3 Biotech (2026) 16:36
https://doi.org/10.1007/s13205-025-04651-5

REVIEW ARTICLE

Advances in nanomedicine strategies for modulating the tumor microenvironment: Recent progress and clinical perspectives

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Received: 30 September 2025 / Accepted: 18 November 2025

Abstract

The tumor microenvironment (TME) significantly impacts tumor development, metastasis, immune evasion, and resistance to conventional treatments. Recent nanomedicine advancements aid the formation of intelligent, multipurpose nanosystems that precisely target and modify various TME elements, including hypoxia, extracellular matrix, tumor-associated macrophages, and immunological checkpoints. The review highlights recent advancements in nanotechnology-based methods for optimizing medication delivery, renewing the TME, and enhancing treatment outcomes. It discusses the impact of nanomedicines on the TME, including immune modulation, stimuli-responsive drug release, and the restoration of abnormal vasculature. It also demonstrates the translational landscape of these methods, focusing on safety profiles, clinical trials, and scaling challenges from preclinical models to clinical applications. Nanomedicine offers personalized cancer treatments by regulating tumor TME, enhancing immunity, restoring tumor vasculature, and targeting multiple TME components through smart nanocarriers. Combination approaches with immunotherapy, photothermal therapy, and chemotherapy show synergistic results. Clinical trials show promise but face scalability and reproducibility issues.

Keywords Tumor microenvironment · Nanomedicine · Targeted drug delivery · Immune modulation · Stimuli-responsive nanoparticles

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Published online: 20 December 2025

Introduction

The tumor microenvironment (TME) comprises tumor cells, stroma, fibroblasts, immune cells, vasculature, and other noncellular tissues, in addition to the invasive immune cells (Wagner et al. 2019). The vascular networks in normal tissues differ significantly from the tumor vasculature. High quantities of vascular endothelial growth factor (VEGF), which is released by rapidly proliferating tumor cells, cause malformations in the leaky vasculature (Tamura et al. 2020). The urgent need for efficient treatment methods is crucial due to the deadly nature of malignant tumors. Tumor treatment has led to the discovery of tumor immunotherapy. Tumor immunotherapy utilizes antigens, checkpoint inhibitors, cytokines, or T cells to enhance immune responses to tumor cells, overcoming immunosuppressive conditions in the immunological microenvironment (Song et al. 2017a; Nam et al. 2019). The immunosuppressive nature of tumor immunotherapy in clinical practice presents challenges such as low response rates and inconsistent patient responses. The extracellular matrix (ECM), blood vessels, immune cells, and other components make up the TME, which is the local environment that surrounds tumor cells. It is essential to the growth and management of malignancies. The TME's hypoxia, low pH, abnormal vascular growth, and high concentration of immunosuppressive cells develop an immunosuppressive microenvironment (Anderson and Simon 2020). The TME is essential to the processes of tumor incidence, invasion, and metastasis, based on ongoing studies on tumor progression (Roma-Rodrigues et al. 2019).

Nanodrugs enhance drug bioavailability, tumor targeting, and reduce side effects, but their inability to target effectively limits therapeutic efficacy and produces negative effects (Chou et al. 2011). Certain nanocarriers, due to their intrinsic characteristics such as light, heat, and activation of immunogenic cell death, can enhance the effectiveness of tumor immunotherapy (Feng et al. 2019; Xu et al. 2020a). Nanomedicine utilizes rapidly developing nanotechnology to provide innovative solutions for pressing biomedical needs (Prabhakar, et al. 2013). Nanoplatforms have been developed as drug/gene nanocarriers to efficiently deliver pharmaceutical agents into tumors, enhancing tumor retention and decreasing non-specific distribution in healthy organs (Bamrungsap et al. 2012; Kang et al. 2015). Nanomedicine has shown the potential to enhance the effectiveness of other therapeutic methods like phototherapy, radiation, and immunotherapy, thereby paving new cancer treatment paths (Liang et al. 2016). Numerous enzymes and nanoparticles (NPs) have been developed to modify the unique characteristics of TME, such as reducing hypoxia, balancing acidic tumor pH, and altering the immunosuppressive microenvironment (Mpekris et al. 2017a; Chen et al. 2015). NPs, including polymers, liposomes, inorganic nanomaterials, and protein-based nanomaterials, have been developed for effective TME modulation (Wang et al. 2018a; Song et al. 2017b). Modulating TME is a less harmful option than directly killing cancer cells and may help increase the effectiveness of already available cancer treatments (Song et al. 2016a). However, TME regulation is an intriguing strategy to enhance cancer treatment based on nanomedicine (Gong et al. 2016). Nanomedicines, like liposomes and micelles, are effective in tumor treatment, but face challenges in the TME, potentially necessitating new chemotherapy regimens and drug reevaluation (Zhang et al. 2017a). Additionally, nanomedicine enhances immunometabolic therapy by improving the targetability, pharmacokinetics, and bioavailability, thereby renewing immune-resistant TME and improving therapy efficacy and side effects (Shi et al. 2017). However, Nanomaterials can enhance the effectiveness of immunotherapy when used in conjunction with radiation therapy, promoting the release of disease-associated molecular patterns and stimulating immune cells (Li et al. 2024a; Li et al. 2024b). Nanomedicine enhances cancer immunotherapy by metabolically altering immunosuppressive TME, targeting stromal and immunological cells using immunometabolic strategies based on nanomedicine-based approaches. (Liu et al. 2024). The review highlights nanomedicine's potential to improve drug delivery, immunosuppression, and therapeutic outcomes by targeting cancer cells and rewiring immune cells in the TME.

The features of the tumor microenvironment

Tumors are complex systems of host cells, ECM, and secreted substances that promote growth and progression. The TME (Fig. 1), a dynamic system involving immune cells, stromal cells, blood vessels, and ECM, actively promotes cancer progression. The process promotes angiogenesis, which replaces oxygen and eliminates metabolic waste, and infiltrates tumors with both innate and adaptive immune cells (Anderson and Simon 2020). Tumors develop in unique microenvironments compared to normal tissues (Polyak et al. 2009). The TME significantly influences tumor development and growth (Fane and Weeraratna 2020). TMEs often have a more acidic microenvironment, higher levels of reactive oxygen species (ROS) and glutathione (GSH), hypoxic status, overexpressed enzymes, and high ATP levels due to their rapid proliferation and metabolism. The TME can cause treatment resistance and failure, promote tumor angiogenesis, and contribute to metastasis (Klemm and Joyce 2015). Hypoxic regions are present in most solid tumors in humans due to the aberrant shape of the vascular network and cancer cell proliferation. Chronic

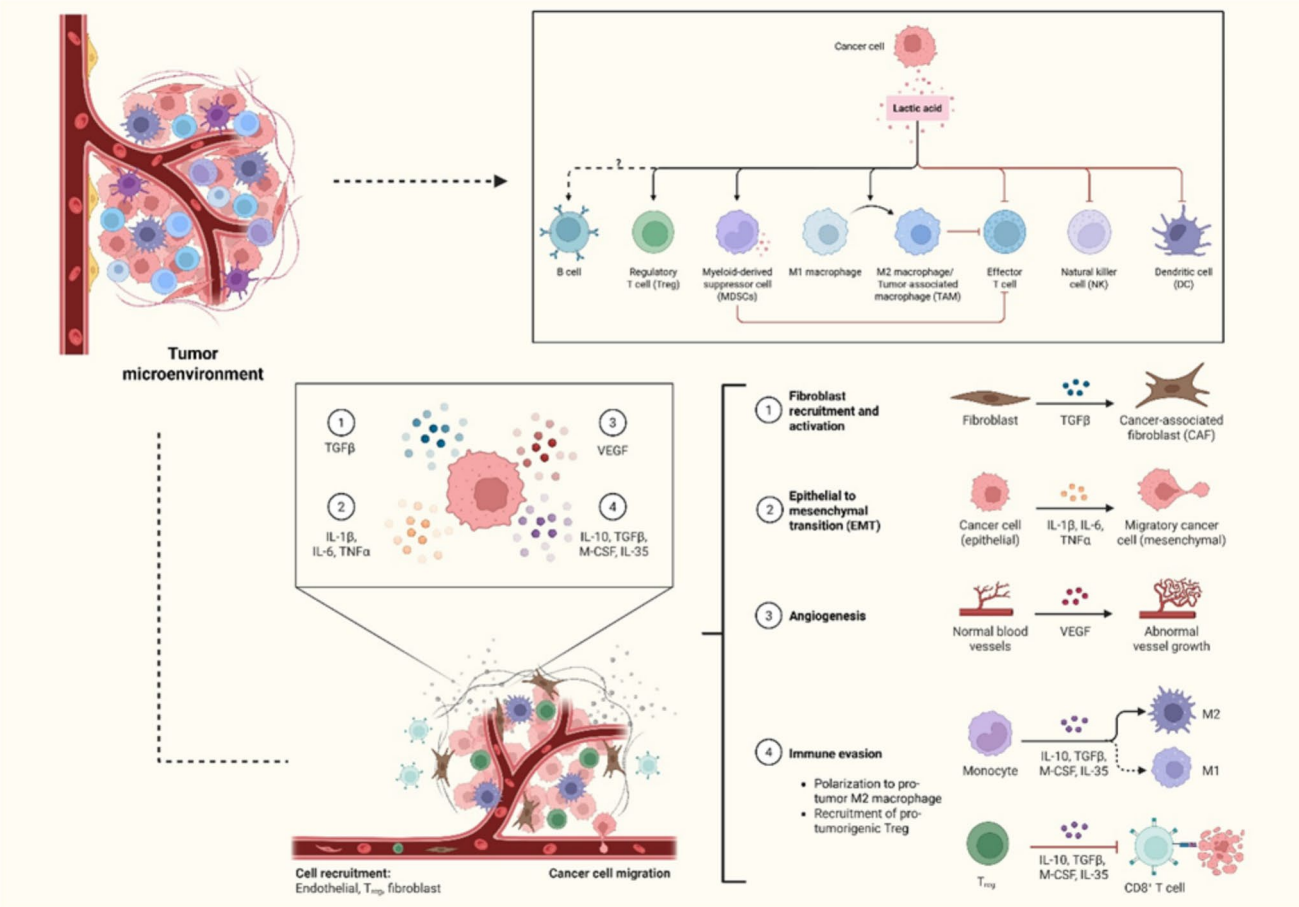

Fig. 1 Schematic representation of the tumor microenvironment

hypoxia affects tumor growth, responsiveness to therapy, and metastasis. Cyclic hypoxia promotes angiogenesis, tumor spread, inflammation, and resistance to anti-cancer therapy more than chronic hypoxia (Michiels et al. 2016). The TME is crucial in cancer development as it contains tumor cells, adipocytes, fibroblasts, lymphocytes, dendritic cells, tumor vasculature, and cancer-associated fibroblasts. These cells interact with neighboring cells via the lymphatic and circulatory systems, affecting the initiation and spread of cancer. The TME also contains cancer stem cells and other substances that aid in tumor growth and spread. Cancer treatment can be effectively managed and result in favorable health outcomes by focusing on and adjusting these cells and elements (Arneth 2019). The TME significantly influences cancer genesis, spread, and management. Recent advancements in systems biology have improved the understanding of the intricate relationships between tumors and their immune milieu. Persistent inflammation and tumor immunoediting are linked to disease onset and progression. A favorable prognosis for cancer patients is correlated with reactivation and maintenance of antitumor responses within the TME (Chew et al. 2012).

Low pH

The ECM of neoplastic tissue exhibits a slightly acidic pH range of 6.5 to 6.8, attributed to uncontrolled energy metabolism, inadequate perfusion, and the Warburg effect (Gerweck and Seetharaman 1996). Recent developments in weak acid-activated nanomedicines or nanoprobes have been attributed to the increased acidity in tumor ECM (Li et al. 2020a; Voskuil et al. 2020). The surface charge changed when cis-maleic monoamides, which were stable at pH 7.4, fully degraded at pH 6.5 for extended periods (Du et al. 2010). The TME has slight acidity, but internal lysosomal and endosomal compartments show a significant pH drop, ranging from 4.5 to 6.5. Both normal and tumor cells have acidic endosome environments, but the significant pH differential between the external environment and endosomes is not exclusive to cancer. The use of acidity as a potential endogenous stimulation could potentially enhance the development of pH-responsive nanomedicine. Tertiary amine groups, which are protonated in acidic environments, often exhibit a sensitive pH-stimuli-responsive property in nanomedicine (Wang et al. 2014). Additionally, the formation of

pH-responsive nanomedicine has been extensively studied using acid-labile linkers such as hydrazones, cis-aconityl, and maleimide (Liu et al. 2010). Barar and Omidi explored the impact of pH dysregulation on solid tumor growth and metastasis. It reveals that overexpression of glucose transporter GLUT-1 and glycolysis-related enzymes worsens the condition. The overexpression of transport mechanism in cancer cells increases lactic acid buildup, leading to a pH imbalance in the cytoplasm and extracellular fluid. This results in a complex TME with high interstitial fluid pressure. The pH dysregulation can increase tumor invasiveness and metastasis, and may lead to resistance to immunotherapy and chemotherapy (Barar and Omidi 2013). TME is influenced by interactions between tumor cells, immune cells, stromal cells, and blood vessels. Recent advancements in cancer immunotherapy have allowed for a more comprehensive study. The primary focus is on the pH regulation of the TME, with lactate, a byproduct of tumor cells, playing a crucial role in tumor development, invasion, and angiogenesis (Hosonuma and Yoshimura 2023).

