REVIEW
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Diseases & Research

Nanocarrier Design Based on the Tumor Microenvironment Target: A Pivotal Direction in Nano-Drug Delivery Strategies

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Abstract: The tumor microenvironment (TME), characterized by its distinct inflammatory profile, acidic pH levels, and hypoxic conditions, holds a pivotal position in regulating tumor behavior, thereby rendering it paramount for devising effective therapeutic strategies. Nanocarriers specifically designed to target the TME have emerged as promising agents in oncology treatment paradigms, attributing to their heightened targeting specificity, extensive drug loading capacity, and versatility in executing multifaceted therapeutic interventions. However, traditional nanoparticles design based on passive targeting are gradually proving to be difficult to achieve efficient delivery. How to design targeting carriers based on the tumor microenvironment and how to achieve rapid and precise delivery by modifying ligands, which here listed as pivotal and challenging issues in nanomedicine development. This comprehensive review delves into the intricate designs of drug delivery systems tailored for the TME, which exhibit specific and microenvironment-responsive characteristics. It explores both passive and active targeting methodologies, highlighting the challenges posed by the tumor's enhanced permeability and retention effects, along with the potential of ligand-mediated active targeting. Furthermore, it applauds the advancements in innovative treatments that capitalize on the unique attributes of the TME to enhance drug efficacy and optimize patient outcomes. Our novelty focused on a comprehensive summary of recent studies concerning nanocarriers that target the tumor microenvironment, proposes future directions and conceptual frameworks for the development of targeting ligands, examines potential targets within the tumor microenvironment, and concludes with a perspective on strategic approaches pertaining to the engineering of pertinent nanocarriers.

Keywords: Tumor microenvironment; Nanocarriers; Passive target; Active target.

Introduction

Biological behaviors such as tumorigenesis, proliferation, metastasis, invasion, and evasion all manifested within the TME. Therefore, isolating and studying any single cell in the TME often failed to reveal the full picture of the tumor in a comprehensive manner[1,2]. According to the current study, the TME was surrounded by non-malignant extratumoral stromal cells, which were interconnected with the external environment via tumor microvessels and microlymphatics. Internally, malignant tumor cells, immune cells, and other stromal cells composed a highly heterogeneous system. The TME had a unique inflammatory profile, acidic PH, and hypoxic environment, which were exacerbated in necrotic tissues as the tumor moves from the outside in. Developing effective tumor treatment strategies required a deeper understanding of these TME properties. Future studies needed to further investigate the complexity of the TME and explore precise therapeutic approaches that target its unique characteristics for enhanced tumor control and treatment efficacy[1].

Nano-based drug-carrying particles have been demonstrated significant potential and advantages in the field of tumor therapy and were regarded as a cutting-edge effective strategy[3-5]. Through fine structural modification, nanocarriers could be engineered to carry ligand molecules that specifically target tumor cells, achieving precise targeting and attack on tumor cells. This property rendered nanocarriers highly targeted and precise in tumor therapy[6-8]. The three-dimensional carrier structure of nanocarriers gave them a considerable loading capacity, enabling them to be synergistically loaded with a variety of different therapeutic agents. This synergy among multiple therapies not only improved the efficacy of drugs but also reduced the side effects and achieves a safer and more effective treatment. During the drug release process, nanocarriers could be released in the desired order, thus enabling multi-pathway cascade therapy. This approach could fully utilize the synergistic effect of various drugs to efficiently kill tumor cells while minimizing the damage to normal cells.

In the present article, we discussed mechanisms of TME-based tumor pathology and potential molecular targets of reported drug delivery strategies (Fig. 1). We also addressed the limitations of passive targeting strategies of nanocarriers, as well as the repor-

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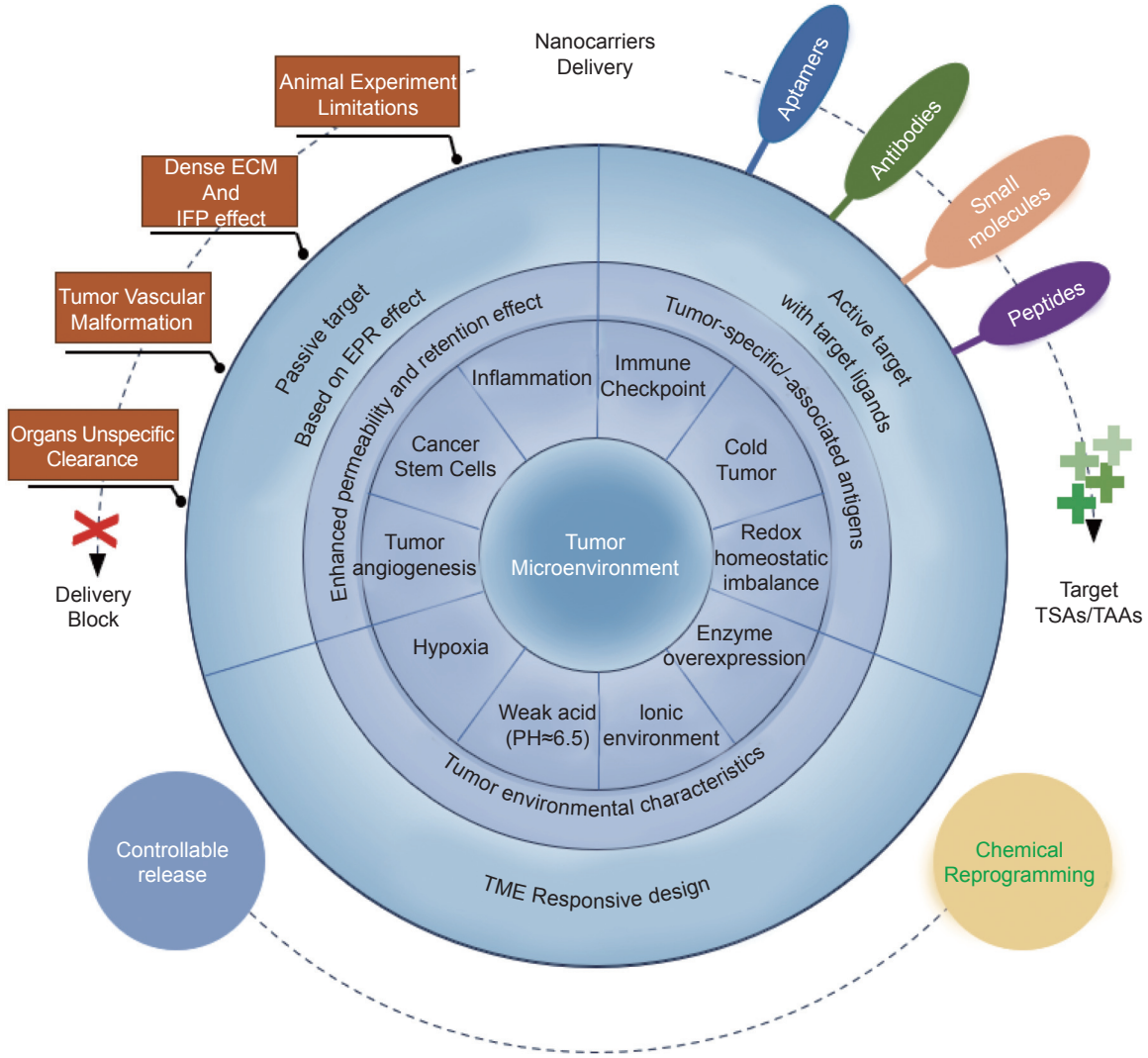

