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TUMOR MICROENVIRONMENT DYNAMICS: MOLECULAR AND GENETIC DETERMINANTS OF CANCER PROGRESSION AND THERAPY RESPONSE

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ABSTRACT

Malignant cells, stromal cells, immunological populations, extracellular matrix elements, and other signalling chemicals make up the tumour microenvironment (TME), a dynamic and intricate ecology that controls cancer initiation, development, metastasis, and treatment response. There is growing evidence that the reciprocal interactions between tumour cells and the tumour microenvironment are critical in defining the course of the illness and the effectiveness of therapy. This review aims to recapitulate the molecular, genetic, epigenetic, and immunological determinants governing tumor microenvironment dynamics, emphasising their contributions to therapeutic resistance, the development of microenvironment-targeted therapy approaches, and the progression of cancer. A literature review was conducted using peer-reviewed articles published in high-impact scientific journals. Relevant studies addressing the molecular architecture of the tumor microenvironment, signaling pathways, immune regulation, tumor heterogeneity, therapeutic resistance, and an integrative picture of current knowledge was produced by critically analysing and synthesising developing technology. and future research directions. The evidence demonstrates that growth factor signalling, inflammatory pathways, hypoxia, metabolic reprogramming, genetic and epigenetic alterations, and extracellular vesicle-mediated communication alter the tumour microenvironment, encouraging tumour growth, metastasis, immune escape, and resistance to immunotherapy, chemotherapy, radiation, and targeted treatment. By enhancing biomarker identification and customised therapy decision-making, emerging technologies including as single-cell multi-omics, spatial transcriptomics, artificial intelligence, organoid models, and liquid biopsy are boosting precision oncology. Targeting the tumor microenvironment alongside malignant cells offers significant opportunities to overcome therapeutic resistance and improve clinical outcomes. Integrating multi-omics technologies with precision medicine methods are anticipated to aid in the creation of individualised, long-lasting, and more potent cancer treatments.

KEYWORDS: Tumor microenvironment, Cancer progression, Therapeutic resistance, Precision oncology, Immunotherapy.

1. INTRODUCTION

The fight against cancer has made significant strides in early detection, molecular characterization, targeted treatments and immunotherapies, nevertheless, cancer remains a leading cause of disease and mortality worldwide. However, the treatment resistance, recurrence and metastasis remain as barriers to long term clinical success. These challenges have shown that the biological environment of the malignant cells surrounding them also performs a important role in the cancer progression. As a result, the focus has turned to the tumor microenvironment (TME), which is a critical component in controlling the behaviour of the tumour and therapeutic response (Desai et al., 2025). Until now, cancer was believed to be caused mainly by progressive genetic changes. But, today, evidence shows that tumors are dynamic, complex, and an interface of malignant cells with surrounding immune and stromal cells occurs daily. The TME is composed of cancer-associated fibroblasts, immune cells, endothelial cells, pericytes, mesenchymal stromal cells, extracellular matrix (ECM), cytokines, chemokines, growth factors, and a number of other signalling chemicals. These do not just provide structural support but actively modulate the initiation and progression of cancers, tumor angiogenesis, invasion, metastasis and sensitivity to therapy via extensive molecular communication (Goenka et al., 2023).

The TME and tumour cells interact in a very intricate and reciprocal way. Numerous cancer cells are continually changing their environment by secreting signaling molecules, remodeling ECM, inducing angiogenesis and changing the function of components of immune system. In turn, the stromal and immune cells generate biochemical and mechanical signals which stimulate tumor proliferation, metabolic adaptation, and survival. Such interactions are bidirectional and occur during the course of disease in the presence of disease stressors like hypoxia, nutrient deprivation, immune surveillance and/or treatment. This adaptive communication facilitates tumors' remarkable ability to survive in harsh environments and gradually gain more aggressive traits (Yuan et al., 2024).

Among the several TME components, immune cells are now understood to be crucial in controlling cancer development and treatment. The tumor immune microenvironment consists of the following cells: Depending on their functional status, cytotoxic T lymphocytes, natural killer cells, dendritic cells, macrophages, neutrophils, regulatory T cells, and myeloid-derived suppressor cells can all have both pro-tumor and anti-tumor effects. A large number of tumours create an immunosuppressive environment which hampers the effective surveillance of the tumour by the immune system and contributes to chronic inflammation, tissue remodelling and immune escape. Immune regulation in the TME is a critical area of current oncology research and forms an important basis for the understanding of the success of immunotherapies, particularly immune checkpoint inhibitors (ICI) (Binnewies et al., 2018).

Cancer is also characterized by lots of molecular and genetic diversity. The continuous genetic instability gives rise to several tumour subclones having distinct biological traits and capacities to interact with nearby stromal and immune cells. The various cell populations compete, cooperate and adapt to environmental and therapeutic pressures. To this end, cancer is now considered as an ecological and evolutionary process in which both the tumor and the local microenvironment continuously adapt to each other. This view gives a fuller picture of the considerable differences in disease course and responses to treatment that can be seen between patients with the same type of tumours (Zahir et al., 2020).

Tumor heterogeneity and the TME are now understood to be a vicious cycle with a significant role in therapeutic resistance. Intra-tumoral genetic diversity creates immune, stromal, metabolic and cytokine signaling niches which can support the survival of resistant tumor cell populations after treatment. At the same time, selective pressures in the TME drive resistant clones to grow after chemotherapy, targeted therapy or immunotherapy. The interconnected processes clearly show that the treatment of cancer cannot only "isolate" the cancerous cells and instead needs to address them in combination with the microenvironment in which they exist (Zhang et al., 2022).

In addition to encouraging the initial tumor's development, the TME also plays a part in its invasion and metastatic dissemination. Tumour cell movement and metastasis colonisation are facilitated by these processes, which include angiogenesis, pre-metastatic niche creation, epithelial-to-mesenchymal transition, ECM remodelling, and activation of cancer-associated fibroblasts. These orchestrated events demonstrate that metastasis is a dynamic process that is not merely a function of tumour cells, but is also dependent on tumour microenvironmental interactions. Knowledge of these mechanisms has thus given rise to new therapeutic opportunities targeting the disruption of tumour–stromal communication (Neophytou et al., 2021).

At the molecular level, the TME is an extremely complicated system, with recent advances in genomics, transcriptomics, spatial biology, and single-cell technologies enhancing our understanding of this complexity. The technologies have shown that the progression of cancer is controlled by the convergence of genetic, epigenetic, metabolic and immune mechanisms within the tumor ecosystem. The therapeutic approaches that are being increasingly implemented in precision oncology will thus target more than just cancer cells, targeting also key components of the tumor microenvironment such as stromal signaling, angiogenesis, immune regulation, and ECM remodeling, will yield better efficacy and counter resistance (Wang et al., 2023).

