Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

NAVIGATING THE TUMOR MICROENVIRONMENT: NANOTECHNOLOGY-DRIVEN STRATEGIES FOR PRECISION CANCER THERAPY

Muhammad Zaigham Javed[*1], Khalid Nadeem Asif[2], Muhammad Shahzad[3], Shahzoob Younis[4], Kashaf Tanzeel[5]

*[*1,3,4,5]Department of Biotechnology, Riphah international University Faisalabad Campus, Punjab, Pakistan. 44000*
[2]Department of Biochemistry, University of Agriculture, Faisalabad Punjab. Pakistan. 38000.

[*1]chzaigham144@gmail.com

DOI: https://doi.org/10.5281/zenodo.21471052

Keywords
tumor microenvironment, nanotechnology, nanoparticles, cancer therapy, drug delivery, stimuli-responsive, precision medicine, immunotherapy

Article History
Received: 01 January 2026
Accepted: 17 June 2026
Published: 28 June 2026

Copyright @Author
Corresponding Author: *
Muhammad Zaigham Javed

Abstract

The tumor microenvironment (TME) is a dynamic, complex milieu that includes cancer cells, stromal cells, immune cells, components of the extracellular matrix, and a network of signaling molecules that interact to drive tumor progression, immune evasion, and therapy resistance. The lack of specific tumor targeting and the presence of non-specific toxicity and poor tumor penetration make conventional cancer therapies (including chemotherapy and radiation) less effective and more urgent than ever before. Within the last twenty years, nanotechnology has become a revolutionary platform for treating cancer and has offered unprecedented control over drug delivery, tumor targeting, and on-demand release of therapeutics in response to TME-specific stimuli. This review gives an overview of the landscape of TME and discusses how several nanotechnology-based approaches, including liposomes, polymeric nanoparticles, inorganic nanocarriers, exosomes and hybrid nanostructures, are being engineered to take advantage of the characteristics of TME, including hypoxia, acidic pH, elevated reactive oxygen species, and aberrant enzyme expression. We also discuss the functions of active and passive targeting, stimuli-responsive drug delivery, immunomodulatory nanomedicine, and combination therapy strategies in overcoming TME-mediated drug resistance. Also, clinical translation issues, regulatory issues, and prospective issues are discussed. Collectively, this review indicates the enormous potential of nanotechnology as a precision-medicine modulator for redefining the TME and enhancing the effectiveness of cancer treatment.

INTRODUCTION

Cancer has been one of the most prominent causes of death in the world, with an estimated 19.3 million new cancer cases and almost 10 million cancer-related deaths reported worldwide in 2020 alone [1]. Although impressive progress has been made in surgery, chemotherapy, radiation therapy, and immunotherapy, the outcomes of treatment of many solid tumors have not yet reached the optimal level, in large part due to the complexity and immunosuppressive effects of the tumor microenvironment (TME) [2]. The TME is not a passive scaffold but an active evolving ecosystem that is bidirectionally communicating with tumor cells, and modulates immune responses as well as provides structural and

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

metabolic support to cancer survival and metastasis [3].

The cellular make-up of the TME includes cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), natural killer cells, and endothelial cells, and they are all found to produce a pro-tumorigenic environment [4]. They produce a huge repertoire of cytokines, growth factors, proteases, and extracellular vesicles which stimulate angiogenesis, remodel the extracellular matrix (ECM), and inhibit the action of anti-tumor immune responses [5]. At the same time, the physical properties of the TME, such as high interstitial fluid pressure, hypoxic gradient, low pH, and dense deposition of ECM, present insurmountable challenges to drug penetration and efficacy [6].

Nanotechnology, a broad concept described as the design and usage of materials and devices having functional frameworks of the nanometer scale (1100 nm), can be a potent associated technology toolkit in overcoming these barriers [7]. The drug delivery systems based on nanoparticles can take advantage of the increased permeability and retention (EPR) effect of tumor vasculature to achieve passive accumulation in the tumor [8]. More sophisticated platforms have active targeting ligands, stimuli-responsive release systems, and immune-modulating payloads to interact with the TME in a highly precise manner [9]. Nanomedicine is thus at the front line of precision cancer therapy due to the convergence of materials science, molecular biology, and clinical oncology [10].

This review critically reviews the main characteristics of the TME and explains the state-of-the-art nanotechnology platforms that are designed to navigate and reprogram these characteristics with therapeutic benefit. We discuss the key categories of nanocarriers, how they can be targeted, and how they can respond to TME-specific stimuli, and their use in combination therapy and immunomodulation. We also discuss current issues and future perspectives of the clinical translation of TME-targeted nanomedicine.

2. The Tumor Microenvironment: Architecture and Functional Significance.

The TME is a very heterogeneous and spatially structured tissue that develops in a dynamic co-evolution between malignant cells and their surrounding stromal components [11]. On the cellular level, the most common non-malignant cell type in many solid tumors is the CAFs, which secrete transforming growth factor-beta (TGF-B), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs) that together promote tumor invasion and angiogenesis [12]. TAMs, which tend to gain an M2 polarization state in the TME, suppress cytotoxic T lymphocyte (CTL) activity by secreting interleukin-10 (IL-10) and arginase-1 and, as a result, allow immune evasion to occur [13].

The ECM of the TME with a greater expression of collagen I, fibronectin, hyaluronic acid, and laminin is fundamentally remodeled in comparison to normal tissue and works to increase tissue stiffness, restrict diffusion of drugs, and activate pro-survival integrin signaling in cancer cells [14]. Mechanotransduction signaling, including YAP/TAZ signaling, is stimulated by mechanical signaling of ECM stiffness [15]. These structural features constitute a physical obstacle that limits the penetration of therapeutic agents such as nanoparticles beyond the perivascular space. The vasculature of tumors is abnormal in nature with disorganized architecture, increased permeability, poor pericyte coverage, and inefficient blood flow [16]. Not only does this vascular abnormality contribute to the hypoxia and interstitial hypertension, but it also contributes to the passive accumulation of nanoparticles by the EPR effect [17]. Hypoxia, which occurs because of insufficient oxygen delivery to compensate for the tumor metabolic demand, stabilizes hypoxia-inducible factor-1 alpha (HIF-1 0), which transcriptionally activates tumor metabolism genes involved in glycolysis, angiogenesis, invasion, and immune suppression [18].

The metabolic reprogramming of tumor cells entails the shift to aerobic glycolysis (the Warburg effect) that produces large amounts of lactic acid, which acidifies the extracellular pH to values that

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

typically range between 6.5 and 6.8 [19]. This acidic environment undermines the effectiveness of weakly basic drugs such as doxorubicin, alters protein function, and creates an immunosuppressive environment by affecting the functioning of the T cell and natural killer cell [20]. High levels of reactive oxygen species (ROS) are also typical of the TME, which are caused by mitochondrial dysfunction, NADPH oxidase activity, and inflammatory cell infiltration [21]. Although high ROS may be cytotoxic, tumor cells are able to adapt, and the gradient of ROS has been utilized as a stimulus trigger in stimuli-responsive nanomedicines [22].