High-level GSH

One of the most prevalent reductive cellular metabolites, GSH, is crucial for preserving the equilibrium of the redox state within cells (Lian et al. 2018). Furthermore, GSH plays an essential role in protein folding by regulating the formation and breakdown of disulfide linkages in various proteins (Bien et al. 2010). Tumor cells often have a GSH content of 5×10^{-3}–10×10^{-3} M, which is significantly greater than that of normal cells (1×10^{-3}–5×10^{-3} M) (Liu et al. 2015). Oxidized glutathione is converted to GSH in the cytosol by GSH reductase and NADPH, resulting in a 1000-fold higher concentration in the cytosol compared to the extracellular environment or plasma (Peng et al. 2019). GSH, a marker widely used in nanomedicine, is utilized to selectively release drugs into the tumor cytosol through disulfide linkages (Men et al. 2018). A 3D stereo fibrous network has been developed to efficiently trap and release circulating tumor cells, despite their fragility. The network, combining liquid-assisted electrospinning, gas foaming, and metal-polyphenol coordination, was able to trap more cancer cells in less time than conventional scaffolds. It also demonstrated enhanced capture ability against heterogeneous cancer cells and could release trapped cells with high viability under physiological stimulation. This TME-inspired 3D stereo fibrous network could aid in rare cell analysis (Luo et al. 2023). Chemodynamic treatment (CDT) is a potential therapeutic strategy for cancer due to elevated redox levels. CDT efficiency is limited by factors such as quick bloodstream clearance, insufficient ferrous ions, and increased anti-oxidative defense. A novel manganese nanocage, resembling a virus, is developed with DHA and a red cell membrane to generate free radicals and enhance the effectiveness of CDT. The nanosystem enhances CDT efficacy by utilizing TME-responsive free radical production and GSH exhaustion, offering a novel approach for targeted drug delivery and synergistic cancer therapy (Lin et al. 2025).

High-level ROS

Numerous physiological functions depend on ROS, particularly hydrogen peroxide (H_2O_2) (Elnakish et al. 2013). ROS are important molecules that affect the formation and incidence of cancers (Srinivas et al. 2019). Through processes involving nicotinamide adenine dinucleotide phosphate oxidase and the mitochondrial respiratory chain, the majority of tumor cells generate more ROS than healthy cells (Panieri and Santoro 2016). Furthermore, alterations in tumor cells' energy metabolic processes and genetic makeup may promote the generation of ROS. The TME is a key component of stimuli-responsive nanomedicine due to its high concentration of H_2O_2, which is 100 times higher than normal tissue levels (Yang et al. 2020). ROS, produced by cellular metabolism, are essential immune signaling messengers in the immune system. Tumor-induced immunosuppression is linked to increased ROS in the TME. T cell-based therapy has been approved for cancer treatment, but ROS can cause T cell activation, death, and hyporesponsiveness. Regulating ROS levels could extend T cell lifespan and boost anticancer activity (Chen et al. 2016a). ROS are crucial for various biological processes, including angiogenesis, apoptosis, proliferation, differentiation, and cell growth. Increased ROS production can damage biomolecules, leading to genetic mutations, genomic instability, and gene expression changes, which can contribute to tumor development. Recent research shows that hyperoxia, EMT, and cancer stem cells are linked to increased ROS production. MiRNAs, which control ROS production, may contribute to cancer development and spread. A new therapeutic approach could focus on ROS mediated by miRNAs or antioxidant compounds like genistein (Bao et al. 2014).

Hypoxia

Hypoxia, an essential TME element, can exacerbate prognosis, accelerate tumor growth, increase aggressiveness, and increase the likelihood of tumor spread (Li et al. 2021a). A characteristic of the majority of solid malignant tumors, hypoxia is important for drug resistance, metastasis, and tumor angiogenesis (Yuan et al. 2021). The majority of nutrients and oxygen are essential within the tumor due to the cancer cells' rapid development. This results in vascular anomalies at the tumor location and the production of

irregular microvessels, which damage the microcirculation. The partial pressure of oxygen steadily drops from the tumor's surface to its center. Tumor tissue has an oxygen partial pressure of 30–40 mm Hg, but in some places it can drop to 0–2.5 mm Hg, forming a hypoxic environment (Wong and Choi 2015). Hypoxia inhibits cell metabolism, prompting tumor cells to adapt by producing various hypoxia-inducible factors (HIF), primarily HIF-1 (Moyer 2012). This adaptation to hypoxia alters the overall biochemical environment around cells and impacts various functions, including transportation (Wang et al. 2009), endocytic receptor internalization (Mosesson et al. 2008), cell energy metabolism (Frezza et al. 2011), and transmembrane receptor recirculation. Hypoxia is becoming the primary emphasis on diagnosis and treatment owing to substantial differences between tumor and normal tissue (Kiyose et al. 2010). Hypoxia can therefore be employed as an endogenous stimulus for imaging and tumor therapy. Quinone, azobenzene, and nitroaromatic derivatives are primary functional groups that respond to hypoxia (Kiyose et al. 2010; Yin et al. 2020). Hypoxia affects the TME in cancer therapy. This resistance is linked to negative patient outcomes through various signaling pathways. Hypoxia targeting may help overcome this resistance, as efflux can give resistance to traditional therapy (Jing et al. 2019). The HIF transcriptional system detects hypoxia in lymphocytes and myeloid cells, affecting immune cell activity and differentiation. The hypoxic response affects key immunotherapy targets, including PD-L1, OX-40, CD137, and FOXP3. Hypoxia promotes T-regulatory cells and supports immunosuppressive actions of tumor-associated macrophages and myeloid cell-mediated inflammation (Labiano et al. 2015).

Overexpressed enzymes

TME significantly influences tumor genesis, development, and metastasis. Metabolic enzymes play a role in TME modulation. Research has shown that glycolytic enzymes control angiogenesis, immunological escape, and stromal cells. Factors contributing to cancer failure include aberrant tumor vascular system, peritumoral stromal cells, and tumor immunosuppressive microenvironment (Xu et al. 2023). A significant component of the biotechnological toolkit, enzymes are a type of protein or RNA that offer potential capabilities and optimal properties to speed up chemical reactions (Mu et al. 2018). Almost all biological and metabolic processes include enzyme-catalyzed reactions, which are the main players in the molecular chemistry of living things because they are extremely efficient and selective toward particular substrates under mild conditions (Hu et al. 2012). Enzymes exhibit varying degrees of expression in a variety of disease-associated microenvironments, including malignancies (Shahriari et al. 2019). Notably, compared to normal tissues, TME shows an overabundance of the enzymes matrix metalloproteinases (MMPs), hyaluronidase (HAdase), γ-glutamyl transpeptidase, and esterase (Qiu et al. 2016). Proteases can break down proteins or peptide substrates. Protein functions are mediated by kinases through the phosphorylation process, while phosphatases regulate dephosphorylation. MMP-2 expression was almost six times higher in breast cancer cells MDA-MB-231 than in normal mammary cells HS578Bst (Li et al. 2017). The expression level of HAse in low-grade bladder cancer and normal bladder tissue was not significantly different, while it was approximately eight times higher in high-grade bladder cancer (Pham et al. 1997). T cells undergo metabolic alterations when exposed to antigens, leading to a metabolic battle between tumors and antitumor T cells. Immunosuppressive enzymes, such as ectoenzymes and those that catabolize essential amino acids, influence the metabolic halo of T cells, causing toxic catabolites, and influencing cancer treatment (Molinier-Frenkel and Castellano 2017). Enzymes are essential for living systems and are used in various diseases. Recently, enzyme types with distinct catalytic properties have emerged for inhibiting tumor growth and enhancing treatment effectiveness by modifying the TME. The study found the formation of enzyme nanoreactors with reduced immunogenicity and improved catalytic performance for tumor OS and cancer treatment (Liu et al. 2021a).

Transport barriers for nanomedicine from the tumor microenvironment

A TME's primary transport hurdles are stromal cells, dense ECM, increased interstitial fluid pressure (IFP), and aberrant tumor vasculature. These elements differed depending on the type of tumor. The study demonstrated highly permeable and highly desmoplastic tumor models to enhance understanding and management of the TME (Stylianopoulos and Jain 2013). Tumor cells are located near tumor vessels in highly permeable tumors, which notably contain a high density of vessels along with specific amounts of ECM, TAFs, and pericytes. However, highly desmoplastic tumors, like those of the pancreas (Cabral et al. 2011), bladder (Zhang et al. 2014), and some breast (Stylianopoulos and Jain 2013), are always hypovascular, with a dense ECM, a high coverage rate of pericytes on the endothelium, and numerous TAFs. Tumor cells are organized into cases by the TAF interacting with the ECM at specific distances from tumor vessels (Feig et al. 2012; Zhang et al. 2016a). A study found the obstacles preventing nanomedicines from penetrating tumors, focusing on the TME (Fig. 2). It suggests potential methods to

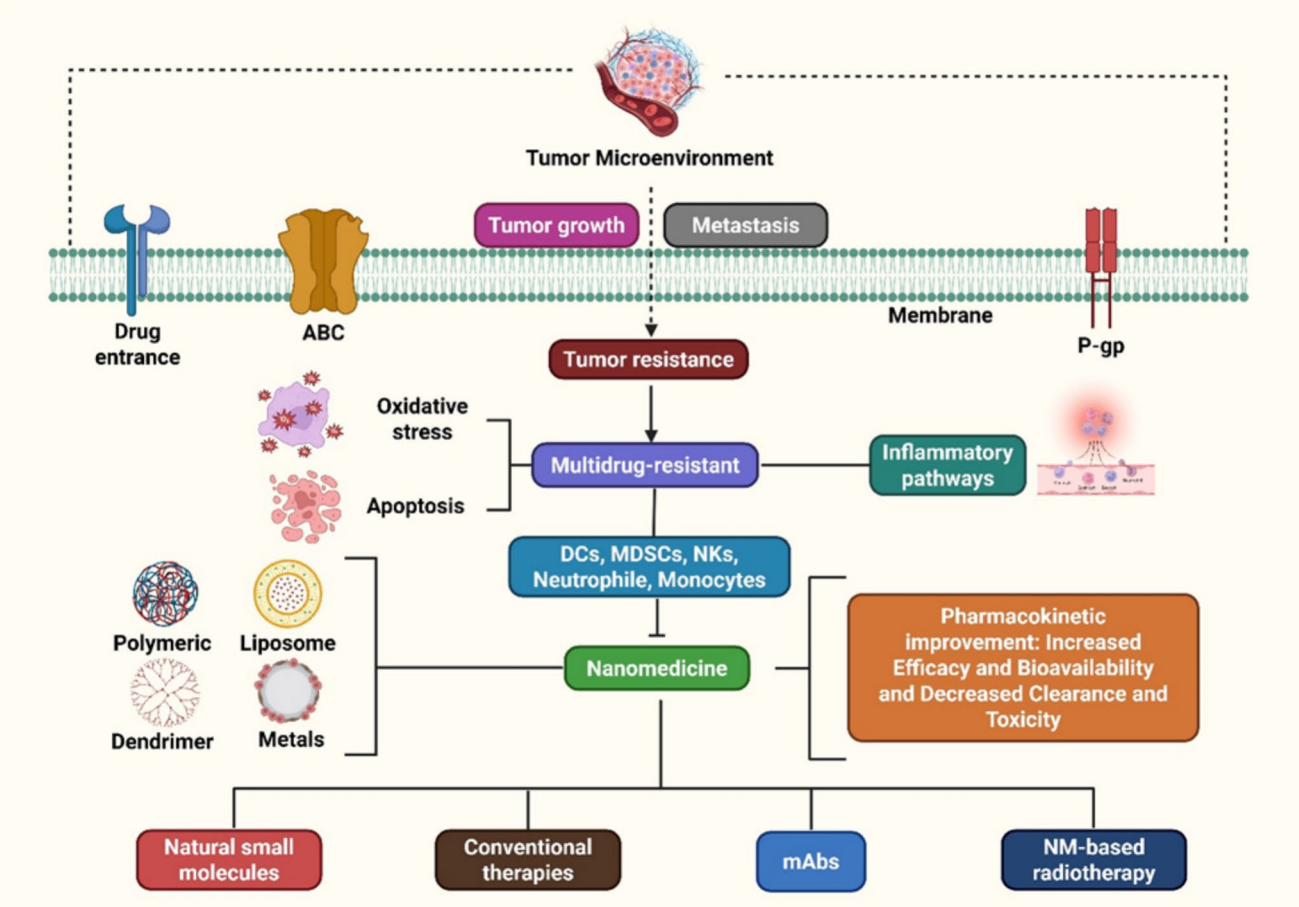

Fig. 2 Nanomedicine combats multidrug resistance through conventional treatments, radiation, mAbs, and natural compounds. Therapeutic medicines use anti-inflammatory, anti-apoptotic, and antioxidant mechanisms to overcome pharmacokinetic restrictions and drug resistance

enhance nanomedicines' penetration, including modifying NP characteristics and repairing tumor stroma and its blood vessels (Liu et al. 2023). NPs improve efficacy and reduce side effects in cancer treatment. However, their therapeutic benefits are limited due to TME anomalies and factors like size, charge, and shape (Wang et al. 2023a). Nanotherapeutics for cancer treatment are well-researched, though limited formulations have advanced to clinical use due to the intricate properties of nanotherapy and the variability in tumor tissues. The study found modeling work related to TME and nanotherapy, including multi-dimensional tumor tissue assessment, vascular flow coupling, in vivo imaging, transport modeling, pharmacokinetic modeling, nano-based hyperthermia, and vasculature binding (Curtis and Frieboes 2016). The human body's primary drug distribution barrier is the imbalance in the tissue microenvironment. Therapeutic agents pass through physical barriers, biological molecules, and cytoprotective mechanisms. Healing damaged physiological barriers is infrequently explored. Maintaining homeostasis and treating disease require both repairing and modifying pathological barriers (Han et al. 2023).

