ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Targeting the tumor microenvironment and mitochondrial dynamics: A theranostic frontier in cancer

Umesh Kumar[1]*, Lakshita Tyagi[2], and Krishnendu Ghosh[3]*

[1]University Centre for Research and Development, Chandigarh University, Mohali, Punjab, India

[2]State Forensic Science Laboratory, Ghaziabad, Uttar Pradesh, India

[3]Department of Pathology, Carver College of Medicine, University of Iowa, Iowa City, Iowa, United States of America

Abstract

The tumor microenvironment (TME) is a dynamic and complex system comprising immune cells, stromal cells, blood vessels, and the extracellular matrix. The cellular and molecular elements can be different among cancer types, but they appear to be crucial for tumor initiation, survival, invasion, and metastasis. During early tumor development, cancer cells create a bidirectional relationship with TME components that allows them to evade immune detection, resist apoptotic processes, and promote angiogenesis and metastasis. Traditionally, cancer progression has been attributed simply to the sequential accumulation of genetic mutations. However, evidence is growing that epigenetic alterations, such as DNA methylation and hydroxymethylation, histone modifications, and microRNA dysregulation, are also important contributors to tumorigenesis. These epigenetic alterations also regulate critical signaling pathways related to apoptosis, autophagy, and cellular differentiation, which have implications for the emergence of aggressive cancer stem-like cells and further metastasis. The recognition of epigenetic regulatory mechanisms has also led to new therapeutic options. Epigenetic drugs, including DNA methyltransferase and histone deacetylase inhibitors, have been shown to reverse the expression of tumor suppressor genes, enhance the efficacy of conventional therapies, block the development of cancer progenitor cells, and reduce recurrence rates. Recognizing epigenetic dysregulation as a hallmark of cancer represents an opportunity to create new biomarkers and targeted treatments. Despite significant advances in surgery, chemotherapy, and radiotherapy, most standard treatments lack precision and typically have significant side effects. The movement toward immunotherapy, targeted therapy, and personalized medicine has allowed for more precise, less invasive, and more tolerable treatment regimens. At the same time, there has been an increasing recognition of the role of mitochondrial dynamics (such as fission, fusion, and mitophagy) as important regulators of tumor metabolism, drug resistance, and apoptosis. Although their clinical significance is still being fully explored, mitochondrial biomarkers and mitochondrial-targeted therapies present diagnostic and therapeutic value. Collectively, the degree to which the TME is responsive to different treatment modalities, the contribution of epigenetics, and the coordinated regulation of mitochondrial dynamics may contribute to a more informed theranostic application toward improving cancer diagnosis, treatment, and patient survival.

Keywords: Tumor microenvironment; Cancer; Mitochondrial dynamics; Theranostic

***Corresponding authors:**
Krishnendu Ghosh (krishnendu-ghosh@uiowa.edu); Umesh Kumar (umesh.e19291@cumail.in)

Citation: Kumar U, Tyagi L, Gjosh K. Targeting the tumor microenvironment and mitochondrial dynamics: A theranostic frontier in cancer. *Tumor Discov*. 2026;5(4):026010002. doi: 10.36922/TD026010002

Received: January 1, 2026

Revised: June 11, 2026

Accepted: June 22, 2026

Published online: July 10, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Cancer is one of humanity's most devastating diseases, and it remains a significant public health challenge, consistently ranking second as a leading cause of death in the world. Evidence of cancer in ancient hominin fossils dates back nearly 2 million years, demonstrating that malignant disease is deeply rooted in human evolutionary history. Osteosarcoma-like lesions have been identified in ancient human fossils in South Africa, demonstrating that this disease existed a long time ago.[1] Unregulated cell proliferation, along with new metastatic properties, characterizes cancer. Generally, the activation of oncogenes and/or the deactivation of tumor suppressor genes result in uncontrolled cell cycle progression and the deactivation of apoptotic mechanisms. Unlike benign tumors, malignant cancers metastasize due to the downregulation of tissue-specific adhesion receptors and the concurrent upregulation of receptors promoting cell motility. Membrane metalloproteases can also provide a mechanism for metastasizing cancer cells to invade other tissues. There are many mechanisms by which these genetic and cellular changes can occur, but generally, the canonical mechanisms are mutation, chromosomal translocation or deletion, and dysregulated expression or activity of signaling pathways. The mutations and resulting changes can activate genes that lead to unregulated cell cycling and/or deactivate apoptotic pathways. The literature discusses these processes comprehensively, with many excellent reviews available on each area of research.[2]

Tumor heterogeneity is the term given to possible variations that may be observed between tumors of the same type, i.e., differences between patients diagnosed with the same cancer and/or differences between a primary and secondary tumor. Tumor heterogeneity is a key contributor to treatment resistance and therapy failure in cancer.[3] Therapy-resistant subclones within a tumor may be capable of surviving therapy, whether chemotherapeutic or targeted in nature, and proliferate after the induced selection for a dominant clone.[4] These cells are further aided by the diverse populations of tumor microenvironment (TME) cells that limit their effective clearance, conferring drug tolerance and the ability to evade immune destruction.[5,6] Tumor heterogeneity, across (inter-tumor) and within (intra-tumor) a single tumor, is increasingly regarded as a major cause of therapeutic failure of cancer therapies. Tumor heterogeneity remodels the TME and is a driver of drug resistance.[7] Tumor heterogeneity can directly affect drug targets but can also remodel the TME to promote drug resistance and treatment failure, impacting all cancer types. This phenomenon explains how small therapy-resistant subclonal populations can survive treatment, expand after clearance of dominant clones, and eventually result in relapse, metastasis, or poor prognosis.[4]

Additionally, heterogeneity impacts the TME, not only the cancer cell compartment, resulting in changes in immune infiltration, stromal cell behavior, and vascular supply, all of which interfere with drug delivery and efficacy.[5] Therefore, failure to effectively treat cancer often stems from not just the development of heterogeneous tumor cell populations evolving under the stress of treatment, but also the supportive microenvironment. Overcoming resistance will likely require strategies that anticipate and target tumor heterogeneity, rather than, or at least in addition to, focusing only on the dominant tumor clone.[6] Tumor heterogeneity contributes to drug resistance, one of the most common causes of therapeutic failure across cancer types and treatment modalities, such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy.[7]

Changes in the biological and host environment, brought about by tumor progression factors, including clonal evolution and tumor heterogeneity, induce a series of alterations to transcriptome expression and cellular crosstalk. Tumor heterogeneity itself is important in drug resistance, which is ubiquitous across all cancer types and treatments. Here, we discuss salient mechanisms of tumor heterogeneity that promote drug resistance in the context of molecularly targeted therapy and immunotherapy in the TME reprogramming.[7]

Theranostics is derived from the combination of two words, therapy and diagnostics, and is one of the most promising areas in precision medicine. It is a medical discipline that combines diagnostic imaging and targeted therapy in the same molecular context and aims to identify, treat, and monitor disease with precision, or personalize medicine. The principal concept of theranostics is "see what you treat and treat what you see," whereby the same agent or target is utilized to identify the disease and to provide therapy.[8] In oncology, theranostics has changed our understanding of and approach to treating cancer. Historically, cancer treatments (e.g., chemotherapy and radiation) have been non-specific and impact healthy and cancer cells alike, which leads to adverse side effects and variability. With theranostics, physicians may visualize specific target molecules on tumor cells using diagnostic radiotracers and then provide therapeutic isotopes or agents directed specifically toward those target cells. Theranostics allows for targeted tumor localization, providing an individualized treatment plan and therapy assessment in real-time.[9]

A significant benefit of theranostics is its capacity to indicate those patients who are most likely to benefit from

specific therapy, thereby eliminating unnecessary treatment while maximizing possible benefits. For instance, using a diagnostic radiopharmaceutical to confirm the expression of the target receptor (e.g., somatostatin receptor) in neuroendocrine tumors, clinicians can determine whether the corresponding therapeutic radioligand is likely to be effective.[10] Personalized care through theranostics promotes the precision of care, potentially reducing toxicity and offering superior follow-up care. In addition, theranostics yields a bridge between molecular imaging and targeted therapy, giving us a means to collect real-time or near-real-time feedback concerning tumor biology, which can help clinicians modify dosages, select new targets of therapy, or modify the delivery of therapy as the disease process evolves.[11] Theranostics lends itself to the concept of adaptive cancer therapy, whereby continuous diagnostic assessments support the therapeutic decision, evolving cancer care into a more dynamic and patient-centered approach.

The concept of theranostics is not limited to oncology and is increasingly being applied to cardiovascular, neurodegenerative, and infectious diseases, where similar principles may be applicable for precision interventions. Nevertheless, in oncology, theranostics is already providing a revolutionary concept of care to move away from traditional "one-size-fits-all" healthcare systems toward a truly predictive and individualized system.[12] Overall, theranostics represents a paradigm shift in modern medicine, one that combines the diagnostic and treatment aspects of care for maximum precision, safety, and efficacy. Theranostics fuses molecular targeting with advanced diagnostic imaging and delivery of therapy, thus developing a platform for the next generation of personalized management of cancer that optimizes patient survival and quality of life around the world.[13]

To optimize the potential of theranostics, it is important to include investigations of how extracellular aspects, specifically the TME, and intracellular systems, with unique attention given to mitochondria and their dynamics, work together to change cancer biology, therapeutic response, and resistance. TME and mitochondria are two key components of cancer biology: one is exogenous/extracellular, and the other is endogenous/intracellular, although both have a significant impact on tumor formation, tumor development, and therapeutic responses. The TME comprised tumor cells, immune cells, endothelial cells, extracellular matrix (ECM) components, soluble growth factors, and mechanical and biochemical cues. This is not a static environment. Rather, it is a continuously changing environment that is engaging with cancer cells and co-evolving with them.[14] For instance, stromal fibroblasts are converted into cancer-associated fibroblasts (CAFs), which produce ECM proteins and remodel the matrix, changing tissue stiffness, creating biochemical gradients, and inhibiting drug delivery.[15] The ECM provides structural support and modulates cell adhesion, polarity, signaling, and migration.[15] Further, the hypoxia and acidic pH common in the TME drive metabolic reprogramming of the tumor cells and confer therapeutic resistance.[16] Therefore, the composition and state of the TME heavily regulate tumor cell proliferation, invasion, metastasis, and response to therapy.[17] These findings establish the TME as a key player rather than a bystander and shift the paradigm of therapy that targets the microenvironment (CAFs, immunosuppressive macrophages, ECM remodelers, etc.) as equally important as targeting tumor cells.[16]

Beyond acting as the "powerhouse" for cellular processes, mitochondria also perform different functions within each cancer cell. Mitochondrial functions include the generation of adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS), management of reactive oxygen species (ROS), signaling apoptosis (programmed cell death), generating biosynthetic precursors for cellular processes, and the integration of responses to cellular stress. Recent evidence emphasizes mitochondrial dynamics, or the cyclical processes of fusion and fission, and their deregulation in cancer.[18] For instance, there is a correlation between excessive mitochondrial fission mediated by dynamin-related protein 1 (DRP1) and increased metastatic potential and chemoresistance.[19] There is also a connection between an elongated, fused mitochondrial network and enhanced OXPHOS, reduced ROS levels, and improved survival of tumor-initiating cells.[20] These alterations in mitochondrial morphology and metabolism allow tumor cells to flexibly adapt to several stressors, including nutrient deprivation, hypoxia, and drugs or immune attack.[21] Therefore, mitochondria serve as intracellular hubs connecting the reprogramming of metabolism to energy generation to the survival of cancer cells.

It is important to understand the TME and mitochondrial function, as they are important points of therapeutic vulnerability. The TME may present a physical and biochemical barrier to drug delivery, an immunosuppressive niche for protecting tumor cells, and a mechanism for promoting metastatic spread.[16] Mitochondrial adaptations allow tumor cells to survive therapy, resist apoptosis, and modify metabolic pathways. However, there is increasing momentum for therapeutic strategies that either attempt to reprogram the TME or directly target mitochondrial vulnerabilities (e.g., fission inhibitors, modulators of mitochondrial metabolism, and

microenvironment-responsive drug delivery).[18,21] Thus, combining TME targeting and mitochondria-targeting could improve the precision and relevance of therapy for cancer.