Figure 1 shows a thematic illustration of the tumor microenvironment (TME) and its major cellular and physicochemical constituents that would be of interest to nanotechnology-based drug delivery. The TME is a diverse cellular ecosystem that includes cancer cells, cancer-associated fibroblasts (CAFs), M2-polarized tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), all of which help to suppress the immune system and promote tumor progression. Physicochemical hallmarks such as hypoxia, extracellular acidosis (pH 6.56.8), high levels of reactive oxygen species (ROS), dense extracellular matrix (ECM), and high interstitial fluid pressure characterize the TME. These attributes both hinder the normal administration of the drug and offer rational targets and triggers to nanotechnology-based therapeutic systems. A combination of passive accumulation of nanoparticles by the enhanced permeability and retention (EPR) effect, which results from aberrant tumor vasculature, and active targeting and stimuli-responsive mechanisms enhances tumor selectivity.

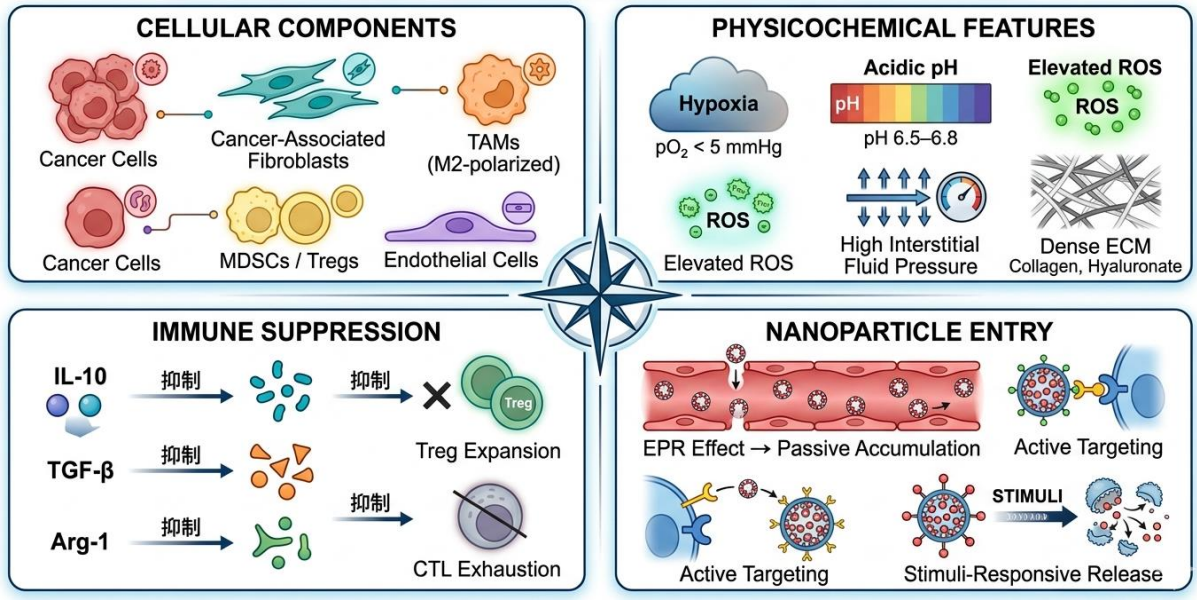


Figure 1: Thematic illustration of the tumor microenvironment (TME) and its major cellular and physicochemical constituents.

3. Nanocarrier-Based Systems of TME-Targeted Drug Delivery.

3.1 Liposomes

Liposomes are spherical vesicles that are constituted of a single or a mixture of phospholipid bilayers, which can also encapsulate both hydrophilic and hydrophobic drugs, making them one of the most clinically advanced nanocarrier systems [23]. Their biocompatibility, capability to imitate cell membranes, and adjustable surface chemistry have led to their extensive use in oncology. Doxil (pegylated liposomal doxorubicin) and Myocet are the first liposomal formulations to be approved to be used

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

clinically in the treatment of breast cancer and Kaposi sarcoma [24].

TME-responsive liposomes have been designed to utilize the acidic extracellular pH by the incorporation of pH-sensitive lipids, including phosphatidylethanolamine (PE) derivatives or dioleoylphosphatidylethanolamine (DOPE), which undergo phase transitions at low pH to destabilize the bilayer and release encapsulated drugs [25]. Activated by mild hyperthermia (40 42 C) induced by focused ultrasound or photothermal agents, thermosensitive liposomes (TSLs) have shown rapid release of drugs in tumor vessels and are currently in Phase III clinical trials of hepatocellular carcinoma [26]. Furthermore, redox-sensitive liposomes containing disulfide bonds in their lipid backbone release their cargo selectively in the intracellular environment rich in glutathione of cancer cells [27].

3.2 Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) made out of biodegradable polymers (such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and poly(caprolactone) (PCL)) are highly versatile in terms of size, surface modification, and drug encapsulation [28]. PLGA nanoparticles that have been approved to deliver paclitaxel (Abraxane) have been shown to exhibit much better safety profiles than conventional taxane formulations by removing the toxic Cremophor EL solvent [29]. The rate of degradation of the PLGA can also be fine-tuned by changing the ratio of lactic to glycolic acids, thus allowing the control of the rate of release of the drug over days to weeks [30].

Amphiphilic block copolymer, e.g., poly (ethylene glycol)-b-poly (lactic acid) (PEG-b-PLA) and poly (ethylene glycol)-b-poly (caprolactone) (PEG-b-PCL), self-assemble to form core-shell micellar structures with a hydrophilic PEG corona that confers stealth properties and extends circulation half-life [31]. Dendrimers are highly branched macromolecules with well-defined architecture and multivalent surface groups that allow high drug loading, conjugation of targeting ligand, and controlled release, but their large-scale synthesis remains technically difficult [32].

3.3 Inorganic Nanocarriers

Inorganic nanocarriers, including gold nanoparticles (AuNPs), mesoporous silica nanoparticles (MSNs), iron oxide nanoparticles (IONPs), and carbon-based nanomaterials, exhibit some distinct optical, magnetic, and structural characteristics that expand the therapeutic repertoire of nanomedicine [33]. AuNPs have tunable surface plasmon resonance in the near-infrared (NIR) window, which is capable of photothermal therapy (PTT), capable of directly ablating tumor cells, and synergizing with chemotherapy [34]. Gold nanoshells and gold nanorods are being evaluated in clinical trials of head-and-neck cancers and other solid tumors, with AuroShell particles showing localized thermal ablation in pilot studies [35].