Given the progress made, this review aims to give a broad picture of the molecular and genetic regulation of TME and how this affects the progression of cancer and treatment response. It highlights the changing describes new treatments that target both the cancer cells and the TME, as well as the dynamics of interactions between the tumour cells and their microenvironment. It also highlights some of the primary processes of tumour growth and therapy resistance. In order to better grasp the potential roles of comprehending the dynamics of TME in the creation of more efficient and individualised cancer therapies, this review attempts to compile the available data.

2. Molecular Architecture of the TME

The TME is a very dynamic environment where various stromal, vascular, immune and extracellular cell types live together with malignant cells. They do not work in isolation, but rather act together and in constant bidirectional communication, with direct cell–cell contacts and soluble factors, that control tumor growth, immune modulation, angiogenesis, invasion, metastasis and therapeutic response. Figure 1 gives an overview of the molecular architecture of the TME, including the major cellular components and the impact of dynamic crosstalk on cancer progression.

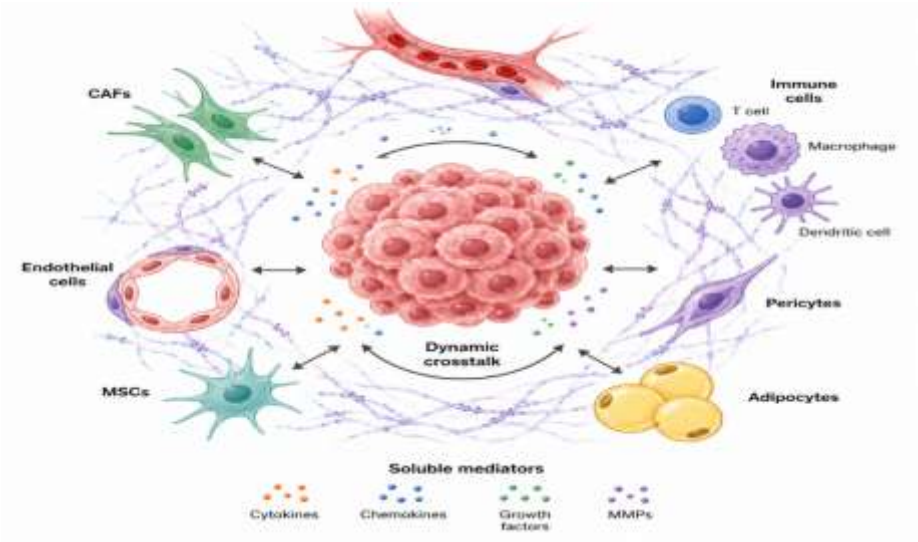

Figure 1. Molecular architecture of the TME

The TME is an integrated system made up of both non-cellular and cellular elements that all contribute to the behaviour of the tumour (as shown in Figure 1). These elements can be highly heterogeneous between tumor types and change with disease progression, continually adapting to genetic changes and environmental signals. The roles of these components and their coordinated interactions must be understood at the individual level, and to decipher the molecular processes that underlie the development of cancer, as well as to create treatment plans that specifically target cancerous cells and the milieu that surrounds them.

2.1 Cellular Composition of the TME

Tumors are composed of cancer cells, which are the engines that drive the growth of the tumor and constantly communicate with other cells in the vicinity by direct contact and paracrine signaling. Through ECM remodelling, cytokine and growth factor secretion, invasion, and angiogenesis, cancer-associated fibroblasts (CAFs) contribute to the formation of tumours. Endothelial cells and pericytes combine to produce the aberrant tumour vasculature, which supplies the tumour with nutrition and oxygen while also creating pathways for metastatic spread. Bioactive molecules are also secreted by adipocytes and MSCs, which promote tumor metabolism, inflammation and tissue remodeling. These cellular populations are extremely diverse, and their composition can be affected by genetic changes inside the tumor cells as well as by interaction between the stromal and the immune compartments, which leads to continuous changes in the TME (Arneth, 2019, Asadi et al., 2024). Furthermore, this cellular organization leads to differential expression of immune checkpoint molecules, such as PD-L1, potentially affecting tumor adaptation and therapeutic responses, from primary to metastatic stages (Shklovskaya & Rizos, 2020).

2.2 Non-Cellular Components

Additionally, a highly dynamic non-cellular network that regulates cell communication and shape makes up the TME. In addition to giving cells mechanical support, the ECM (ECM) controls cell adhesion, migration, proliferation, and differentiation. Cytokines and chemokines create signaling networks which control the recruitment of immune cells, inflammatory responses and communication between tumor and stromal cells. Growth factors including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and fibroblast growth factor (FGF) induce angiogenesis, cell survival, cell proliferation, and tissue remodelling. The ECM is continually remodeled by matrix remodeling enzymes (MREs), particularly matrix metalloproteinases (MMPs), which can promote tumor invasion and metastatic spread, and also can release signaling molecules that are bound in the ECM. These acellular components are also dynamic, allowing tumor cells to change their phenotype in the presence of environmental stress and adapt to therapy, thus contributing to the phenomenon of phenotypic plasticity (Ahmed & Haass, 2018). Moreover, constant fluctuations in cytokine, chemokine and growth factor signaling can impact the activity of immune checkpoints and therapeutic sensitivity, highlighting the biochemical context of the TME as an important factor affecting therapy outcomes (Lin et al., 2019).

3. Molecular Determinants Driving TME Dynamics

Multiple interconnected molecular pathways control the dynamic behavior of the TME that control the pro-angiogenic, pro-inflammatory, metabolic adaptation and intercellular communication processes. These signaling pathways all affect tumor progression, immune regulation, metastasis dissemination and therapeutic responsiveness. The key molecular factors that affect the dynamics of TME, some of the mediators they represent, the major biological functions they play and the clinical relevance are summarized in Table 1.

Table 1. Major molecular determinants regulating TME dynamics and their functional significance

Molecular determinant	Representative mediators	Key role in the TME	Clinical significance	Reference
Growth factor	VEGF, PDGF, TGF-β,	Angiogenesis, stromal	Promotes progression	Franco et al.

signaling	EGF, FGF	activation, EMT, proliferation	and therapy resistance	(2020)
Inflammatory signaling	IL-6, IL-1β, TNF-α, NF-κB, JAK/STAT	Inflammation, immune modulation, cell survival	Drives immune evasion and treatment resistance	Tahmasebi Birgani & Carloni (2017)
Hypoxia & metabolic reprogramming	HIF-1α, lactate, acidosis	Metabolic adaptation, angiogenesis, immune suppression	Enhances metastasis and therapy resistance	Vuong et al. (2019)
Extracellular vesicle communication	Exosomes, miRNAs, proteins, lipids	Intercellular signaling, stromal remodeling, immune regulation	Facilitates metastasis and serves as biomarker source	Mittal et al. (2018); Hirata & Sahai (2017)

Table 1 summarizes that the molecular architecture of the TME is regulated by interconnected signaling pathways and not by single mechanisms. These determinants work together to control the growth of tumors, immune system reorganisation and the development of new blood vessels, metabolic remodeling, and communication between cells. Each molecular determinant is described in detail below focusing on its mechanism of action and how it contributes to the regulation of TME and the therapeutic response.