Networks of abnormal tumor vasculature

Tumor cells form solid tumors, characterized by irregular blood flow, leakage, and elevated interstitial fluid pressure. These anomalies form a barrier that prevents therapeutic medicines from reaching tumors and may promote metastasis. Abnormal microcirculation reduces the effectiveness of anti-tumor treatments. The imbalance between pro- and anti-angiogenic factors is governed by host-tumor interactions. Restoring the balance can help tumor vasculature normalize and operate better. Combining cytotoxic therapy and anti-angiogenic treatment can achieve this (Fukumura and Jain 2007). Tumor cells require more nutrients due to their division, making angiogenesis possible by increasing blood flow and delivering oxygen and nutrients. Cancer can be cured by reducing blood flow to tumor cells. Approaches include genetic models, pharmacological inhibition of angiogenesis, and NP-based therapy. Monitoring vascular normalization is crucial for selecting the best tumor vascular normalization method (Taleb et al. 2022). Proangiogenic chemicals like VEGF and endogenous antiangiogenic

molecules like sVEGFR1 and thrombospondins are exquisitely counterbalanced in normal tissues (Carmeliet and Jain 2000; Jain 2003). However, pathological angiogenesis occurs in unorganized tumor tissues, with the proangiogenic impact being amplified abnormally. Tumor vasculature has a diverse basement membrane, large endothelial gaps, and a very erratic and chaotic structure in comparison to normal vessels (Carmeliet and Jain 2011a). Tumor blood vessels, composed of endothelial and mural cells, exhibit morphological and functional anomalies that support the TME and mediate cell spread. They lack hierarchy, form large sinusoidal tubes, and have a heterogeneous density (Ribatti et al. 2007). Tumor microcirculation is heterogeneous, potentially leading to hypoxic areas and reduced treatment effectiveness. This study investigates the impact of aberrant adaptable reactions to regional hemodynamic and metabolic stressors on tumor microcirculation using computational simulations. Intravital microscopy captured the topology, vascular diameter, length, and red blood cell velocity of tumor and normal mesenteric vascular networks. Tumor networks had greater oxygen delivery deficits and diameter mismatches compared to normal networks. The study suggests weak structural adaptability may be the primary cause of these aberrant characteristics (Pries et al. 2009). The development of a tumor is contingent upon the interaction among cancer cells and their surroundings, including neovessels. The vascular network is the primary pathway for cancer cell spread, aiding metastasis. Vascular normalization, which removes unnecessary structures and stabilizes aberrant vasculature, is beneficial for anti-cancer therapy. Understanding this relationship and modifying the vasculature can improve disease treatment (Magnussen and Mills 2021).

Elevated IFP

Cancer genesis is complex and involves more than just genetic anomalies. Solid tumors' abnormal interstitium and irregular microvasculature create barriers against treatment modalities. Innovative approaches should target TME bioelements holistically. Large molecular processes develop during oncogenesis, forming a lenient TME for tumor progression. Solid tumors have resistance to conventional chemotherapy and immunotherapy drugs due to their self-regulation and coadaptation. Cancerous cells form a microenvironment that leads to altered extracellular pH, distorted ECM, disrupted immune functions, and abnormal microvasculature (Omidi and Barar 2014). Milosevic et al. found the impact of invasive needle assessments on human malignancies, particularly cervical cancer, where elevated tumor IFP is a significant independent prognostic factor (Milosevic et al. 2004). IFP is a kind of fluid-induced stress that is consistently raised throughout the bulk of many tumors. Three mechanisms include fluid flow: the lymphatic veins drain excess fluid, the fluid flows across the tumor interstitium, and the fluid flows along the tumor vasculature (Jain et al. 2014). Elevated IFP results from abnormalities in the TME about these three processes. Excess fluid and plasma macromolecules can extravasate into the tumor interstitium due to the leaky tumor vasculature. In healthy tissues, an efficient lymphatic network could discharge extra fluid to keep the interstitial pressure of the tissues balanced. IFP is higher in tumor tissues, nevertheless, since lymphatic drainage in tumors is malfunctioning. In addition to anomalies in lymphatic and tumor blood arteries, aberrant hydraulic conductivity also regulates IFP, particularly in severely desmoplastic tumors. The volume fraction, surface charge, chemical makeup, and fiber arrangement in the tumor interstitial space all affect hydraulic conductivity (Stylianopoulos et al. 2008). The hydraulic conductivity of tumors with high collagen content may be an order of magnitude lower than that of tumors with low collagen content (Netti et al. 2000). The depletion of glycosaminoglycans by MMPs-1 and -8 leads to an increase in hydraulic conductivity and interstitial fluid velocity (Mok et al. 2007). High density of stromal and tumor cells may decrease interstitial space for fluid flow, increasing IFP and fluid resistance. IFP ranges from 0 to 3 mm Hg in healthy tissues. But IFP is high in human and experimental solid tumors, usually between 5 and 40 mmHg, and up to 75–130 mmHg in highly desmoplastic pancreatic tumors (Milosevic et al. 2004; Provenzano et al. 2012).

ECM

The non-cellular substance that is extensively found in all tissues and organs is called the ECM. Proteoglycans (PGs) and fibrous proteins are the two primary macromolecule categories that make up the ECM (Järveläinen et al. 2009; Schaefer and Schaefer 2010). Most of the tissue's extracellular interstitium is filled with PGs like hyaluronan, which take the shape of a hydrated gel. Collagens, elastins, fibronectins, and laminins are examples of fibrous ECM proteins (Dequidt et al. 2007). ECM is a very dynamic structure that is continuously being reconstructed, either enzymatically or non-enzymatically, and a wide range of post-translational changes regulate its final components. Additionally, ECM is tissue-specific and differs significantly among various tissues, including malignant ones (Frantz et al. 2010). The ECM's distinct structure and composition act as a growth regulator. Cell survival and dynamic homeostasis are maintained by the regulation of cell proliferation and differentiation by ECM and ECM-associated enzymes and growth factors (Li et al. 2010). However, in conditions like cancer,

the ECM frequently undergoes deregulation, and disarray occurs. Numerous cancer types exhibit fibrosis as a result of either insufficient ECM turnover or excessive ECM synthesis. A dense ECM consisting of collagen, hyaluronan, and fibronectin is consistently found in highly desmoplastic tumors, such as pancreatic cancer and certain breast cancers (Stylianopoulos and Jain 2013; Feig et al. 2012). Tumors with a lot of blood vessels always have a low ECM content. Platelet-derived growth factor (PDGF), Hedgehog signaling, and TGF-β were among the signaling pathways implicated in the synthesis of ECM. Heparanase, cysteine proteases, 6-O-sulfatases, urokinase, and many MMPs are among the enzymes that cause ECM turnover to undergo remolding (Egeblad et al. 2010; Lu et al. 2012). The dense ECM in tumors groups cancer cells into clusters away from collapsed arteries, which obstructs the effective penetration and uniform distribution of nanomedicine in three main ways (Bailey et al. 2008; Miao et al. 2015). A dense network consists of large matrix molecules, a high stromal fraction, and limited interstitial volume (Padera et al. 2004). This effectively reduces blood flow and limits the convection of nanomedicine. The diffusion of nanomedicine is influenced by factors such as collagen thickness, mesh size, and fibrillar structure. The size of nanomedicine has an inverse relationship with its diffusion capacity. In solid tumors, the matrix mesh size varies from 20 to 40 nm. The ECM selectively permits the passage of small particles, completely halting larger ones, while partially restricting those near the mesh size (Nichols and Bae 2012). The indirect structure of the interstitial space in nanomedicines increases the diffusion path from blood arteries to tumor cells, posing challenges for various sizes (Chauhan et al. 2009). Highly desmoplastic tumors are the primary source of nanomedicine delivery resistance from the ECM. Nanomedicine can penetrate tumor tissues in tumors with a tumor-vessel structure due to reduced abundance, density, and stiffness of the ECM (Cabral et al. 2011). Human cancers exhibit thicker and denser ECM compared to rat models (Miao and Huang 2015).

Stromal cells

Tumor-associated macrophages (TAM), pericytes, and TAF are examples of stromal cells. Endothelial cells, hematopoietic stem cells, resident tissue fibroblasts, bone marrow-derived mesenchymal stem cells, and epithelial cells are likely the genesis of TAF (Shiga et al. 2015). TAF generates a significant amount of ECM to form a nest of tumor cells. It plays a crucial role in the binding-site barrier that facilitates the interstitial transport of nanomedicine. High TAF, linked to dense ECM, compresses tumor arteries, posing a threat to nanomedicine's vascular transport. TAF's uptake of the anisamide ligand-modified nanomedicine was seven times more than that of the other cells. The TAF and other cells exhibited different levels of sigma receptor expression (Miao et al. 2016). The prognosis of various cancer types is greatly affected by TAM, the main inflammatory cells associated with cancer, which primarily originate from monocytes. Myeloid-derived suppressor cells, dendritic cells, and granulocytes are significant inflammatory cells in the TME (Mocellin et al. 2001; Hu et al. 2016). TAM enhances immune evasion and angiogenesis, accelerating tumor growth when the TME polarizes it towards an anti-inflammatory state (Cieslewicz et al. 2013). The phagocytic nature of inflammatory cells means that nanomedicines may have an off-target effect. The study found that despite TAM comprising only 1% of total tumor cells, the relationship between TAM and NP was four times stronger than that of cancer cells (Roode et al. 2016). Another significant subset of stromal cells that are mostly found in the perivascular region and have an impact on the distribution of nanomedicines are pericytes. Nanomedicines should be transported using either over-mature capillaries with high pericyte coverage or leaky, immature vasculature with low coverage. In highly vascularized tumors, excessively leaky arteries primarily impair blood perfusion and, consequently, the vascular transfer of nanomedicine (Stylianopoulos and Jain 2013). Highly desmoplastic tumors often have extensive pericyte coverage, narrowing the endothelial gap and limiting nanomedicine's transvascular transport, particularly for larger nanomedicine (Cabral et al. 2011).

Immune cell alteration in the TME

Antigen recognition by the TCR in the presence of costimulatory factors initiates metabolic transformation in T cells. During T-cell activation, aerobic glycolysis is used to supply energy and nutrients more effectively than oxidative phosphorylation (Chang et al. 2013). PI3K/Akt/mTOR and c-Myc are two significant signaling pathways that enhance the expression of glucose transporter-1, which encourages glycolysis in T-effs (Jiang and Yan 2016). However, decreased glutamine and leucine metabolism in the TME may jeopardize these two pathways, which would hinder T-cell activation (Patel and Powell 2017). The actions of T-effs also depend critically on lipid metabolism. Activated CD8+T cells have been shown to have higher cholesterol levels, which increases TCR clustering and signaling (Yang et al. 2016). Maintaining CD8+T cell activity in the starved TME would benefit from increased fatty acid catabolism (Zhang et al. 2017b). For instance, CD8+T cells contain the cholesterol esterification enzyme acetyl-CoA acetyltransferase-1 (ACAT-1), which lowers free cholesterol levels and