MSNs have a highly porous interior structure with a huge surface area (up to 1000 m 2 g -1) and adjustable pore sizes (250 nm g -1), enabling the easy loading of a wide variety of therapeutic molecules such as small-molecule drugs, proteins, nucleic acids, etc. [36]. The silanol groups on the MSN surface enable facile chemical functionalization with targeting ligands, stimuli-responsive gatekeepers, and polymer coating [37]. IONPs, in particular superparamagnetic iron oxide nanoparticles (SPIONs), can be used to deliver drugs with magnetic resonance imaging (MRI) guidance and are currently being actively investigated as magnetically targeted therapy of cancer [38].

3.4 Exosomes and Bio-inspired Nanocarriers.

Exosomes are naturally occurring extracellular vesicles (30150 nm) that are secreted by literally all types of cells and that play key roles in intercellular communication by transporting between cells proteins, lipids, mRNA, and microRNA [39]. They are endogenous and therefore have inherent biocompatibility, low immunogenicity, and natural cell tropism, which makes them very attractive vehicles in drug and gene delivery [40]. Exosomes derived from tumors can be engineered or repurposed to deliver chemotherapeutics, siRNA, or immune-stimulatory molecules to homotypic tumor cells by exploiting their inherent homing properties [41].

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Cell membrane-camouflaged nanoparticles have been developed inspired by the immune evasion strategy used by pathogens, where synthetic nanoparticle cores are covered with membranes derived from either red blood cells, platelets, cancer cells, or macrophages [42]. The nanoparticles coated with membrane-coated red body cells provide an extended circulation because they express CD47 ('don't eat me' signal), which inhibits the phagocytosis of macrophages [43].

Table 1. Overview of major nanocarrier classes (organic, inorganic, and bio-inspired) used for TME-targeted cancer therapy, highlighting their structural features and triggered drug release mechanisms.

Table 1. Major classes of nanocarrier platforms for TME-targeted cancer therapy.

Nanocarrier Type	Representative Example	TME-Targeted Mechanism	Clinical Status
Liposomes	Doxil (PEG-liposomal doxorubicin)	pH-sensitive, thermosensitive lipid bilayer disruption	FDA-approved
Polymeric NPs	Abraxane (albumin-paclitaxel)	Passive EPR, receptor-mediated uptake	FDA-approved
Gold NPs	AuroShell (gold nanoshells)	NIR-triggered photothermal therapy	Phase I/II trials
MSNs	MSN-based siRNA/drug conjugates	Redox/pH-gated pore opening	Preclinical/Phase I
Exosomes	Tumor-derived exosome carriers	Homotypic targeting, immune camouflage	Early-phase trials

4. Precision Delivery into the TME targeting strategies.

4.1 Passive Targeting and EPR Effect.

Passive targeting uses the natural pathophysiological properties of solid tumors, most notably the EPR effect, to preferentially accumulate nanoparticles [45]. Firstly described by Matsumura and Maeda in 1986, the EPR effect is caused by two main characteristics of tumor vasculature, namely: (i) gaps between endothelial cells ranging between 200 and 2000 nm, which allow nanoparticle extravasation and (ii) defective lymphatic drainage that prevents the clearance of accumulated macromolecules [46]. The effect of EPR is size-dependent, and nanoparticles in the size range between 20-200 nm are generally considered optimal to passively accumulate in tumors [47].

Nevertheless, the EPR effect is very heterogeneous in tumor types and individual patients, and its clinical relevance has been a matter of significant debate [48]. Radiolabeled nanoparticles have been used in studies that have shown that, on average, only 0.7 percent of the delivered dose actually accumulates in the tumor [49]. Tumor vascular normalization by anti-VEGF therapy, ultrasound-mediated vascular disruption, and tumor priming agent application, including transforming growth factor-beta blockers to decrease interstitial fluid pressure, can be considered as strategies to enhance EPR [50].

4.2 Active Targeting Strategies

Active targeting involves decorating the surface of a nanoparticle with ligands that specifically bind to receptors that are overexpressed on tumor cells or TME stromal cells, thereby enhancing cellular internalization and index of therapeutic actions [51]. The folate receptor (FR-a) targeted by folic acid is overexpressed in ovarian, breast, and cervical cancers, and allows receptor-mediated endocytosis of FR-targeted nanoparticles [52]. Transferrin-conjugated nanoparticles take advantage of the overexpression of transferrin receptors (TfR) in rapidly proliferating tumor cells, with clinical formulations such as CALAA-01 (siRNA-loaded cyclodextrin NPs conjugated with

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

transferrin) entering Phase I trials in solid tumors [53].

Antibody-conjugated nanoparticles (immunoliposomes and immunonanoparticles) are a highly specific family of targeted nanomedicines. Conjugated liposomes containing trastuzumab targeting the breast cancer cells overexpressing the HER2/neu antigen have been shown to have improved cellular delivery and antitumor effects in preclinical models [54]. Single-stranded nucleic acid ligands selected through the SELEX process, aptamers, have the following benefits over antibodies: smaller size, reduced immunogenicity, and chemical stability [55]. The docetaxel-laden PSMA aptamer-functionalized PLGA nanoparticles demonstrated promising pharmacokinetics and early-phase clinical activity in prostate cancer patients [56].

Besides tumor cell surface receptors, further entry points include tumor stromal TME components, for precision delivery. To achieve stromal targeting, which can disrupt the desmoplastic barrier and increase drug penetration, peptide ligands that bind to CAF-expressed fibroblast activation protein (FAP) or platelet-derived growth factor receptor-bet 2 (PDGFR-bet 2) have been conjugated to nanoparticles [57]. The antibodies have been conjugated to liposomes to serve as vascular-targeted delivery and exploit the greater genetic stability of the endothelium over tumor cells [58].

5. Stimuli-Responsive Nanomedicine: Exploiting TME Triggers.

5.1 pH-Responsive Systems

The acidic pH of the TME (at least in the extracellular space) has been widely used as a stimulus to release smart drugs. pH-sensitive nanoparticles utilise ionisable polymers, including poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA), poly(L-histidine), and polyethylenimine (PEI), which undergo protonation-driven conformational changes at low pH, destabilising the nanocarrier structure and allowing release of the drug [59]. Mixed-shell micelles made to switch between negative and positive surface charge in response to tumor acidity improve tumor cell membrane interaction and intracellular uptake in the tumor site without tumor cell stealth being compromised in circulation [60].