3.1 Growth Factor Signaling Networks

Growth factor-mediated signalling facilitates information exchange between tumour cells and their surroundings. Angiogenesis is stimulated by vascular endothelial growth factor (VEGF), a substance that causes endothelial cells to proliferate and causes the vessels to become more permeable, allowing oxygen and nutrients to reach growing tumors. Platelet-derived growth factor (PDGF) is involved in recruiting fibroblasts and pericytes in stromal remodeling and vascular stabilization. Tumour suppression during early carcinogenesis, stimulation of the epithelial-mesenchymal transition (EMT), immunological suppression, and metastatic spread in late illness are all context-dependent functions of transforming growth factor-β (TGF-β). Fibroblast growth factor (FGF) induces angiogenesis, tissue healing, and cell proliferation, whereas epidermal growth factor (EGF) activates receptor tyrosine kinase signalling to enhance tumour cell migration, proliferation, and survival. In concert, these interrelated signalling pathways create a molecular network that constantly reshapes the TME, and plays a role in targeted therapy resistance, making them valuable targets for precision oncology (Franco et al., 2020).

3.2 Inflammatory Signalling

Chronic inflammation has long been recognised as a characteristic of the TME and a crucial component of tumour maintenance. Pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumour necrosis factor-α (TNF-α), regulate immune cell recruitment while simultaneously promoting tumour cell proliferation, angiogenesis, and metastatic potential. These cytokines initiate intracellular signalling pathways, including Janus kinase/signal transducer and activator of transcription (JAK/STAT) and nuclear factor-κB (NF-κB), which control the transcription of genes involved in cell survival, chronic inflammation, immune evasion and resistance to apoptosis. Active of these pathways create a self-sustaining inflammatory state which facilitates interactions between the malignant cells and stromal elements. Furthermore, inflammatory signalling plays a role in therapeutic resistance through increasing the adaptability of tumors and decreasing efficient anti-tumor immune reactions, suggesting inflammatory and immunomodulatory combinations that target these pathways as a potential therapeutic strategy. (Tahmasebi Birgani & Carloni, 2017).

3.3 Hypoxia and Metabolic Reprogramming

Tumors often grow too quickly to keep up with blood supply, producing hypoxic areas that have a significant impact on TME. Hypoxia-Inducible factors (HIFs) are genes regulated by oxygen deprivation which regulate genes related to angiogenesis, cell survival, glucose metabolism, and metastatic spread. The tumor cells develop a glycolytic phenotype, producing excess lactate and thus lowering the pH of the extracellular environment. This acidic microenvironment inhibits immune cell function, promotes degradation of ECM and tumors invade through it. At the same time, however, both malignant and stromal cells scavenge for glucose, amino acids, lipids, and oxygen, further altering nutrient availability and consequently immune function and cell metabolism. These metabolic adaptations not only ensure the survival of the tumor under adverse conditions but also decrease its therapeutic sensitivity, through the induction of cellular plasticity and survival. Therefore, there is a need to target hypoxia-associated pathways and metabolic vulnerabilities to enhance the effectiveness of treatment and avoid treatment resistance (Vuong et al., 2019).

3.4 Extracellular Vesicles and Exosome-Mediated Communication

Extracellular vesicles (EVs) and exosomes in particular have become important mediators of intercellular communication in the TME. The membrane-bound vesicles carry proteins, lipids, messenger RNAs, microRNAs, and other bioactive molecules within them between the tumor cells and neighbouring stromal, endothelial and immune cells. This molecular payload allows exosomes to effect recipient cells' behaviour, induce the creation of new blood vessels (angiogenesis), change immune responses, stimulate initiation of fibroblasts, and promote remodelling of the ECM. They also help form pre-metastatic niches and vital role in the adaptation of tumours to therapeutic stress by shuttling molecules associated with resistance between tumor cells. Given the dynamic nature of the fields of exosomes and their communication to continually influence the biology of the TME, they are important contributors to disease progression, metastatic dissemination, and treatment response. Recent studies have shown that EVs could also be used as minimally invasive

cancer diagnostic, prognostic, and therapeutic monitoring biomarkers and as targets for novel anti-cancer therapies (Hirata & Sahai, 2017; Mittal et al., 2018).

4. Genetic and Epigenetic Determinants of Tumor–Microenvironment Interactions

TME interactions are significantly influenced by genetic and epigenetic modifications, which in turn impact cellular signaling, ECM remodeling, immune regulation and response to treatment. These molecular modifications also continually remodel the biological environment of the TME, leading to the emergence of phenotypic plasticity, ITH, and resistance to treatment. Based on the above, the key genetic and epigenetic factors that regulate TME dynamics are summarized, and their role in the major cancer-related biological processes is highlighted in figure 2.