By examining the TME, mitochondrial physiology, and combined theranostics, this review provides a holistic perspective on current cancer research and its potential to improve future patient outcomes.

2. Tumor microenvironment: Biology and therapeutic relevance

The TME represents a complex and dynamic ecosystem in which cancer cells are intimately engaged with surrounding non-cancerous cells, ECM, blood vessels, and immune components (Figure 1). Rather than being a passive background, the TME actively participates and aids tumor initiation, progression, metastasis, and resistance to therapy.[22] The TME's relevance stems both from its biological functions and the fact that it simultaneously offers multiple therapeutic targets for intervention.

The TME is a heterogeneous blend of cellular and non-cellular components. The cellular fraction includes a mixture of CAFs, endothelial cells (which give rise to the vasculature), immune cells (tumor-associated macrophages [TAMs], T cells, myeloid-derived suppressor cells [MDSCs]), and pericytes. The non-cellular fraction is primarily composed of the ECM (collagens, proteoglycans, glycoproteins), growth factors, cytokines, and metabolic by-products. All these components function in tandem through reciprocal communication with tumor cells. For example, CAFs secrete ECM proteins and enzymes that remodel the ECM to induce stiffness in the matrix, thus facilitating invasion while also limiting drug delivery.[22] On the other hand, immune cells within the TME are usually reactive against tumor cells themselves, but depending on local signals, may be reprogrammed by tumor cells to inactivate anti-tumor immunity.[23] In addition, hypoxic, acidic, and nutrient-poor niches develop as the TME progresses, which lead to genetic and epigenetic alterations advantageous to tumor survival and resistance.[22]

The significance of the TME in cancer progression is evidenced in several ways: it promotes angiogenesis (via vascular endothelial growth factor [VEGF] signaling), provides support for both invasion and metastasis (via matrix metalloproteinases [MMPs] and ECM remodeling), and helps in immune evasion (via checkpoint ligands, regulatory T-cell recruitment).[24,25] For example, stiffened ECM can hamper the penetration of chemotherapy, and hypoxia can induce hypoxia-inducible factor 1-alpha (HIF-1α) mediated survival pathways in tumor cells. This microenvironmental support also allows for dormancy of cancer cells and protects them from conventional therapies, leading to relapse.[25] Thus, the TME is not a passive scaffold but an active driver of malignancy. Table 1 depicts the specific components and their attributes in TME.

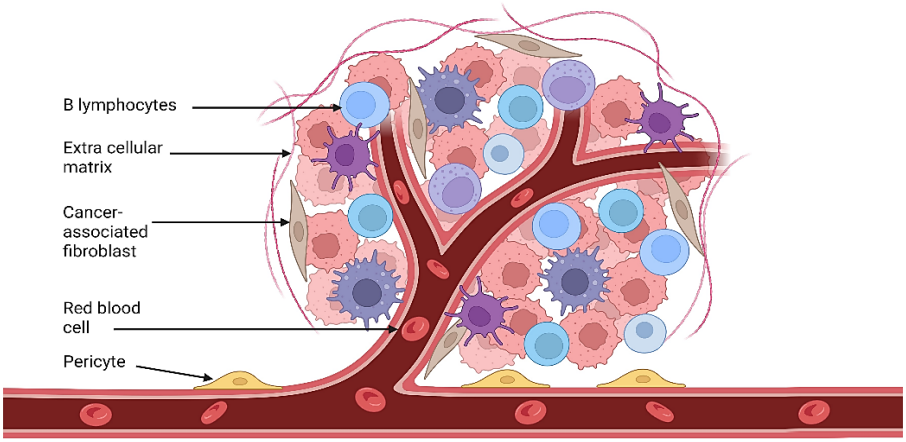

Figure 1. Components of tumor microenvironment (TME): TME is a diverse community of cellular and non-cellular elements that together drive tumor development. Important constituents include cancer-associated fibroblasts, immune cells (B-lymphocytes), endothelial cells, pericytes, red blood cells, and the extracellular matrix. The constituents are dynamic and intercommunicate to enhance angiogenesis, immune escape, and metastatic potential. The image depicts the structural and cellular organization surrounding tumor vasculature, specifically the cellular interactions and involvement from either stromal or immune populations that provide support and remodel the tumor. Created in BioRender. Ghosh, K. (2026). https://BioRender.com/8ebkqmr.

Table 1. Key components of the TME and their roles in cancer progression

Component	Origin/type	Major functions/mechanisms	Therapeutic relevance
CAFs	Derived from resident fibroblasts, mesenchymal stem cells, or pericytes	Secrete TGF-β, IL-6, ECM proteins, and matrix metalloproteinases; remodel ECM; increase stiffness; promote tumor invasion, angiogenesis, and immune evasion	Targeting CAF signaling or ECM remodeling may improve drug delivery and reduce metastasis
TAMs	Differentiated macrophages polarized toward an M2-like phenotype	Secrete IL-10, VEGF, and arginase-1; promote angiogenesis, tissue remodeling, and immunosuppression	Depleting or reprogramming TAMs enhances anti-tumor immunity
MDSCs	Immature myeloid lineage cells expanded under chronic inflammation	Suppress T-cell activation via reactive oxygen species, nitric oxide, and immunosuppressive cytokines	Inhibition of MDSC recruitment or function restores immune surveillance
Hypoxia	Microenvironmental oxygen deficiency	Stabilizes HIF-1α; upregulates VEGF and glycolytic genes; promotes metastasis and therapy resistance	HIF inhibitors and oxygenation strategies enhance treatment efficacy
Acidosis	Accumulation of lactate and acidic metabolites via the Warburg effect	Enhances ECM degradation, immune escape, and metastasis; reduces chemotherapy response	Buffer therapy and lactate-targeting drugs may improve outcomes
ECM stiffness	Excess collagen deposition and cross-linking	Increases mechano-transduction, migration, stemness, and resistance	Anti-fibrotic or ECM-normalizing agents sensitize tumors to therapy
Angiogenesis	Endothelial proliferation induced by VEGF signaling	Generates leaky, abnormal vasculature; fosters hypoxia and metastasis	Anti-VEGF therapies aim to normalize vessels and enhance drug delivery
Immune checkpoints	PD-L1/PD-1 and CTLA-4 pathways in TME immune cells	Inhibits T-cell activation, enabling tumor immune evasion	Immune checkpoint inhibitors restore anti-tumor immunity

Abbreviations: CAFs: Cancer-associated fibroblasts; CTLA-4: Cytotoxic T-lymphocyte–associated protein 4; ECM: Extracellular matrix; HIF-1α: Hypoxia-inducible factor 1-alpha; IL: Interleukin; MDSCs: Myeloid-derived suppressor cells; PD-1: Programmed cell death protein 1; PD-L1: Programmed death ligand 1; TAMs: Tumor-associated macrophages; TGF-β: Transforming growth factor-beta; TME: Tumor microenvironment; VEGF: Vascular endothelial growth factor.

From a therapeutic standpoint, the TME presents various actionable targets. Therapies can target tumor cells directly and can also alter or normalize the TME through the following approaches: (i) manipulating immune infiltrates (e.g., reprogramming immunosuppressive TAMs toward pro-inflammatory phenotypes); (ii) normalizing vasculature to improve drug delivery; (iii) targeting the ECM to enhance therapeutic-agent penetration; and (iv) modulating metabolic parameters (e.g., reducing hypoxia or acidity).[26] Biomaterial-based TME systems that can induce TME remodeling (e.g., remodeling ECM stiffness or delivering immunomodulators) have been shown to enhance the efficacy of immunotherapies in preclinical models.[27] The advantage of targeting TME is that it might bypass some resistance mechanisms that occur when you only target tumor cells.

Although the TME is recognized for its possible therapeutic significance, the field faces considerable hurdles. The inherent heterogeneity of the TME, both between patients and within the same tumor, adds to the complexity of targeting. Furthermore, some TME-modifying strategies also have risks; altering the ECM and/or vasculature can inadvertently enhance the extent of metastasis if not precisely controlled.[27] It is worth emphasizing that the TME is dynamic and evolves over time; therefore, static targeting strategies may be insufficient, and adaptive, real-time targeting may be required. Novel experimental models (three-dimensional co-cultures, organoids) and computational approaches (spatial transcriptomics, single-cell sequencing) are currently being developed to help characterize the underlying complexity of this phenomenon.[22] Ultimately, combining TME targeting with tumor cell-directed therapies/diagnostics could improve therapy outcomes by attacking cancer in numerous ways.

2.1. Components of tumor microenvironment

The TME is a heterogeneous network of cellular and non-cellular elements that work together to dictate the processes of cancer initiation, progression, and metastasis, as well as therapeutic resistance. These components do not function in isolation but are in constant communication with tumor cells to establish a dynamic ecosystem that increasingly

changes throughout the progression of cancer.[28] Investigating CAFs, immunosuppressive myeloid cells, and physicochemical features such as hypoxia, acidosis, ECM stiffness, angiogenesis, and immune checkpoints is essential for identifying therapeutic vulnerabilities.

2.1.1. Cancer-associated fibroblasts

Cancer-associated fibroblasts are among the most numerous stromal cells in solid tumors. CAFs can arise from resident fibroblasts, mesenchymal stem cells, or pericytes and acquire a pro-tumor phenotype by producing growth factors (e.g., transforming growth factor beta [TGF-β], interleukin 6 [IL-6], ECM proteins, and matrix-remodeling enzymes such as MMPs).[29] This behavior directly supports cancer cell proliferation, invasion, and metastasis. Additionally, CAF remodeling of the ECM increases tissue stiffness, which affects integrin signaling and contributes to malignant behavior.[30] Finally, CAFs affect immune evasion by secreting chemokines (to recruit immunosuppressive cells) or forming physical barriers to immune cell entry. Thus, CAFs exhibit diverse functions that establish them as central regulators of tumor behavior and as promising therapeutic targets.

2.1.2. Tumor-associated macrophages and myeloid-derived suppressor cells

Immune cells residing in the TME often take on modified functional states that increasingly support tumor growth rather than anti-tumor immunity. TAMs are often polarized to an M2-like phenotype that supports angiogenesis, tissue remodeling, and immune suppression via the secretion of interleukin-10 (IL-10), VEGF, and arginase-1.[31] High TAM infiltration is associated with poor prognosis in many cancers. MDSCs are another important immunosuppressive population in the TME. MDSCs suppress T-cell activation via the production of ROS, nitric oxide, and immunomodulatory cytokines.[32] TAMs and MDSCs are recruited to the TME via tumor-derived chemokines and are often expanded in conditions of chronic inflammation, thereby reinforcing an immunosuppressive niche, which allows tumor cells to escape immune detection. Given these coordinated roles, therapies directed against myeloid cells are emerging as important strategies in cancer immunotherapy, as shown in Table 1.

2.1.3. Hypoxia, acidosis, extracellular matrix stiffness, angiogenesis, and immune checkpoints

Non-cellular elements of the TME contribute equally to tumor progression through physicochemical changes.

(a) Hypoxia: Hypoxia occurs following rapid tumor proliferation exceeding blood perfusion. Low oxygen levels stabilize HIF-1α, which promotes the expression of angiogenic, glycolytic, and metastasis-related genes.[33] Hypoxic niches are also associated with therapy resistance as they limit drug penetration and promote metabolic adaptation.

(b) Acidosis: Cancer cells rely on aerobic glycolysis (the Warburg effect), which generates an abundant supply of lactate that, in turn, acidifies the TME. Further, acidic conditions promote ECM degradation and immune evasion and lead to a more favorable environment for metastasis, as well as decreased efficacy of several chemotherapies.[34]

(c) ECM stiffness: The ECM of tumors becomes abnormally stiff due to an increased deposition of collagen along with cross-linking. The stiffening of the ECM influences aspects of mechano-transduction pathways that heighten tumor cell motility, stemness, and resultant resistance to treatment.[35]

(d) Angiogenesis: Abnormal angiogenesis is primarily driven by VEGF secretion and subsequent vascular proliferation from tumor and stromal cells. Newly formed vessels are often grossly irregular and have an increased permeability that may lead to hypoxia or an inability to facilitate drug delivery.[36] Anti-angiogenic therapies are thought to normalize and create more functional vascular networks to enhance anti-tumor treatment efficacy.