To enable pH-dependent drug release, acid-labile chemical linkages have been commonly applied as prodrug nanoconjugates and polymer-drug conjugates [61]. Conjugation of doxorubicin to nanoparticles with the help of hydrazone bonds releases the drug selectively at pH 5.0 (lysosomal) in addition to extracellular TME activation [62]. These dual intracellular–extracellular pH–responsive systems have shown superior tumor specificity and reduced systemic toxicity in animal models [63].

5.2 Redox-Responsive Systems

The concentration of intracellular glutathione (GSH) (2-10 mM) in cancer cells is up to 1000-fold higher than the concentration in blood plasma (2-20 mmHg), which provides a steep redox gradient that has been exploited to release selective intracellular drugs [64]. Nanocarriers with disulfide bonds are disassembled by thiol-disulfide exchange during the nanocarrier's presence in environments rich in thiols (GSH) [65]. Dithiodipropionic acid (DTDPA)-cross-linked micelles, selenide-containing polymeric vesicles, as well as disulfide-bridged mesoporous silica nanoparticles have all proved to be GSH-responsive in release profile, and highly tumor specific [66].

Boronic acid esters, thioketal linkages, and poly (propylene sulfide) (PPS) moieties, which are oxidized and hydrolyzed in the presence of ROS, are used to prepare these systems [67]. Interestingly, some ROS-sensitive nanoparticles can eliminate TME-related ROS as a component of their therapeutic action, thereby disrupting redox homeostasis in cancer cells and amplifying the oxidative stress-mediated cell death [68].

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

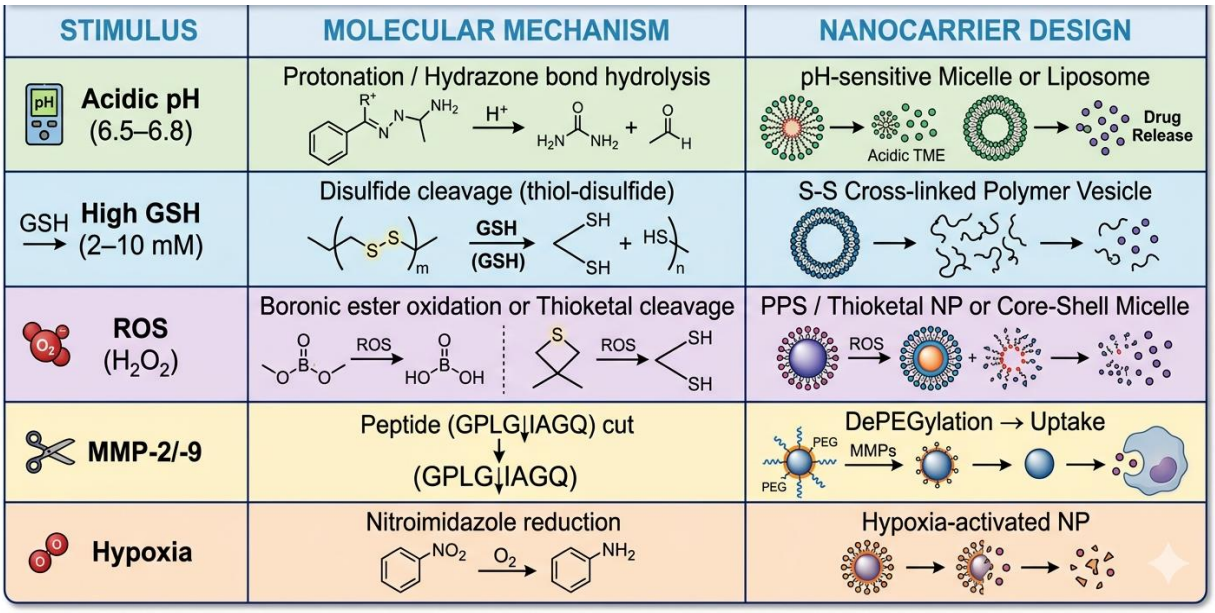


Figure 2 shows that the TME contains five major physicochemical and biochemical stimuli that can serve as selective triggers of the release of an engineered nanocarrier of a drug. Protonation-induced conformational changes and hydrolysis of hydrazone bonds of pH-sensitive polymeric micelles and liposomes occur at acidic extracellular pH (6.56.8). The large intracellular glutathione concentration (GSH; 210 mM) selectively breaks disulfide bonds of redox-responsive vesicles. High concentrations of reactive oxygen species (ROS), especially H 2 O 2, oxidise boronic ester and thioketal moieties in ROS-responsive nanoparticles. Overexpression of matrix metalloproteinases (MMP-2 and MMP-9) cleaves particular peptide sequences incorporated into the nanoparticle shell, which induces dePEGylation and increased uptake by tumor cells. The nanoparticles are enzyme-activated by hypoxic areas through enzyme-based reduction by cellular nitroreductases. All the mechanisms allow spatially and temporally regulated drug release at the tumor site.

Figure 2. Thematic diagram of key TME-specific stimuli and the molecular processes and nanocarrier architectures that can be exploited for stimulus-responsive drug delivery.

5.3 Enzyme-Responsive Systems

The TME overexpresses a wide range of enzymes such as MMPs (MMP-2, MMP-9), cathepsin, hyaluronidase, urokinase plasminogen activator (uPA), which collectively facilitate ECM degradation and tumor invasion [69]. These enzymes are selective inactivators of prodrug activation and disassembly of nanocarriers. PEGylation Linkers PEGylation linkers (e.g., GPLGIAGQ) have been incorporated to enable the dePEGylation of linkers and the subsequent uptake of the nanoparticle core by tumor cells [70]. Hyaluronic acid (HA)-coated nanoparticles have a dual purpose since they target CD44 receptors of cancer cells, but are degraded in the TME by hyaluronidase to release the therapeutic payload [71].

5.4 Hypoxia-Responsive Systems

The utilisation of nitroimidazole, azobenzene, and nitrobenzyl moieties that undergo reductive metabolism at low oxygen tension by cellular nitroreductases and azoreductases [72]. Nanoparticles conjugated with nitroimidazole are selective to release their cargo in hypoxic tumor areas that are also linked with the highest therapeutic resistance and stem cell phenotype [73]. Moreover, hypoxia-inducible promoters have been combined with gene therapy vectors to achieve transcriptionally targeted expression of therapeutic genes, specifically in hypoxic tumor

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

regions, which is a genetic-level exploitation of the TME [74].

Table 2 categorizes nanocarrier systems according to the major physicochemical and biological hallmarks of the tumor microenvironment (TME).