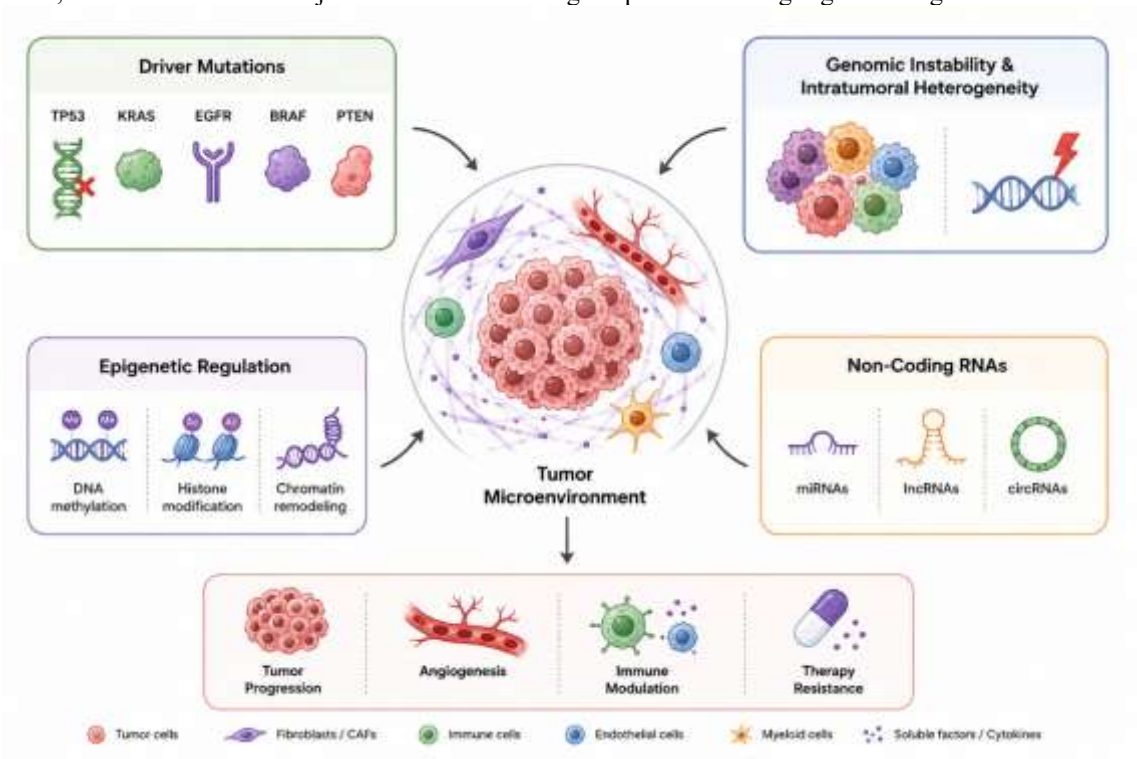

Figure 2. Genetic and epigenetic determinants shaping tumor–microenvironment interactions

The development of the TME is driven by coordinated epigenetic and genetic changes and not by individual molecular events as shown in Figure 2. These mechanisms are connected and affect the behavior of the cancerous cells, as well as stromal remodeling, immune response, and cell communication in the TME. The determinants are discussed separately, with a focus on how each contributes to the mechanism of tumor progression and how they are relevant to therapeutic intervention.

4.1 Driver Mutations Shaping the TME

In addition to driving malignant transformation, driver mutations also vital role in actively modifying the TME through changes in cell signaling and stromal interactions. The mutations in TP53 block genomic surveillance and generate inflammatory cytokines and immune escape. In addition to increasing the release of pro-inflammatory mediators that attract stromal and immune cells, aberrant KRAS signalling also causes metabolic alterations. Activated EGFR stimulates the growth of the tumor, its vascularization and the expression of immunological checkpoints, whereas oncogenic BRAF mutations modify the immune landscape via controlling T cell invasion and cytokine generation. By triggering the PI3K/AKT pathway and altering the tumor/stromal cell interaction, loss of PTEN also plays a crucial part in subsequent immune system suppression. Together, these genetic changes create a niche of cells that favors the progression of a tumor, its spread to other organs and tissues as metastases and resistance to treatment, and illustrate how oncogenic mutations can alter both the intrinsic biology of the tumor and the local cellular environment (Wu & Dai, 2017).

4.2 Genomic Instability and Intratumoral Heterogeneity

Intratumoral heterogeneity is a hallmark of cancer, and genomic instability a crucial role in its development. The accumulation of genetic changes creates multiple subpopulations of tumour cells that have different phenotypes and functions. These heterogenous clones can generate different types of microenvironments with various fibroblasts, endothelial cells, immune cells, and extracellular matrix elements, resulting in a microenvironment that varies both in space and time within the same tumour. This diversity fosters the evolution of resistance to the therapeutic agent and allows resistant strains to flourish and spread after exposure to the therapy. The use of single-cell multi-omics has shed light on the evolutionary processes of cancer, highlighting that both genetic changes and non-genetic cellular plasticity play a role in cancer evolution, highlighting the dynamic communication between TME and cancer cells. To enhance precision oncology and therapeutic resistance, it is crucial to understand this complexity (Nam et al., 2021).

4.3 Epigenetic Regulation

The control of gene expression is regulated by epigenetic mechanisms, which do not change the underlying sequence of DNA and are crucial in determining TME dynamics. Epigenetic modifications have the potential to regulate both immune recognition and inflammatory signaling as well as to inhibit tumor suppressor genes. Similarly, chromatin remodeling complexes alter programs of transcription that allow tumor cells to respond to environmental stress and therapeutic intervention. These epigenetic changes are reversible and affect both the malignant cells and the stromal and immune cells, which in turn affect the interactions of the TME. Epigenetic changes are reversible and have become increasingly attractive therapeutic targets to increase the sensitivity of treatment and to improve the delivery of drugs to cancer by altering the biological properties of the TME (Stapleton et al., 2017).

4.4 RNAs' Non-Coding

The role of non-coding RNA as important regulators of intercellular communication in the TME has become clear. Long non-coding RNAs (lncRNAs) regulate chromatin, transcriptional activity and signal transduction pathways that regulate stromal activation and immune regulation. Circular RNAs (circRNAs) are closed-loop RNAs that are not degraded by enzymes and act as molecular sponges for miRNAs, which regulate gene expressions associated with tumor growth and metastasis. These non-coding RNAs are involved in cellular plasticity, metastatic dissemination and therapeutic resistance by interacting with stromal and immune cells. Their differential expression in the different subpopulations of tumors also suggests that they serve as good markers of molecular heterogeneity of the TME and offer potential therapeutic opportunities in precision cancer therapy (Ge et al., 2022).

5. Mechanisms of Immune Escape and Landscape

Innate and adaptive immunity work together to create the TME's immunological environment, immune checkpoint pathways and immune suppressing cytokine networks. Immune surveillance helps to control the growth of tumors but persistent remodeling of immune components allows for malignant cells to outsmart the host's immunity and become resistant to treatment. The main immune components that regulate tumor immune escape, their biological roles and what they contribute to tumor immune escape are summarized in Table 2.

Table 2. Major immune components and mechanisms contributing to immune escape within the TME

Immune component	Major mediators/cells	Primary function in the TME	Contribution to immune escape	Reference
Innate immunity	TAMs, neutrophils, dendritic cells, NK cells	Antigen recognition, inflammation, stromal remodeling	Suppresses cytotoxic immunity and promotes tumor progression	Sherman & Beatty (2023)
Adaptive immunity	$CD8^+$ T cells, $CD4^+$ T cells, Tregs, B cells	Antigen-specific immune responses	T-cell exhaustion and immune tolerance	Bhat et al. (2024)
Checkpoints of Immune	CTLA-4, LAG-3, PD-1/PD-L1, TIGIT, TIM-3,	Regulate immune homeostasis and activation of T cells	Reduce immunotherapy efficacy and inhibit anti-tumor responses	Li et al. (2021)
Immunosuppressive cytokines	TGF-β, IL-10, VEGF, CSFs	Immune regulation, angiogenesis, stromal activation	Promote immune suppression, metastasis	Kundu et al. (2024)

Immune escape is not the failure of one cell type in the immune system, it is the coordinated failure of multiple immune and stromal mechanisms (Table 2). Innate and adaptive immunity, immune checkpoint signaling and immunosuppressive cytokine networks act in concert to create a tumor immune microenvironment that fosters tumor progression and restricts the effectiveness of therapeutics. These immune determinants will be covered in further detail below, highlighting their mechanistic functions in driving the TME and implications for immunotherapies.