(e) Immune checkpoints: The TME has high levels of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4, which inhibit T-cell activation and drive immune evasion. Immune checkpoint inhibitors have shown considerable therapeutic efficacy, emphasizing the relevance of TME-induced immune modulation.[37]

2.2. Tumor microenvironment-associated molecular biomarkers

Within TME, there exist many molecular biomarkers that reflect and drive malignant progression. Some of the most prominent molecular biomarkers are VEGF, PD-L1/programmed cell death protein 1 (PD-1), IL-6, TGF-β, and HIF-1α. Each plays a unique, although interrelated, role in remodeling the TME and driving treatment responsiveness.

2.2.1 Vascular endothelial growth factor

Vascular endothelial growth factor serves as a major contributor to angiogenesis, promoting the development of new blood vessels to support the needs of rapidly growing tumors. In addition to its effects on blood vessel growth, VEGF induces immune suppression, resulting in impaired

dendritic cell maturation, the recruitment of MDSCs, and an increase in immune checkpoint molecules such as PD-L1.[38,39] Therefore, higher VEGF levels are associated with poorer prognosis and greater treatment resistance. Blocking VEGF/vascular endothelial growth factor receptor (VEGFR) signaling has been a cornerstone of anti-angiogenic strategies; however, a more recent focus is on combining immunotherapy with anti-VEGF therapeutics due to the immunomodulatory role of VEGF.[39]

2.2.2. Programmed death-ligand 1/Programmed cell death protein 1

The PD-L1/PD-1 axis is an important immune-checkpoint pathway allowing tumor cells to escape T-cell killing. In response to inflammatory cytokines, exosomes, hypoxia, and other signals, tumor and stromal cells in the TME upregulate PD-L1 expression. PD-L1 expression level can act as a biomarker indicating appropriate candidates for immunotherapy and represents a real-time read-out of the TME immune status. As PD-L1 expression is regulated by TME factors, PD-L1 detection can also convey microenvironmental state and predict response to PD-1/PD-L1 inhibitors.[40]

2.2.3. Interleukin-6

Interleukin-6 is a pleiotropic cytokine commonly increased within the TME, and it is associated with chronic inflammation, tumor growth, and therapeutic resistance. Elevated IL-6 levels in plasma or tumor tissue from a patient are linked to worse clinical outcomes and a reduced response to immune checkpoint blockade.[41] IL-6 can also promote angiogenesis via the activation of the VEGF axis, thereby leading to a pro-tumorigenic microenvironment.[42] Consequently, IL-6 is increasingly viewed as a prognostic biomarker and a therapeutic target for combination therapy.

2.2.4. Transforming growth factor beta

Transforming growth factor beta is a multifunctional cytokine with context-dependent behavior in cancer, acting as a tumor suppressor during the early stages and promoting progression in later stages. Within the TME, TGF-β regulates immunosuppression, stroma activation (such as CAF formation), ECM remodeling, epithelial–mesenchymal transition, and metabolic reprogramming.[43] Due to its widespread impacts, TGF-β levels and signaling are considered biomarkers of aggressive disease and treatment resistance. Therapeutic strategies focusing on TGF-β signaling are actively being investigated.[44]

2.2.5. Hypoxia-inducible factor 1-alpha

Hypoxia-inducible factor 1-alpha is a primary transcriptional regulator that is activated in response to hypoxia, an intrinsic feature of several solid tumors. Stabilized HIF-1α activates transcription of several genes involved in angiogenesis (e.g., VEGF), glycolysis, cell survival, invasion, and immune suppression.[42] Thus, HIF-1α acts as a biomarker to indicate regions of aggressive tumor hypoxia and is associated with therapeutic resistance, metastasis, and poor prognosis. Therefore, HIF-1α provides a molecular perspective into hypoxia-driven TME states that may aid therapeutic decisions.

2.3. Theranostic targeting of tumor microenvironment

Theranostics, which refers to the combined use of diagnostics and therapy, is increasingly being applied to the TME. Because TME can influence drug distribution, immune response, metabolism, and eventually tumor behavior, incorporating imaging and therapeutic approaches within the context of the TME could greatly enhance precision oncology. The following subsections demonstrate how imaging modalities and therapeutic approaches based on the TME are developing to synergize into cancer theranostics.

2.3.1. Imaging of the tumor microenvironment

Advanced imaging modalities provide critical diagnostic insights into the TME; imaging modalities can visualize stromal, vascular, metabolic, and immune characteristics. For instance, magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging probes can be engineered to target TME markers, such as fibroblast activation protein (FAP) on CAFs, or integrin expression on endothelial/stromal compartments, for the purpose of mapping the TME *in vivo*.[45] In one example, radiolabeled FAP-targeting probes preferentially accumulated in CAF-rich regions of xenograft tumors, demonstrating the feasibility of TME-targeted PET imaging.[45] Concurrently, photoacoustic imaging can be integrated with fluorescently labeled nanoparticle probes that respond to TME conditions (e.g., hypoxia, acidic pH, or matrix stiffness), enabling high spatial resolution and read-out of multiple TME states.[46] This imaging approach not only identifies patients who may be suitable candidates for TME-directed therapies but also provides a means of monitoring treatment response and adaptation in real time, thereby addressing the diagnostic aspect of the theranostic paradigm.

2.3.2. Therapeutic targeting of the tumor microenvironment

Beyond diagnostics, the therapeutic aspect of TME-specific theranostics is emerging rapidly. Immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) directly target immune suppression within the TME and are a proven effective

treatment modality for various tumor types. TME imaging can support their integration into theranostic workflows by helping select patients, monitor immune infiltration, and predict treatment response.[8] Anti-angiogenic agents (such as VEGF/VEGFR inhibitors) are another cornerstone: mediated by their normalization of abnormal tumor vasculature to improve perfusion and drug and immune-cell access, they target the vascular subsystem of the TME.[47] Hypoxia-activated prodrugs target the low-oxygen microenvironment of tumors, and while they are inert and non-cytotoxic in normal oxygen levels, they become cytotoxic and engage a unique metabolism solely in hypoxia, leading to a targeted attack on hypoxic tumor niches, which are often linked to resistance.[47] Finally, ECM-modulating enzymes (collagenase conjugates or MMP modulators) can reduce ECM stiffness and interstitial pressure, thereby improving nanoparticle penetration, immune-cell infiltration, and therapeutic distribution.[46] This combined use of imaging and therapy, viewing the TME, determining targeted strategies, and assessing response is the definitive example of theranostics.

2.3.3. Integration of the concept

The strength of TME-targeted theranostics lies in their ability to integrate multiple microenvironmental factors. Imaging can detect targetable microenvironmental vulnerabilities, guide therapies directed at these vulnerabilities, and subsequently reassess response or inform adaptive therapeutic changes. For example, PET imaging of FAP expression could be used to identify patients who may benefit from FAP-directed therapy, and follow-up imaging could then determine whether the stromal compartment has been modified or whether FAP expression has decreased. This approach creates a feedback loop for treatment scheduling, dose adjustment, and rational combination therapy. However, clinical translation remains difficult because of treatment tolerability, inter- and intrapatient heterogeneity, dynamic changes in TME vulnerabilities during therapy, and off-target effects of stromal or niche-targeted agents.[45,47] Future studies should explore multimodal imaging probes, dual-function nanoparticles that combine imaging and therapy, and real-time feedback systems to optimize TME-targeted therapeutics.

3. Mitochondrial dynamics in cancer

Mitochondria are ever-changing organelles that can alter their shape, position, and functional state through cycles of fusion, fission, and mitophagy that are coordinately regulated. Collectively termed "mitochondrial dynamics," these processes are critical for cellular bioenergetics, redox homeostasis, apoptosis regulation, and metabolic adaptation. Dysregulation of mitochondrial dynamics in cancer is becoming increasingly appreciated as an important component of tumor progression, therapeutic resistance, metastasis, and the maintenance of cancer stem cell properties.[48,49]

Mitochondrial fusion is mediated primarily by the dynamin-like GTPases known as mitofusin 1 and 2 (MFN1 and MFN2) on the outer mitochondrial membrane and optic atrophy 1 (OPA1) on the inner mitochondrial membrane. Fusion enables mixing of mitochondrial contents, diluting damaged proteins and mitochondrial DNA, and supporting OXPHOS under nutrient-limiting conditions.[48] In contrast, fission achieves the fragmentation of the mitochondrial network and is orchestrated primarily by the cytosolic DRP1 and its receptors on the outer mitochondrial membrane. Fission is important for the mitotic segregation of mitochondria and for isolating segments of dysfunctional mitochondria that are subsequently degraded by mitophagy.[49,50] The basic dynamic of mitochondrial fusion-fission has been schematically represented in Figure 2.

In cancer cells, the equilibrium of fission and fusion is disrupted. Elevated fission is associated with higher proliferation, apoptosis resistance, and metastatic behavior in several cancer types; for instance, DRP1 activation was associated with cell cycle progression and worse outcomes in hepatocellular carcinoma and other cancers.[50] Conversely, elevated fusion may enhance mitochondrial respiration and biosynthesis in tumor subpopulations that depend on OXPHOS, such as stem-like and therapy-resistant cells.[51]

Mitophagy, or the selective autophagic clearance of damaged mitochondria, occurs via multiple routes, notably through the PTEN-induced putative kinase 1 (PINK1)/Parkin ubiquitin-dependent system, and through a receptor-mediated pathway such as B-cell lymphoma 2 (BCL2)/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), which acts in conjunction with the ubiquitin-proteasome system. Mitophagy serves as a double-edged sword in cancer: while the selective removal of dysfunctional mitochondria via mitophagy may protect against excess ROS accumulation and genomic instability (a tumor-suppressive function), excessive mitophagy may allow cancer cells to adapt to metabolic stress and resist cytotoxic therapies.[52,53] Due to the context-dependent effects of mitophagy, the same pathway can in one context suppress tumor development, and in another, support tumor survival/maintenance or resistance to therapy.[53,54] Table 2 summarizes key mitochondrial proteins involved in fusion, fission, and mitophagy and their alterations across cancer subtypes.

Table 2. Overview of major mitochondrial dynamics mechanisms and their roles in cancer

Process	Key proteins	Normal functional physiology in non-cancerous cells	Primary role in cancer	Representative findings	Associated cancer types
Fusion	MFN1, MFN2, OPA1	MFN1/MFN2 mediates outer mitochondrial membrane fusion while OPA1 mediates inner mitochondrial membrane fusion. In healthy normal cells, fusion interconnects the mitochondrial network, enabling the sharing of mitochondrial DNA, metabolites, and membrane potential; collectively catering to respiratory efficiency and addressing organelle damage under physiological stress conditions.	Promotes metabolic efficiency, stress resistance, and cell survival.	High OPA1 expression correlates with tumor progression and therapy resistance.	Breast cancer (MFN2 downregulation driving tumor growth); Hepatocellular carcinoma (MFN2 tumor suppressor and is frequently silenced); Glioblastoma (OPA1 overexpression contributes to tumor cell survival); Lung adenocarcinoma (OPA1 upregulation contributes to poor prognosis); Colorectal cancer (MFN1/MFN2 loss linked to faster disease progression); Pancreatic cancer (MFN2 downregulation results in aggression).
Fission	DRP1, FIS1	DRP1 is recruited from the cytosol to the outer mitochondrial membrane, where it polymerizes to constrict and cut mitochondria; FIS1 acts as a receptor/adaptor facilitating DRP1 docking. In healthy normal cells, fission enables proper mitochondrial distribution during cell division, segregates damaged segments for mitophagy, and allows rapid morphological adaptation to mitigate energy demands.	Enhances proliferation, migration, and metastasis.	DRP1 hyperactivation promotes mitochondrial fragmentation and aggressive tumor growth.	Breast cancer (DRP1 overexpression links metastasis and poor survival); Glioblastoma (DRP1-driven fragmentation results in invasion); Melanoma (aberrant DRP1 phosphorylation helps in tumor progression); Non-small cell lung carcinoma (DRP1 hyperactivation associated with chemoresistance); Colorectal cancer (elevated DRP1 linked to tumor aggression); Acute myeloid leukemia (altered fission dynamics result in disease progression)
Mitophagy	PINK1, Parkin	PINK1 accumulates on the outer membrane of depolarized mitochondria and phosphorylates ubiquitin, recruiting and activating Parkin, which ubiquitinates outer membrane proteins, enabling autophagic degradation. In normal cells, this pathway selectively clears dysfunctional mitochondria, preventing reactive oxygen species accumulation and maintaining cellular homeostasis.	Maintains mitochondrial quality control and contributes to drug resistance.	Overactive mitophagy supports tumor survival under hypoxia and chemotherapy.	Lung cancer (Parkin acts as a tumor suppressor and is frequently deleted); Colorectal cancer (Parkin loss of function accelerates tumor growth); Hepatocellular carcinoma (PINK1 overexpression promotes hypoxia-driven cell survival); Glioblastoma (upregulated mitophagy results in resistance to temozolomide); Ovarian cancer (dysregulated mitophagy under hypoxic tumor microenvironment); Pancreatic cancer (mitophagy-mediated therapeutic resistance)

Abbreviations: DRP1: Dynamin-related protein 1; FIS1: Mitochondrial fission 1 protein; MFN1: Mitofusin 1; MFN2: Mitofusin 2; OPA1: Optic atrophy 1; PINK1: PTEN-induced kinase 1.