Table 2. Stimuli-responsive nanocarrier systems targeting TME hallmarks

TME Stimulus	Responsive Material	Drug/Cargo Delivered	Key Outcome
Acidic pH (extracellular)	Poly(L-histidine) micelles	Doxorubicin	4× tumor uptake vs. non-responsive
High GSH (intracellular)	Disulfide cross-linked PLGA	Paclitaxel + siRNA	90% drug release at 10 mM GSH
ROS (H_2O_2)	Boronic ester PEG-PCL micelles	Curcumin / cisplatin	Selective cancer cell apoptosis
MMP-2/-9 (pericellular)	GPLGIAGQ peptide-linked NPs	siRNA (survivin)	Tumor growth inhibition 70%
Hypoxia (intratumoral)	Nitroimidazole-PLGA NPs	Tirapazamine	Synergistic killing in hypoxic zones

6. Nanomedicine and Tumor Immune Microenvironment.

6.1 Reprogramming Tumor-Associated Macrophages

TAMs are one of the most numerous populations of immune cells in the TME and are important orchestrators of immunosuppression, angiogenesis, and metastasis [75]. Plasticity of macrophages provides a promising therapeutic option: re-polarization of M2-type TAMs to the anti-tumor pro-inflammatory M1-phenotype can restore anti-tumor immune surveillance and increase the efficacy of checkpoint inhibitors [76]. The syngeneic tumor can be regressed and re-polarized in the murine model by lipid nanoparticles loaded with a TLR4 agonist, lipopolysaccharide (LPS), or CpG oligonucleotides (TLR9 agonists) [77].

M2-to-M1 reprogramming agents, such as IL-12, anti-IL-10 siRNA, or CSF1R inhibitors, can selectively target TAMs by using nanoparticles that target mannose receptors (CD206) [78]. Moreover, anti-PD-1 checkpoint blockade, combined with nanoparticle-delivered colony-stimulating factor 1 receptor (CSF1R) siRNA, depletes immunosuppressive TAMs and recruits inflammatory macrophages, which, together with anti-PD-1 checkpoint blockade, deplete tumor cells, leading to long-lasting tumor clearance in glioblastoma models [79].

6.2 Nanoparticle-Enhanced Cancer Immunotherapy

Anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies with immune checkpoint blockade (ICB) have shown lasting response in melanoma, non-small cell lung cancer, and other malignancies, but the response rates are modest across many tumor types due to poor tumor immunogenicity and immunosuppressive tumor microenvironment (TME) [80]. Nanotechnology can be used in a variety of complementary measures to enhance the efficacy of ICB. Immunogenic cell death (ICD)-inducing agents, e.g., oxaliplatin or anthracyclines, are delivered by nanoparticles and promote the release of damage-associated molecular patterns (DAMPs), stimulating tumor antigen presentation by dendritic cells (DCs) (81).

Cancer vaccines that are based on neoantigens and which are formulated in lipid nanoparticles or polymeric nanoparticles represent an exciting convergence of personalized oncology and nanomedicine [82]. mRNA nanoparticle vaccines that encode tumor-specific neoantigens, which are delivered together with adjuvants such as STING agonists, have shown strong priming of CD8+ T cells and synergy with anti-PD-1 therapy in preclinical models of melanoma [83]. Further stimulation of the oncology use of this platform has been generated by the clinical success of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

COVID-19 mRNA lipid nanoparticle vaccines [84].

Coadministration of systemic checkpoint antibodies and cytotoxic drugs through nanoparticles has been shown to generate synergetic anti-tumor effects at the same time reducing the systemic immune toxicity that would be generated when the systemic checkpoint antibodies were administered systemically [85]. Photothermal tumor ablation by inorganic nanoparticles has also been demonstrated to induce in situ release of tumor antigens as well as prime abscopal immune responses, in effect converting the primary tumor into a therapeutic cancer vaccine [86].

7. Combinations Therapy Strategies using Nanoparticle-Mediated Combinations Therapy Strategies.

The complexity and flexibility of the TME render single-agent therapies a fundamental inadequacy in the long-term tumor control in most clinical settings. Combination therapy, especially when it is co-formulated into a single nanocarrier, allows the simultaneous delivery of drugs to a tumor site, it allows the exploitation of synergistic mechanisms of action, and it reduces the risk of sequential development of resistance [87]. Nanoparticles are especially well adapted to combination therapy, due to the ability of co-encapsulation of drugs with vastly dissimilar physicochemical properties [88].

PEG-b-PLA micelles containing doxorubicin and lapatinib have been shown to be more effective in terms of anti-tumor efficacy in PEG-b-PLA micelles in HER2-overexpressing breast cancer models, compared to either of the two drugs, and the anti-tumor effect is due to synergistic inhibition of both DNA replication and HER2-driven pro-survival signaling [89]. Likewise, co-delivery of paclitaxel and VEGF siRNA in lipid-polymer hybrid nanoparticles simultaneously inhibited proliferation of tumor cells and angiogenesis of the TME, and produced significantly greater tumor growth inhibition as compared to either form of monotherapy in ovarian cancer xenograft models [90].

The platforms Chemo-photodynamic therapy (chemo-PDT) platforms combine photosensitizers (such as chlorin e6 (Ce6) or porphyrin derivatives) with chemotherapeutic agents in a single nanocarrier to enable spatiotemporally controlled tumor ablation through a combination of ROS generation upon light irradiation and direct cytotoxicity [91]. They have shown high efficacy in tumors in the superficial areas and are being extended to deep tumors by the use of X-ray-activated photosensitizers and upconverting nanoparticles that convert NIR light to visible wavelengths that can be used in PDT [92].

The combination of gene therapy and chemotherapy that is developed as nanoparticles has the potential of reversing the mechanisms of chemoresistance by silencing drug efflux pumps or anti-apoptotic genes that accompany the administration of chemotherapy [93]. The co-delivery of Bcl-2 siRNA and doxorubicin by lipid nanoparticles restored drug sensitivity in multidrug-resistant breast cancer cells, and in vivo studies confirmed a significantly greater tumor regression compared to either agent alone [94].

Table 3 shows representative nanoparticle-based combination therapy strategies targeting distinct TME hallmarks including platform design, drug combinations, and key findings..

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 3. Selected nanoparticle-based combination therapy strategies targeting the TME.