Fig. 1. It was underscored the significance of TME-targeted drug delivery systems in advancing novel therapeutic strategies for cancer treatment. The distinctive characteristics of the TME and how these features could be leveraged through both passive and active targeting approaches to enhance the efficiency of nanocarrier-mediated drug delivery, thereby overcoming the challenges posed by the TME.

ted active targeting-based nanocarriers. Additionally, we discussed the specificity of the tumor microenvironment and microenvironment-responsive design. The objective of this review is to assess recent reports and to propose potential avenues for the advancement of targeting nanocarriers in response to the characteristics of the tumor microenvironment.

Tumor microenvironment and delivery strategy

Microenvironment-responsive drugs showed great potential in tumor therapy as an innovative therapeutic approach[6-8]. The TME markedly differed from the normal cellular environment (Fig. 2), exhibiting the following characteristics[1,2]: (1) A weakly acidic microenvironment (pH ≈ 6.5). (2) Overexpression of enzymes, such as matrix metalloproteinase 2 (MMP-2), histone B (Cathepsin B), and alkaline phosphatase. (3) Imbalance in redox homeostasis, as evidenced by a substantial increase in the disparity between intra- and extracellular oxidation-reduction potentials. The redox potential difference between the intracellular and extracellular environments in the TME resulted in a hypoxic and reducing state, characterized by disruptions in glutathione metabolism and elevated intracellular oxidative stress levels. (4) Elevated inflammation levels were attributed to the release of inflammatory factors and chemokines from a significant number of apoptotic or necrotic tumor cells, which subsequently recruit numerous inflammation-associated cells to infiltrate the TME, leading to a robust inflammatory response. (5) Ionic homeostasis imbalance was characterized by high extracellular concentrations of ions (e.g., Na + , K + , etc.) in the TME, which maintained the intracellular microenvironment and regulate the physiological state of the cells. (6) Immunosuppression was evident through immune checkpoint-mediated mechanisms in the TME, resulting in reduced inflammation and diminished infiltration of immune cells, leading to the characteristic features of “cold” tumors.

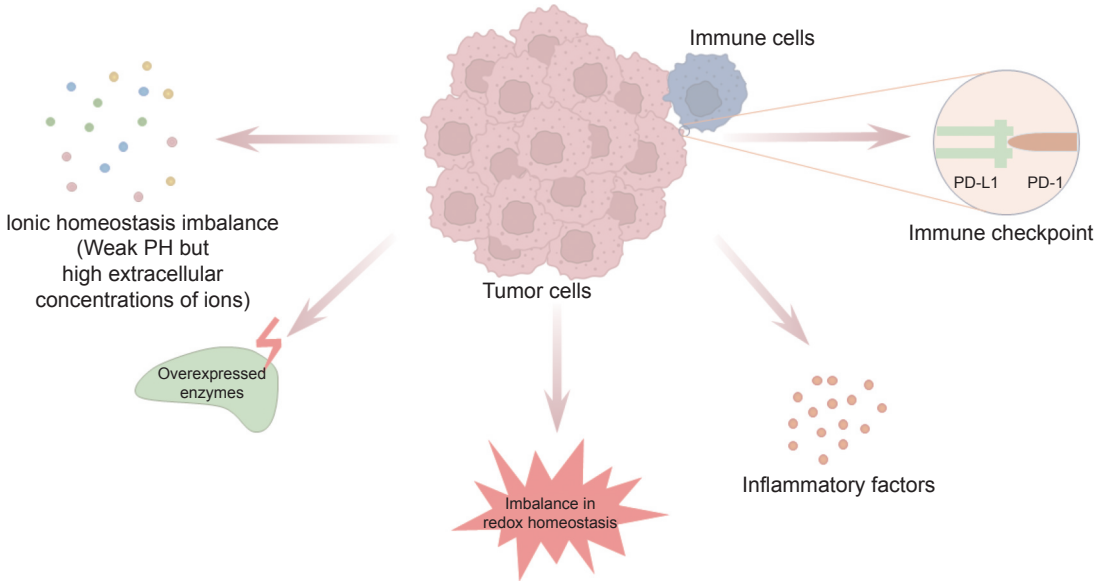

Fig. 2. The TME markedly differed from the normal cellular environment with ionic homeostasis imbalance, overexpressed secrete enzymes, redox homeostasis imbalance, upregulated inflammatory factors and overexpressed immune checkpoints. These features mediate TME different from normal extracellular matrix in chemical, physical and biological aspects.