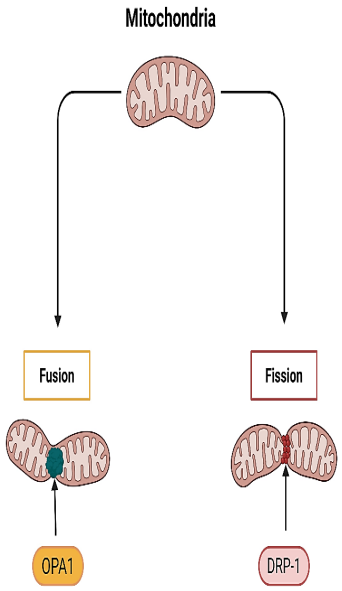

Figure 2. Mitochondrial dynamics: Mitochondrial shape and function are balanced by two opposing but coordinated processes: fission and fusion. Fission is mediated by dynamin-related protein 1 (DRP1) and creates smaller organelles that allow for mitosis, metabolic changes, and the removal of damaged mitochondria. In contrast, fusion is regulated by optic atrophy protein 1 (OPA1) and mitofusins (MFN1/2) to elongate mitochondria and facilitate the exchange of mitochondrial DNA and proteins, resulting in improved bioenergetic stability and stress resistance. The figure shows how the balance between fission and fusion can determine mitochondrial quality control and how this can confer cancer cell survival and metabolic plasticity. Created in BioRender. Ghosh, K. (2026). https://BioRender.com/j1qy2rm.

Mitochondrial dynamics are closely connected to metabolic reprogramming in tumors (Figure 3). Mitochondria are often fragmented in tumor cells with glycolytic phenotypes and are resistant to apoptosis. In contrast, networks of fused mitochondria support OXPHOS, ATP production, and antioxidant capacity in a subset of cells.[48,49] Notably, cancer stem cells and populations of minimal residual disease exhibit adaptive mitochondrial phenotypes resulting from altered fusion/fission balance and increased mitophagy, which promote their survival advantages during chemotherapy or targeted therapy.[51] Such adaptive changes of mitochondrial dynamics fuel intra-tumoral heterogeneity and, in part, relapse following a successful course of treatment.

Because mitochondrial dynamics impact critical vulnerabilities of cancer cells, they are attractive targets for therapeutic strategies. Several approaches are being tested: small-molecular-weight inhibitors of DRP1 to inhibit unfavorable fission, modulators of MFN/OPA1 to disrupt fusion, and agents that manipulate mitophagy (either inhibiting adaptive mitophagy to sensitize tumors or inducing mitophagy to eliminate damaged mitochondria in some circumstances).[49,50] For example, preclinical studies have demonstrated that DRP1 inhibition suppresses tumor growth and increases sensitivity to chemotherapy and radiotherapy, while inhibiting OPA1 has led to re-sensitization in resistant cancer models to targeted agents.[55] Nonetheless, mitochondrial modulators need to be carefully developed, as mitochondria are critical to normal tissues, which present challenges of therapeutic windows and delivery specificity.

Key challenges in advancing mitochondrial dynamics targeted therapies revolve around the contextual dependency of mitochondrial functions across tumor types, mitochondrial heterogeneity within a tumor, and toxicity to healthy tissues. Looking ahead, future work must focus on:

(a) robust biomarkers reflecting mitochondrial states *in vivo* (e.g., imaging or circulating mitochondrial signatures)
(b) combination regimens that target mitochondrial dynamics at the same time as either metabolic or immunologic therapies
(c) selective delivery strategies (e.g., tumor-targeted nanoparticles) to achieve specificity without off-target effects.[48,50,54]

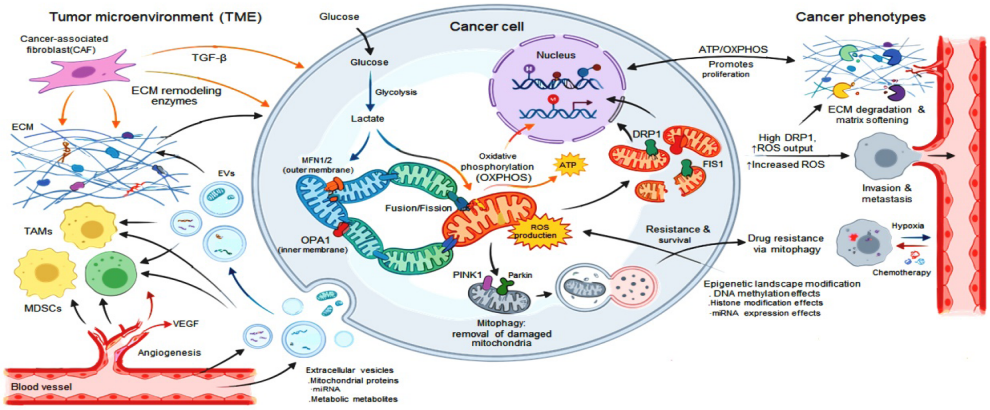

Figure 3. Differential role of mitochondrial dynamics in cancer: CAFs secrete TGF-β and ECM remodeling enzymes that modify the tumor stroma and release EVs. These signals influence TAMs and MDSCs, while VEGF promotes angiogenesis from blood vessels. Within the cancer cell, glucose uptake fuels glycolysis (producing lactate) and OXPHOS via mitochondrial ATP production and ROS generation. Mitochondrial dynamics are regulated by fusion/fission proteins (MFN1/2, OPA1) and quality control through PINK1/Parkin-mediated mitophagy. The DRP1-FIS1 axis and elevated ROS contribute to cancer phenotypes, including ATP/OXPHOS-driven proliferation, ECM degradation, and matrix softening leading to invasion and metastasis, drug resistance via mitophagy under hypoxic and chemotherapeutic stress, and epigenetic landscape modifications that support tumor progression.
Abbreviations: DRP1: Dynamin-related protein 1; ECM: Extracellular matrix; EVs: Extracellular vesicles; FIS1: Mitochondrial fission 1 protein; MDSCs: Myeloid-derived suppressor cells; MFN1/2: Mitofusin 1/2; OPA1: Optic atrophy 1; PINK1: PTEN-induced kinase 1; ROS: Reactive oxygen species; TAMs: Tumor-associated macrophages; VEGF: Vascular endothelial growth factor. Created in BioRender. Ghosh, K. (2026) https://BioRender.com/zwa2cib

Additionally, connecting mitochondrial characteristics to treatment outcomes and designing adaptive, person-centered approaches will also rely on a combination of assessing high-resolution single-cell and spatial omics, as well as functional mitochondrial tests.

3.1. Role of mitochondria in cancer progression

Metabolic reprogramming is a hallmark of tumor progression and is exemplified by the Warburg effect, in which many tumor cells preferentially convert glucose to lactate even in the presence of sufficient oxygen, rather than relying on OXPHOS.[56] This "aerobic glycolysis" provides rapid ATP generation and biosynthetic precursors for cell proliferation.[21,56] Interestingly, while there are early proposals that mitochondrial dysfunction is key to the Warburg effect, evidence shows that many cancer cells retain functional mitochondria and can switch between glycolysis and OXPHOS.[57] For example, in scenarios of nutrient deprivation or metastatic stress, tumor cells readily switch back to OXPHOS to maximize ATP generation and ultimately redox balance. In this way, the interplay between glycolysis and mitochondrial respiration gives tumors metabolic flexibility to promote cell survival and tumor progression under variation in microenvironmental conditions.

Mitochondria are significant sources of ROS through electron leak in the electron transport chain during OXPHOS. While moderate levels of ROS function as signaling molecules to promote growth and survival pathways, high levels of ROS lead to mitochondrial permeability transition, cytochrome c release, and subsequent apoptosis.[58,59] Cancer cells take advantage of this duality; they lessen their reliance on apoptotic pathways (i.e., through downregulation or mutation of BCL-2 family proteins), increase antioxidant defenses, and alter mitochondrial dynamics to avoid apoptosis and proliferate.[59] For example, decreased mitochondrial OXPHOS can reduce the generation of ROS and, in turn, reduce the sensitivity to anoikis (detachment-induced apoptosis) and support metastasis. Thus, mitochondria are metabolic powerhouses but also play a role in regulating cell survival in cancer.

The mitochondrial microenvironment axis is increasingly acknowledged as fundamental to the progressive nature of cancer. TME presents specific conditions (e.g., hypoxia, nutrient limitation, acidosis, and reactive species) that will affect mitochondrial function and regulation.[60] Likewise, mitochondrial metabolic outputs (e.g., lactate, ROS, oncometabolites) can modulate the TME by altering cellular signaling, immune infiltration, and stromal-cell behavior.[61] For example, HIF-1α stabilized in the hypoxic TME suppresses mitochondrial

pyruvate oxidation, shifting cells toward preferential reliance on glycolysis, thereby altering mitochondrial metabolic choice. CAFs or immune cells present in the TME can "feed" tumor cells through metabolites that use the tumor's mitochondrial networks as a means of processing and movement of metabolites, a phenomenon known as the "reverse Warburg effect."[62] This bidirectional communication allows tumor cells to dynamically adapt and persist in inhospitable microenvironmental niches, gain resistance to therapy, and metastasize. Figure 3 describes the role of mitochondrial dynamics in cancer cells and TME.

