abundant astrocytes in the brain into missing dopamine neurons in Parkinson's disease. Since it uses a cell transformation method rather than correcting the disease-causing mutation, this last example illustrates the wide range of CRISPR treatment applications. In fact, several treatment options for CRISPR have already been developed that can prevent or reverse the course of the disease through biomedical research. However, it is important to establish appropriate delivery methods to translate these treatments. In a variety of clinical contexts, such as cancer, genetic diseases, and infectious diseases, nucleic acids that facilitate gene silencing, expression, and modification hold promise for much use as genetic therapies. Both viral and non-viral delivery methods are used to help nucleic acids target cells due to their undesirable pharmacological properties. For the safe and effective management of genetic drugs, lipid nanoparticles (LNPs) are the most advanced non-viral delivery system. In fact, the FDA in 2018 [17] approved Onpetro, the first small drug for RNA interference, and the mRNA vaccines currently available to protect against the SARS-CoV-2 virus, which led to the COVID-19 pandemic. These technologies have been made possible by LNPs. Despite these advances, the therapeutic use range of (IV) LNPs delivered to the arteries is significantly limited because they are usually accumulated in the liver and absorbed by hepatocytes. [13][14][22]

Immunotherapy for Cancer

Active immunotherapy uses the immune system to target cancer cells. Examples include CAR-T cells, targeted antibody therapies, and therapeutic cancer vaccines — also known as therapeutic vaccines. These vaccines are aimed at strengthening the body's immune system and fighting cancer. On the other hand, passive immunotherapy enhances the immune system's ability to fight rather than directly targeting cancer cells. Cytokines and checkpoint inhibitors are two examples. By identifying specific markers. Active cell treatments called antigens try to eliminate cancer cells. Medical experts are developing new immunotherapy drugs to treat other cancers. The immune system is an effective protective mechanism, but it can sometimes be overly effective. In order to prevent overreactions to invaders and damage to healthy cells, there are checkpoints in the body. For example, white blood cells known as T lymphocytes, or T cells, are produced by bone marrow. T lymphocytes fight cancer cells and protect the body from diseases. T cell surface proteins bind to immune checkpoints. T lymphocytes receive signals from checkpoint proteins and other proteins that control the timing of activation and inactivation. (Consider traffic monitors that control traffic flow by activating and disabling stop signals.) To destroy cancer cells, T-lymphocytes are stimulated. In order to protect healthy cells from damage, they are inactive. Protein cells cannot tell T cells to deactivate them if the link is broken. In this way, T cells continue to kill cancer cells. [14][23]

Resistance to treatment

Effective cancer treatment prevents the development of drug resistance. Most cancer patients acquire resistance during chemotherapy, radiation, molecular targeted therapy and immunotherapy, hampering their long-term survival. Drug resistance and treatment failure can be easier for a variety of reasons. Drug resistance may be due to pre-existing genetic changes in tumors or genetic changes acquired during treatment, but malignant tumors can also evade drug response through non-genetic processes. and epigenesis. Tumor heterogeneity within or among individuals, which support variable or limited treatment response, and the effects of the tumor microenvironment, which can alter drug exposure and response, are additional factors that cause treatment resistance. It is very important to understand that drug sensitivity and resistance in cancer, as well as different resistance mechanisms, can coexist in the same tumor or in separate metastatic cancers in the same patient. A complex clinical syndrome, drug resistance in breast cancer arises from various molecular changes. Although receptor-targeting drugs have shown great hope in the fight against hormone-positive breast cancer in recent years, several studies have shown that selective pressure for treatment can affect tumor growth. To further complicate matters, resistance due to targeted therapies may be a factor, and vice versa, because chemotherapy is often used clinically in conjunction with targeted therapy for subtypes ER+ or HER-2+. 121–123 [24][25]. Each resistance mechanism requires a

unique set of treatment plans and medications tailored to specific clinical conditions. Initial clinical investigations specifically call for vehicles targeting each route. For example, verapamil inhibits the drug flow pump, while rapamycin targets resistance to hormone therapy. One of the main challenges of effective cancer treatment is acquired resistance to treatment. In the early stages of tumor growth, when genetic changes lead to abnormalities in conventional caspase-dependent apoptosis, a partial resistance pathway provides a growth advantage by protecting normally transformed cells from various stimuli that cause apoptosis, including the host immune system and the mutated cells themselves. During development and eventually, through treatments that trigger apoptosis, cells affected by apoptosis disorders are selected. When cancer cells with effective effusion escape treatment, multidrug resistance is produced, a different type of resistance. [15]