Limitations of passive targeting strategies of nanocarriers

The EPR effect was mainly based on two histologically based premises: Firstly, the high permeability due to the laxity of the endothelial interstitial space of the tumor's neoplastic vascular system allowed optimal access to the tumor tissue for drug particle sizes of 6-8 nm, or greater than 40 kDa[9,10]; And secondly, the obstruction of lymphatic reflux caused by defects in the tumor lymphatic system was the primary reason for the accumulation of drug particles within the TME[10].

It had been pointed out that current studies of EPR effects in tumor tissues tend to oversimplify the complexity. This was because the highly heterogeneous nature of human tumor tissues and the complexity of the TME collectively influence the efficiency of tumor drug delivery based on the EPR effect, primarily due to the dense extracellular matrix (ECM) and elevated interstitial fluid pressure (IFP) levels of tumor tissues. The ECM could be divided primarily into the basement membrane (BM), which supported the epithelial cells, and the interstitial matrix (IM)[1]. The BM is a thin, pliable membrane that must firstly be breached during the spread of tumor cells. Tumor cells secreted ECM remodeling enzymes (e.g., matrix metalloproteinases) to penetrate and destroy the basement membrane. However, from this perspective, the BM of the tumor ECM did not appear to differ much structurally from that of normal tissues and was therefore unlikely to pose a significant obstacle to drug delivery. On the other hand, the interstitial matrix (IM) was looser and consists of collagen fibers, elastin fibers, glycoproteins, and so on. With in some of the tumor intracellular environment, the collagen fiber layer becomes thicker, more ordered, and denser as collagen fiber deposition increased. This change not only promoted tumor invasion but also posed a great obstacle to nanomedicine delivery[1]. Additionally, the compression of the surrounding normal tissues by the dense ECM and proliferating tumor mass resulted in higher levels of interstitial fluid pressure (IFP) in the TME. High levels of IFP not only promoted tumor cell migration and invasion, accelerating cancer progression[11,12], but also significantly reduced the delivery efficiency of targeted drugs. From a kinetic point of view, a pressure difference should be overcome while drugs have been delivered from a blood vessel to a target tissue. However, since the IFP of tumor tissues was similar to its surrounding microvascular levels, this resulted in difficulties for the drug to diffuse efficiently into the interior of the tumor tissue and penetrate the ECM into the central region[13]. Therefore, high IFP was considered to be a key factor preventing the targeting of nanocarriers to tumor tissues. Lowering IFP was considered a potential strategy to enhance the EPR effect.

Notably, when discussing the EPR effect of nanocarriers targeting tumors, we tended to assume that nanocarriers should be efficiently delivered to the periphery of tumor tissues through the bloodstream. However, the aberrant structure of the tumor vascular system challenged the premise. Although the mechanism of tumor angiogenesis was not been fully clarified, it had been suggested that tumor vascularization was closely related to the hypoxic state of the TME and the regulation of angiogenesis by VEGF secreted by a variety of cells in the TME[9,14-16]. During tumorigenesis and progression, over-proliferating tumor cells were often in a state of high oxygen consumption and nutrient deficiency, leading to a hypoxic microenvironment tin the TME[9]. Under well-oxygenated conditions, HIF-1α and HIF-2α were hydroxylated by PDH and FIH-1 and degraded via the proteasome-mediated ubiquitination pathway. However, in the hypoxic microenvironment of tumors, the activity of FIH-1 and PHDs was reduced and failed to hydroxylate HIF-1/HIF-2α, resulting in the intracellular accumulation of these proteins. The accumulated HIF-1/HIF-2α dimer entered the nucleus and activates genes related to angiogenesis (e.g., VEGFA, VEGFR1, MMP2, ANGPT), thereby promoting angiogenesis in tumors[14]. On the other hand, due to hypoxia, the expression of VEGF/VEGFR was upregulated, and these factors mediated the abnormal growth of vascu-

lar endothelial cells by activating the RAF/MEK/MAPK and PI3K/AKT signaling pathways to regulate the processes of cell proliferation, migration, and invasion[15,16], resulting in an increase in the density of capillaries that exhibited a multibranched morphology and disorganized orientation[17,18]. Overall, vascular disorganization at the tumor margins not only hindered oxygen delivery and exacerbated hypoxia in the TME but may also leaded to vascular necrosis in the central region of the tumor. Together, these factors obstruct blood flew within the TME, thereby limiting the effective delivery of nanocarriers[19].

Nanocarriers delivery strategies based on active targeting ligands

There had been documented a variety of targeting ligands, each with distinct attributes, enabling their application to diverse nanocarriers tailored to specific clinical or experimental requirements. Here enumerated and detailed currently available mature ligand species for recognition.

Monoclonal antibodies demonstrated highly selective binding to target cell surface antigens through antigen-antibody specific binding reactions, particularly when directed against molecular markers overexpressed on the surface of tumor cells. Leveraging this property, monoclonal antibody-drug conjugates (ADCs) had been developed and shown significant potential in tumor therapy. ADCs not only markedly reduced the side effects of drugs and enhanced their efficacy but also achieved efficient and precise drug delivery[6-8].