3.2. Mechanisms of mitochondrial dynamics

Mitochondrial fusion entails the combination of the outer and inner mitochondrial membranes, which enables the exchange of various mitochondrial contents such as metabolites, proteins, and mitochondrial DNA. This process is mediated by MFN1/2 on the outer membrane and OPA1 on the inner membrane.[63] Fusion enhances mitochondrial complementation, allowing cells to accommodate oxidative or metabolic stress through the redistribution of damaged components and maintaining mitochondrial membrane potential, as shown in Table 2.[64] In cancer, increased fusion is implicated in sustaining life despite depletion of nutrients while inducing drug resistance to chemotherapy, which is facilitated through fused mitochondria that promote more efficient OXPHOS and ATP generation.[65] Increased OPA1 expression has been associated with poor prognosis in certain cancer types, including blood cancer, suggesting a role for OPA1 in tumor cell viability.[64-66]

The reverse process, mitochondrial fission, is mediated by DRP1, a cytosolic GTPase that translocates to the outer mitochondrial membrane through adaptor proteins such as mitochondrial fission 1 protein, mitochondrial fission factor, and mitochondrial dynamics proteins 49 and 51. DRP1 assembles into spirals around the mitochondria to constrict and divide them.[67] Under normal physiology, fission is used to ensure equal mitochondrial segregation during cell division and to help remove damaged organelles through mitophagy. In cancer, however, excessive fission leads to increased tumor aggressiveness and metastasis. For example, hyperactivation of DRP1 was shown to parallel increased fragmentation of mitochondrial networks, drive glycolytic metabolism, and promote rapid proliferation and migration in breast and liver cancers.[50] Furthermore, DRP1 overexpression is associated with advanced tumor grade and poor patient survival, indicating the relevance of mitochondrial fragmentation in signaling and mediating therapeutic resistance.[50,68]

Mitophagy is a third important aspect of mitochondrial dynamics. The canonical pathway for mitophagy is the PINK1–Parkin pathway. Under normal conditions, PINK1 enters mitochondria and is degraded by mitochondrial proteins. However, when mitochondria lose membrane potential due to stress or damage, PINK1 accumulates on the outer mitochondrial membrane and recruits the E3 ubiquitin ligase Parkin, leading to the ubiquitination of mitochondrial proteins and marking them for degradation through autophagy.[69] In the case of cancer, mitophagy has a context-dependent function: modest levels of mitophagy eliminate dysfunctional mitochondria and, importantly, prevent the excessive accumulation of ROS, and thereby the development of genomic instability.[52] On the flip side, excessive levels of growth factor-related mitophagy, or dysregulated mitophagy, allow cancer cells to tolerate hypoxia or the stress of chemotherapy by preserving mitochondrial homeostasis.[70,71] Therefore, adaptive mitophagy contributes to therapy resistance, especially when the tumor's microenvironment is hypoxic and nutrient-limited.

3.3. Mitochondrial theranostic strategies

Mitochondria have recently been recognized as major regulators of cancer metabolism and apoptosis, once again establishing them as a pertinent theranostic target to connect cancer imaging with therapeutic modalities that take advantage of tumor mitochondrial changes. Theranostics that engage mitochondrial features leverage the unique characteristics of cancer mitochondria, considering mitochondrial dynamics and functions that are related to bioenergetics or changes in structure. These theranostic strategies employ hyperpolarized mitochondrial membrane potential, altered redox state, or mitochondrial dynamics to allow imaging and targeting. Mitochondrial imaging can inform the metabolic activity of tumors, distinctions between viable and non-viable cells, and the treatment response of tumors to specific therapeutic interventions. These mitochondrial imaging strategies use common fluorescent molecules; for example, 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide (JC-1), tetramethylrhodamine ethyl ester, tetramethylrhodamine methyl ester, and MitoTracker dyes are often used to monitor mitochondrial membrane potential ($\Delta\Psi m$), an indicator of mitochondrial function and potential cellular viability. JC-1 is a fluorescent probe that behaves as a potential-dependent two-component molecule, where red-fluorescent aggregates form in healthy cells and green-fluorescent monomers are generated in depolarized mitochondrial space, making it very useful for detecting early events of the apoptotic pathway. [72-74]

Molecular imaging advances have been applied to PET using mitochondria-targeted tracers, such as to visualize OXPHOS in tumor tissue through the selective binding to mitochondrial complex I.[75] These improvements not only provide enhanced sensitivity in tumors but also allow for real-time assessments of treatment efficacy and drug resistance pathways related to mitochondrial metabolism.[72] Interventions targeting mitochondria aim to impair energy metabolism, activate apoptosis, or prevent drug resistance from recurring in cancer cells. DRP1 inhibitors such as Mdivi-1 have been shown to inhibit mitochondrial fission as a means of restoring mitochondrial networks, ultimately inhibiting tumor growth and metastasis.[76,77] In particular, the antidiabetic agent metformin's inhibition of mitochondrial complex I generates reduced ATP and affects apoptotic cell death via AMP-activated kinase-dependent pathways in metabolically active tumors.[78]

Lonidamine is another agent that is directed to the mitochondria that impairs glycolysis and enhances the action of chemotherapeutics by disrupting the interaction of hexokinase II with the outer mitochondrial membrane.[79] In addition, cationic triphenylphosphonium (TPP^+) conjugates have been used to deliver either chemotherapeutic or antioxidant agents directly to mitochondria, chiefly due to the enhanced membrane potential of cancerous cells, leading to heightened drug selectivity and decreased systemic toxicities.[80] One new type of approach is mitochondria-targeting photodynamic therapy, which involves photosensitizers, for example, MitoTracker-Red or TPP^+-conjugated porphyrins, that become concentrated in the mitochondria and, upon light activation, generate ROS that bring about irreversible mitochondrial damage leading to apoptosis. This strategy enables spatially controlled destruction of cancer cells and represents a promising precision-oncology approach. Additionally, mitochondrial imaging paired with targeted therapeutics allows for a new dynamic platform that facilitates real-time information regarding the delivery and response to therapy. Several of these theranostics can further establish greater specificity in anticancer therapies while limiting off-target toxicity and are ushering in an era of personalized mitochondrial medicine in oncology.

4. Dual theranostic targeting: Integrating tumor microenvironment and mitochondria

The intricate nature of cancer and its various forms calls for multi-dimensional solutions that can target both the TME and the inherent machinery of mitochondria in cancer cells. New findings propose that a dual theranostic approach that includes the simultaneous targeting of both TME and mitochondrial function is a potential path forward in precision oncology, improving diagnostic specificity and therapeutic effectiveness with minimized off-target toxicity.[81] This integrative theranostic method considers the importance of TME and mitochondria because, as the common key sites for mechanistic development and propagation of cancer, they both represent targets for alterations in cancer metabolism, immune evasion, and treatment resistance.

The mitochondria and TME are interrelated via a cycle of metabolic and signaling pathways. Due to hypoxic and nutrient-deprived tumor niches, mitochondrial reprogramming permits cancer cells to alter glycolysis and OXPHOS to survive and metastasize within hypoxic and nutrient-deprived niches. The TME cells, including CAFs and immune cells, as well as endothelial cells, provide metabolites, such as lactate and glutamine, which serve to fuel mitochondrial pathways in tumor cells. On the cellular level, mitochondrial dysfunction produces ROS and HIF-1α. Increased ROS activates HIF-1α, which maintains the relationship between TME and mitochondrial processes, promoting angiogenesis, epithelial–mesenchymal transition, and immune suppression.[82] This type of bidirectional reciprocity provides the basis for the simultaneous targeting of both compartments with the intention of disrupting metabolic homeostasis within the tumor.

4.1. Design concept of dual target systems

The creation of dual-target theranostics represents a cutting-edge frontier in precision oncology, combining capabilities to diagnose, deliver, and act selectively within TME and organelles such as the mitochondria. These systems aim to address key challenges in cancer therapy, including inadequate drug penetration, systemic toxicity, and adaptive resistance, by combining environment-responsive nanocarriers with organelle-targeting ligands.[83]

The TME is characterized by abnormal biochemical gradients that include an acidic pH (≈6.5), hypoxia, and elevated levels of ROS, and presents some of the best markers for selective drug release. As demonstrated, smart nanocarriers can be developed to sense these stimuli and deliver therapeutic payloads selectively in tumor compartments to limit off-target effects in normal tissue.[84] For instance, pH-sensitive liposomes and polymeric micelles leverage acid-labile bonds (e.g., hydrazone, imines, or acetal linkages) that hydrolyze in acidic conditions, ultimately leading to drug release into the TME.[85] Hypoxia-responsive nanocarriers similarly can contain nitroimidazole or azobenzene moieties that are reductively cleaved in low oxygen, which, in turn, elicits site-specific activation of prodrugs.[86]

In addition, ROS-responsive nanoplatforms take advantage of the oxidative nature of tumors through the incorporation of thioketal or boronic ester linkages that degrade in high levels of ROS, leading to controlled release of the drug and improved accuracy of the therapy.[87] The combination of these responsive mechanisms allows a more spatiotemporal controlled theranostic delivery with the physiological profile of the TME.

Outside of environmental responsiveness, molecular targeting is an essential step to enhance the specificity of dual-target systems. To leverage location specificity, nanocarriers can be functionalized with ligands that recognize receptors that are overexpressed in the TME. For instance, nanocarriers can be functionalized with integrin-binding arginine–glycine–aspartic (RGD) peptides, antibodies specific to tumors, or folate ligands.[88] These moieties allow active targeting via receptor-mediated endocytosis and uptake in tumors, leading to accumulation of nanoparticles in the tumor vasculature and tumor stroma.

After cellular uptake, targeting motifs can guide the payload to mitochondria, known to be the energy centers important for apoptosis and metabolic reprogramming. Mitochondria-targeting vectors, including TPP^+ cations, mitochondria-penetrating peptides, or rhodamine derivatives, are based on the properties of the organelle; a generally negative membrane potential can be leveraged to selectively accumulate TPP^+.[89] Conjugation of TPP^+ with chemotherapeutic agents or imaging agents would theoretically provide both mitochondrial disruption and imaging in real-time. This provides a two-phase advantage in the dual diagnostic and potential therapeutic, deciphering the true nature of theranostics.

The ability to target both the TME and mitochondrial compartments in a single platform ultimately provides a hierarchical delivery cascade that first navigates the extracellular tumor niche and then penetrates and acts in subcellular compartments. This enables a multi-stage delivery approach to ultimately ensure that the therapeutic payload can overcome biological barriers (e.g., dense extracellular matrices and multidrug resistance mechanisms) and maintain maximal efficacy at the intracellular level.[90,91] Moreover, these nanoplatforms can be designed to co-deliver chemotherapeutic agents, photosensitizers, or immunomodulators and facilitate combination therapies that simultaneously modulate the TME and induce mitochondrial-mediated apoptosis. In addition, these nanoplatforms may also include a diagnostic component, such as near-infrared fluorescent probes or MRI contrast, that can allow researchers to track biodistribution, drug release, and therapeutic response in real time and bring together targeted therapy with precision imaging.[92] In summary, the design of dual-target systems exemplifies a sophisticated next step in nanomedicine for cancer treatment, which integrates the premise of spatial targeting, biological responsiveness, and controlled *in vivo* monitoring for intelligent, adaptive theranostic interventions. Table 3 represents various approaches to dual theranostic interventions.

4.2. Types of nanoplatforms

Theranostic nanomedicine is a growing field of research, which has led to various nanoplatforms intended to simultaneously diagnose and treat cancer by targeting both the TME and mitochondria. Liposomes and exosomes can use biological compatibility for dual targeting, while polymeric and metal–organic framework-based nanocarriers provide stimuli-responsive and controlled delivery with multimodal action. New hybrid systems and exosome-mimetic systems are paving the way for precision nanomedicine systems that can deliver multiple drugs or biologics while enabling diagnostic monitoring within a single nanoplatform.

5. Clinical translation: Opportunities and challenges

5.1. Current clinical activity: Trials targeting the tumor microenvironment and mitochondria

Translating TME-directed and mitochondria-directed strategies into the clinic is well underway, especially regarding immune and vascular targets. Numerous clinical trials combine anti-angiogenic agents with immune checkpoint blockade (targeting both VEGF and PD-1/PD-L1 axes) to simultaneously modulate the TME and enhance anti-tumor T cell immunity.[93] For example, AK112 (a bispecific PD-1/VEGF antibody) is undergoing clinical evaluation in patients with non-small cell lung cancer.[94] In comparison, direct mitochondria-targeting agents are less advanced in clinical development. Repositioned metabolic drugs like metformin have gone into many cancer clinical trials (as monotherapy or adjunct therapy) because of their effects on mitochondrial complex I and their safety profiles, but clinical evidence is more equivocal and highly context dependent.[95,96] Experimental compounds modulating mitochondrial dynamics (e.g., DRP1 inhibitors such as Mdivi-1) have demonstrated compelling preclinical efficacy but remain mainly in preclinical or early translational research due to questions about specificity and mechanism.[97] Thus, while components of the TME arm of theranostics are already advancing into late-phase trials, mitochondria-targeting theranostics are mostly in early clinical or preclinical phases that still

pursue a combination treatment strategy with established TME modifiers.[97] Table 4 briefly depicts some of the key clinical trials with dual theranostic approaches across different cancer types.