hence suppresses T-cell activation (Yang et al. 2016). Tumor cell and T cell glucose metabolism is significantly impacted by immune checkpoint signaling. Antibodies or NPs binding PD-1/PD-L1, 4-1BB, or CTLA-4 can control the Akt/mTOR signaling pathway, raising glucose levels in the TME, aiding T-cell glycolysis and cytokine production (Chang et al. 2015; Mi et al. 2018; Choi et al. 2017). Poly (β-L-malic acid) nanoconjugates were formed to help transport checkpoint inhibitory antibodies to brain gliomas over the BBB (Galstyan et al. 2019). The TME promotes T-reg recruitment and differentiation, and unlike T-effs, T-regs are crucial for the immunological escape of malignancies (Barsoum et al. 2014; Kouidhi et al. 2017). It has been demonstrated that a significant rise in T-regs in the TME is a characteristic of many solid cancers. The migratory and inhibitory effects of T-regs in the TME are enhanced by HIF-1α in T-regs during hypoxia (Miska et al. 2022). Unlike stiff T-effs, T-regs can adapt their metabolic processes to thrive in a lactate-rich, glucose-restricted environment, enhancing their proliferation and function. T-regs outperform T-effs in glucose competition and glycolysis execution, leading to T-cell fatigue alongside tumor cells (Ho et al. 2015; Liu et al. 2018a). Apart from glucose competition, T-regs utilize fatty acid oxidation (FAO) to absorb fatty acids in the TME, aiding their growth and inhibitory functions (Muroski et al. 2017; Cluxton et al. 2019). The critical functions of glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR, CD357) in activated T cells and T-reg cells have been emphasized (Zappasodi et al. 2019). Agonistic antibodies targeting GITR demonstrate therapeutic benefits by reducing T-regs and enhancing CD8+T cell activity through the downregulation of PD-1 and LAG-3 expression (Mahne et al. 2017). Anti-GITR monotherapy may not be adequate for achieving significantly improved clinical outcomes (Zappasodi et al. 2019). In a preclinical tumor model resistant to anti-PD1, combining anti-GITR and anti-PD1 therapy decreased T-reg immunosuppression caused by radiation therapy, leading to enhanced survival and tumor elimination (Schoenhals et al. 2018). A preclinical melanoma model was utilized to evaluate photodynamic/thermal therapy, agonistic monoclonal antibodies, and imatinib, a molecular medication that inhibits T-reg cells and the IDO pathway in tumor cells (Balachandran et al. 2011; Larmonier et al. 2008; Ou et al. 2018). MDSCs, a diverse group of immature myeloid cells, migrate to primary and metastatic tumors after being produced in bone marrow due to the release of cytokines or immune mediators (Gabrilovich et al. 2012). Polymorphonuclear and monocytic MDSCs demonstrate enhanced nonspecific suppressive activity at tumor sites compared to peripheral lymphoid tissues in both humans and animals (Kumar et al. 2016). Tumor-infiltrating MDSCs are compelled to use FAO and OXPHOS as their primary metabolic pathways in the acidic and hypoxic TME (Kumar et al. 2016; Hossain et al. 2015). Additionally, MDSCs quickly develop into TAMs and increase the production of iNOS and arginase 1 (Gabrilovich 2017). MDSCs inhibit T-cell activities by reducing essential nutrients like arginine, cysteine, and tryptophan (Kumar et al. 2016). The induction of T-regs in the TME has been associated with MDSCs (Huang et al. 2006). MDSCs exhibit M1 and M2 phenotypes, just like TAMs (Kodumudi et al. 2010). M2-type MDSCs inhibit T lymphocytes or NK cells by secreting TGF-β, IL-10, and arginase, while M1-like cells produce TNF-α, IL-12, and nitric oxide (Waldron et al. 2013). MDSC repolarization may represent a new strategy for enhancing current cancer immunotherapy methods. Toll-like receptor (TLR) signaling ligands prevent MDSCs from having their immunosuppressive effects (Li et al. 2015; Forghani and Waller 2015). Research indicates that sunitinib pretreatment reduces MDSCs and T-regs while enhancing cytotoxic T cells and Th1 cytokine profiles, thereby augmenting antitumor immunity (Zhao et al. 2015). Together with T-regs and MDSCs, TAMs make up a sizable fraction of the cell populations in the TME and are important immune cells that promote tumor growth (Noy and Pollard 2014). The M1 phenotype of macrophages produces more proinflammatory cytokines and is cytotoxic. By inhibiting MHC-mediated antigen presentation and promoting lymphocyte death, M2-like TAMs secrete immunosuppressive cytokines like IL-10 and TGF-β, contributing to tumor progression and resistance to chemotherapy (Mosser and Edwards 2008; Pathria et al. 2019). Furthermore, poor long-term survival, increased angiogenesis, and metastasis are linked to TAM density (Sawa-Wejksza and Kandefer-Szerszeń 2018). Consequently, one factor influencing the effectiveness of cancer immunotherapy is the proportion of M2 to M1 phenotype macrophages in tumors. Lipid NP-encapsulated siRNA silencing in inflammatory monocytes has been used to deplete TAM (Leuschner et al. 2011). Biocompatible NPs with nuclease stability can deliver siRNA to the immune system more effectively, providing advantages in reducing immunostimulation during delivery. Moreover, TAMs can adapt into the proimmunogenic M1 phenotype due to their inherent flexibility. TLR agonist-loaded NPs were used to polarize the protumorigenic M2 phenotype toward the antitumorigenic M1 phenotype. R848, a TLR7/8 agonist, was incorporated into β-cyclodextrin NPs (CDNP-R848) and utilized as a strong inducer of the M2 to M1 phenotypic conversion (Rodell et al. 2018). NPs enhance medication delivery through TAM targeting. Mannose and folate enhance NP surface modifications aimed at targeting TAMs, leading to improved cellular absorption (Yu et al. 2013; Turk et al. 2004; Ai et al. 2019). A study found polymeric NPs coated with M2pep

(YEQDPWGVKWWY) to improve the selectivity of TAM targeting. These NPs preferentially bind to murine M2-like TAMs through an adhesive layer of tannic acid-Fe3+complex on their surface (Pang et al. 2019). Hyaluronidase pretreatment of tumors enhances the absorption of liposomal doxorubicin by degrading the ECM and forming a transcapillary pressure gradient (Eikenes et al. 2005). Drug penetration into solid tumors was improved by priming them with an apoptotic inducer, which decreased cell density (Jang et al. 2001a, 2001b). Lu et al. found that apoptosis-inducing tumor priming with PTX-loaded polymeric microparticles increased interstitial space, produced a 16 times higher PTX concentration, and had lower toxicity (Lu et al. 2008). Furthermore, Kuhn et al. found that by decreasing nonspecific NP adherence to the ECM, PEG surface coating of superparamagnetic NPs with a radius of 145 nm enhanced NP transport and biodistribution (Kuhn et al. 2006). Large amounts of ECM proteins are produced by TAFs, which are prevalent in desmoplastic tumors and establish barriers that prevent NP transport (Miao et al. 2016). Several types of NPs have been developed to improve the interstitial transport and distribution of nanomedicines for TAF depletion. Lipid/calcium/phosphate nanoparticles were developed to enhance quercetin accumulation and improve its metabolic stability (Hu et al. 2017).

Immunosuppressive TME modification for improved cancer treatment

Numerous immune cells typically infiltrate solid tumors (Iida et al. 2013). Cancer cells can promote immunological tolerance by imitating certain immune system signaling pathways, which enables them to survive, spread, and evade immune responses (Jochems and Schlom 2011). Additionally, a significant number of immune-suppressive cells, including TAMs, Tregs, and MDSCs, are used by cancer cells (Schmid et al. 2011). The immunosupportive M1-like phenotype and the immunosuppressive M2-like phenotype are both present in TAMs, which are the dominant myeloid cells (Schmid et al. 2011; Rolny et al. 2011). T cells that suppress the activity of other immune cells to prevent immunological responses are known as Treg cells (Shevach 2004). Activated granulocytes and myeloid cells, two phenotypically diverse cell populations represented by MDSCs, may also inhibit immunological function (Rodriguez et al. 2004). White blood cells known as macrophages can take up and break down foreign materials, cell debris, and even cancer cells (Gordon 2003). TAMs would polarize from immunosupportive M1-type TAMs to immunosuppressive M2-type TAMs due to the distinct TME, particularly the hypoxia (Mantovani et al. 2002; Qian and Pollard 2010). TAM polarization in the TME promotes tumor growth and progression by declining anti-tumor immunity (Mantovani et al. 2002). Modifying macrophage polarization through anti-angiogenesis treatment can improve tumor vasculature, enhance blood perfusion, and decrease hypoxia. Huang et al. indicated that low doses of anti-VEGFR2 antibody can reduce tumor hypoxia, improve tumor vasculature distribution, and modify the immunosuppressive TME, which promotes the infiltration of CD4+and CD8+T-cells, thus enhancing the effectiveness of chemotherapy (Huang et al. 2012). Erlotinib, an EGFR inhibitor, was used to normalize tumor vasculature, improve oxygenation and perfusion, and transform the immunosuppressive TME into an immunosupportive one (Chen et al. 2017a). A method to promote macrophage utilization and polarization in tumors is forming oxygen in situ, alongside normalizing tumor vasculature to alter the immunosuppressive TME (Chen et al. 2015; Casazza et al. 2013). Song et al. reprogrammed M2 TAMs to anticancer M1 macrophages using HA-modified manganese dioxide NPs, which react with hydrogen peroxide in the TME to produce oxygen (Song et al. 2016b). Furthermore, Yang et al. found an intelligent nanoplatform for drug loading and TME regulation based on hollow manganese dioxide nanoshells (Yang et al. 2017). Important pathways are linked to the processes of immune cell formation, activation, differentiation, and function (Chiarle et al. 2008). The immunosuppressive TME is linked to immunologically suppressive immune cells like Tregs and MDSCs, the production of negative stimulatory ligands like PDL1, and inhibitory cytokines like IL-10 (Rabinovich et al. 2007; Ko et al. 2009). Therefore, the administration of immunomodulatory drugs can enhance various immune responses in cancer treatment, including boosting T cell activation and effector function, promoting tumor antigen presentation, and mitigating immunosuppressive activities (Hähnel et al. 2008; Seeger et al. 2010). A key polypeptide, TGF-, is involved in the activation, proliferation, and differentiation of various immune cells (Derynck and Akhurst 2007). TGF- functions as a cancer cell suppressor in healthy epithelial cells; however, within the TME, it promotes tumor growth, invasion, and metastasis (Nagaraj and Datta 2010). Therefore, blocking the TGF pathway may prevent tumor cells from proliferating and invading. The study suggests that a small molecule TGF-inhibitor, used at the appropriate dosage, can alter tumor neovasculature and modify the TME, leading to enhanced extravasation of nanomedicine. Therefore, doxil and a polymeric micelle containing adriamycin show strong growth inhibition when used together with a TGF-inhibitor (Kano et al. 2007). The enzyme indoleamine-2,3-dioxygenase (IDO) serves as an immunomodulator by degrading tryptophan and increasing metabolites in the tumor microenvironment, which may

lead to immunosuppressive effects. Different IDO inhibitors are utilized alongside conventional chemotherapies and other immunotherapies to reduce IDO expression in tumors and inhibit their growth (Bilir and Sarisozen 2017). The tumor margin develops by up-regulating heat shock protein, IDO, and PDL1, despite modest PTT causing partial cancer cell necrosis and clearance. PTT treatment combined with immunotherapy using NLG919/IR780 nano-micelles can effectively inhibit IDO activity and enhance T lymphocyte activation, which may limit tumor margin development. Recent studies indicate that therapeutic responses of tumor treatments may improve through the regulation of immunosuppressive TME by NPs with IDO inhibitors (Cheng et al. 2018; Kuang et al. 2018; Wang et al. 2018b).

Targeting the tumor biological microenvironment

Extracellular matrix

The non-cellular part of cells in all tissues is called the ECM. Collagen, enzymes, and glycoproteins are among the many extracellular macromolecules that make up this intricate network. Cellular proliferation and differentiation rely on the biochemical and physical support provided by the ECM surrounding the cells (Frantz et al. 2010; Engin et al. 2017). Tumor growth and metastasis can be aided by the ECM in tumor tissue, which is usually denser and more rigid compared to normal cells (Reid et al. 2017). ECM can inhibit the delivery and penetration of NPs in heterogeneous tumor tissues due to its difficulty and density (Engin et al. 2017). Several methods, including the use of collagenase and hyaluronidase, have been explored to enhance the anti-tumor efficacy of nanomedicines by overcoming the biological barrier of the ECM (McKleroy et al. 2013). The stimulation of collagen degradation (Pan et al. 2018), inhibition of collagen synthesis (Liu et al. 2012; Li et al. 2016a), and repair of collagen cross-linking are common strategies to target collagen (Kanapathipillai et al. 2012). The enzyme collagenase improves the penetration of the NPs by breaking down collagen. Collagenase enhances medication delivery in the treatment of cancer (Eikenes et al. 2004; Murty et al. 2014). Collagenase was administered intravenously to improve gene expression and lipoplex accumulation in a lung tumor xenograft model, followed by liposome/plasmid DNA complex treatment (Kato et al. 2012). In a 3D spheroid culture model of breast cancer cells, collagenase and metformin-conjugated gold NPs demonstrated enhanced cytotoxicity (Abdolahinia et al. 2019). A polymeric micelle formulation modified with collagenase was used to improve NP penetration into tumor tissue by degrading collagen fibers. Furthermore, the pharmaceutical delivery system uses a pH-sensitive ligand that enables NPs to expand in the tumor microenvironment, increasing their retention time. Cisplatin NPs effectively released medication into cancer cell mitochondria, demonstrating exceptional anticancer activity in a mouse model (Xu et al. 2020b). In a 4T1 syngeneic mouse breast tumor model, PLGA-PEG NPs coupled with hyaluronidase showed improved tumor penetration and anti-tumor activity. Complicated chemical conjugation reactions are frequently needed for these techniques (Zhou et al. 2016). An A549 tumor mouse model's thick ECM was broken down by pulsed high-intensity focused ultrasound, which improved drug-loaded NP tumor penetration. The high-intensity focused ultrasound treatment significantly improved tumor targeting efficiency by 2.5 times compared to the control group (Lee et al. 2017). Lingasamy et al. developed an Ft peptide to target neuropilin-1 in glioma cells, neovasculature, and tenascin-C in the ECM. In a glioblastoma mouse model, paclitaxel-loaded Ft NPs increased the antitumor activity, with a longer survival rate (Lingasamy et al. 2019). Another study formed the bi-specific peptide PL1, which can target both fibronectin and tenascin-C. The study shows that PL1 nanoscale model payloads, including metallic silver NPs and iron oxide nanoworms, accumulate in prostate cancer and glioblastoma models. In a glioblastoma mouse model, PL-1 nanoworm treatment resulted in decreased tumor development and improved survival (Lingasamy et al. 2019).