Aptamers, also known as nucleic acid aptamers, were short-stranded oligonucleotide sequences obtained through in vitro screening techniques. They exhibited high affinity and specificity for particular receptors, making them effective tools for efficient and rapid recognition and binding of overexpressed antigens. Additionally, aptamers possessed advantages such as low molecular weight, low immunogenicity, stable structure, and ease of synthesis and modification[20,21]. Small molecule ligands offered advantages over large molecule antibody ligands due to their ease of modification, small molecular weight, stable structure, and low immunogenicity. Short sequence peptides, commonly referred to as targeting peptides or homing peptides, were frequently utilized as ligands for nanoparticle modification. Targeting peptides offered significant advantages due to their high affinity and specificity for target receptors.

Monoclonal antibodies and nanobodies ligands

Monoclonal antibodies themselves possessed diverse tumor cell-killing mechanisms, such as mediating antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)[22,23], while also binding to membrane antigenic epitopes of tumor cells with high affinity, thus mitigating their mediated immunosuppression and immune escape[24,25]. Consequently, nanocarriers conjugated with monoclonal antibodies often exhibited higher efficacy than standalone drugs. Presently, the development of monoclonal antibodies was well-established, enabling the creation of antibodies targeting specific tumor surface overexpression antigens[26-35] in Table 1. These antibodies had also become valuable raw materials for the semi-synthesis of nanocarriers. Notably, monoclonal antibody nanocarrier platforms targeting immune checkpoints (ICBs) presented a promising strategy for immune reprogramming of the tumor microenvironment. These drugs not only modulated the immunosuppressive state but also delivered drugs that, in synergy with loaded chemotherapeutic drugs or photosensitizers, could cascade to induce tumor cell death. ICBs overexpressed on the tumor surface include CTLA-4, PD-L1, TIM-3, B7-1, BTLA, VISTA, LAG-3, among others, with nanocarriers designed based on PD-L1 and CTLA-4 becoming the most common platforms for immune-suppression modulation by targeting ICBs[36-37].

Additionally, a "rapidly assembled" monoclonal antibody-modified nanocarrier technology had garnered significant attention. This approach employed aPD-L1 monoclonal antibody to modify PLGA carriers, crosslinking the antibody Fc fragment with the carrier drug during nanoparticle preparation, and subsequently combining the active Fab segment with Fc-PLGA as needed. This innovative method offered a new strategy for drug discovery characterized by rapid preparation, immediate use, extended storage time, and ease of transportation[38]. In addition to monoclonal antibodies, nanobodies (Nbs) had garnered attention for their outstanding solubility, stability, antigen affinity, and deep tissue penetration, offering new possibilities in the realm of tumor therapy[39].

Aptamers targeting ligands

The aptamer screening process relied on SELLEX technology, which enabled precise construction of target antigens through data mining and structural analysis[8]. For instance, Kianpour et al.[40] investigated the potential inducing effect of CEMIP2 on cancer cell metastasis. Through data mining and structural domain deletion localization analysis, they identified the role of the PANDER structural domain of CEMIP2 in mediating tumor migration. Subsequently, they successfully screened the specific

Table 1. The nanocarriers based on monoclonal antibodies targeting tumor specific or associated antigens.

Monoclonal Antibodies	Targeting TSAs/TAAs	References
Cetuximab	EGFR	[24,25]
Trastuzumab	HER-2	[26-28]
Bevacizumab	VEGF	[29,30]
Rituximab	CD20	[31]
Anti-CD147 monoclonal antibody	CD147	[32,33]

aptamer aptCEMIP2-100 using Cell-SELLEX technology and developed a mesoporous nano-loading platform carrying doxorubicin based on this finding. The range of targets recognized by aptamers was extensive[41-48] , as shown in Table2.

Table 2. The nanocarriers modified aptamers targeting tumor specific or associated antigens.

Aptamers	Targeting TSAs/TAAs	References
AS1411 aptamer	Nucleolin	[41-43]
HApt aptamer	HER-2	[44]
Sgc8c aptamer	PTK7	[45]
EPCAM DNA aptamer	EPCAM	[46]
5TR1 aptamer	MUC-1	[47,48]

Despite their potential, aptamers also exhibited limitations, such as susceptibility to degradation by nucleases, renal clearance, potential chemical and immunogenic toxicity during synthesis, and possible conformational changes in the tumor microenvironment, affecting their pharmacokinetic properties[49]. To address these limitations, protecting and structurally modifying aptamers showed crucial. Modification strategies based on specific responses to the TME for drug release were considered effective solutions. For instance, Yang et al.[45] utilized a homo-structured $mSiO_2$ material to protect the sgc8c aptamer, enabling drug release in response to pH changes in the TME, thereby achieving the desired therapeutic effect with reduced toxicity.

Small molecules and short sequence peptides ligands

These characteristics facilitated the entry of small molecules into the TME, thereby reducing toxicity and side effects in the circulatory system[6-8,49]. Folic acid served as a commonly used small-molecule targeting ligand due to its dependence on folate metabolism, particularly in metabolically active tumor cells[50-52]. Moreover, small molecule ligands targeting tissue-specific antigens or receptors represented a promising strategy[53-62] in Table 3. However, small molecule ligands encountered challenges due to their small molecular weights, including off-target effects resulting from high mobility and difficulty in achieving effective receptor contact due to their small binding area.

The wide application of random peptide sequence strategies in peptide ligand design had enabled researchers to develop targeting peptide ligands with high compatibility and selectivity against specific antigens found in various organs, tissues, or cell types[6-8,63]. One of the most well-known targeting peptides was the cRGD peptide, composed of three amino acid residues-Arg-Gly-Asp-capable of binding specifically to the integrin receptor αVβ3, which exhibited high expression in the endothelium of neoplastic tumor vessels. Nanocarriers designed using cRGD as a basis had shown notable selectivity and specificity in targeting diverse malignant tumors including ovarian cancer, non-small cell lung cancer, colon cancer, breast cancer, and osteosarcoma[63]. Several targeting peptides had been documented[64-68], which had been shown in Table 4. Nonetheless, current challenges revolved around achieving a substantial accumulation of peptide-drug couplings at the target site and ensuring effective target recognition at the molecular level.