5.2. Limitations and safety concerns: Toxicity, biodistribution, immune interactions, and heterogeneity

The clinical translation of nano-theranostics and mitochondrial drugs faces several interrelated obstacles:

(a) Toxicity and off-target effects: Nanomaterials and mitochondria-active drugs can cause unintended effects in non-tumor tissues that have high reliance on mitochondrial functioning (heart, liver, kidney). In the case of mitochondrial modulators, careful and selective delivery to the tumor site and dose optimization are required to minimize potential cardiometabolic toxicities and narrow therapeutic windows.[96,98] In relation to nanocarriers, systemic accumulation and organ retention (liver, spleen) in the body should be considered as they act as a safety concern.[99]

(b) Biodistribution and delivery efficiency: There are challenges to achieving sufficient mitochondrial and tumor delivery within humans, which are more difficult than in preclinical models. Tumors in humans do not consistently display the enhanced permeability and retention effect. In addition, physical barriers to effective nanoparticle delivery, such as dense tumor ECM or abnormal vasculature, hinder penetration.[47,100] Therefore, even the most promising preclinical biodistribution parameters do not always result in clinical benefit.

Table 3. Types of nanoplatforms for dual theranostic targeting

Platform type	Composition & structure	Theranostic function	Mechanism of TME/ mitochondrial targeting	Key advantages
Liposomes & exosomes	Lipid bilayer vesicles (synthetic or cell-derived); encapsulate both hydrophilic and hydrophobic molecules	Dual delivery of drugs and contrast agents to both TME and mitochondria for simultaneous therapy and imaging	Modified with TME-responsive ligands (e.g., RGD peptides) or mitochondrial-penetrating molecules (e.g., TPP^+); exosomes possess intrinsic tumor-homing abilities	Biocompatible, low immunogenicity, efficient drug encapsulation, suitable for multimodal imaging
Polymeric nanoparticles	Constructed from biodegradable polymers like PLGA, PEG–PLA, or chitosan	Controlled, stimuli-responsive release of therapeutic agents in the TME	Designed to respond to TME stimuli (pH, redox, hypoxia); surface modification with mitochondria-targeting peptides enhances subcellular localization	Tunable degradation rates, high drug loading, customizable targeting properties
Metal–organic frameworks	Porous crystalline networks composed of metal ions and organic linkers	Photothermal/photodynamic therapy (PTT/PDT) and multimodal imaging (magnetic resonance imaging, computed tomography, fluorescence)	Functionalized with mitochondria-targeting moieties (e.g., TPP^+); photoactivation induces reactive oxygen species generation and mitochondrial collapse	Large surface area, tunable pore size, high loading capacity, and optical/magnetic responsiveness
Hybrid nanoparticles	Composite systems combining polymeric, lipidic, and inorganic cores or shells	Enable co-targeted drug delivery, imaging, and synergistic therapy (PDT/PTT + chemotherapy)	Outer layer targets TME (via pH or enzyme sensitivity), while core targets mitochondria using active molecules like TPP^+	Multifunctional, improved therapeutic precision, reduced systemic toxicity
Exosome-mimetic nanoplatforms (emerging class)	Engineered exosome-like vesicles produced through membrane extrusion from donor cells	Mimic natural exosomes for combined TME and mitochondrial delivery and imaging	Combine exosomal homing capability with synthetic mitochondrial-targeting ligands or peptides	Enhanced biodistribution, long circulation, potential for personalized and cell-derived therapies

Abbreviations: PDT: Photodynamic therapy; PEG–PLA: Poly(ethylene glycol)–poly(lactic acid); PLGA: Poly(lactic-co-glycolic acid); PTT: Photothermal therapy; RGD: Arginine–glycine–aspartic acid; TME: Tumor microenvironment; TPP^+: Triphenylphosphonium.

(c) Immune recognition and rejection: The immune system may recognize and clear some nanoparticles, resulting in decreased time in circulation and thus less therapeutic effect; conversely, some nanomaterials may result in undesired immune suppression or activation.[101] Additionally, immune response to delivery vehicles may also complicate delivery for repeat doses and when administered along with immunotherapies.

(d) Tumor heterogeneity and adaptive resistance: Inter- and intratumor heterogeneity mean that within a patient's lesions or throughout the course of therapy, there may not be a single theranostic target or metabolic vulnerability. Tumors can adapt their metabolism and microenvironmental phenotype, leading to the failure of therapies that do not account for such plasticity.[47]

5.3. Manufacturing, scale-up, and regulatory hurdles

Transitioning nano-theranostics and mitochondrial agents from a lab environment to a clinical-grade product adds reproducible manufacturing, robust characterization, and purposeful quality control features into the process. Regulatory agencies such as the Food and Drug Administration and European Medicines Agency require detailed information around composition, stability, impurities, sterility, pharmacokinetics, and toxicology. Nanomedicines have additional intricacies because slight changes in properties like surface chemistry, size, or charge result in biological modifications, and therefore, developers must take care to standardize production and demonstrate lot-to-lot consistency.[100,102] Guidance documents for nanotechnology-based products do exist, as documentation is always evolving, and there is some uncertainty for developers around suitable preclinical models or methods for monitoring immunotoxicity and clinical endpoints.[102] Close engagement with regulatory agencies and addressing manufacturability at the outset are necessary to minimize late-stage failures that might otherwise be costly.

5.4. Ethical and economic considerations

Clinical translation must also address ethical and economic limitations, beyond the bounds of biology and regulation. For example, theranostic platforms frequently employ expensive imaging agents, development of unique delivery systems, and advanced manufacturing, raising questions regarding equitable access to these health technologies in resource-limited settings.[103] It raises equity concerns if

Table 4. Key clinical trials using dual theranostic approaches across cancer types

Cancer	Trial (NCT Nos.) & phase	Agent(s)	Targets: TME/metabolic	Diagnostic modality	Reference
mCRPC	VISION/ PLUVICTO (03511664), phase III	[^{177}Lu] Lu-PSMA-617	PSMA; beta-radiation alters mitochondrial apoptosis	^{68}Ga-PSMA-11 PET/CT	104
GEP-NETs (midgut)	NETTER-1 (01578239), phase III	[^{177}Lu]Lu-Dotatate	SSTR2; radiation drives mitochondrial apoptosis	^{68}Ga-DOTATATE PET/CT	105
GEP-NETs (1L)	NETTER-2 (03972488), phase III	[177Lu] Lu-Dotatate	SSTR2; somatostatin-mediated metabolic suppression	68Ga-DOTATATE PET/CT	106
NSCLC (EGFR mutant)	HARMONi-A (05184712), phase III	Ivonescimab (SMT112 or AK112) injection	Hypoxic mitochondrial stress	PD-L1 IHC; RECIST; serum VEGF	107
HCC (unresectable, 1L)	IMbrave150 (03434379), phase III	Atezolizumab + Bevacizumab	PD-L1 + VEGF; anti-VEGF blocks mitochondrial HIF-1α	RECIST 1.1; PD-L1 IHC	108
RCC (ccRCC)	CheckMate 214 (02231749), phase III	Nivolumab + Ipilimumab	PD-1 + CTLA-4; drives T-cell-mediated mitochondrial reprogramming	RECIST; PD-L1 IHC; TMB	109
AML (R/R)	02882321, phase I	IACS-010759	Interfere mitochondrial C-I OXPHOS; TME immune modulation	Serum lactate/OXPHOS; ^{18}F-FDG PET	110

Abbreviations: 1L: First-line; AML: Acute myeloid leukemia; ccRCC: Clear-cell renal cell carcinoma; C-I: Complex I; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; GEP-NETs: Gastroenteropancreatic neuroendocrine tumors; HCC: Hepatocellular carcinoma; HIF-1α: Hypoxia-inducible factor-1 alpha; IHC: Immunohistochemistry; mCRPC: Metastatic castration-resistant prostate cancer; NSCLC: Non-small cell lung cancer; OXPHOS: Oxidative phosphorylation; PD-1/PD-L1: Programmed death-1/ligand-1; PSMA: Prostate-specific membrane antigen; RECIST: Response Evaluation Criteria in Solid Tumors; R/R: Relapsed/refractory; SSTR2: Somatostatin receptor 2; TME: Tumor microenvironment; TMB: Tumor mutational burden; VEGF: Vascular endothelial growth factor. EGFR: Epidermal growth factor receptor. ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography. ^{68}Ga: Gallium-68. PET/CT: Positron emission tomography/Computed tomography. ^{177}Lu: Lutetium-177.

modern, cutting-edge theranostic care becomes accessible only to patients in wealthy health systems, as this could worsen disparities in health status and life expectancy among patients in resource-limited settings. Because novel nanomaterials, mitochondrial modulators, and other emerging theranostic approaches may have uncertain safety profiles, clinical and preclinical studies must carefully assess potential benefits and risks to ensure that participants or animals are not exposed to avoidable harm. Each human clinical study must properly document the informed consent process and communicate all relevant uncertainties, potential benefits, and risks to patients.[100] Finally, reimbursement and pricing policies will have a huge impact on the way that new health technologies are adopted and provide equitable access to patients. For these technologies to gain broad clinical uptake, health services, policymakers, and funding bodies must be shown to improve survival, quality of life, or cost-effectiveness.

5.5. Opportunities and paths forward

Despite challenges, there are numerous opportunities that can expedite translational mitochondria-based theranostics that includes (i) repurposing clinically approved drugs with mitochondrial activity (e.g., metformin) as adjuvants in biomarker-selected populations; (ii) rational combination trials of TME modulators (anti-angiogenic or immune checkpoint agents) with mitochondrial or nanocarrier strategies to elicit synergy; (iii) improved predictive preclinical models (patient derived organoids, tumor-on-chip, and spatial omics) to better recapitulate human TME and biodistribution; (iv) standardized manufacturing platforms and early engagement with regulators to facilitate scale-up. With a coordinated scientific, regulatory, and economic effort, dual theranostic strategies targeting the TME and mitochondria are a real opportunity to benefit patients.

6. Conclusion

The interplay of mitochondrial dynamics with the TME is of fundamental importance to the expansion, dissemination, and therapy resistance of cancer cells. These systems interact to promote tumor-cell survival under oncogenic stress, while also evading programmed cell death and manipulating surrounding cells. Understanding these interactions between mitochondria and the TME offers the foundation to design novel strategies that will facilitate more precise and effective treatment of cancer. Theranostic methods that merge therapy with diagnostics are opening new avenues in precision oncology. Rather than simply targeting tumors, these approaches allow simultaneous tumor detection and therapy and allow real-time monitoring of therapeutic response while limiting off-target systemic toxicity in healthy tissues. By integrating imaging into the treatment modality, theranostic approaches facilitate a more data-informed approach to cancer management and treatments. The emergence of dual-targeting strategies that focus therapeutic efforts in both mitochondria-mediated and TME-mediated mechanisms provides an innovative approach for next-generation cancer therapeutics. Dual-targeting strategies, when properly executed, may lead to multifocal perturbation of tumor biology, greater clinical efficacy, and reduced likelihood of resistance or recurrence of tumors. With the continued advancement of biocompatible nanotechnology and molecular medicine, dual theranostic targeting appears to hold promise in the development of more personalized and effective cancer therapy in the not-too-distant future.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Umesh Kumar, Krishnendu Ghosh
Visualization: Umesh Kumar, Krishnendu Ghosh
Writing–original draft: Umesh Kumar, Lakshita Tyagi
Writing–review & editing: Krishnendu Ghosh

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy. *Discov Oncol.* 2025;16(1):607.

   doi: 10.1007/s12672-025-02198-8

2. Sarkar S, Horn G, Moulton K, *et al.* Cancer Development, Progression, and therapy: An Epigenetic overview. *Int J Mol Sci.* 2013;14(10):21087-21113.

doi: 10.3390/ijms141021087

3. Fu YC, Liang SB, Luo M, Wang XP. Intratumoral heterogeneity and drug resistance in cancer. *Cancer Cell Int*. 2025;25(1):103.