Endothelial cells and angiogenesis

One important element of the TME is the vascular niche (Fan et al. 2012). Angiogenesis, the growth of blood vessels, is a potential cancer treatment target owing to its significant function in tumor growth and metastasis (Teichert et al. 2017). Anti-angiogenic drugs with clinical approval, including pazopanib, sorafenib, sunitinib, bevacizumab, and thalidomide, have significantly improved cancer treatment (Fan et al. 2012). To efficiently provide anti-angiogenic medicines to the TME with the least amount of systemic damage, angiogenesis-targeted delivery systems **(**Fig. 3**)** have been thoroughly investigated (Wei et al. 2014). For instance, angiogenesis can be stopped by targeting receptors that are excessively expressed during the process (Cruijsen et al. 2005; Minder et al. 2015). The main process of angiogenesis relies on interactions between the endothelium cells, pericytes, and stoma cells that make up the ECM (Fan et al. 2012; Chung et al. 2010). Antiangiogenic treatments often target endothelial cells, and a range of ligands, including peptides, antibodies, and cationic components, can be employed to do this (Sakurai et al. 2019). Angiogenesis is typically indicated by the overexpression of αv integrins on

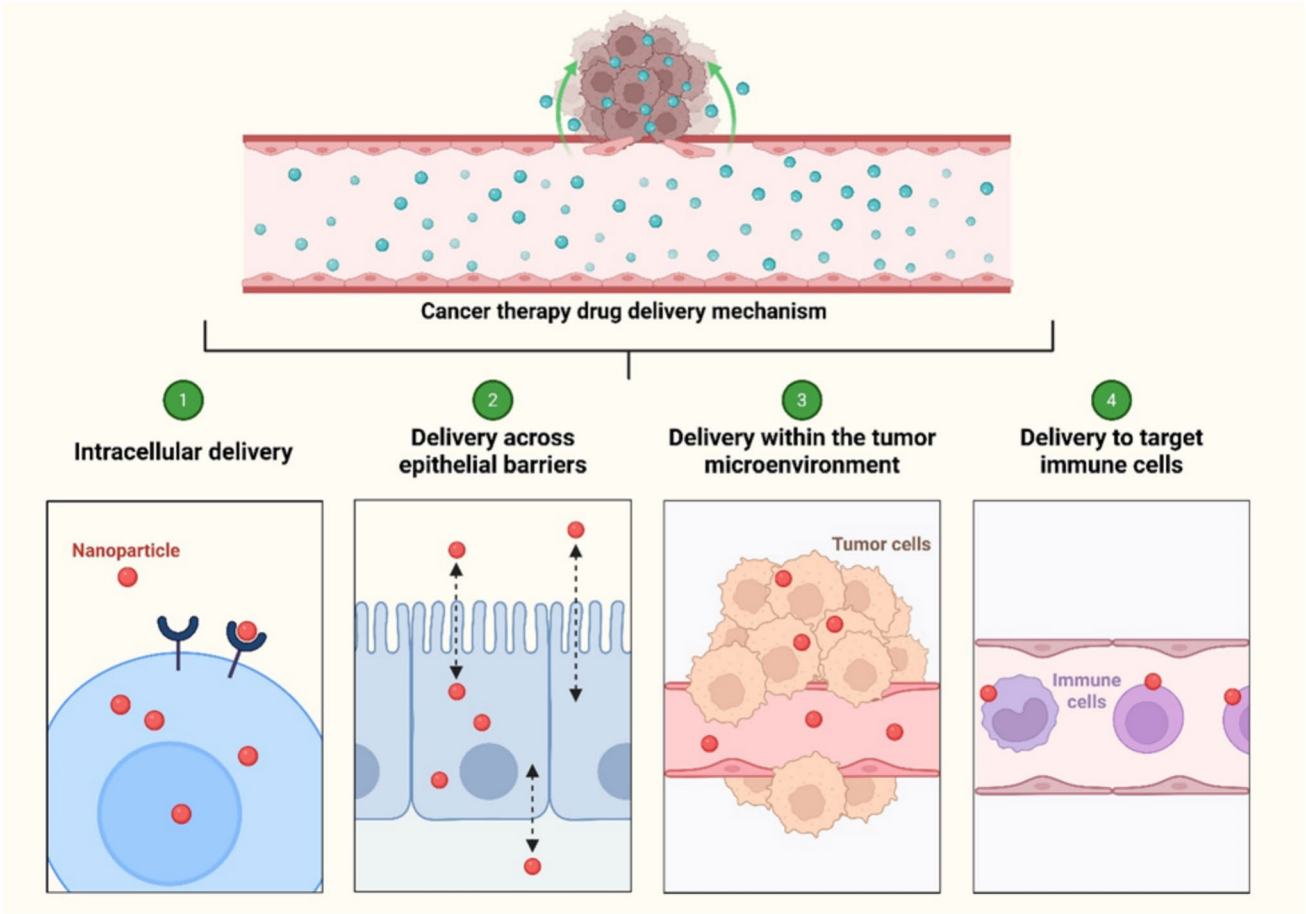

Fig. 3 Illustration of nanoparticle-based drug delivery within the tumor microenvironment

the surface of endothelial cells. By binding to tumor ECM proteins and/or nearby cells, the integrins promote the formation of new blood vessels (Weis and Cheresh 2011). The study developed cyclic RGD-modified PEG-PLA micelles loaded with paclitaxel, which enhanced anti-glioblastoma effects in U87MG glioblastoma xenografts and extended median survival time, demonstrating the potential of drug delivery systems for cancer therapy (Zhan et al. 2010). Sakurai et al. utilized RGD-LNP to encapsulate anti-angiogenic siRNA, resulting in increased overall survival of metastasized lung model mice through continuous administration (Sakurai et al. 2018). Cancer nanomedicines must enter tumors and accumulate within the vascular network of the TME. Facilitating the distribution of the nanomedicine is therefore crucial. Antiangiogenic therapy has demonstrated promising outcomes in numerous preclinical investigations. Therapy activation of various signaling pathways, such as the vascular endothelial growth factor pathway, may lead to drug resistance, neoplastic invasion, and metastasis (Ebos et al. 2009; Abdalla et al. 2018). Furthermore, Abdalla et al. found elevated FGF2 levels in a bevacizumab-resistant xenograft model, indicating that upregulation of FGF-2, a pro-angiogenic factor, induces tumor resistance to cancer treatment (Abdalla et al. 2018).

Pericytes

Another intriguing target for anti-cancer therapy is pericytes (Chen et al. 2017b). The perivascular cells known as pericytes envelop the capillary and artery endothelium. Pericytes are crucial biological elements of the TME that interact with endothelial cells (Martin et al. 2019). For instance, it has been discovered that pericytes use the vascular endothelial growth factor signaling pathway to modulate angiogenesis and endothelial cell proliferation (Franco et al. 2011; Eilken et al. 2017). Drug administration for brain tumor treatment faces significant challenges due to the need to penetrate the BBB. The integrity of the BBB is maintained by pericytes. Pericyte-deficient mouse models showed improved cerebral permeability of both high and low molecular tracers (Armulik et al. 2010). Peptide-modified drug delivery systems that adhere to particular proteins on pericytes have demonstrated increased anti-cancer efficiency in a number of studies. Docetaxel-loaded NPs (TH10-DTX-NP) have been linked

to the TH10 peptide (TAASGVRSMH) (Guan et al. 2014). Roy Chaudhuri et al. demonstrated that Erismodegib, a smoothened inhibitor, significantly enhances the accumulation of doxorubicin-loaded NPs in adenocarcinoma cell tumor regions. Smoothened inhibitors have the potential to deactivate tumor fibroblasts by interfering with the hedgehog-signaling pathway (Roy Chaudhuri et al. 2016). The current understanding of pericytes' identity, ontogeny, and progeny is insufficient, making it challenging to target them for cancer therapy (Armulik et al. 2011). Depletion of pericytes may also result in unexpected tumor growth and failure to enhance the anti-tumor impact (Nisancioglu et al. 2010). Furthermore, a poor prognosis and tumor metastasis have been linked to insufficient pericyte coverage (Armulik et al. 2011; Ramaswamy et al. 2003).

Cancer-associated fibroblasts

The mesenchymal stromal cells known as cancer-associated fibroblasts (CAFs) are prevalent in the TME and are implicated in the progression of cancer (Zhang et al. 2017a; Brennen et al. 2012). Important in stroma remodeling, CAFs give tumor cells physical support and are the primary cellular type involved in collagen synthesis and crosslinking, which contributes to increased ECM stiffness (Liu et al. 2019a). CAFs are also linked to tumorigenesis and immune evasion (Liu et al. 2019b). Zhang et al. improved the distribution of paclitaxel-loaded micelles using celecoxib, a therapeutically relevant cyclooxygenase-2 (COX-2) inhibitor. Celecoxib improves tumor perfusion, disrupts the fibronectin bundle, and lowers CAFs. In human lung A549 tumor xenografts, this led to better paclitaxel-loaded micelle penetration and accumulation, as well as improved therapeutic effects (Zhang et al. 2017c). Additionally, Chen et al. modified nanoliposomes loaded with peptide FH (FH-SSL-Nav) with navitoclax. The peptide FH can attach to tenascin-C specifically, and the small drug navitoclax can cause CAFs to undergo apoptosis. In a Hep G2 tumor mouse model, the peptide liposome FH-SSL-Nav demonstrated enhanced anticancer activity along with higher cellular uptake and cytotoxicity in vitro (Chen et al. 2016b). Gold-core silver-shell hybrid nanomaterials can reduce the tumor cell-promoting activity of CAFs. The nanomaterial had increasing results in preventing tumor spread in the in vivo investigation (Kovács et al. 2020). The lack of a clear nomenclature for CAFs and fibroblast subtypes poses a significant challenge in CAF research for broader application in stromal biology and cancer. Strong indicators for the clinical identification of CAFs are also lacking. Understanding CAFs' origin, diverse functions, heterogeneity, and adaptability is crucial for modifying them for anti-cancer therapy (Sahai et al. 2020).

Platelets

Anucleate blood cells called platelets are found in the TME. Platelets have been shown to promote tumor growth and metastasis in addition to their function in blood coagulation (Schlesinger 2018; Yan and Jurasz 2016). There are various methods by which platelets interact with tumor cells. To put it briefly, tumors that depend on the vascular network for growth can cause the platelets that flow via the tumor vasculature to aggregate, activate, and secrete (Yan and Jurasz 2016). In addition to protecting tumor cells from immune cell-mediated destruction and blood stress (Palacios-Acedo et al. 2019). Platelets are also involved with other elements of the TME, including fibroblasts, endothelial cells, pericytes, and immune cells, which promote inflammation and tumor growth (Ho-Tin-Noe et al. 2009). In order to distribute the platelet inhibitor ticagrelor, a study developed NPs modified with the tumor-homing pentapeptide CREKA (Cys-Arg-Glu-Lys-Ala). In a mouse model of mammary tumor xenograft, these NPs were found to effectively inhibit platelet-tumor cell contact and prevent tumor cell transformation into mesenchymal-like invasive cells (Zhang et al. 2017d). Platelets loaded with conjugated doxorubicin and anti-CD22 monoclonal antibodies for tumor targeting. Doxorubicin's half-life was extended by the platelet drug transporters. In vitro and in vivo, increased anticancer activity was noted (Xu et al. 2017). In comparison to uncoated groups (CS-pPLGA/Bu NPs), mice with H22 hepatocellular carcinoma tumors treated with platelet membrane-coated NPs showed augmented aggregation of the NPs and more efficient suppression of neoplastic proliferation (Wang et al. 2019). The preclinical outcomes of the platelet-like NPs have been increasing. However, in order to adapt the technology, scale-up manufacturing and a comprehensive safety evaluation are still pending. Cancer patients' hemostasis may be suppressed if platelets are the target of cancer treatment (Haemmerle et al. 2018).