Combination Strategy	Nanocarrier Platform	Target/Tumor Model	Key Result
DOX + Lapatinib	PEG-b-PLA polymeric micelle	HER2+ breast cancer	3× improved tumor growth inhibition
Paclitaxel + VEGF siRNA	Lipid-polymer hybrid NPs	Ovarian cancer xenograft	Anti-tumor + anti-angiogenic synergy
Chemo + PDT (Ce6)	Porphyrin-PLGA NPs	Hepatocellular carcinoma	>80% tumor volume reduction
Dox + anti-PD-L1	pH-sensitive liposomes	Melanoma syngeneic model	Restored immune tumor killing
Bcl-2 siRNA + DOX	Cationic lipid nanoparticles	MDR breast cancer	Sensitization to chemotherapy

8. ECM Barriers: Nanoparticle Design to Penetrate Deep into Tumors.

The thick ECM of desmoplastic tumor types, including pancreatic ductal adenocarcinoma (PDAC), breast cancer, and some colorectal cancer types, is one of the most daunting physical barriers to nanoparticle penetration [95]. The size and shape of nanoparticle permeability are restricted by collagen fibers and hyaluronic acid matrices that trap nanoparticles larger than about 60100 nm confined to the perivascular space and leaving hypoxic and necrotic tumor cores largely inaccessible [96]. Two key strategies of ECM penetration have been devised: ECM-degrading enzyme co-delivery and size-switchable nanoparticle architectures.

It has been demonstrated that enzyme-loaded nanoparticles of collagenase, hyaluronidase, or losartan-conjugated ECM-disrupting agents can be used to deplete the collagen and hyaluronic acid content of tumor stroma, reducing the interstitial fluid pressure and enhancing the intratumoral distribution of subsequently administered nanoparticles [97]. One landmark study has shown that PEGylated recombinant human hyaluronidase (PEGylated recombinant human hyaluronidase) significantly improved the tumor accumulation of gemcitabine nanoformulations, leading to enhanced antitumor efficacy in animal models [98].

The combination of size switchable cascade nanoparticles can be used to achieve the penetration-internalization paradox, where large nanoparticles (>100 nm) accumulate via EPR but fail to penetrate the ECM, whereas smaller nanoparticles (<20 nm) penetrate freely but are rapidly cleared. A two-step system, where large gelatin matrix nanoparticles (130 nm) are degraded by MMP-2 to release small drug-loaded quantum dot nanoparticles (10 nm) at the tumor site, showed a superior tumor penetration and anticancer efficacy compared to either size category alone [99]. This is a graceful strategy that dissociates accumulation that depends on EPR, and penetration of ECM, and in the same tumor, they are achieved sequentially [100].

9. Challenges in clinical translation and perspectives in the future.

Although extraordinary scientific breakthroughs in TME-targeted nanomedicine have been reported over the last two decades, the clinical transfer of the platforms into clinically approved products has been significantly slower than expected. Several interrelated issues are leading to this translation bottleneck. First, the EPR effect, which most passive targeting strategies are basing their predictions on, is highly tumor-type, patient population, and lesion-specific in the same patient, rendering clinical efficacy predictions unreliable by relying solely on preclinical data [45].

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Further limiting the predictive validity of preclinical results, the use of immunocompromised xenograft mouse models, which do not have the complex immune microenvironment of human tumors.

Second, the complex nanoparticle formulations produced at Good Manufacturing Practice (GMP) scale with reproducible size, drug encapsulation effectiveness, polydispersity, and stability present formidable technical and economic challenges [66]. Regulatory requirements require a large amount of characterization of critical quality attributes (CQAs) and demonstration of batch-to-batch consistency (which can be especially difficult with self-assembled polymeric systems or bioinspired carriers such as exosomes [82]. The absence of unified techniques of characterization and regulatory advice that are specific to nanomedicines has further complicated the approval process.

Third, the immunological interactions of nanoparticles with the mononuclear phagocyte system (MPS), including opsonization of nanoparticles by serum proteins (formation of protein corona), uptake by Kupffer cells, and activation of complement, all reduce the fraction of the administered dose that is deposited in the tumor and can provoke infusion-related hypersensitivity reactions [43]. The dynamically changing surface properties and accessibility to targeting ligands of the protein corona that forms on nanoparticles when exposed to blood change dynamically in response to changes in blood serum composition [50]. Some of the strategies that can be used to mitigate the effects of protein corona are surface modification with zwitterionic polymers, incorporation of cell membrane coatings, and the use of anti-fouling polysaccharides.

In the future, machine learning (ML) and artificial intelligence (AI) combined with nanomedicine would bring radically new opportunities to accelerate nanoparticle design, predict tumor-specific accumulation patterns, and identify optimal patient subpopulations for TME-targeted therapies [88]. The emergence of patient-derived tumor organoid (PDO) and microfluidic tumor-on-a-chip model is likely to significantly enhance the predictive validity of preclinical nanoparticle testing by recapitulating the complexity of the TME, including stromal architecture, immune cell composition, and mechanical properties [92].

The ultimate goal of precision cancer therapy is personalized nanomedicine, in which the formulations of nanoparticles are optimally designed to the molecular and immunological profile of the TME of an individual patient. New tools of single-cell RNA sequencing, spatial transcriptomics, and proteomics are yielding high-resolution maps of TME heterogeneity, which can be used to inform the rational design of patient-specific nanoparticle therapies [95]. Combining these technologies with synthetic biology, materials science, and immunology has the potential to really individualize nanomedicine platforms that will adapt to the dynamic evolution of the TME during and after treatment [100].

10. Conclusion

The microenvironment of tumors poses a great challenge and an equally great opportunity for precision cancer therapy. Nanotechnology has shown a special ability to overcome these obstacles by rational design of size, surface chemistry, targeting ligands, and release by stimuli-responsive release mechanisms that are specifically matched to the physicochemical and biological properties of the TME. Since the dawn of hope that EPR-based passive targeting represented by liposomal doxorubicin, the discipline has since evolved to include highly sophisticated active targeting platforms, multi-stimulus-responsive nanocarriers, immunomodulatory nanomedicines, and bioinspired delivery systems that mimic endogenous cellular communication.

The polyclonal and adaptive character of tumor evolution is overcome by the combination of therapeutic strategies into single nanocarrier platforms, and ECM-remodeling strategies unlock the physical barriers that confine therapeutic nanoparticles to the periphery of the tumor. Nanomedicine Immuno-oncology applications of nanomedicine, such as TAM reprogramming, neoantigen vaccine delivery, and checkpoint inhibitor co-formulation, represent particularly promising frontiers that hold the promise of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

transforming immunosuppressive tumors that are considered immunologically cold to immunologically hot immunomodulatory environments responsive to durable immune control.

Nevertheless, to realize the clinical translation of TME-targeted nanomedicines, concerted efforts are needed to address the scalability of manufacturing, the management of protein corona, TME heterogeneity, and the need to develop more predictive preclinical models. The new integration of artificial intelligence, spatial omics, and patient-derived tumor models into the nanomedicine development pipeline is likely to make a significant acceleration in the bench-to-bedside translation of the next-generation TME-responsive platforms. As a continued interdisciplinary effort across the fields of chemistry, materials science, oncology, and immunology, nanotechnology-based precision cancer therapy is poised to have a meaningful impact on clinical outcomes of patients with challenging-to-treat solid tumors.