Table 3. The nanocarriers connected with small molecular ligands which target tumor specific or associated antigens.

Small Molecules	Targeting TSAs/TAAs	References
Folic acid	Folic acid receptor	[50-52]
Glucose derivatives	GLUT-1	[53,54]
Urea derivatives	PSMA	[55,56]
Glycyrrhizic acid derivatives	GA-R	[57,58]
Hyaluronic acid	CD44	[59,60]
Phenylboronic acid	sialic acid	[61,62]

Table 4. The nanocarriers coupled with short sequence peptides which target tumor specific or associated antigens.

Short Sequence Peptides	Targeting TSAs/TAAs	References
cRGD peptide	Integrin receptor αvβ3	[63]
F56 peptide	VEGFR1/3	[64,65]
Esbp peptide	E-selectin	[66]
F3 peptide	Nucleolin	[67,68]

Opportunities and Challenges

Broadly speaking, the development of nanocarriers specifically tailored to the TME represented a promising and valuable field of study. On the one hand, the TME's unique characteristics, which amplified the uniqueness of tumor cells from the cellular level to

the tissue level, offered innovative avenues for the tracking and diagnosis of exogenous drug probes. Furthermore, the engineering of TME-responsive nanocarriers, informed by the TME's physicochemical properties and employing multi-level targeting strategies, held the potential to actualize the paradigm of integrated diagnosis and therapy. On the other hand, the distinct physicochemical and biological attributes of the TME facilitated a diverse array of options for the modification of targeting ligands and the encapsulation of therapeutic agents, thereby enhancing the efficacy of combined therapeutic approaches.

Nevertheless, akin to the challenges encountered by many novel anti-tumor drugs, TME-based nanocarriers confronted the critical challenge of clinical translation, compounded by the inherent uncertainties regarding their therapeutic efficacy and potential toxicity. These issues underscored the necessity for rigorous preclinical assessments and comprehensive clinical investigations to address the complexities and paved the way for their eventual clinical application.

Conclusion

The mechanisms that underpin TME-based tumor pathology and the molecular targets implicated in reported drug therapeutic strategies were systematically summarized. Limitations had been critically assessed inherent to passive targeting strategies of nanocarriers and underscored the significant advancements in the development of active targeting-based nanocarriers. The specificity of the tumor microenvironment and the critical role of microenvironment-responsive design were emphasized. There had been documented a variety of design strategies for TME-targeted drugs, which enhanced therapeutic efficacy by responding to specific microenvironmental cues, such as acidic PH, hypoxia, enzyme overexpression, and reductive conditions. To surmount the challenges related to drug distribution and efficacy at the tumor site, researchers had proposed actively targeted nanodrugs and environmentally responsive drug delivery strategies that were specifically tailored to the characteristics of the TME. The microenvironment- responsive drug release affect the targeting of internal tumor cells within the TME that the ligands on the surface of nanocarriers effectively could recognize antigens or receptors specific to the microenvironment, the capabilities of nanorobotics for targeted drug delivery and these systems be seamlessly integrated into biological processes were also summarized and discussed. The development of drug-loaded nanoparticles targeting tumor microenvironment has also gained attention. The emerging development of conventional chemotherapeutic drug delivery systems based on nanocarriers provides a viable option for a new generation of low-toxicity, high-precision, and high-efficacy oncology therapeutic strategies[69-73].

Overall, our study delivered an exhaustive overview regarding the distinctive physicochemical and biological characteristics of the tumor microenvironment that underpins the design of nanocarriers. Furthermore, this paper also reviewed the existing targeting ligands comprehensively across distinct sections, as well as their respective benefits and drawbacks. With ongoing advancements in research and technological developments, it was anticipated that more innovative therapies would be translated into clinical practice in the future. These developments held the promise of overcoming current limitations and improving patient outcomes in the realm of oncology.

Abbreviations

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; AKT, protein kinase B; ANGPT, Angiopoietin; RAF, serine/threonine kinase; B7-1, B-lymphocyte activation antigen 7; BM, basement membrane; BTLA, B and T lymphocyte attenuator; CD, cluster of differentiation; CDC, complement dependent cytotoxicity; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; EPR effect, enhanced permeability and retention effect; FIH, factor Inhibiting HIF; GA-R, glycyrrhizinic acid receptor; GLUT-1, glucose transporter 1; HER-2, human epidermal growth factor receptor 2; HIF, hypoxia inducible factor; ICB, immune checkpoint blockade; IFP, interstitial fluid pressure; IM, interstitial matrix; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MMP-2, matrix metalloproteinase 2; MUC-1, mucins 1; Nbs, nanobodies; SELLEX, systematic evolution of ligands by exponential enrichment; CEMIP2, cells in motion program 2; PANDER, pancreatic-derived factor; PDH, pyruvate dehydrogenase; PD-L1, programmed cell death 1 ligand 1; PH, pondus hydrogenii; PI3K, phosphoinositide 3-kinase; PIK7, protein tyrosine kinase 7; PLGA, poly(lactic-co-glycolic acid); PSMA, prostate-specific membrane antigen; TIM-3, T cell immunoglobulin domain and mucin domain-3; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor; VISTA, V-type immunoglobulin domain-containing suppressor of T cell activation; LAG-3, lymphocyte activation gene 3.

Conflicts of interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Figures and tables were created by ourselves originally.