5.1 Innate Immune Components

The innate immune compartment is the first level of resistance to tumor development and also plays a part in sculpting TME remodeling. Tumor-associated macrophages (TAMs) secrete cytokines and growth factors which promote angiogenesis, ECM remodeling, and immune suppression, especially those with M2-like phenotype. Neutrophils exhibit functional plasticity, having an anti-tumor or pro-tumor activity depending on the microenvironmental signals. Although dendritic cells are essential antigen-presenting cells that trigger an adaptive immune response, the tumour microenvironment frequently compromises their function, which leads to inadequate T cell activation. Natural killer (NK) cells are cytotoxic cells that kill transformed cells without the need for antigen presentation, but whose cytotoxic activity is often suppressed by inhibitory signals in the TME. These innate immune populations are coordinately dysregulated, allowing for immune escape, thereby creating a conducive environment for tumor progression, and they are appealing therapeutic targets for restoration of anti-tumor immunity (Sherman and Beatty, 2023).

5.2 Adaptive Immunity

Antigen-specific surveillance of malignant cells is accomplished by adaptive immunity, and is often impaired during the progression of tumors. CD8+ cytotoxic T cells kill the tumor cells via the direct killing of the cells through the activity of perforin and granzymes, whereas CD4+ helper T cells modulate cytokine secretion and increase the cytotoxic activity of CD8+ cells. On the other hand, regulatory T cells (Tregs) are types of cells which suppress the function of effector T cells and generate immune tolerance within the TME. B cells are responsible for adaptive immune response through the production of antibodies, antigen presentation, and cytokine secretion, and certain subtypes of B cells also possess

inhibitory functions within anti-tumor immunity. The ratio of effector: suppressor lymphocytes determine the efficacy of immune surveillance and could be a determining factor in the response to immunotherapeutic agents (Bhat et al., 2024).

5.3 Checkpoints of Immune System

These checkpoint pathways are important in maintaining immune homeostasis and cancer cells often exploit these paths to evade immune destruction. Programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) is responsible for the Inhibition of Cytotoxic T-Cells after the binding of the PD-1 ligand, and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) suppresses early T-cell activation during antigen presentation. Post-translational changes that impact receptor stability and signalling efficacy, including as phosphorylation, glycosylation, ubiquitination, and acetylation, closely regulate their expression and function. In spite of the successful therapeutic blockade of these checkpoints that has significantly revolutionised the treatment of cancer, adaptive resistance mechanisms within the TME are still one of the biggest clinical challenges (Li et al., 2021).

5.4 Immunosuppressive Cytokine Networks

Abnormalities in the immunosuppressive cytokine network create a biochemical environment which allows the tumor to escape from effective anti-tumor immunity and to progress. Other inhibitory receptors, such as lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T-cell immunoreceptor with Ig and ITIM domains (TIGIT), also have an impact on T-cell exhaustion and reduced immune surveillance. Receptor expression and function are tightly controlled by post-translational modifications such phosphorylation, glycosylation, ubiquitination, and acetylation that affect receptor stability and signalling efficiency. These molecules also promote the remodeling of the ECM, the development of angiogenesis and activation of the stromal compartment, consolidating the immune exclusion and therapeutic resistance. Cytokine signaling and matrix remodeling mechanisms and inflammatory pathways create an immunologically tolerant microenvironment that supports metastatic dissemination. Therefore, the use of cytokine-targeted therapies alongside immune checkpoint inhibitors has become a promising approach to boost the anti-tumor immune response and increase therapeutic efficacy in various types of cancer (Kundu et al., 2024; Pearce et al., 2018).

6. TME in Cancer Progression and Metastasis

The TME actively promotes cancer progression, orchestrating angiogenesis, EMT, ECM remodeling, maintenance of cancer stem cells and pre-metastatic niche formation. All these processes work together to facilitate invasion of the tumor, its spread, and colonization of distant organs. A summary of the main microenvironmental mechanisms that favour metastatic progression is shown in Figure 3.

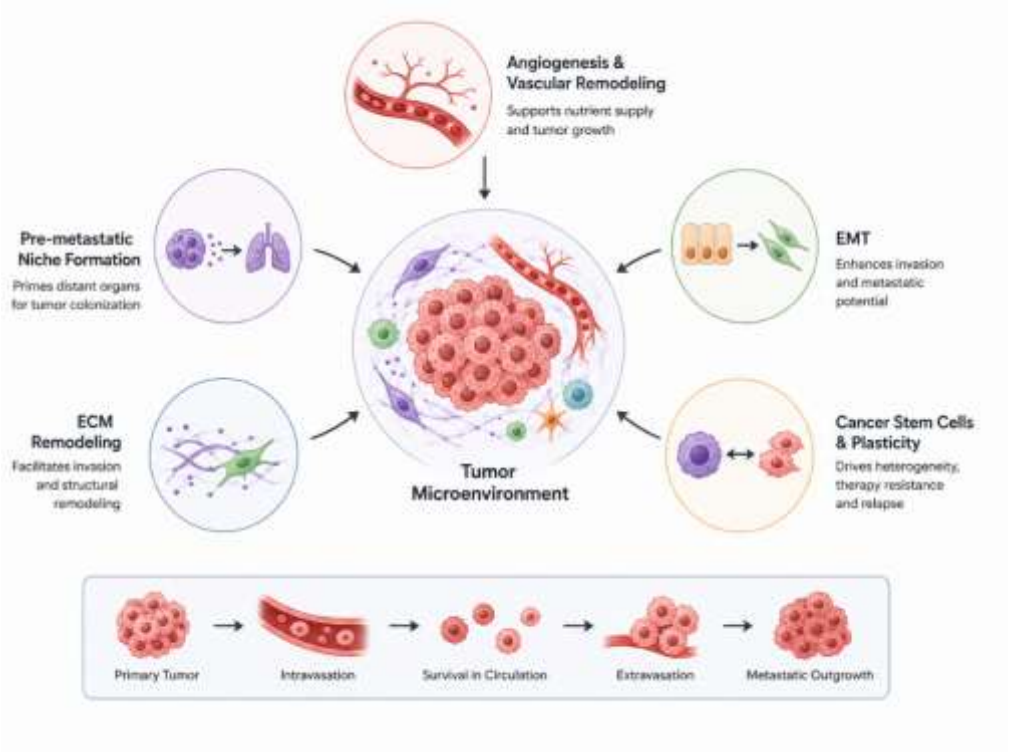

Figure 3. TME–mediated mechanisms driving cancer progression and metastasis

Metastatic evolution is not solely driven by changes in tumor intrinsic properties, but occurs as a result of a coordinated interaction between cancerous cells and the surrounding microenvironment, as it is depicted in Figure 3. The interplay of vascular remodeling, cellular plasticity, ECM reorganization, and preparation of distant niches creates conditions conducive to tumor dissemination and metastatic colonization. Each of these processes and mechanistic contribution to cancer progression is discussed in more detail below.