Nanomedicine controls the TME to enhance immunotherapy

The advantages of nanomedicine

Advancements in nanotechnology and nanomedicine have significantly influenced the use of nanomaterials in drug delivery, targeted therapy, and tumor diagnostics (Chen et al. 2017c). NPs as carriers enhance medication solubility, bioavailability, and compatibility, prolong circulation duration, and prevent immune system recognition and elimination. Nanodrugs are often coated with polyethylene glycol (PEG), forming a defense barrier that reduces

immune system detection. The PEG alteration can enhance the bioavailability of nanodrugs by prolonging their circulation within the body (Wilhelm et al. 2016). Furthermore, nanomaterials prevent harmful side effects, precisely control drug release, and enhance drug dispersion throughout the body (Martin et al. 2020). Additionally, by improving tumor permeability and retention, nanomaterials can passively target tumors. They can also improve active targeting by altering the surface with targeting molecules (Martin et al. 2020; Mi et al. 2020). Nanodrugs are drug particles at the nanoscale that can deliver drugs through chemical bonding and physical embedding. Liposomes, carbon nanotubes, quantum dots, dendritic macromolecules, micelles, polymer NPs, and other forms are currently classified under nanomedicine (Peer et al. 2020). There are numerous benefits to using nanodrugs to treat cancers. First, there are disadvantages to some chemotherapy drugs, including poor water solubility, high toxicity and adverse effects, and a brief in vivo metabolism period. Through PEG modification, nanodrugs can lengthen the duration of a drug's circulation and slow its elimination in vivo. Drugs can be passively targeted, their toxicity to healthy tissues can be decreased, and their adverse effects can be minimized through nanodrug delivery. The use of different targeting groups can alter the specific surface area of NPs, promoting proactive targeting and aggregation of anticancer medications in tumor tissues (Chou et al. 2011). Medication combinations, in addition to single-treatment strategies, can effectively prevent tumor growth and overcome the limitations of single-drug therapies in clinical practice (Ghodeif et al. 2025; Zhang et al. 2016b). Despite the potential benefits, issues like limited therapeutic effects persist when drug combinations are delivered via nanomaterials due to varying solubilities and pharmacokinetic parameters (Zhang et al. 2016b). The biological barrier inhibits drug therapy efficacy due to insufficient drug accumulation in tumor sites, necessitating the development of novel NPs designs. Additionally, achieving optimal medication release and therapeutic effects is more challenging due to the TME's intricacy. Concerns include inadequate drug release due to poor stimulation signals in tumor tissues, detoxification processes in tumor tissues, and potential systemic drug leakage causing systemic toxicity and adverse effects (Chen et al. 2020). Currently, about ten types of nanomedicine are approved for use in clinical settings to treat cancerous tumors (Wicki et al. 2015). Drug encapsulation using nanocarriers enhances drug bioavailability, delays rapid drug degradation, and facilitates the transport of medications, including chemotherapeutic medicines, to tumor tissues (Parveen et al. 2019). The immunosuppressive microenvironment may potentially be reprogrammed by nanomedicine carriers. Nanomedicine carriers like liposomes can prolong a drug's half-life by modifying their surface, such as through PEGylation, to contain medications. This alteration reduces the impact of the immunosuppressive microenvironment and increases medication accumulation within tumors (Shi et al. 2017). The anticancer medication doxorubicin is delivered via liposomal carriers such as Doxil (doxorubicin liposomes). The study developed liposome LPDp by loading MMP and PD-L1 inhibitors into liposomes and combining them with adriamycin, a low-dose chemotherapeutic medication. It exhibited the highest tumor inhibitory efficiency (~78.7%) in the mice used in the experiments, which implied that it might improve the anti-tumor efficacy (Liu et al. 2019c). Polymeric NPs: made of biocompatible polymers, polymeric NPs are drug carriers. Polymers can be modified to regulate medication release, enhancing drug targeting and enhancing the effectiveness of immunotherapy by altering their characteristics (Reddy et al. 2006). Photothermal therapy can enhance immunotherapy by using metal NPs like gold and silver. The efficacy of NPs can be enhanced by heating tumor tissues locally (Dreaden et al. 2009). Multifunctional NPs are carriers that often possess advantageous properties like drug release, imaging, and targeting. Customized design can enhance the efficacy of immunotherapy by reprogramming the immunosuppressive microenvironment (Kroll et al. 2017). Furthermore, nanodelivery technologies utilize passive/active targeting techniques to reduce harmful effects on healthy tissues and cells while increasing medication concentration in tumor cells (Acharya et al. 2009). Nanodrug delivery systems (Table 1) provide numerous advantages over chemotherapy and alternative drug delivery methods mediated by NPs in tumor immunotherapy (Fan and Moon 2015). Furthermore, some nanocarriers' intrinsic properties can also be utilized to improve tumor immunotherapy (Feng et al. 2019; Xu et al. 2020a).

Nanomedicine techniques to control the TME and enhance immunotherapy

Improving tumor hypoxia

A natural feature of the majority of solid tumors is hypoxia. The effectiveness of nonsurgical tumor treatments can be considerably reduced by severe tumor hypoxia, which can also result in drug resistance and tumor metastases. Additionally, the hypoxic microenvironment can reduce the effectiveness of anticancer treatment by affecting the efficacy of radiotherapy, chemotherapy, and photodynamic therapy (PDT) in eradicating tumor cells (Liu et al. 2018b). PDT is a method that utilizes photosensitizers to generate oxygen radicals, which are responsible for the death of cancer cells. However, the efficiency of PDT is reduced in hypoxic conditions due to the limited generation of oxygen

Table 1 An overview of nanodrug delivery systems that can be utilized to modulate the TME

Purpose	Delivery platform	Strategy	Advantages and limitations	Examples	Ref
Normalizing blood vessels	Nanomaterials with EGFR and VEGF inhibitors	Focusing on vascular growth factors like VEGF	Nanomedicines can effectively target VEGF through surface modification or drug carrier design, reducing their impact on healthy tissues and enhancing therapy accuracy	PHCL-Lip/ETOsiVEGF; PLGA	Osswald et al. 2017; Li et al. 2019)
	TAM polarization to M1 is promoted by nanomedicines	Regulation of TAMs	Inflammatory proteins, including TNF-α and IL-1β, are released when type M1 is triggered, aiding in immune system activation and triggering immune cells to identify and target tumor cells. But in TME, M1 might be immune-tolerant	Erlotinib and NPs	Chen et al. 2017a)
Modulating acidity	$NaHCO_3$-loaded nanomaterials	Neutralizing the TME's acidity	$NaHCO_3$ can rapidly reduce tumor acidosis, but its effects are temporary	$NaHCO_3$	Banerjee and Bose 2019)
	Nanocarriers with inhibitors of glycolysis	Stopping the process of aerobic glycolysis	Nanocarriers are essential for enhancing targeting and improving the tumor hyperacidic environment effectively	Inhibitors of glycolysis LND	Liu et al. 2021b)
Ameliorating tumor hypoxia	Exploring strategies for inhibiting mitochondrial respiration and other methods that are not reliant on endogenous oxygen generation	Additional strategies to reduce hypoxia in tumor tissue	Self-delivery nanosystems that generate oxygen without relying on endogenous H_2O_2 for extended periods	Ti2C(OH)2-Ce6; HBO	Liu et al. 2021b; Liu et al. 2021c)
	CAT-loaded mesoporous nanomaterials or those possessing CAT-like characteristics	In situ oxygen delivery to tumor tissues using an oxygen-self-sufficient nanosystem	The oxygen production effect of the treatment is influenced by the H_2O_2 content of the tumor site, resulting in longer-lasting improvements in hypoxia	mZCD; PPy@MnO2-PEG-MB	Zou et al. 2018; Li et al. 2021b)
Inhibition of immunosuppressive cells and factors	Drug-loaded nanocarriers that lower immunosuppressive cells	Suppression of immune-suppressive cells, such as MDSCs and Tregs	Direct inhibition of immunosuppressive cells can effectively reduce the release of immunosuppressive substances, thereby enhancing tumor immunotherapy	Gel/(REG+NG/LY); CLCeMOF	Li et al. 2020b; Feng et al. 2023)
	Drug-loaded nanocarriers that lower immunosuppressive factors	Inhibition of immunosuppressive substances, such as IDO1 and TGF-β	The direct inhibition of immunosuppressive factors secreted by immunosuppressive cells can significantly improve tumor immunotherapy	OTX+IDOI@MPDAs; Gel/(REG+NG/LY	Tian et al. 2023; Li et al. 2022)
Reprogramming TAMs	Chemokine-loaded nanocarriers that are resistant to M2-type TAM recruitment induction	M2-TAM recruitment inhibition	Lowering the origin of pro-tumorigenic TAM types to effectively improve immunotherapy	Anti-CSF-1R called M2NPs	Qian et al. 2017)
	TAM apoptosis may be impacted by nanocarriers loaded with other nanocarriers	Direct M2-TAM consumption	The most effective strategy for modulating tumor TAMs and improving the TME is through direct methods	CaZol@pMNPs; nano-PROTAC	Zang et al. 2019; Zhang et al. 2022)

radicals. Consequently, enhancing immunotherapy involves raising the oxygen content of tumor tissue and reducing the hypoxic environment of malignancies. Numerous nanodelivery systems have been developed to enhance nanomaterials that target tumor hypoxia (Chao and Liu 2023). Nanodrug delivery carriers increase oxygen content in tumor tissues through blood substitutes and catalyzing hydrogen peroxide breakdown. These methods include NPs based on manganese dioxide or catalase, which produce oxygen through antioxidant enzymes (Sahu et al. 2020). Numerous nanomaterial researchers are developing various oxygen-carrying delivery systems, including hemoglobin and perfluorocarbons. NPs can transport oxygen to hypoxic tumor tissues by altering their surface characteristics, adding oxygen-carrying molecules, or improving their oxygen-transport efficacy through various alterations. This enhances the oxygen content in the tumor site, reverses hypoxic conditions in the TME, and enhances the therapeutic efficacy in removing malignancies (Wang et al. 2015). Hemoglobin is a naturally occurring oxygen carrier that is mostly utilized in artificial blood. However, due to its high oxygen affinity and organ toxicity, it is easily oxidized and broken down into dimers during circulation, resulting in toxic substances like high iron (Rummer et al. 2013). Hemoglobin must therefore be altered or encapsulated to function as an oxygen transporter. For example, by activating the antioxidant mechanism of red blood cells, glutaraldehyde is utilized to cross-link hemoglobin to superoxide dismutase (SOD). In order to supply oxygen to mouse breast cancer tumors (4T1) and mouse colon cancer tumors (CT26), the resultant polymers can act as antioxidant blood replacements (D'Agnillo and Chang 1998). PFC provides superior biological safety and good histocompatibility due to the low polarization of fluorine (Castro and Briceno 2010). However, PFCS's use in cancer treatment is restricted by its hydrophobic nature. The development of nanodelivery methods that utilize PFC for oxygen delivery is crucial to combat hypoxia (Sahu et al. 2020). A study developed mesoporous iron-based NPs, loaded with glucose oxidase and PFC, an oxygen-carrying agent. This system can enhance anticancer effects when combined with starvation therapy, photothermal therapy, and chemokinetic therapy (Wang et al. 2023b). A study developed a nanodelivery system using hollow PEG-Bi2SE3 NPs for anticancer drugs, improving oxygen supply to tumors and radiosensitization therapy (Song et al. 2016c). Oxygen circulation is insufficient in tumor tissues because of aberrant blood arteries and the distance that most tumor cells are from these vessels. Therefore, techniques to improve the hypoxic TME by introducing oxygen into tumor tissues are limited. In order to stimulate the breakdown of endogenous H_2O_2 to produce O_2, researchers have been concentrating on forming a novel type of nanodelivery technology in recent years. This method aims to enhance the hypoxic TME by increasing the oxygen content of tumor tissues. Inorganic NPs like MnO_2 can break down H_2O_2 in tumor tissues, enhancing oxygen concentration and improving the hypoxic microenvironment (Li et al. 2021b). The content of H_2O_2 in tumor tissues is greater than in healthy tissues due to the aberrant metabolism of tumor cells (Chen et al. 2017d). When H_2O_2 catalyzes the breakdown of tumors, oxygen molecules are produced, which can help reduce tumor hypoxia (Gu et al. 2011). A study developed a self-delivery vector for CAT to prevent hydrolysis by circulatory system proteases, increasing therapeutic effects and alleviating hypoxia in tumor lesions. By inhibiting the quick degradation of CAT and increasing its effective growth at the neoplastic locus, this delivery method improves the effectiveness of PDT and chemotherapy via in situ oxygen administration (Cheng et al. 2016). A study embedded catalase and doxorubicin in a pH-sensitive zeolite imidazolate framework. This oxygen-producing biomimetic core–shell nanoplatform can improve chemotherapy efficacy, decrease PD-L1 expression, and enhance outcomes by accumulating in tumors and downregulating HIF-1α expression (Zou et al. 2018). Some inorganic substances, like MnO_2, Pb, and Pt, have CAT-like characteristics and can efficiently catalyze the breakdown of H_2O_2 to produce O_2 (Yang et al. 2018). Unique materials provide better physicochemical stability than CAT for in situ oxygen administration to alleviate hypoxia in the TME. Pb and Ce6 were co-loaded into a mesoporous organic silicon dioxide NP delivery system to increase PDT efficacy through O_2 self-generation (Fan et al. 2011). Furthermore, it has been shown that metal oxides with CAT-like activity, such as MnO_2, are effective at generating O_2 to enhance TME hypoxia. The study found PPy@MnO_2-PEG-MB nanostructures by anchoring MnO_2 nanosheets to polypyrrole (PPy) NPs using in situ redox processes. These then connected the methylene blue photosensitizer and PEG modifier via electrostatic interactions. The study demonstrates a novel multifunctional nanotherapeutic approach for tumor PTT/PDT, utilizing polypyridine NPs to enhance PTT effects and MnO_2 nanosheets to improve tumor hypoxia (Li et al. 2021b; Zheng et al. 2018). A hollow mesoporous manganese dioxide nanoplatform coloaded with doxorubicin and chlorin e6 was formed. The tumor's hypoxic circumstances considerably improved after this nanoplatform treatment. The study found that the nanoplatform's abundant O_2 supply enhanced the therapeutic effects of PDT and chemotherapy. ICD was subsequently brought on by PDT and chemotherapy, which increased T-cell activation and dendritic cell (DC) maturation. The immunosuppressive TME was reshaped at the same time that the tumor-associated M_2 phenotype in TAMs changed to an anticancer M1 phenotype (Yang et al. 2017).