Authors' contributions

ZRZ wrote the manuscript, prepared all tables and figures, and conducted the most of the work. XYK assisted in analysis of all data and revised the manuscript. ZJW assisted in preparation of figures and tables and revised the manuscript. YHC provided the initiate thought and assisted in idea design. JL designed and raised up the idea, and revised the manuscript. All authors read and approved the final manuscript.

References

[1] de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell, 2023, 41(3): 374-403.

[2] Lu Q, Kou D, Lou S, et al. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. J Hematol Oncol, 2024, 17(1): 16.

[3] Holghoomi R, Kharab Z, Rahdar A, et al. Harnessing the power of green synthesis of nanomaterials for anticancer applications: A review. Coordin Chem Rev, 2024, 513: 215903.

[4] Pourmadadi M, Shaghaghi M, Arshad R, et al. Polymeric and non-polymeric oxaliplatin nanomedicine for cancer therapy: A comprehensive review. Eur Polym J, 2024, 208: 112870.

[5] Alipournazari P, Pourmadadi M, Abdouss M, et al. Enhanced delivery of doxorubicin for breast cancer treatment using pH-sensitive starch/PVA/g-C3N4 hydrogel. Int J Biol Macromol, 2024, 265: 130901.

[6] Xin Y, Huang Q, Tang JQ, et al. Nanoscale drug delivery for targeted chemotherapy. Cancer Lett, 2016, 379(1): 24-31.

[7] Yang J, Zhao Y, Zhou Y, et al. Advanced nanomedicines for the regulation of cancer metabolism. Biomaterials, 2022, 286: 121565.

[8] Da J, Di X, Xie Y, et al. Recent advances in nanomedicine for metabolism-targeted cancer therapy. Chem Commun, 2024, 60(18): 2442-2461.

[9] Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer, 2003, 3(6): 401-410.

[10] Choi HS, Liu W, Misra P, et al. Renal clearance of quantum dots. Nat Biotechnol, 2007, 25(10): 1165-1170.

[11] Kanapathipillai M, Brock A, Ingber DE. Nanoparticle targeting of anti-cancer drugs that alter intracellular signaling or influence the tumor microenvironment. Adv Drug Deliv Rev, 2014, 79-80: 107-118.

[12] Khawar IA, Kim JH, Kuh HJ. Improving drug delivery to solid tumors: priming the tumor microenvironment. J Control Release, 2015, 201: 78-89.

[13] Gao X, Zhang J, Huang Z, et al. Reducing Interstitial Fluid Pressure and Inhibiting Pulmonary Metastasis of Breast Cancer by Gelatin Modified Cationic Lipid Nanoparticles. ACS Appl Mater Interfaces, 2017, 9(35): 29457-29468.

[14] Paul SA, Simons JW, Mabjeesh NJ. HIF at the crossroads between ischemia and carcinogenesis. J Cell Physiol, 2004, 200(1): 20-30.

[15] Liu ZL, Chen HH, Zheng LL, et al. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduct Target Ther, 2023, 8(1): 198.

[16] Dianat-Moghadam H, Nedaeinia R, Keshavarz M, et al. Immunotherapies targeting tumor vasculature: challenges and opportunities. Front Immunol, 2023, 14: 1226360.

[17] Höckel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. J Natl Cancer Inst, 2001, 93(4): 266-276.

[18] Vaupel P, Mayer A, Höckel M. Tumor hypoxia and malignant progression. Methods Enzymol, 2004, 381: 335-354.

[19] Stylianopoulos T, Munn LL, Jain RK. Reengineering the Tumor Vasculature: Improving Drug Delivery and Efficacy. Trends Cancer, 2018, 4(4): 258-259.

[20] Kim M, Kim DM, Kim KS, et al. Applications of Cancer Cell-Specific Aptamers in Targeted Delivery of Anticancer Therapeutic Agents. Molecules, 2018, 23(4).

[21] Agwa MM, Elmotasem H, Moustafa RI, et al. Advent in proteins, nucleic acids, and biological cell membranes functionalized nanocarriers to accomplish active or homologous tumor targeting for smart amalgamated chemotherapy/photo-therapy: A review. Int J Biol Macromol, 2023, 253: 127460.

[22] Van Wagoner CM, Rivera-Escalera F, Jaimes-Delgadillo NC, et al. Antibody-mediated phagocytosis in cancer immunotherapy. Immunol Rev, 2023, 319(1): 128-141.

[23] Wong JKM, Dolcetti R, Rhee H, et al. Weaponizing natural killer cells for solid cancer immunotherapy. Trends Cancer, 2023, 9(2): 111-121.

[24] Salik B, Smyth MJ, Nakamura K. Targeting immune checkpoints in hematological malignancies. J Hematol Oncol, 2020, 13(1): 111.

[25] Park JE, Kim SE, Keam B, et al. Anti-tumor effects of NK cells and anti-PD-L1 antibody with antibody-dependent cellular cytotoxicity in PD-L1-positive cancer cell lines. J Immunother Cancer, 2020, 8(2).

[26] Shukla VN, Vikas, Mehata AK, et al. EGFR targeted albumin nanoparticles of oleanolic acid: In silico screening of nanocarrier, cytotoxicity and pharmacokinetics for lung cancer therapy. Int J Biol Macromol, 2023, 246: 125719.

[27] Elechalawar CK, Gulla SK, Roy RV, et al. Biodistribution and therapeutic efficacy of a gold nanoparticle-based targeted drug delivery system against pancreatic cancer. Cancer Lett, 2024, 589: 216810.

[28] Myat YY, Sahatsapan N, Rojanarata T, et al. Antibody-decorated chitosan-iodoacetamide-coated nanocarriers for the potential delivery of doxorubicin to breast cancer cells. Int J Biol Macromol, 2024, 258(Pt 1): 128797.