6.1 Angiogenesis and Vascular Remodeling

Angiogenesis is an essential process, which allows tumor masses to grow beyond the capacity of oxygen and nutrient supply via diffusion. The development of abnormal blood vessels is encouraged by a complicated network of signals between the tumour, stromal, and invading immune cells. Tumor associated vessels are structurally disorganized, leaky and inefficient, leading to hypoxia and unevenly distributed blood flow. These vascular alterations facilitate dissemination of tumour cells and hinder the delivery of therapeutic agents. Remodelling of the vascular network also occurs continuously, allowing interactions between endothelial cells, immune cells and fibroblasts which support the progression towards metastasis. This means that angiogenesis is not only a way to get nutrients into the tumour but it is also a dynamic part of the TME that influences invasion, immune evasion, and treatment response in all stages of cancer (De Visser and Joyce, 2023).

6.2 Epithelial–Mesenchymal Transition (EMT)

Epithelial tumour cells can acquire mesenchymal characteristics through a biological process called epithelial-mesenchymal transition (EMT), which encourages migration and invasion. The transition is controlled by several signaling pathways, such as Wnt, TGF-β and inflammatory mediators, as well as by transcription factors like SNAIL, TWIST and ZEB family proteins. Tumour cells are able to exit the main tumour due to increased cytoskeletal reorganisation and reduced cell-cell adhesion and invade nearby tissues, a mechanism known as EMT. In TMEs, EMT is further stimulated by stromal cells and signals from immune cells, which promote metastatic dissemination and resistance to conventional therapies. The EMT process is reversible, and cells that have undergone EMT can at the distant metastatic site assume epithelioid features as well, emphasizing the importance of tumor plasticity and progression (Patel et al., 2019; Vishnoi et al., 2020).

6.3 Cancer Stem Cells and Tumor Plasticity

A particular kind of tumour cell known as cancer stem cells (CSCs) is capable of multilineage differentiation, self-renewal, and long-term tumour maintenance. Specialized microenvironmental niches that provide molecular signals favouring stemness and cellular plasticity play a significant role in their survival. CSCs can withstand therapeutic stress and retain their tumor-initiating ability via interactions with ECM elements, immune cells, and stromal cells. This plasticity allows for dynamic phenotypic switching between differentiated and stem-like states and is responsible for intratumoral heterogeneity, recurrence and resistance to treatment. Furthermore, the immune dysfunction that occurs with cancer progression plays a role in the persistence of CSCs by also compromising immune surveillance, allowing metastatic colonization and providing a measure of resistance to anti-cancer therapies (Zhang et al., 2022).

6.4 ECM Remodeling

The ECM provides extracellular support and plays an active role in biochemical and biomechanical signalling of tumor progression. Fibroblasts, macrophages and tumour cells constantly deposit, degrade and reorganise matrix proteins during cancer development. These changes change tissue rigidity, activate integrin-mediated signalling and establish migration avenues leading to tumor invasion. The remodeling of the matrix also can affect the amount of cytokines and growth factors that are available in the ECM, which can affect angiogenesis, immune cell recruitment and metastatic dissemination. The renovated ECM can now adopt a more active role in regulating cellular communication and tumor evolution processes, serving not just as a physical scaffold, but as a crucial therapeutic target to block tumor progression (Wang et al., 2021).

6.5 Pre-Metastatic Niche Formation

The process of metastasis starts before circulating tumor cells have reached the distant organs by creating pre-metastatic niches. The main tumour secretes cytokines, growth factors, extracellular vesicles, and other soluble mediators that draw bone marrow cells, modify local ECM, and inhibit immune surveillance at metastatic sites. These alterations create permissive micro environments that allow for the survival of tumor cells, their colonization, and outgrowth after dissemination. Pre-metastatic niches are organ-, and cancer-specific, reflecting context-specific interactions between the tumour-derived factors and resident stromal and immune cells within the organ. These organ-specific remodellings are associated with the metastatic efficiency and with systemic therapy resistance. Therefore, knowledge of the molecular mechanisms involved in pre-metastatic niche formation is crucial to design strategies to prevent metastatic disease and improve patients' long-term prognosis (Falcomata et al., 2023).

7. TME and Therapeutic Response

Aside from molecular changes in cells within the tumor, the therapeutic sensitivity of cancer can be influenced by dynamic interactions in and between the TME. The efficacy of treatment, as well as resistance, are all influenced by stromal cells, immune components, ECM remodeling, metabolic adaptation, and intercellular signaling. Table 3 details the key mechanisms involved in TME that influence the response to current anti-cancer therapeutics and identifies representative biomarkers that could be used in clinical practice.

Table 3. TME-mediated mechanisms influencing therapeutic response and resistance

Therapeutic modality	Major TME determinants	Impact on therapy	Representative biomarkers/targets	Reference
Chemotherapy	CAFs, ECM, stromal cytokines	Reduced drug penetration and enhanced survival	Stromal activation, ECM remodeling	Tilsed et al. (2022)
Radiotherapy	Hypoxia, inflammatory signaling, abnormal	Decreased radiosensitivity and	HIF signaling, hypoxic markers	Tao et al. (2021)

	vasculature	enhanced DNA repair		
Targeted therapy	Stromal signaling, EMT, metabolic adaptation	Activation of compensatory pathways and acquired resistance	EMT-associated pathways, stromal mediators	Li et al. (2022)
Immunotherapy	Immunosuppressive cells, metabolic competition, inhibitory cytokines	T-cell dysfunction and immune escape	Immune metabolic signatures	Wegiel et al. (2018)
Predictive biomarkers	circRNAs and TME-derived molecular signatures	Patient stratification and therapy prediction	circRNAs, immune and stromal biomarkers	Zhang et al. (2020)

The therapeutic efficacy is heavily dependent on several mechanisms associated with TME and which are active in different therapeutic approaches as summarized in Table 3. All of these pathways work together to modulate drug delivery, immune activation, metabolic adaptation and cellular survival, affecting the way drugs are responded to and can lead to treatment resistance. The remainder of these sections will explore the impact of the TME on individual therapeutic strategies and explore new biomarkers that could enable precision oncology.