Declarations

Author Contributions

conceived the review, conducted the literature search, wrote and revised the manuscript. The author read and approved the final version.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The author declares no conflict of interest.

REFRENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–674.
3. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022;12(1):31–46.
4. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423–1437.
5. Balkwill FR, Capasso M, Hagemann T. The tumor microenvironment at a glance. J Cell Sci. 2012;125(23):5591–5596.
6. Stylianopoulos T, Munn LL, Jain RK. Reengineering the physical microenvironment of tumors to improve drug delivery and efficacy: from mathematical modeling to bench to bedside. Trends Cancer. 2018;4(4):292–319.
7. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017;17(1):20–37.
8. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. J Control Release. 2000;65(1–2):271–284.
9. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol. 2007;2(12):751–760.
10. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer. 2005;5(3):161–171.
11. Turley SJ, Cremasco V, Astarita JL. Immunological hallmarks of stromal cells in the tumour microenvironment. Nat Rev Immunol. 2015;15(11):669–682.
12. Bhowmick NA, Neilson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. Nature. 2004;432(7015):332–337.
13. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;14(7):399–416.
14. Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. EMBO Rep. 2014;15(12):1243–1253.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

15. Dupont S, Morsut L, Aragona M, et al. Role of YAP/TAZ in mechanotransduction. Nature. 2011;474(7350):179–183.

16. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011;473(7347):298–307.

17. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005;307(5706):58–62.

18. Semba H, Takeda N, Isagawa T, et al. HIF-1α-PDK1 axis-induced active glycolysis plays an essential role in macrophage migratory capacity. Nat Commun. 2016;7:11635.

19. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer. 2004;4(11):891–899.

20. Damaghi M, Wojtkowiak JW, Gillies RJ. pH sensing and regulation in cancer. Front Physiol. 2013;4:370.

21. Szatrowski TP, Nathan CF. Production of large amounts of hydrogen peroxide by human tumor cells. Cancer Res. 1991;51(3):794–798.

22. Trachootham D, Alexandre J, Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? Nat Rev Drug Discov. 2009;8(7):579–591.

23. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4(2):145–160.

24. O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004;15(3):440–449.

25. Simões S, Moreira JN, Fonseca C, Düzgüneş N, de Lima MC. On the formulation of pH-sensitive liposomes with long circulation times. Adv Drug Deliv Rev. 2004;56(7):947–965.

26. Rizzitelli S, Giustetto P, Faletto D, et al. The release of Doxorubicin from ThermoDox-activated by MRI-guided focused ultrasound is mediated by acoustic cavitation. J Control Release. 2016;241:granting enhanced local therapy.

27. Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. Biomaterials. 2009;30(12):2180–2198.

28. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release. 2012;161(2):505–522.

29. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794–7803.

30. Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev. 2012;64(Suppl):72–82.

31. Wei X, Shao B, He Z, et al. Cationic nanocarriers induce cell necrosis through impairment of Na(+)/K(+)-ATPase and cause subsequent inflammatory response. Cell Res. 2015;25(2):237–253.

32. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Prog Polym Sci. 2014;39(2):268–307.

33. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013;12(11):991–1003.

34. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. Chem Soc Rev. 2012;41(7):2740–2779.

35. Schwartz JA, Shetty AM, Price RE, et al. Feasibility study of particle-assisted laser ablation of brain tumors in orthotopic canine model. Cancer Res. 2009;69(4):1659–1667.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

36. Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery. Adv Mater. 2012;24(12):1504–1534.

37. Li Z, Barnes JC, Bosoy A, Stoddart JF, Zink JI. Mesoporous silica nanoparticles in biomedical applications. Chem Soc Rev. 2012;41(7):2590–2605.

38. Wahajuddin, Arora S. Superparamagnetic iron oxide nanoparticles: magnetic nanoplatforms as drug carriers. Int J Nanomedicine. 2012;7:3445–3471.

39. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol. 2002;2(8):569–579.

40. Syn NL, Wang L, Chow EK, Lim CT, Goh BC. Exosomes in cancer nanomedicine and immunotherapy: prospects and challenges. Trends Biotechnol. 2017;35(7):665–676.

41. Zhu L, Kalimuthu S, Gangadaran P, et al. Exosomes derived from natural killer cells exert therapeutic effect in melanoma. Theranostics. 2017;7(10):2732–2745.

42. Luk BT, Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. J Control Release. 2015;220(Pt B):600–607.

43. Hu CM, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc Natl Acad Sci USA. 2011;108(27):10980–10985.

44. Hu Q, Sun W, Qian C, Wang C, Bomba HN, Gu Z. Anticancer platelet-mimicking nanovehicles. Adv Mater. 2015;27(44):7043–7050.

45. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting. Adv Enzyme Regul. 2001;41:189–207.

46. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46(12 Pt 1):6387–6392.

47. Cabral H, Matsumoto Y, Mizuno K, et al. Accumulation of sub-100 nm polymeric micelles in poorly permeable tumours depends on size. Nat Nanotechnol. 2011;6(12):815–823.

48. Danhier F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? J Control Release. 2016;244(Pt A):108–121.

49. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016;1(5):16014.

50. Chauhan VP, Stylianopoulos T, Boucher Y, Jain RK. Delivery of molecular and nanoscale medicine to tumors: transport barriers and strategies. Annu Rev Chem Biomol Eng. 2011;2:281–298.

51. Bazak R, Houri M, El Achy S, Hussein W, Refaat T. Passive targeting of nanoparticles to cancer: a comprehensive review of the literature. Mol Clin Oncol. 2014;2(6):904–908.

52. Sudimack J, Lee RJ. Targeted drug delivery via the folate receptor. Adv Drug Deliv Rev. 2000;41(2):147–162.

53. Davis ME, Zuckerman JE, Choi CH, et al. Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. Nature. 2010;464(7291):1067–1070.

54. Kirpotin DB, Drummond DC, Shao Y, et al. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. Cancer Res. 2006;66(13):6732–6740.

55. Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. Nat Rev Drug Discov. 2010;9(7):537–550.

56. Hrkach J, Von Hoff D, Mukkaram Ali M, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci Transl Med. 2012;4(128):128ra39.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

57. Miao L, Liu Q, Lin CM, et al. Targeting tumor-associated fibroblasts for therapeutic delivery in desmoplastic tumors. Cancer Res. 2017;77(3):719–731.

58. Ran R, Liu Y, Gao H, et al. Enhanced gene delivery efficiency of cationic liposomes coated with PEGylated hyaluronic acid for anti P-glycoprotein siRNA: a potential candidate for overcoming multi-drug resistance. Int J Pharm. 2014;477(1–2):150–158.