Significant improvements in oxygen delivery have been made possible by the application of inorganic NPs having CAT-like activity. However, it is difficult to maintain O_2 generation during prolonged tumor therapy since oxygen transport to the TME is heavily reliant on H_2O_2 (Zheng et al. 2018). Self-delivery nanosystems can effectively address restrictions in treating tumor hypoxia by eliminating the need for endogenous H_2O_2. $Ti_2C(OH)_2$-Ce_6 can improve the hypoxic environment by blocking mitochondrial respiration and continually supplying oxygen. $Ti_2C(OH)_2$-Ce_6 significantly reduces tumor hypoxia by interacting with the cancer cell surface, suppressing mitochondrial respiration, and continuously generating O_2. PDT generates $1O_2$ to destroy cancer cells, while PTT efficiently converts light energy into heat, enhancing oncological therapy efficacy (Huang et al. 2021). HBO therapy improves oxygen transport to tissues in TME by increasing plasma oxygen concentration, eliminating the need for hemoglobin (á. Gill and Bell 2004). HBO, by reducing major ECM constituents like collagen and fibronectin, may facilitate the transport of anti-PD-1 Ab and T-cell infiltration into the tumor site. HBO-anti-PD-1 Ab combination is a promising clinical treatment for solid tumors due to HBO's ability to enhance the anticancer effect of anti-PD-1 Ab (Liu et al. 2021c).

Normalizing blood vessels

One significant feature of solid tumors is abnormal blood vessel growth. Hypoxia in the TME can stimulate tumor growth by stimulating the formation of new blood vessels and providing necessary nutrients for indefinite tumor growth. Abnormal tumor blood vascular proliferation is often due to factors such as angiopoietin, VEGF, vascular maturation, pericyte infiltration, proangiogenic mechanisms, and regulation of disorganization factors in tumor vasculature (Carmeliet and Jain 2011b). Furthermore, elevated tissue fluid pressure in the TME is caused by the leaky nature of tumor arteries (Jain 2013; Deng et al. 2021). Both drug delivery and immune cell infiltration are greatly impacted by the aberrant growth of tumor blood vessels. For example, drug delivery is limited by the atypical configuration of these abnormal blood arteries in malignancies. Medications often get caught in stromal tissue surrounding tumors, reducing local medication concentration and treatment effectiveness (Jain 2013). Abnormal vascular structure in tumor tissue reduces immune cell entry, leading to fewer immune cells in the TME, suppressing the antitumor immune response (Binnewies et al. 2018). Elevations in VEGF and other vascular growth factors have been shown in a number of preclinical investigations to result in vascular abnormalities (Chung et al. 2010). Inhibiting VEGF and other angiogenic factors can normalize tumor vascularity in the TME and enhance vaccine-based antitumor immunotherapy effectiveness (Huang et al. 2012). A study developed an injectable nanosystem for cancer treatment, consisting of PLGA microspheres, a VEGF inhibitor, and a poly (N-isopropyl acrylamide) hydrogel. The study revealed that 60% of mice treated with anti-VEGF-loaded DDS showed significantly lower lesion areas compared to untreated animals throughout the investigation (Osswald et al. 2017). Another study found PHCL-Lip/ETO-siVEGF, a pH/redox-sensitive polymer-based siVEGF and etoposide drug delivery vector that has the dual benefits of preventing angiogenesis and destroying tumors. Metastatic non-small cell lung cancer may be treated with this vector (Li et al. 2019). Gold NPs have shown promising results in short-term tumor targeting, resulting in transient vascular normalization, reduced permeability, improved vascular integrity, and increased blood perfusion (Li et al. 2016b). The combination of DC101 and combretastatin A4 NPs enhances anti-PD-1 therapy in hepatocellular carcinoma, promoting tumor vascular breakdown and normalization (Bao et al. 2021). Peptide amphipathic NPs containing an immune checkpoint blocking peptide and an antiangiogenic peptide can enhance the anticancer treatment efficacy (Taleb et al. 2021). NO is essential for maintaining vascular homeostasis and controlling angiogenesis. NanoNO, a nanosized carrier, enhances chemotherapeutic drug delivery, tumor vasculature normalization, and tumor immunotherapy efficacy in hepatocellular carcinoma, normalizing tumor vasculature and transforming immunosuppressive TME into an immunostimulatory phenotype. These delivered NO donors and therapeutic drugs using liposomes and PLGA-based nanocarriers (Sung et al. 2019). The release of NO in mice's H22 liver tumors restored tumor vasculature, enhancing the efficacy and delivery of chemotherapy drugs. Furthermore, two-dimensional ZnFe(CN)5NO nanosheets can be formed by combining Zn^{2+} with sodium nitroprusside, a therapeutic antihypertensive medication (Tian et al. 2019). TAMs significantly impact malignant tumor development and spread, contribute to tumor angiogenesis, promote immune evasion, and are predominantly polarized towards the M2 phenotype in the TME. M2 TAMs have been demonstrated to cause vascular abnormalities (Carmeliet and Jain 2011b). TAM M2 polarization can be blocked to efficiently ameliorate tumor vascular anomalies and enhance immunotherapy effects. The study demonstrated that targeting the M1 phenotype with TAM polarization could improve anti-tumor immunity and restore the tumor vascular system, which would prevent tumor growth and metastasis (Rolny et al. 2011). Histidine-rich glycoprotein overexpression may enhance the effectiveness of vascular normalization therapy and, consequently, the effects of immunotherapy (Theek et al. 2018). A study utilized erlotinib to increase TAM M1

polarization to normalize blood vessels and enhance the effectiveness of immunotherapy (Chen et al. 2017a).

Modulating acidity

Tumor cells preferably use glucose to make lactate and undergo ion exchange on their membrane due to their particular aerobic glycolysis circumstances. This leads to the formation of numerous acidic chemicals during the tumor advancement process. Weak acidity has been identified as a crucial feature of the TME. Normal cells cannot survive in acidic environments, and hypoxia is often present in acidic TMEs, which can further promote tumor growth. Furthermore, acidosis can result in neovascularization, and lactic acid can cause immunosuppression by preventing effector T cells from responding to the immune system. The common alkaline reagent that can lessen tumor-induced acidosis is sodium bicarbonate ($NaHCO_3$) (Pillai et al. 2019). Despite the fact that $NaHCO_3$ injection only temporarily neutralizes pH, it increases T-cell infiltration. Additionally, oral $NaHCO_3$ has been shown to neutralize the acidity of the TME in preclinical mice, preventing tumor growth and dissemination (Wang et al. 2021). The proton pump vesicular ATPase (V-ATPase) causes an acidic TME because it can move H^+ to the extracellular space. Therefore, inhibiting pH-regulating enzymes is an alternative, direct way to treat acidosis (Li et al. 2021c). The combination of BPTES and KM91104 in a ZIF-based nanodelivery system can significantly improve cancer treatment effectiveness by preventing proton efflux and reducing energy supply (Wang et al. 2022). Furthermore, buffered nanosystems based on NPs are a simple method to mitigate tumor acidity (Dong et al. 2016). Zhu et al. utilized calcium carbonate's properties to target azithromycin and NLG919, aiming to alter the TME and achieve effective immunotherapeutic efficacy (Zhu et al. 2021). Stopping aerobic glycolysis in tumor cells can enhance the TME's acidity and the effectiveness of tumor therapy. The study discovered a dimer-based nanosystem that synergistically increases tumor therapeutic benefits by combining the immune checkpoint inhibitor NLG919 with the glycolysis inhibitor lonidamine (Liu et al. 2021b). A nanodelivery system targeting mitochondria, containing dichloroacetate to normalize the TME and PDK1 suppressor, selectively inhibited glycolysis in cancer cells. The nanosystem was found to enhance immune responses when used in conjunction with anti-PD-1 treatment (Kolb et al. 2020). Suppressing lactate generation and excretion is an effective strategy for correcting the acidic environments of the TME, as lactic acid is a crucial component (Li et al. 2020c). Moreover, Zhao et al. improved colorectal cancer immunotherapy by self-assembling Ce6, SB505124, and Lon into TerBio biological regulators, modifying the tumor microenvironment with photodynamic therapy to initiate immune cascades (Zhao et al. 2022).

Reprogramming the ECM

Collagen, hyaluronic acid, proteins, enzymes, and other macromolecules produced by cells make up the complex network known as the ECM. The primary physical barrier preventing cells and medications from entering tumors is the ECM (Pickup et al. 2014). Encapsulated NPs with enzymes target ECM components in tumor lesions, improving treatment efficiency. The system consists of a nanoscale coordination polymer imbued with collagenase CLG and PEG. The system can rapidly degrade and release collagenase in the TME's low pH environment, resulting in a nearly seven-fold decrease in collagen content. It enhances the effectiveness of medication delivery and has a tumor-killing effect (Liu et al. 2018c). The development of rHuPH20, a new tumor treatment system, utilizes a lactate-glycolic acid-polyethylene glycol NP delivery system. The delivery mechanism enhances tumor permeability by breaking down HA in the ECM (Zhou et al. 2016). Furthermore, high IFP and dense ECM are common in tumor treatment and drug administration. A study discovered that MCdS-HA, a nanosystem targeting HA, can effectively control IFP in the TME and enhance tumor therapy results (He et al. 2021). Tumor cells release various growth and stimulatory molecules to influence the formation of the ECM. TGF-β is a protein that can stimulate proteases to produce CAFs, which aid in the synthesis and regulation of ECM proteins (Bonnans et al. 2014). A study developed self-assembling HES-Ce6, which consists of Ce6, hydroxyethyl starch, and TGF-β inhibitor LY2157299 to prevent TGF-β-mediated control of the tumor ECM and improve the results of photodynamic treatment (Chen et al. 2021). Chen et al. improved the TME by simultaneously blocking signals related to tumor cell ECM development (Chen et al. 2022).

Reprogramming TAMs

TAMs, a prevalent immune cell type in solid tumors, play a crucial role in carcinogenesis, growth, invasion, and metastasis. TAMs can be categorized into two groups: M1-TAMs, which exhibit anticancer properties, and M2-TAMs, which exhibit tumor-promoting characteristics (Biswas and Mantovani 2010). The most effective method for regulating tumor regression is to directly deplete TAMs, which are crucial for tumor angiogenesis, metastasis, and immune evasion. TAM depletion enhances local anticancer immune responses, prevents angiogenesis, tumor growth, and metastasis, according to research. There are two ways to start TAM depletion. Colony-stimulating factor 1 (CSF1) regulates

macrophage populations, with its tyrosine kinase receptor, CSF1R, enhancing survival, proliferation, and differentiation of monocytes and macrophages (O'Brien et al. 2021). Consequently, TAM depletion targets CSF1R. Bisphosphonates can inhibit new angiogenesis, induce apoptosis in TAMs, and ultimately prevent tumor development and spread. Researchers have utilized bisphosphonate liposomal formulations or NPs to target TAMs. Lipid-coated calcium zoledronate NPs were developed to precisely target TAMs and induce their death (Zang et al. 2019). A multipurpose nanoscale proteolytic chimera (nano-PROTAC) may target tumor-associated macrophages as well as lung cancer cells. The BRD4 super tail domain dBET6 was loaded onto the pH/glutathione responsive polymer DS-PLGA to form an agent capable of targeting lung cancer cells. Then, tumor-associated macrophages were specifically targeted using plasmid transfection (Zhang et al. 2022). Chemokines are crucial for TAM recruitment, and increased CCL2 production by tumor cells is often linked to poor prognosis (Mantovani et al. 2004). Chemoattractants, such as chemokines, cytokines, and CSF-1R, are common inducers that attract monocytes and M-MDSCs to tumor sites, promoting the development of TAMs (Argyle and Kitamura 2018). The development of TAM may be limited by targeting the related chemokines. NPs effectively prevented the development of TAMs, thereby extending the lifespan of tumor-bearing animals. Anti-CSF-1R siRNA was delivered for tumor immunotherapy (Qian et al. 2017). NF-κB, activator of STAT6, and STAT3 signaling are closely associated with TAM M2-like polarization (Genard et al. 2017). Blocking signaling pathways may prevent macrophages from polarizing into the M2 phenotype, which would inhibit tumor growth. The study developed a nanodrug that possessed dual properties of active targeting and TME responsiveness. First, they used pH-sensitive polyethylene glycol to encase the M2-targeting peptide. The nanomedicine, containing siRNAs targeting NF-κB kinase inhibitor (IKKβ) and STAT6 inhibitor AS1517499, was modified using this technique to form nanocomposites. The M2-targeting peptide is exposed to the tumor site when the nanocomplex reaches it, as it sheds its protective PEG shell under acidic TME conditions. The medication is delivered specifically to M2 macrophages, causing a phenotypic change and reducing side effects, resulting in a safe and efficient immunotherapy (Xiao et al. 2020). Kulkarni et al. supramolecular agent that can self-assemble into NPs with particular chemicals and bind selectively to SIRPα while blocking CSF-1R. TAMs can polarize macrophages towards the M1 phenotype by targeting them, inhibiting SIRPα receptor interaction, and disrupting the CSF-1R signaling pathway (Kulkarni et al. 2018). Resveratrol inhibits STAT3 activity, which lowers the M2-like polarization of TAMs (Sun et al. 2017). TAMs typically exhibit a protumor phenotype, but macrophages are significant phagocytes capable of presenting antigens. TAMs can transition from a protumor to an antitumor phenotype during tumor development and treatment, triggering the immune system to inhibit tumor growth (Shapouri-Moghaddam et al. 2018). There are various methods for achieving TAM repolarization. Blocking CD47/SIRPα signaling can repolarize TAMs, enhance their phagocytic capabilities, and reestablish the tumor cell clearance pathway. TLR agonists can polarize tumor antigen-presenting cells towards an anticancer phenotype by imitating microbial signals via TLRS. TLR activation by bacterial particles or viral nucleic acids can trigger the immune system, causing macrophages to polarize towards a proinflammatory M1 phenotype. Cancer can be prevented by controlling key kinases in signaling pathways linked to macrophage phenotypic polarization, such as PI3Kγ. Epigenetics can be used to induce TAM repolarization. The study developed a porous hollow iron oxide modified with mannose to target 3-methyladenine P13Kγ, a tumor-killing inhibitor, without affecting systemic immunity (Li et al. 2020d). Kim et al. found a nanoemulsion-based nanodelivery system. TLR7/8a agonists are administered using this delivery method in tumor immunotherapy (Kim et al. 2019). The promotion of effector T-cell proliferation, TAM polarization, and recruitment and proliferation can lead to effective anticancer immune responses and reduced side effects. A multifunctional UCCG nanocatalyst reverses TAM polarization and provides positive cancer immunotherapeutic properties by generating ROS through intracellular GSH reduction, allowing M2 macrophages to become M1 macrophages (Wang et al. 2023b). Furthermore, Song et al. demonstrated albumin NPs with paclitaxel and a PI3Kγ inhibitor in Science Translational Medicine. Researchers discovered that combining it with anti-programmed death 1 can enhance anti-tumor immunotherapy, leading to the remission of breast cancer tumors in mice (Song et al. 2022).