7.1 Influence on Chemotherapy Resistance

The TME has a significant part in the effectiveness of chemotherapy, both physically and biochemically protecting the malignant cells. The combination of fibroblasts associated cancer, tumor infiltrating leukocytes, ECM proteins, and abnormal blood vessels all impair drug delivery and activate survival pathways to prevent chemotherapy-induced cell death. The tumor cells also survive cytotoxic stress through the activation of DNA repair pathways by stromal-derived cytokines and growth factors, which are known to promote cellular plasticity. Furthermore, the metabolic environment of the TME affects the availability of drugs and sensitivity of cells, helping in the development of acquired resistance after multiple drug treatments. Such dynamic tumor–stromal interactions highlight the role of stromal context on the therapeutic responses to chemotherapy and the importance of developing therapeutic approaches that will also target the stromal compartment (Tilsed et al., 2022).

7.2 Radiotherapy Resistance

The biological features of the TME significantly affect the therapeutic effect of radiotherapy. Reduced oxygen levels continue to be one of the main reasons for radio resistance as it minimizes radiation-induced DNA damage. Additionally, stromal cells, the remodeling of the ECM, and inflammatory signaling stimulate pathways that allow the survival of tumor cells after irradiation. Radiation can also impact the microenvironment itself by affecting infiltration of immune cells, vascular integrity, and cytokine production, which can impact subsequent therapeutic responses. These adaptive changes help to cause tumor recurrence and reduce long-term treatment outcomes. As a result, a combination of radiotherapy and TME normalization/improving tissue oxygenation has become an attractive option to increase the radiosensitivity and minimize treatment failure (Tao et al., 2021).

7.3 Targeted Therapy Resistance

Targeted therapies selectively target one or more oncogenic signaling pathways, but often these therapies fail to achieve a durable response due to adaptive changes that occur in the TME. Tumor cells activate compensatory signaling pathways which enable them to evade therapeutic inhibition by stromal cells, immune populations and ECM components. Phenotypic plasticity, EMT and metabolic adaptation also provide the microenvironment with a continuous remodeling which enables the survival of resistant cells during therapy. Additionally, tumour-stromal interactions further promote the survival signals and promote disease progression even in the presence of molecularly targeted therapies. The observations suggest that combination therapy approaches are needed to overcome targeted therapy resistance, and that these need to target both oncogenic signaling and the supportive nature of the TME (Li et al., 2022).

7.4 Immunotherapy Response and Resistance

The effectiveness of immunotherapy is highly dependent upon the immune profile and metabolism of the TME. The combination of immunosuppressive cell populations, inhibitory cytokines, nutrient deprivation and hypoxia combine to create a multi-faceted effect of inhibiting the activation of the cytotoxic T cell and allowing immune escape to occur. Metabolic competition between cancerous cells and immune cells also impacts on the availability of glucose and amino acids, which is detrimental for anti-tumour immunity and limits immune checkpoint blockade efficacy. Tumors with 'metabolically hostile' microenvironments may also show low sensitivity to immune cell infiltrate, even with good infiltration. Therefore, therapeutic approaches to restore metabolic balance and reverse immune suppression are actively being investigated to enhance the efficiency and sustainability of cancer immunotherapy (Wegiel et al., 2018).

7.5 Emerging Biomarkers Predicting Therapy Response

Being able to identify reliable biomarkers is crucial for predicting therapeutic response and guiding precision oncology. In addition to traditional genomic markers, there is growing interest in microenvironment-associated markers which are associated with immune activity, stromal remodeling, metabolic adaptation, and intercellular communication. Of these, circular RNAs (circRNAs) have become a promising class of regulators of cell signaling and gene expression in the TME. They are extremely stable, and have tissue specific expression patterns making them an attractive choice for non-invasive diagnosis, prognosis and monitoring of treatment. The combination of circRNA signatures with molecular, immune and clinical data may help stratify patients and aid in personalised therapeutic choices. With the continued improvement of biomarkers discovery, multi-parameter approaches are likely to yield better prediction of treatment outcomes for a variety of malignancies. (Zhang et al., 2020)

8. Therapeutic Strategies Targeting the TME

There are several strategies currently under way that do not target a single pathway, but rather attempt to remodel the TME, restore anti-tumor immunity, normalize tumor architecture, and enhance the efficacy of therapy. The major therapeutic strategies targeted to the TME and their main mechanism of action and clinical relevance are summarized in Table 4.

Table 4. Major therapeutic strategies targeting the TME

Therapeutic strategy	Primary target	Major therapeutic effect	Reference
Immune checkpoint inhibitors	PD-1/PD-L1, CTLA-4 axis	Restores anti-tumor immunity and converts immune-cold tumors into immune-responsive tumors	Khosravi et al. (2024)
Anti-angiogenic & metabolic targeting	VEGF signaling, hypoxia, tumor metabolism	Normalizes tumor vasculature, improves oxygenation, and enhances therapeutic response	Okafor et al. (2024)
CAF- and ECM-targeted therapy	Cancer-associated fibroblasts and ECM	Reduces stromal support, ECM stiffness, and improves drug penetration	Alkasalias et al. (2018)
Cytokine/Chemokine & epigenetic modulation	Inflammatory mediators, DNA methylation, histone modification	Restores immune activity and enhances treatment sensitivity	Yang et al. (2023)
Combination therapeutic strategies	Immune, stromal, vascular, and metabolic pathways	Overcomes multi-mechanistic resistance and improves clinical outcomes	Khosravi et al. (2024)

Increasingly, therapeutic approaches that target multiple aspects of the TME are becoming integral to the effective management of cancer. These strategies can combine the effects of immune modulation, stromal remodeling, vascular normalization, metabolic interventions, and combination therapies to establish a cure and achieve long-term clinical benefits. Each TME-targeted therapeutic approach is described in greater detail below, with a focus on the translational relevance.

8.1 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs), which disrupt inhibitory receptors including PD-1, PD-L1, and CTLA-4 to restore anti-tumor immunity by T cells, have revolutionised cancer treatment. But there's a wide variation in therapeutic efficacy due to the fact that many tumors have an immunologically "cold" microenvironment with low immune infiltration and high immunosuppression. Therapeutic strategies recently developed are designed to make cold tumors immune-reactive through the use of methods that increase antigen presentation, recruit T cells, and decrease suppressive immune cells. Microenvironment (TME) directed immunotherapy has proven to be a critical approach in combination with ICIs to achieve higher immune activation and sustain clinical results (Khosravi et al., 2024).