[29] Zhao L, Chang F, Tong Y, et al. A Multifunctional Bimetallic Nanoplatform for Synergic Local Hyperthermia and Chemotherapy Targeting HER2-Positive Breast Cancer. Adv Sci, 2024, 11(16): e2308316.

[30] Yin Q, Gao X, Zhang H, et al. Fe_3O_4-Cy5.5-trastuzumab magnetic nanoparticles for magnetic resonance/near-infrared imaging targeting HER2 in breast cancer. Biomed Mater, 2024, 19(3).

[31] Di Filippo LD, Lobato Duarte J, Hofstätter Azambuja J, et al. Glioblastoma multiforme targeted delivery of docetaxel using bevacizumab-modified nanostructured lipid carriers impair in vitro cell growth and in vivo tumor progression. Int J Pharm, 2022, 618: 121682.

[32] Salvanou EA, Kolokithas-Ntoukas A, Prokopiou D, et al. ^{177}Lu-Labeled Iron Oxide Nanoparticles Functionalized with Doxorubicin and Bevacizumab as Nanobrachytherapy Agents against Breast Cancer. Molecules, 2024, 29(5).

[33] Khodakarami A, Kashani MA, Nazer A, et al. Targeted Silencing of NRF2 by rituximab-conjugated nanoparticles increases the sensitivity of chronic lymphoblastic leukemia cells to Cyclophosphamide. Cell Commun Signal, 2023, 21(1): 188.

[34] Tian H, Huang Y, He J, et al. CD147 Monoclonal Antibody Targeted Reduction-Responsive Camptothecin Polyphosphoester Nanomedicine for Drug Delivery in Hepatocellular Carcinoma Cells. ACS Appl Bio Mater, 2021, 4(5): 4422-4431.

[35] Tian H, Yu L, Zhang M, et al. Dextran-doxorubicin prodrug nanoparticles conjugated with CD147 monoclonal antibody for targeted drug delivery in hepatoma therapy. Colloids Surf B Biointerfaces, 2023, 228: 113400.

[36] Yu Y, Li J, Song B, et al. Polymeric PD-L1 blockade nanoparticles for cancer photothermal-immunotherapy. Biomaterials, 2022, 280: 121312.

[37] Da X, Mo J, Li Q, et al. Targeted co-delivery of PD-L1 monoclonal antibody and sorafenib to circulating tumor cells via platelet-functionalized nanocarriers. Biochem Biophys Res Commun, 2023, 671: 335-342.

[38] Zhang Z, Zhang H, Cui L, et al. An MMAE-loaded PDL1 active targeting nanomedicine for the precision treatment of colon cancer. Biomater Sci, 2023, 11(15): 5195-5204.

[39] Qu C, Yuan H, Tian M, et al. Precise Photodynamic Therapy by Midkine Nanobody-Engineered Nanoparticles Remodels the Microenvironment of Pancreatic Ductal Adenocarcinoma and Potentiates the Immunotherap-0.1. ACS Nano, 2024, 18(5): 4019-4037.

[40] Kianpour M, Huang CW, Vejvisithsakul PP, et al. Aptamer/doxorubicin-conjugated nanoparticles target membranous CEMIP2 in colorectal cancer. Int J Biol Macromol, 2023, 245: 125510.

[41] Zhang C, Tang S, Wang M, et al. "Triple-Punch" Strategy Exosome-Mimetic Nanovesicles for Triple Negative Breast Cancer Therapy. ACS Nano, 2024.

[42] Yu J, Zhang Y, Xu M, et al. Innovative gelatin-based micelles with AS1411 aptamer targeting and reduction responsiveness for doxorubicin delivery in tumor therapy. Biomed Pharmacother, 2024, 174: 116446.

[43] Seo K, Hwang K, Nam KM, et al. Nucleolin-Targeting AS1411 Aptamer-Conjugated Nanospheres for Targeted Treatment of Glioblastoma. Pharmaceutics, 2024, 16(4).

[44] Khorshid M, Varshosaz J, Rostami M, et al. Anti HER-2 aptamer functionalized gold nanoparticles of dasatinib for targeted chemo-radiotherapy in breast cancer cells. Biomater Adv, 2023, 154: 213591.

[45] Yang A, Luo D, Jia Y, et al. Targeted delivery of AZD5363 to T-cell acute lymphocytic leukemia by mSiO(2)-Au nanovehicles. Colloids Surf B Biointerfaces, 2023, 230: 113505.

[46] Tarin M, Babaei M, Eshghi H, et al. Targeted delivery of elesclomol using a magnetic mesoporous platform improves prostate cancer treatment both in vitro and in vivo. Talanta, 2024, 270: 125539.

[47] Zavareh HS, Pourmadadi M, Moradi A, et al. Chitosan/carbon quantum dot/aptamer complex as a potential anticancer drug delivery system towards the release of 5-fluorouracil. Int J Biol Macromol, 2020, 165: 1422-1430.

[48] Lv J, Chang S, Chen HY, et al. A multi-channel responsive AuNP@COF core-shell nanoprobe for simultaneous subcellular profiling of multiple cancer biomarkers. Biosens Bioelectron, 2023, 234: 115325.

[49] Wei G, Wang Y, Yang G, et al. Recent progress in nanomedicine for enhanced cancer chemotherapy. Theranostics, 2021, 11(13): 6370-6392.

[50] Soltany P, Miralinaghi M, Pajoum Shariati F. Folic acid conjugated poly (Amidoamine) dendrimer grafted magnetic chitosan as a smart drug delivery platform for doxorubicin: In-vitro drug release and cytotoxicity studies. Int J Biol Macromol, 2024, 257(1): 127564.