Liver metastasis

This makes metastasis more noticeable. Once removed, they appear as black holes in strong perenicyma. Although imaging is part of the standard screening system for monitoring cancer patients, computerized tomography (CT) scans are commonly used with PVP. Since computed tomography is easily accessible, it can reach a large number of patients who need this surgery. However, these large sets of surveillance are beyond the capacity of CEUS facilities. In this group, CT and MRI can lead to unclear results. One of the primary tasks of CEUS is to effectively address these outcomes. While each process has a different mechanism, they all have an effect on each other. Clinical symptoms and imaging tests are the main methods used to diagnose liver metastasis in breast cancer. Surgical removal is the primary treatment for these metastases, and may also include chemotherapy and interventional therapy. While more research is needed to validate this, immunotherapy is now being developed to treat liver metastasis in breast cancer. Two strategies are needed to prevent liver metastasis in triple-negative breast cancer: first, the cancer's primary lesion should be suppressed through surgery, chemotherapy and radiation therapy. Second, immunotherapy and radiofrequency ablation can also inhibit and slow liver metastasis in triple-negative breast cancer. Future TNBC treatment will be facilitated by the creation of new targeted drugs and a better understanding of the tumor microenvironment. Many primary tumors have the potential to spread to the liver, such as melanoma, colorectal, breast, kidney, and pancreatic cancer. Appropriate treatment for such individuals depends on the accurate identification of liver metastases. While patients with liver metastasis may require systemic chemotherapy or rhesectomy, people without liver and metastasis may benefit from definitive surgical treatment. Therefore, it is important to accurately diagnose liver metastasis in people with primary malignant tumors. The liver is a common site for metastasis from malignant solids. This diagnosis is usually made when imaging shows multiple liver lesions in a normal liver. In only 20% of cases, liver metastases appear as a single lesion and usually affect both lobes of the liver. 77 The most common causes of liver metastasis include pancreatic and gastrointestinal (often stomach and colon) cancer. [16][17][26]

Survival of cancer

The survival rate for cancer is usually five years. Usually, the survival rate is given as a percentage. For example, the total survival rate for five-year bladder cancer is that 77% of bladder cancer patients live up to five years after their diagnosis. On the other hand, after being diagnosed with bladder cancer, 23 out of every 100 people die within five years. It has been used in research. Data collected from hundreds or thousands of patients with a particular type of cancer are used to calculate cancer survival rates. Regardless of age or health status, people with a particular form of cancer are included in the overall survival rate. It includes both those who are diagnosed early and very late. Depending on the stage of cancer, a healthcare professional may be able to provide more accurate information. For example, 61% of early-stage lung cancer patients live for at least five years after their diagnosis. Whether cancer survivors continue treatment after five years is not reflected in the overall survival rate. They don't even say if they have recovered from the disease. Additional survival rates providing more detailed data include categories: this is the percentage of patients who do not develop cancer after treatment. This is the percentage of patients whose cancer does not worsen after treatment. People who were treated after treatment are included in this. It also covers people who still have cancer but treatment disrupts their growth. Five-year survival rates are often used to calculate cancer survival rates [27]. That doesn't stop cancer from returning after five years. After identification and treatment, some tumors may recur years later. If you don't do this within five years of the original diagnosis, some malignant tumors are much less likely to recur. Discuss with your doctor the possibility of a cancer relapse. The potential for cancer treatment is known as diagnosis. Other variables, such as age and overall health, may also influence this diagnosis. Cancer survival figures can be disappointing. People with some type of cancer may have a survival rate based on thousands of cases. Under these circumstances most people can get a basic idea of cancer survival rates. However, they are unable to predict specific chances of healing or remission. As a result, some individuals ignore cancer survival data. Other medical issues are not taken into account in the survival data. There are other limitations in survival rates. For example, they can't do the following: Talk about the latest treatments. The latest cancer data includes those who received their diagnosis five years ago. At least five years will pass before any new treatment is developed which will affect the survival rate. Suggest which treatment to choose. Survival rates do not provide information about the conditions. On the other hand,

some patients want to know more about cancer. When evaluating options and starting treatment, having more knowledge about cancer can help you feel less anxious. [17][28] [29]

Conclusion

Advances in understanding the molecular mechanisms that drive metastasis, such as immune cell infiltration, angiogenesis, ECM remodeling, and EMT, have dramatically improved our ability to target metastatic cancer as a treatment. Immunotherapy and targeted therapy have revolutionized the treatment of various metastatic cancers, providing hope for long-term remission and improved survival outcomes. In addition, innovations in early diagnosis, such as liquid biopsy and advanced imaging techniques, have made it possible to identify metastases in the early stages, allowing for more effective treatment strategies. However, despite these great measures, challenges such as treatment resistance and complexity of the tumor microenvironment persist. Future research to overcome these barriers, including developing personalized treatments and exploring more TMEs, will be critical to improving the prognosis of metastatic cancer patients and ultimately reducing cancer-related deaths.

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