8.2 Anti-Angiogenic Therapies

Anti-angiogenic strategies are used to block abnormal tumor blood vessels and thus the spread of metastasis. Blocking of vascular endothelial growth factor (VEGF) signaling slows neovascularization and normalizes vessels, increasing tissue oxygenation and drug delivery. In addition to blocking the formation of vessels, vascular normalization is also important for infiltration of immune cells and better effectiveness of chemotherapy and immunotherapy. However, therapeutic advantages are often restricted by adaptive angiogenic mechanisms and compensatory pathways that are stimulated by hypoxia.

8.3 CAF-Targeted Strategies

CAFs are therapeutic targets that has a chief role in ECM remodeling, immune suppression and therapeutic resistance. The strategies currently being used to combat CAFs are not to eradicate them, but to specifically inhibit their tumor-promoting activity while leaving their physiological functions in tissue homeostasis intact. Tumor stromal desmoplasia, drug penetration and re-establishment of anti-tumor immune responses have been targeted through strategies focusing on CAF-derived cytokines, signaling pathways and fibroblast activation proteins. This functional reprogramming of CAFs may thus be a more promising approach to stromal mediated therapeutic resistance than indiscriminate depletion (Alkasalias et al., 2018).

8.4 ECM Remodeling Approaches

The ECM represents a significant physical and biochemical barrier to infiltration by immune cells and to therapeutic delivery. The therapeutic strategies aimed at ECM remodeling aim to soften the matrix, normalize tissue architecture, and enhance vascular perfusion. Drug penetration may be facilitated and invasive behavior minimized due to inhibition of matrix metalloproteinases, collagen cross-linking enzymes and pathways associated with fibrosis. ECM-directed therapies also alter the biomechanical signaling within the TME, improving the efficacy of chemotherapy, immunotherapy and targeted therapies in combination therapeutic approaches.

8.5 Targeting Tumor Metabolism

The idea of metabolic targeting has emerged as a potential approach to break the supportive conditions that are set within the TME. Tumor cells compete for nutrients with immune cells and generate hypoxia and acidification that negatively affect immune function. Therapeutic modalities that act on glycolysis and lactate production, amino acid metabolism, mitochondria and oxidative stress aim to restore metabolic balance and boost anti-tumor immunity. Such strategies can

not only inhibit tumour growth, but also improve the sensitivity to traditional treatments by overcoming metabolic adaptations that promote drug resistance.

8.6 Cytokine and Chemokine Modulation

Tumor cells, stromal cells and immune populations communicate through cytokines and chemokines. Blocking these signaling pathways can inhibit chronic inflammation, decrease immune evasion and improve immune-mediated tumour clearance. Furthermore, epigenetic modification is a promising approach to modulate cytokine expression and immune-related signaling pathways in the TME. Targeting chromatin remodeling, histone modifications, and DNA methylation can restore anti-tumor immune responses and enhance sensitivity to targeted treatment and immunotherapy, offering new precision oncology opportunities (Yang et al., 2023).

8.7 Combination Therapeutic Strategies

Single agents rarely achieve long-term clinical benefit in the TME. The combination strategies include the treatment of immunotherapeutic agents, anti-angiogenic agents, metabolic inhibitors, stromal-targeted therapies and epigenetic modulators, which are being explored in order to address several mechanisms of resistance. Recent data also suggest modulation of the microbiome and management of microbial dysbiosis can enhance treatment efficacy by affecting immune responses and decreasing inflammation in the TME. Integrated approaches should improve therapeutic durability, reduce the risk of resistance and facilitate more personalized cancer therapy in the future (Okafor et al., 2024).

9. Emerging Technologies, Current Challenges, and Future Perspectives

Advancements in technology are rapidly revolutionizing TME research, with the ability to characterize the molecular, cellular and spatial complexity of the TME as well as answer key questions in precision oncology. Single-cell multi-omics combines genomic, transcriptomic, epigenomic, and proteomic data at the single-cell level, while spatial transcriptomics maintains tissue structure to identify the interactions between different types of cells within a specific tissue microenvironment. Liquid biopsy technologies, including circulating tumor DNA, tumor cells (CTCs), extracellular vesicles and exosomes, also provide minimally invasive means for tracking tumor evolution, treatment response, and therapeutic resistance and could help guide real-time clinical decisions (Li & Nabet, 2019).

Although all these advances have been made, there are still a few problems to clinical translation of research in TME. The presence of large tumor heterogeneity, the shift in tumor microenvironment over time, and the large inter-patient variability, makes it difficult to accurately identify markers and predict therapeutic response. Moreover, there is no consensus on the use of biomarkers and harmonized analytical methods that allow for the reproducible results between different studies and for clinical implementation. Integration of multi-omics technologies into AI-driven computational strategies to enhance patient stratification, uncover dynamic therapeutic targets, and refine personalized treatment strategies will drive future progress. Further, understanding of immune cell crosstalk, context-dependent microenvironmental interactions and extracellular vesicle-mediated communication will help facilitate development of novel combination therapies. A multidisciplinary approach to tackle these gaps is expected to drive forward precision oncology and improve personalized cancer care (Di Spirito et al., 2025; Bikfalvi et al., 2023).

10. CONCLUSION

The TME is now recognized as much more than the passive framework of the tumor; it is a key player in the initiation, progression, metastasis, and response to therapy of cancer. Tumor evolution and clinical outcome are the result of dynamic interactions between tumour cells, stromal cells and populations, immune cells and components, ECM and various molecular signaling networks. Breakthroughs in understanding the genetic, epigenetic, metabolic and immunological processes have shown that responses to cancer therapy must be targeted at both the tumor cells and the tumor microenvironment. Immuno-therapy, anti-angiogenic therapy, stromal modulation, metabolic intervention and the use of combination strategies have demonstrated great promise in the ability to bypass microenvironmental resistance and to enhance the efficacy of therapy. Furthermore, new technologies like single-cell multi-omics, spatial transcriptomics, artificial intelligence, organoid technologies, and liquid biopsy are offering new understandings of heterogeneity and complexity of the TME, which are enabling the discovery of new biomarkers and precision oncology. However, many challenges still exist, such as intratumoral heterogeneity, temporal evolution of the TME, inter-patient variability, and the need for the establishment of predictive biomarkers. A multi-omics framework and sophisticated computational methods should be combined to gain deeper insight into the dynamic tumor ecosystem and to facilitate personalized therapeutic interventions in the future. Developing effective, durable and individualized methods for the treatment of cancer will rely on a thorough understanding of cancer biology in TME that will lead to better patient survival and long-term clinical outcomes.

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