59. Du JZ, Du XJ, Mao CQ, Wang J. Tailor-made dual pH-sensitive polymer-doxorubicin nanoparticles for efficient anticancer drug delivery. J Am Chem Soc. 2011;133(44):17560–17563.

60. Zhou Z, Li L, Yang Y, Xu X, Huang Y. Tumor targeting by pH-sensitive, biodegradable, cross-linked N-(2-hydroxypropyl) methacrylamide copolymer micelles. Biomaterials. 2014;35(24):6622–6635.

61. Lee ES, Gao Z, Bae YH. Recent progress in tumor pH targeting nanotechnology. J Control Release. 2008;132(3):164–170.

62. Kurtoglu YE, Navath RS, Wang B, Kannan S, Romero R, Kannan RM. Poly(amidoamine) dendrimer-drug conjugates with disulfide linkages for intracellular drug delivery. Biomaterials. 2009;30(11):2112–2121.

63. Aubry J, Gangloff A, de Waal E, et al. Tumor pH and the tumor microenvironment influence both the pharmacokinetics and pharmacodynamics of acid-labile prodrugs. J Control Release. 2011;153(3):204–211.

64. Kim D, Lee ES, Oh KT, Gao ZG, Bae YH. Doxorubicin-loaded polymeric micelle overcomes multidrug resistance of cancer by double-targeting folate receptor and early endosomal pH. Small. 2008;4(11):2043–2050.

65. Yin W, Ke W, Chen W, et al. Integrated block copolymer prodrug nanoparticles for combination of tumor oxidative stress amplification and ROS-responsive drug release. Biomaterials. 2019;195:63–74.

66. Wu H, Zhu L, Torchilin VP. pH-sensitive poly(histidine)-PEG/DSPE-PEG co-polymer micelles for cytosolic drug delivery. Biomaterials. 2013;34(4):1213–1222.

67. Sun X, Zhang G, Wu B, et al. Mitochondria-targeted cancer therapy based on functional peptide-modified nanoplatform. Small. 2022;18(30):e2200023.

68. Peng J, Xiao Y, Li W, et al. Photosensitizer micelles together with IDO inhibitor enhance cancer photothermal therapy and immunotherapy. Adv Sci. 2018;5(5):1700891.

69. Huo M, Yuan J, Tao L, Wei Y. Redox-responsive polymers for drug delivery: from molecular design to applications. Polym Chem. 2014;5(5):1519–1528.

70. De la Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. Adv Drug Deliv Rev. 2012;64(11):967–978.

71. Olson OC, Joyce JA. Cysteine cathepsin proteases: regulators of cancer progression and therapeutic response. Nat Rev Cancer. 2015;15(12):712–729.

72. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell. 2010;141(1):52–67.

73. Choi KY, Saravanakumar G, Park JH, Park K. Hyaluronic acid-based nanocarriers for intracellular targeting: interfacial interactions with proteins in cancer. Colloids Surf B Biointerfaces. 2012;99:82–94.

74. Meng F, Cheng R, Deng C, Zhong Z. Intracellular drug release nanosystems. Mater Today. 2012;15(10):436–442.

75. Guo M, Yan Y, Zhang H, et al. Magnetic and pH-responsive nanocarriers with enhanced cytotoxicity to HeLa cells. J Mater Chem. 2008;18(42):5104–5112.

76. Chen H, Tian J, He W, Guo Z. H_2O_2-activatable and O_2-evolving nanoparticles for highly efficient and selective photodynamic therapy against hypoxic tumor cells. J Am Chem Soc. 2015;137(4):1539–1547.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

77. Hatakeyama H, Akita H, Harashima H. The polyethyleneglycol dilemma: advantage and disadvantage of PEGylation of liposomes for systemic genes and nucleic acids delivery to tumors. Biol Pharm Bull. 2013;36(6):892–899.

78. Ruan S, He Q, Gao H. Matrix metalloproteinase triggered size-shrinkable gelatin-gold fabricated nanoparticles for tumor microenvironment sensitive penetration and diagnosis of glioma. Nanoscale. 2015;7(21):9487–9496.

79. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol. 2002;23(11):549–555.

80. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets. Cell Immunol. 2012;280(1):57–64.

81. Irvine DJ, Hanson MC, Rakhra K, Tokatlian T. Synthetic nanoparticles for vaccines and immunotherapy. Chem Rev. 2015;115(19):11109–11146.

82. Rodell CB, Arlauckas SP, Cuccarese MF, et al. TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. Nat Biomed Eng. 2018;2(8):578–588.

83. Zhu S, Niu M, O'Mary H, Bhattacharya P, Zhang Y, Bhattacharya R. Targeting of tumor-associated macrophages made possible by PEG-sheddable, mannose-modified nanoparticles. Mol Pharm. 2013;10(9):3525–3530.

84. Peng J, Yang Q, Li W, et al. Eradicating unresectable large tumors through combined photothermal and immunotherapy using aggregation-induced emission nanoparticles. ACS Nano. 2021;15(5):9052–9066.

85. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56–61.

86. Casares N, Pequignot MO, Tesniere A, et al. Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death. J Exp Med. 2005;202(12):1691–1701.

87. Hu Z, Leet DE, Allesoe RL, et al. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. Nat Med. 2021;27(3):515–525.

88. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222–226.

89. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–416.

90. Mi Y, Shao Z, Vang J, Cahan H, Salem AK. Application of nanotechnology to cancer radiotherapy. Cancer Nanotechnol. 2016;7(1):11.

91. Chen Q, Xu L, Liang C, Wang C, Peng R, Liu Z. Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. Nat Commun. 2016;7:13193.

92. Langer R, Weissleder R. Nanotechnology. JAMA. 2015;313(2):135–136.

93. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res. 2008;14(5):1310–1316.

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

95. Meng H, Zhao Y, Dong J, et al. Two-wave nanotherapy to target the stroma and optimize gemcitabine delivery to a human pancreatic cancer model in mice. ACS Nano. 2013;7(11):10048–10065.

96. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. Nat Mater. 2013;12(11):958–962.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

97. Huang X, Teng X, Chen D, Tang F, He J. The effect of the shape of mesoporous silica nanoparticles on cellular uptake and cell function. Biomaterials. 2010;31(3):438–448.

98. Stylianopoulos T, Martin JD, Snuderl M, Mpekris F, Jain SR, Jain RK. Coevolution of solid stress and interstitial fluid pressure in tumors during progression: implications for vascular collapse. Cancer Res. 2013;73(13):3833–3841.

99. Provenzano PP, Cuevas C, Chang AE, Bhatt DK, den Brok MH, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012;21(3):418–429.

100. Jacobetz MA, Chan DS, Neesse A, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut. 2013;62(1):112–120.