   doi: 10.1186/s12935-025-03734-w

4. Safri F, Nguyen R, Zerehpooshnesfchi S, George J, Qiao L. Heterogeneity of hepatocellular carcinoma: from mechanisms to clinical implications. *Cancer Gene Ther*. 2024;31(8):1105-1112.

   doi: 10.1038/s41417-024-00764-w

5. Salemme V, Centonze G, Avalle L, *et al.* The role of tumor microenvironment in drug resistance: emerging technologies to unravel breast cancer heterogeneity. *Front Oncol*. 2023;13:1170264.

   doi: 10.3389/fonc.2023.1170264

6. Khan SU, Fatima K, Aisha S, Malik F. Unveiling the mechanisms and challenges of cancer drug resistance. *Cell Commun Signal*. 2024;22(1):109.

   doi: 10.1186/s12964-023-01302-1

7. Zhang A, Miao K, Sun H, Deng CX. Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. *Int J Biol Sci*. 2022;18(7):3019-3033.

   doi: 10.7150/ijbs.72534

8. Burkett BJ, Bartlett DJ, McGarrah PW, *et al.* A review of Theranostics: Perspectives on emerging approaches and clinical advancements. *Radiol Imaging Cancer*. 2023;5(4):e220157.

   doi: 10.1148/rycan.220157

9. Sedlack AJH, Meyer C, Mench A, *et al.* Essentials of Theranostics: A guide for physicians and medical physicists. *Radiographics*. 2024;44(1):e230097.

   doi: 10.1148/rg.230097

10. Shrivastava S, Jain S, Kumar D, Soni SL, Sharma M. A review on Theranostics: An approach to Targeted diagnosis and therapy. *Asian J Pharm Res Dev*. 2019;7(2):63-69.

    doi: 10.22270/ajprd.v7i2.463

11. Korol P, Tkachenko M. THERANOSTICS – a UNIQUE CONCEPT OF NUCLEAR MEDICINE. REVIEW. *Med Sci Ukr*. 2018;13(3-4):76-80.

    doi: 10.32345/2664-4738.3-4.2017.12

12. Viana AF, Cannarozzo E. Theranostics explained: A personalized approach to cancer care. *J Nucl Med*. 2026;67(4):494-495.

    doi: 10.2967/jnumed.125.271895

13. Gutiérrez VM, Trujillo PB, Rodríguez GU. Teranóstico en medicina nuclear: ¿qué es y qué experiencia tenemos en Colombia? *Rev Colomb Radiol*. 2021;32(2):5554-5557.

    doi: 10.53903/01212095.133

14. Anderson NM, Simon MC. The tumor microenvironment. *Current Biol*. 2020;30(16):R921-R925.

    doi: 10.1016/j.cub.2020.06.081

15. Almazrouei KM, Mishra V, Pandya H, Sambhav K, Bhavsar SN. Tumor Microenvironment and its Role in Cancer progression: An Integrative review. *Cureus*. 2025;17(9):e92707.

    doi: 10.7759/cureus.92707

16. Garemilla SSS, Gampa SC, Garimella S. Role of the tumor microenvironment in cancer therapy: unveiling new targets to overcome drug resistance. *Med Oncol*. 2025;42(6):202.

    doi: 10.1007/s12032-025-02754-w

17. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. *J Cell Sci*. 2012;125(23):5591-5596.

    doi: 10.1242/jcs.116392

18. Vona R, Mileo AM, Matarrese P. Microtubule-Based mitochondrial dynamics as a valuable therapeutic target in cancer. *Cancers*. 2021;13(22):5812.

    doi: 10.3390/cancers13225812

19. Ma Y, Wang L, Jia R. The role of mitochondrial dynamics in human cancers. *Am J Cancer Res*. 2020;10(5):1278-1293

20. Trotta AP, Chipuk JE. Mitochondrial dynamics as regulators of cancer biology. *Cell Mol Life Sci*. 2017;74(11):1999-2017.

    doi: 10.1007/s00018-016-2451-3

21. Wang SF, Tseng LM, Lee HC. Role of mitochondrial alterations in human cancer progression and cancer immunity. *J Biomed Sci*. 2023;30(1):61.

    doi: 10.1186/s12929-023-00956-w

22. Tiwari A, Trivedi R, Lin SY. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. *J Biomed Sci*. 2022;29(1):83.

    doi: 10.1186/s12929-022-00866-3

23. Bei R, Masuelli L. Novel therapeutic targets for tumor microenvironment in cancer. *Int J Mol Sci*. 2023;24(8):7240.

    doi: 10.3390/ijms24087240

24. Chen F, Zhuang X, Lin L, *et al.* New horizons in tumor microenvironment biology: challenges and opportunities. *BMC Med*. 2015;13(1):45.

    doi: 10.1186/s12916-015-0278-7

25. Li Y, Zhang C, Jiang A, *et al.* Potential anti-tumor effects of regulatory T cells in the tumor microenvironment: a review. *J Transl Med*. 2024;22(1):293.

    doi: 10.1186/s12967-024-05104-y

26. Guven H, Székely Z. Leveraging the tumor microenvironment

as a target for cancer therapeutics: A Review of Emerging Opportunities. *Pharmaceutics*. 2025;17(8):980.

doi: 10.3390/pharmaceutics17080980

27. Kim M, Lee NK, Wang CPJ, *et al.* Reprogramming the tumor microenvironment with biotechnology. *Biomater Res.* 2023;27(1):5.

doi: 10.1186/s40824-023-00343-4

28. Buenrostro D, Mulcrone PL, Owens P, Sterling JA. The Bone Microenvironment: A Fertile Soil for Tumor Growth. *Curr Osteoporos Rep.* 2016;14(4):151-158.

doi: 10.1007/s11914-016-0315-2

29. Kalluri R. The biology and function of fibroblasts in cancer. *Nature Rev Cancer*. 2016;16(9):582-598.

doi: 10.1038/nrc.2016.73

30. Sahai E, Astsaturov I, Cukierman E, *et al.* A framework for advancing our understanding of cancer-associated fibroblasts. *Nature Rev Cancer*. 2020;20(3):174-186.

doi: 10.1038/s41568-019-0238-1

31. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. *Nat Rev Drug Discov.* 2018;17(12):887-904.

doi: 10.1038/nrd.2018.169

32. Gabrilovich DI. Myeloid-Derived suppressor cells. *Cancer Immunol Res*. 2017;5(1):3-8.

doi: 10.1158/2326-6066.cir-16-0297

33. Semenza GL. The hypoxic tumor microenvironment: A driving force for breast cancer progression. *Biochim Et Biophys Acta (BBA) Mol Cell Res*. 2016;1863(3):382-391.

doi: 10.1016/j.bbamcr.2015.05.036

34. Corbet C, Feron O. Tumour acidosis: from the passenger to the driver's seat. *Nature Rev Cancer*. 2017;17(10):577-593.

doi: 10.1038/nrc.2017.77

35. Kalli M, Stylianopoulos T. Defining the role of solid stress and matrix stiffness in cancer cell proliferation and metastasis. *Front Oncol*. 2018;8:55.

doi: 10.3389/fonc.2018.00055

36. Carmeliet P, Jain RK. Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. *Nature Rev Drug Discov*. 2011;10(6):417-427.

doi: 10.1038/nrd3455

37. Herbst RS, Soria JC, Kowanetz M, *et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528):563-567.

doi: 10.1038/nature14011

38. Tamura R, Tanaka T, Akasaki Y, Murayama Y, Yoshida K, Sasaki H. The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications. *Med Oncol.* 2019;37(1):2.

doi: 10.1007/s12032-019-1329-2

39. Patel SA, Nilsson MB, Le X, Cascone T, Jain RK, Heymach JV. Molecular mechanisms and future implications of VEGF/VEGFR in cancer therapy. *Clin Cancer Res.* 2022;29(1):30-39.

doi: 10.1158/1078-0432.ccr-22-1366

40. Jiang X, Wang J, Deng X, *et al.* Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Mol Cancer*. 2019;18(1):10.

doi: 10.1186/s12943-018-0928-4

41. Liang Y, Shao Y, Gu W. Role of interleukin-6 in resistance to tumor therapy. *Discov Oncol.* 2025;16(1):1791.

doi: 10.1007/s12672-025-03644-3

42. Bandopadhyay S, Patranabis S. Mechanisms of HIF-driven immunosuppression in tumour microenvironment. *J Egypt Natl Cancer Inst*. 2023;35(1):27.

doi: 10.1186/s43046-023-00186-z

43. Deng Z, Fan T, Xiao C, *et al.* TGF-β signaling in health, disease and therapeutics. *Signal Transduct Target Ther*. 2024;9(1):61.

doi: 10.1038/s41392-024-01764-w

44. Garg P, Pareek S, Kulkarni P, Horne D, Salgia R, Singhal SS. Exploring the potential of TGFβ as a diagnostic marker and therapeutic target against cancer. *Biochem Pharmacol*. 2024;231:116646.

doi: 10.1016/j.bcp.2024.116646

45. Loureiro LR, Hoffmann L, Neuber C, *et al.* Immunotheranostic target modules for imaging and navigation of UniCAR T-cells to strike FAP-expressing cells and the tumor microenvironment. *J Exp Clin Cancer Res.* 2023;42(1):341.

doi: 10.1186/s13046-023-02912-w

46. Xu Y, Jiang D, Chen W. Editorial: Tumor microenvironment targeted nanomedicine: a feasible strategy for cancer imaging and theranostics. *Front Oncol*. 2023;13:1228910.

doi: 10.3389/fonc.2023.1228910

47. Roma-Rodrigues C, Mendes R, Baptista PV, Fernandes AR. Targeting tumor microenvironment for cancer therapy. *Int J Mol Sci*. 2019;20(4):840.

doi: 10.3390/ijms20040840

48. Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. *Signal Transduct Target Ther*. 2023;8(1):333.

doi: 10.1038/s41392-023-01547-9

49. Wu Z, Xiao C, Li F, Huang W, You F, Li X. Mitochondrial fusion–fission dynamics and its involvement in colorectal cancer. *Mol Oncol*. 2024;18(5):1058-1075.

doi: 10.1002/1878-0261.13578

50. Adhikary A, Mukherjee A, Banerjee R, Nagotu S. DRP1: at the crossroads of dysregulated mitochondrial dynamics and altered cell signaling in cancer cells. *ACS Omega*. 2023;8(48):45208-45223.

doi: 10.1021/acsomega.3c06547

51. Xing J, Qi L, Liu X, Shi G, Sun X, Yang Y. Roles of mitochondrial fusion and fission in breast cancer progression: a systematic review. *World J Surgical Oncol*. 2022;20(1):331.

doi: 10.1186/s12957-022-02799-5

52. Youle RJ, Narendra DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol*. 2010;12(1):9-14.

doi: 10.1038/nrm3028

53. Wang S, Long H, Hou L, *et al*. The mitophagy pathway and its implications in human diseases. *Signal Transduct Target Ther*. 2023;8(1):304.

doi: 10.1038/s41392-023-01503-7

54. Macleod KF. Mitophagy and mitochondrial dysfunction in cancer. *Annu Rev Cancer Biol*. 2019;4(1):41-60.

doi: 10.1146/annurev-cancerbio-030419-033405

55. Woo SM, Min KJ, Kwon TK. Inhibition of Drp1 Sensitizes Cancer Cells to Cisplatin-Induced Apoptosis through Transcriptional Inhibition of c-FLIP Expression. *Molecules*. 2020;25(24):5793.

doi: 10.3390/molecules25245793

56. Liberti MV, Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem Sci*. 2016;41(3):211-218.

doi: 10.1016/j.tibs.2015.12.001

57. Vyas S, Zaganjor E, Haigis MC. Mitochondria and cancer. *Cell*. 2016;166(3):555-566.

doi: 10.1016/j.cell.2016.07.002

58. Brandl N, Seitz R, Sendtner N, Müller M, Gülow K. Living on the Edge: ROS homeostasis in cancer cells and its potential as a therapeutic target. *Antioxidants*. 2025;14(8):1002.

doi: 10.3390/antiox14081002

59. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS release. *Physiol Rev*. 2014;94(3):909-950.