Reprogramming CAFs

CAFs not only inhibit immune cell activation but also prevent medications and immune cells from penetrating deep tumor tissues, thereby reducing the effectiveness of tumor treatment. A new method for cancer treatment involves tumor inhibition through CAF modulation or bypassing their barrier function. The development of nanocarriers is a key focus in tumor treatment research, aiming to target and regulate CAFs to prevent tumor progression and enhance therapeutic accumulation. It explores the use of nanocarriers to target CAFs for tumor treatment and presents innovative ideas to enhance tumor immunotherapy outcomes. Three treatment strategies are available for reprogramming CAFs:

directly killing CAFs, disrupting CAF function, and disrupting CAF activation (Chen and Song 2019). CAF depletion can greatly enhance the transport of nanomedicine and chemotherapeutic medications to cancer locations in addition to inhibiting tumor growth (Mpekris et al. 2017b). CAFs secrete collagen and other ECM proteins, forming a physical barrier that prevents medicines from infiltrating tumor tissue. Drugs have a higher chance of penetrating tumor tissue when CAFs are depleted due to decreased abundance of matrix components. Additionally, CAFs can increase the tumor's interstitial pressure, which could inhibit medication diffusion and blood flow. The distribution of drugs is enhanced when interstitial pressure decreases due to the depletion of CAF. The effects of different cytotoxic medicines on CAFs were tested using liposomes as carriers. Paclitaxel and acridine yellow effectively kill CAFs and prevent 3D tumor sphere formation in fibroblast and cancer cell coculture systems (Fourniols et al. 2020). Nicolas-Boluda et al. used Fe3O4-Au hybrid NPs to target liver cancer CAFs, then exposed them to laser radiation and photothermal effects to remove the tumor (Nicolás-Boluda et al. 2020). Moreover, Zhao et al. developed M-CPA/PTX, a nanosystem loaded with cyclopamine and paclitaxel, to treat pancreatic tumors by reducing connective tissue matrix proliferation, potentially improving chemotherapy antitumor effects, and preventing tumor growth (Zhao et al. 2018). CAF activation is the process by which tumor-secreted stimulatory substances like TGF-β/PDGF activate static fibroblasts. Interfering with stimulatory substances like TGF-β/PDGF is a promising method for inactivating CAFs, which are crucial for CAF activation. For instance, blocking the TGF-β/Smad/ROS pathway, boosting free fatty acid expression Blocking the TGF-β/Smad/ROS pathway, increasing free fatty acid expression, and using bromodomain protein 4 inhibitors can prevent CAF activation, while excessive TGF-β activation may increase ROS generation (Hossen et al. 2019).

Inhibition of immunosuppressive cells and factors

The interaction between neoplastic cells and host immune cells forms an immunosuppressive microenvironment, protecting tumor cells from immunological attack. This leads to immunosuppression and promotes tumor growth. Tumor growth, T-cell proliferation inhibition, and tumor immune evasion are all facilitated by immunosuppressive cells' continual secretion of immunosuppressive chemicals (such as TGF-β) (Binnewies et al. 2018). Tregs, MDSCs, and other cells are among these cells. Tregs play a crucial role in immunotherapy by secreting immunosuppressive mediators TGF-β and IL-10, and controlling the activity of CD4+and CD8+cells. MDSCs can suppress the immune system by producing cytokines that inhibit the function of antitumor immune cells, including T cells (Gabrilovich and Nagaraj 2009). A study formed an immunomodulatory nanoagent (FX/siPD-L1@HP) that inhibits CXCR4. Immunotherapy involves reducing MDSCs/Tregs in the TME, promoting tumor cell calreticulin expression, inducing T-cell infiltration, and working with siPD-L1. The study suggests that nanocomplexes blocking CXCR4 can reduce tumor fibrosis, promote T-cell infiltration, ease immunological suppression, and alter the immune system, thereby enhancing the effectiveness of immunotherapy. This drug enhances immune response, positive modulation by promoting dendritic cell maturation, antigen presentation, and increasing calreticulin exposure on tumor cell surfaces (Li et al. 2020b). Another study developed a nanoplatform using a cerium metal–organic framework and reloaded with CB839 and LOX. A ROS-responsive nanogel, infused with regorafenib and TGF-β inhibitors, has been developed to enhance tumor immunotherapy by reducing immune-suppressive cells and promoting killer cell infiltration (Feng et al. 2023). Furthermore, a study developed a nanomodulator, OTX+IDOI@MPDAs, using a dual immunosuppressant loaded with mesoporous polydopamine NPs, which effectively treats various diseases. The nanosystem enhanced the benefits of immunotherapy by promoting CTL activation, controlling M2 macrophage polarization, and greatly inhibiting the immunosuppressive actions of PD-L1/CD47/Tregs (Tian et al. 2023). Moreover, another study developed a ROS-responsive nanogel loaded with regorafenib and TGF-β inhibitors to enhance tumor immunotherapy by reducing immune-suppressive cells and promoting killer cell infiltration. Regorafenib, which prevents tumor growth and increases the generation of ROS, is the first medication that this nanosystem can accurately distribute sequentially. The substance produces LY, a TGF-β inhibitor, which prevents cancer cells from bypassing the immune system and undergoing the EMT triggered by elevated TGF-β. The sequential release process reduces tumor-associated macrophage and MDSC recruitment, boosts CD8+T cell infiltration, and promotes M2 to M1-type macrophage polarization. This nanosystem significantly enhances the effectiveness of tumor immunotherapy by targeting immune-suppressive cells (Li et al. 2022).

Nanomedicine enhances the TME by reprogramming metabolism

Modifying key nodes in tumor cell metabolism may mitigate the hostile TME by overexpressing transporters and enzymes, allowing tumor cells to absorb and catabolize numerous nutrients. These also release a variety of

immunosuppressive compounds. Additionally, altering the metabolism of CAFs and immune cells can strengthen anti-tumor immunity. Nonetheless, due to their limited absorption and significant toxicity from off-target effects, metabolism-modulating drugs are difficult to use. Nanomedicine can be utilized to provide metabolic modulators to specific cell types. NPs can passively gather in tumor areas owing to increased EPR effect, but can actively bind to certain cells via ligand-receptor interactions, like 2-Deoxyglucose (Minor et al. 2010). However, 2-DG nanovesicles that target tumor cells have the potential to eradicate lung cancer cells and show no noticeable harm to major organs 14 days after therapy (Li et al. 2023). Targeting immune cells within the TME can potentially modulate an immunosuppressive TME, as they are an essential constituent of the TME (Xiao et al. 2023; Xu et al. 2022). After treatment-induced tumor cell death, antigens are usually released to start a tumor–immunity cycle. These antigens can be absorbed and processed by immature DCs, which then mature. Mature DCs stimulate T lymphocytes by presenting antigen in tumor-draining lymph nodes. The circulatory system enables the entry of activated T lymphocytes into tumor sites. The most potent anti-tumor immune cells are CTLs, which secrete granzyme B, IFN-γ, and the Fas/FasL pathway. The tumor-immunity loop can sustainably continue due to the release of antigens from newly deceased tumor cells (Liu and Sun 2021). Glycolysis mediates DC and T cell activation. Restoring glycolytic components to DCs directly may be an efficient alternative. F-16BP MPs, containing melanoma antigens and an immune adjuvant, phagocytosed DCs, restoring glycolysis and increasing the CTL/Treg ratio, strengthening the immune response against melanoma (Inamdar et al. 2023). Additionally, aberrant lipid metabolism affects T cell priming and antigen cross-presentation in DCs. TOFA, a commonly used drug to inhibit FAS by reducing ACC, is less effective when taken orally due to its poor absorption and solubility in water. The study developed TPOP, a nanovaccine designed to manipulate lipid metabolism, composed of PLGA NPs loaded with TOFA and bacterial outer membranes. DCs effectively phagocytosed TPOP due to pattern recognition receptors that can identify pathogen-associated molecular patterns on the bacterial outer membrane. The TPOP nanovaccine may specifically target DCs. TPOP and DOX were delivered, causing the ICD effect to release tumor-associated antigens, which were then ensnared using the Michael addition process. The TPOP nanovaccine enhanced DC maturation and antigen presentation while lowering intracellular levels of triglycerides and cholesterol esters. The TPOP nanovaccine effectively suppressed primary tumor and distant lesions in B16F10 tumor-bearing mice by increasing effector memory T cell populations and anti-tumor cytokine levels (Qin et al. 2023). Phosphoenolpyruvate increases T cell activation and cytotoxic effector molecule production (Ho et al. 2015). Furthermore, CD8+T lymphocytes upregulate FAO and peroxisome proliferator-activated receptor-α (PPAR-α) to sustain their anti-tumor activity in a glucose-deficient environment (Zhang et al. 2017b). Kim et al. incorporated fenofibrate, a PPAR-α agonist, into modified NPs (aCD3/F/ANs) with anti-CD3e f (ab')2 fragments for targeted T cell delivery. It was shown that CD3+T cells exclusively absorbed aCD3/F/ANs. By upregulating the expression of the associated enzymes and transporters, aCD3/F/ANs activated PPAR-α, which in turn increased FAO in T cell mitochondria. The nanomedicine significantly inhibited the growth of B16F10 tumors by increasing the number of tumor-infiltrating CD8+T cells and enhancing their cytokine production (Kim et al. 2021).

Conclusion and future perspectives

Nanotechnology's potential to revolutionize cancer treatment has been evidenced in preclinical models and early clinical trials through its application to TME-targeted strategies. Nanomedicine's progress in clinical use is hindered by issues such as scalability, safety, regulatory approval, and tumor heterogeneity, despite advancements in laboratory research. Nanomedicine is a revolutionary approach in oncology that provides innovative solutions to the persistent challenges of the TME. Researchers are using smart, multifunctional nanocarriers to enhance therapeutic outcomes, overcome physical and biological barriers in the TME, and reconfigure immunosuppressive elements. The review highlights the development of intelligent nanocarriers, which are stimuli-responsive NPs that enable precise drug release within the TME. Nanomedicine platforms can enhance anti-tumor immunity by rewiring immunosuppressive elements of the TME, such as regulatory T cells and TAMs. Nanotherapeutics can improve medication delivery and oxygenation by restoring normalcy to aberrant tumor vasculature. Multimodal therapy, a combination of nanomedicine, immunotherapy, photothermal therapy, and chemotherapy, effectively targets multiple TME components simultaneously. Clinical trials are started for TME-targeting nanomedicine formulations, promising for treatment and safety, but still grappling with scalability and reproducibility issues. The future advancements in nanomedicine should focus on precision, customization, and predictability. Advancements in biomimetic nanocarriers, AI-driven nanomedicine design, and patient-specific TME profiling are expected to drive personalized treatment solutions. Standardized manufacturing procedures, reliable 3D tumor models, and therapeutically relevant animal models are crucial to bridge the gap

between preclinical results and human applications. Prioritize multimodal therapies that combine nanomedicine with immunotherapy, gene therapy, and phototherapy to target the TME in performance. The increasing interdisciplinary cooperation between materials scientists, oncologists, and clinicians could lead to nanomedicine becoming a crucial component of precision oncology in the future.

Acknowledgements The authors are thankful to their own institutions and to the Deanship of Research and Graduate Studies, King Khalid University, Abha, Saudi Arabia, for financially supporting this work through the Large Research Group Project under Grant no. R.G.P.2/543/46.

Funding This research received no external funding.

Data availability All data supporting the findings of this study are available in the paper.

Declarations

Conflict of interest The authors declare no conflict of interest.

Human ethics and consent to participate Not applicable.

Institutional review board statement Not applicable.

Informed consent statement Not applicable.

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