[51] Jia W, Jin B, Xu W, et al. pH-Responsive and Actively Targeted Metal-Organic Framework Structures for Multimodal Antitumor Therapy and Inhibition of Tumor Invasion and Metastasis. ACS Appl Mater Interfaces, 2023, 15(43): 50069-50082.

[52] Chen Y, Tan Q, Tang Y, et al. Sorafenib and tetrakis (4-carboxyphenyl) porphyrin assembled nanoparticles for synergistic targeted chemotherapy and sonodynamic therapy of hepatocellular carcinoma. Biomater Sci, 2024, 12(7): 1864-1870.

[53] Jiang X, Xin H, Ren Q, et al. Nanoparticles of 2-deoxy-d-glucose functionalized poly(ethylene glycol)-co-poly(trimethylene carbonate) for dual-targeted drug delivery in glioma treatment. Biomaterials, 2014, 35(1): 518-529.

[54] Abolhasani A, Biria D, Abolhasani H, et al. Investigation of the Role of Glucose Decorated Chitosan and PLGA Nanoparticles as Blocking Agents to Glucose Transporters of Tumor Cells. Int J Nanomedicine, 2019, 14: 9535-9546.

[55] Wu J, Lee HJ, You L, et al. Functionalized NIR-II Semiconducting Polymer Nanoparticles for Single-cell to Whole-Organ Imaging of PSMA-Positive Prostate Cancer. Small, 2020, 16(19): e2001215.

[56] Lim J, Guan B, Nham K, et al. Tumor Uptake of Triazine Dendrimers Decorated with Four, Sixteen, and Sixty-Four PSMA-Targeted Ligands: Passive versus Active Tumor Targeting. Biomolecules, 2019, 9(9).

[57] Cui L, Wang X, Liu Z, et al. Metal-organic framework decorated with glycyrrhetinic acid conjugated chitosan as a pH-responsive nanocarrier for targeted drug delivery. Int J Biol Macromol, 2023, 240: 124370.

[58] Yang W, Zhang Y, Wang J, et al. Glycyrrhetinic acid-cyclodextrin grafted pullulan nanoparticles loaded doxorubicin as a liver targeted delivery carrier. Int J Biol Macromol, 2022, 216: 789-798.

[59] Shanmugam L, Venkatasubbu GD, Jayaraman M. Hyaluronan-based nano-formulation with mesoporous silica enhances the anticancer efficacy of phloroglucinol against gastrointestinal cancers. Int J Biol Macromol, 2024, 265: 130856.

[60] Gao M, Deng H, Zhang Y, et al. Hyaluronan nanogel co-loaded with chloroquine to enhance intracellular cisplatin delivery through lysosomal permeabilization and lysophagy inhibition. Carbohydr Polym, 2024, 323: 121415.

[61] Jeong JY, Hong EH, Lee SY, et al. Boronic acid-tethered amphiphilic hyaluronic acid derivative-based nanoassemblies for tumor targeting and penetration. Acta Biomater, 2017, 53: 414-426.

[62] Qian X, Ge L, Yuan K, et al. Targeting and microenvironment-improving of phenylboronic acid-decorated soy protein nanoparticles with different sizes to tumor. Theranostics, 2019, 9(24): 7417-7430.

[63] Qin W, Chandra J, Abourehab MAS, et al. New opportunities for RGD-engineered metal nanoparticles in cancer. Mol Cancer, 2023, 22(1): 87.

[64] Xu QH, Shi JY, Zhang J, et al. Comparison of tumor neovasculature-targeted paramagnetic nanoliposomes for MRI in mice xenograft models. Clin Transl Oncol, 2014, 16(4): 395-401.

[65] Wang C, Zhao M, Liu YR, et al. Suppression of colorectal cancer subcutaneous xenograft and experimental lung metastasis using nanoparticle-mediated drug delivery to tumor neovasculature. Biomaterials, 2014, 35(4): 1215-1226.

[66] Liu Y, Yang B, Zhao X, et al. E-Selectin-Binding Peptide-Modified Bovine Serum Albumin Nanoparticles for the Treatment of Acute Lung Injury. AAPS PharmSciTech, 2019, 20(7): 270.

[67] Kumar H, Gupta NV, Jain R, et al. F3 peptide functionalized liquid crystalline nanoparticles for delivering Salinomycin against breast cancer. Int J Pharm, 2023, 643: 123226.

[68] Lopes R, Shi K, Fonseca NA, et al. Modelling the impact of nucleolin expression level on the activity of F3 peptide-targeted pH-sensitive pegylated liposomes containing doxorubicin. Drug Deliv Transl Res, 2022, 12(3): 629-646.

[69] Pourmadadi M, Ghaemi A, Shaghaghi M, et al. Cabazitaxel-nano delivery systems as a cutting-edge for cancer therapy. J Drug Delivery Sci Technol, 2023, 82: 104338.

[70] Pourmadadi M, Eshaghi MM, Shaghaghi M, et al. Nano-scale drug delivery systems for carboplatin: A comprehensive review. OpenNano, 2023, 13: 100175.

[71] Mustafa G, Hassan D, Ruiz-Pulido G, et al. Nanoscale drug delivery systems for cancer therapy using paclitaxel—A review of challenges and latest progressions. J Drug Delivery Sci Technol, 2023, 84: 104494. s

[72] Karami MH, Abdouss M, Rahdar A, et al. Graphene quantum dots: Background, synthesis methods, and applications as nanocarrier in drug delivery and cancer treatment: An updated review. Inorg Chem Commun, 2024, 161: 112032.

[73] Mukhtar M, Ezra Manicum A-L, Shojaei Barjouei M, et al. Nanocarriers for methotrexate delivery/codelivery in the frame of cancer diagnostics and treatment: a review. Front Biomater Sci, 2023, 2.