doi: 10.1152/physrev.00026.2013

60. Wang R, Zhuang J, Zhang Q, *et al*. Decoding the metabolic dialogue in the tumor microenvironment: from immune suppression to precision cancer therapies. *Exp Hematol Oncol*. 2025;14(1):99.

doi: 10.1186/s40164-025-00689-6

61. Kay EJ, Zanivan S. The tumor microenvironment is an ecosystem sustained by metabolic interactions. *Cell Rep*. 2025;44(3):115432.

doi: 10.1016/j.celrep.2025.115432

62. Benny S, Mishra R, Manojkumar MK, Aneesh TP. From Warburg effect to Reverse Warburg effect; the new horizons of anti-cancer therapy. *Med Hypotheses*. 2020;144:110216.

doi: 10.1016/j.mehy.2020.110216

63. Chan DC. Mitochondrial dynamics and its involvement in disease. *Annu Rev Pathol Mech Dis*. 2020;15(1):235-259.

doi: 10.1146/annurev-pathmechdis-012419-032711

64. Yao CH, Wang R, Wang Y, Kung CP, Weber JD, Patti GJ. Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation. *eLife*. 2019;8.

doi: 10.7554/elife.41351

65. Boulton DP, Caino MC. Mitochondrial fission and fusion in tumor progression to metastasis. *Front Cell Dev Biol*. 2022;10:849962.

doi: 10.3389/fcell.2022.849962

66. Doshi S, Glytsou C. Mitochondrial dynamics in blood cancer development and progression. *Current Pharmacol Rep*. 2025;11(1):53.

doi: 10.1007/s40495-025-00431-0

67. Zerihun M, Sukumaran S, Qvit N. The DRP1-Mediated Mitochondrial Fission Protein interactome as an emerging core player in mitochondrial dynamics and cardiovascular disease therapy. *Int J Mol Sci*. 2023;24(6):5785.

doi: 10.3390/ijms24065785

68. Borankova K, Solny M, Krchniakova M, Skoda J. Depleting chemoresponsive mitochondrial fission mediator DRP1 does not mitigate sarcoma resistance. *Life Sci Alliance*. 2025;8(2):e202402870.

doi: 10.26508/lsa.202402870

69. Pickrell AM, Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron*. 2015;85(2):257-273.

doi: 10.1016/j.neuron.2014.12.007

70. Vara-Perez M, Felipe-Abrio B, Agostinis P. Mitophagy in Cancer: A Tale of adaptation. *Cells*. 2019;8(5):493.

doi: 10.3390/cells8050493

71. Denisenko TV, Gogvadze V, Zhivotovsky B. Mitophagy in carcinogenesis and cancer treatment. *Discov Oncol*. 2021;12(1):58.

doi: 10.1007/s12672-021-00454-1

72. Qian K, Gao S, Jiang Z, Ding Q, Cheng Z. Recent advances in mitochondria-targeting theranostic agents. *Exploration*.

2024;4(4):20230063.

doi: 10.1002/exp.20230063

73. Du H, Xu T, Yu S, Wu S, Zhang J. Mitochondrial metabolism and cancer therapeutic innovation. *Signal Transduct Target Ther.* 2025;10(1):245.

doi: 10.1038/s41392-025-02311-x

74. Rout SK, Priya V, Setia A, *et al.* Mitochondrial targeting theranostic nanomedicine and molecular biomarkers for efficient cancer diagnosis and therapy. *Biomed Pharmacother.* 2022;153:113451.

doi: 10.1016/j.biopha.2022.113451

75. Tsukada H, Kanazawa M, Ohba H, Nishiyama S, Harada N, Kakiuchi T. PET Imaging of Mitochondrial Complex I with 18F-BCPP-EF in the Brains of MPTP-Treated Monkeys. *J Nuclear Med*. 2016;57(6):950-953.

doi: 10.2967/jnumed.115.169615

76. Deng Y, Ngo DTM, Holien JK, Lees JG, Lim SY. Mitochondrial Dynamin-Related Protein Drp1: a New Player in Cardio-oncology. *Current Oncol Rep*. 2022;24(12):1751-1763.

doi: 10.1007/s11912-022-01333-w

77. Peng J, Yuan C, Lin Y, *et al.* Targeting the MTFR1–DRP1 pathway inhibits tumor growth and enhances chemosensitivity in breast cancer. *Genes Dis*. 2026:102027.

doi: 10.1016/j.gendis.2025.102027

78. Wheaton WW, Weinberg SE, Hamanaka RB, *et al.* Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. *eLife*. 2014;3:e02242.

doi: 10.7554/elife.02242

79. Floridi A, Paggi MG, Marcante ML, Silvestrini B, Caputo A, De Martino C. Lonidamine, a Selective Inhibitor of Aerobic Glycolysis of Murine Tumor Cells. *J Nation Cancer Inst*. 1981;66(3):497-499.

doi: 10.1093/jnci/66.3.497

80. Murphy MP. Targeting lipophilic cations to mitochondria. *Biochim Et Biophys Acta (BBA) Bioenerg.* 2008;1777(7-8):1028-1031.

doi: 10.1016/j.bbabio.2008.03.029

81. Gao Y, Tong H, Li J, *et al.* Mitochondria-Targeted Nanomedicine for Enhanced Efficacy of cancer therapy. *Front Bioeng Biotechnol.* 2021;9:720508.

doi: 10.3389/fbioe.2021.720508

82. Muz B, De La Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia*. 2015;3:83-92.

doi: 10.2147/hp.s93413

83. Omidian H, Gill EJ. Multifunctional nanoplatforms bridging diagnostics and therapeutics in cancer. *Micromachines*. 2025;16(12):1323.

doi: 10.3390/mi16121323

84. Carvalho IC, Mansur A a. P, Carvalho SM, Mansur HS. Nanotheranostics through Mitochondria-targeted Delivery with Fluorescent Peptidomimetic Nanohybrids for Apoptosis Induction of Brain Cancer Cells. *Nanotheranostics*. 2021;5(2):213-239.

doi: 10.7150/ntno.54491

85. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. *Nanoscale*. 2014;6(21):12273-12286.

doi: 10.1039/c4nr04249b

86. Xia Y, Duan S, Han C, Jing C, Xiao Z, Li C. Hypoxia-responsive nanomaterials for tumor imaging and therapy. *Front Oncol*. 2022;12:1089446.

doi: 10.3389/fonc.2022.1089446

87. Kashyap BK, Singh VV, Solanki MK, Kumar A, Ruokolainen J, Kesari KK. Smart nanomaterials in Cancer Theranostics: Challenges and opportunities. *ACS Omega*. 2023;8(16):14290-14320.

doi: 10.1021/acsomega.2c07840

88. Yang G, Phua SZF, Bindra AK, Zhao Y. Degradability and clearance of inorganic nanoparticles for biomedical applications. *Adv Mater*. 2019;31(10):e1805730.

doi: 10.1002/adma.201805730

89. Ali M, Gowda BJ, Shukla R, Kesharwani P. Triphenylphosphine-Based mitochondrial targeting nanocarriers: Advancing cancer therapy. *Clin Pharmacol Adv Appl.* 2025;Volume 17:119-141.

doi: 10.2147/cpaa.s526895

90. Xu Z, Liu S, Li Y, *et al.* Engineering strategies of sequential drug delivery systems for combination tumor immunotherapy. *Acta Pharm Sin B.* 2025;15(8):3951-3977.

doi: 10.1016/j.apsb.2025.05.039

91. Chen H, Fang Z, Song M, Liu K. Mitochondrial targeted hierarchical drug delivery system based on HA-modified liposomes for cancer therapy. *Eur J Med Chem*. 2022;241:114648.

doi: 10.1016/j.ejmech.2022.114648

92. Sun L, Liu H, Ye Y, *et al.* Smart nanoparticles for cancer therapy. *Signal Transduct Target Ther*. 2023;8(1):418.

doi: 10.1038/s41392-023-01642-x

93. Hack SP, Zhu AX, Wang Y. Augmenting anticancer immunity through combined targeting of angiogenic and PD-1/PD-L1 pathways: challenges and opportunities. *Front Immunol*. 2020;11:598877.

doi: 10.3389/fimmu.2020.598877

94. Zhao Y, Chen G, Chen J, *et al.* AK112, a novel PD-1/VEGF bispecific antibody, in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): an open-label, multicenter, phase II trial. *eClinicalMedicine*. 2023;62:102106.

doi: 10.1016/j.eclinm.2023.102106

95. Zhu L, Yang K, Ren Z, Yin D, Zhou Y. Metformin as anticancer agent and adjuvant in cancer combination therapy: Current progress and future prospect. *Translational Oncol*. 2024;44:101945.

doi: 10.1016/j.tranon.2024.101945

96. Galal MA, Al-Rimawi M, Hajeer A, Dahman H, Alouch S, Aljada A. Metformin: a Dual-Role player in cancer treatment and Prevention. *Int J Mol Sci.* 2024;25(7):4083.

doi: 10.3390/ijms25074083

97. Ahn SI, Choi SK, Kim MJ, Wie J, You JS. Mdivi-1: Effective but complex mitochondrial fission inhibitor. *Biochem Biophys Res Commun.* 2024;710:149886.

doi: 10.1016/j.bbrc.2024.149886

98. Singh A, Faccenda D, Campanella M. Pharmacological advances in mitochondrial therapy. *eBioMedicine*. 2021;65:103244.

doi: 10.1016/j.ebiom.2021.103244

99. Albalawi F, Hussein MZ, Fakurazi S, Masarudin MJ. Engineered Nanomaterials: The challenges and opportunities for nanomedicines. *Int J Nanomedicine*. 2021;16:161-184.

doi: 10.2147/ijn.s288236

100. Hua S, De Matos MBC, Metselaar JM, Storm G. Current Trends and Challenges in the Clinical translation of nanoparticulate Nanomedicines: Pathways for translational development and Commercialization. *Front Pharmacol*. 2018;9:790.

doi: 10.3389/fphar.2018.00790

101. Ray P, Haideri N, Haque I, *et al.* The impact of nanoparticles on the immune system: a gray zone of nanomedicine. *J Immunol Sci*. 2021;5(1):19-33.

doi: 10.29245/2578-3009/2021/1.1206

102. Desai N, Rana D, Patel M, Bajwa N, Prasad R, Vora LK. Nanoparticle Therapeutics in Clinical perspective: Classification, marketed products, and regulatory landscape. *Small*. 2025;21(29):e2502315.

doi: 10.1002/smll.202502315

103. Imani S, Moradi S, Faraj TA, *et al.* Nanoparticle technologies in precision oncology and personalized vaccine development: Challenges and advances. *Int J Pharm X*. 2025;10:100353.

doi: 10.1016/j.ijpx.2025.100353

104. Sartor O, de Bono J, Chi KN, *et al.* Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2021;385(12):1091-1103.

doi: 10.1056/NEJMoa2107322

105. Strosberg J, El-Haddad G, Wolin E, *et al.* Phase 3 trial of 177 Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med* 2017;376(2):125-135.

doi: 10.1056/nejmoa1607427

106. Singh S, Halperin D, Myrehaug S, *et al.* [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2–3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403(10446):2807-2817.

doi: 10.1016/s0140-6736(24)00701-3

107. HARMONi-A Study Investigators; Fang W, Zhao Y, Luo Y, *et al.* Ivonescimab plus Chemotherapy in Non–Small cell lung cancer with EGFR variant. *JAMA*. 2024;332(7):561-570.

doi: 10.1001/jama.2024.10613

108. Finn RS, Qin S, Ikeda M, *et al.* Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New Engl J Med*. 2020;382(20):1894-1905.

doi: 10.1056/nejmoa1915745

109. Motzer RJ, Tannir NM, McDermott DF, *et al.* Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *New Engl J Med*. 2018;378(14):1277-1290.

doi: 10.1056/nejmoa1712126

110. Yap TA, Daver N, Mahendra M, *et al.* Complex I inhibitor of oxidative phosphorylation in advanced solid tumors and acute myeloid leukemia: phase I trials. *Nature Med*. 2023;29(1):115-126.

doi: 10.1038/s41591-022-02103-8