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Review **RRJODDD**

Nanomedicine in the Tumor Microenvironment: Physiological Modulation Through Tissue Engineering Approaches

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Abstract

The integration of nanomedicine and tissue engineering offers transformative strategies for cancer therapy by directly modulating the physiological processes within the tumor microenvironment (TME). This review emphasizes recent advances in nanomedicine that enable precise drug delivery, controlled release, and real-time monitoring of key physiological parameters influencing tumor progression, angiogenesis, and immune evasion. Tissue-engineered 3D tumor models provide physiologically relevant platforms that better mimic in vivo conditions than traditional 2D cultures, facilitating enhanced understanding of tumor biology and therapy resistance. Advances in stimuli-responsive nanoparticles, organ-on-chip platforms, and biomaterials allow researchers to study and manipulate the TME in ways that have direct translational potential for personalized medicine. By focusing on the physiological mechanisms and applied approaches, this review underscores the synergistic role of nanomedicine and tissue engineering in advancing therapeutic strategies and improving cancer treatment outcomes.

Keywords: Nanomedicine, Tumor Microenvironment, Tissue Engineering, 3D Tumor Models, Targeted Drug Delivery, Applied Physiology, Personalized Therapy

INTRODUCTION

Tumors are intricate and heterogeneous entities that play a central role in the initiation and progression of cancer. Recent breakthroughs in tumor biology have significantly advanced our understanding of these entities, shedding light on their evolution and interactions within the surrounding microenvironment [1]. A tumor primarily consists of malignant cells that proliferate uncontrollably, leading to neoplastic growth. These cancerous cells engage in complex interactions with their surrounding environment, known as the tumor microenvironment (TME), which includes non-cancerous cells, signaling molecules, and the extracellular matrix (ECM) [2]. Understanding these interactions is crucial for comprehending tumor growth, invasion, and metastasis [2]. The TME plays a pivotal role in the initiation, progression, and therapeutic response of cancer, providing biochemical and biophysical cues to tumor cells that influence key processes such as angiogenesis, metastasis, and drug resistance [3, 4]. Tissue engineering offers an advanced approach to replicate and study these complex TME interactions. This involves developing three-dimensional (3D) models that incorporate cancer cells, ECM-mimicking scaffolds, and other essential components that modulate tumor behavior and growth [5]. The integration of nanomedicine with tissue engineering presents substantial potential for enhancing cancer therapy by specifically targeting the TME. Unlike

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conventional treatments such as chemotherapy and radiotherapy, which primarily target rapidly dividing tumor cells, nanomedicine provides a precise strategy aimed at modifying the TME to improve therapeutic efficacy while mitigating resistance and adverse effects. Traditional therapies often encounter challenges such as drug resistance and systemic toxicity, partly due to the TME's complexity, which includes diverse cell types like fibroblasts, immune cells, and endothelial cells that collectively support tumor progression [6]. Moreover, conventional treatments can induce a senescence-associated secretory phenotype (SASP) in cancer-associated fibroblasts (CAFs), potentially exacerbating inflammation and promoting tumor progression and therapeutic resistance [7]. In contrast, nanomedicine can be engineered to selectively target specific TME components. For instance, nanoparticles can modulate the TME by generating reactive oxygen species, altering pH, and depleting glutathione, thereby disrupting tumor-supportive mechanisms [8]. The synergy of nanomedicine and tissue engineering offers transformative potential in cancer therapy, enhancing precision, reducing systemic toxicity, and improving diagnostic capabilities, marking a significant advance toward personalized cancer care. Despite challenges in clinical translation, ongoing progress in nanotechnology continues to expand the therapeutic arsenal against cancer [9].

COMPONENTS OF THE TUMOR MICROENVIRONMENT

The development, progression, and metastasis of cancer are profoundly influenced by the tumor microenvironment (TME), a complex ecosystem composed of both cellular and non-cellular components. The TME includes adipocytes, fibroblasts, endothelial cells, neoplastic cells, pericytes, stem and progenitor cells, extracellular matrix (ECM) components, and diverse immune cells [10]. These components interact through intricate mechanisms to regulate tumor behavior and therapeutic outcomes. The TME is highly dynamic, with its constituents capable of either promoting or inhibiting tumor growth depending on local and systemic conditions [11]. For example, immune cells such as dendritic cells, lymphocytes, macrophages, and myeloid-derived suppressor cells can exert both pro- and anti-tumorigenic effects, as observed in gastric cancer [12]. Additionally, biomechanical forces within the TME—such as growth-induced solid stresses, increased matrix stiffness, and altered interstitial flow—play a critical role in influencing cell behavior and tumor progression [13].

TUMOR MICROENVIRONMENT ROLE IN CANCER PROGRESSION AND METASTASIS

The tumor microenvironment (TME) plays a pivotal role in cancer progression and metastasis across multiple cancer types. In breast cancer, the TME critically influences tumor development, progression, and metastatic spread, with diverse immune cell populations contributing to both anti-tumor and pro-tumor activities [14]. Biophysical interactions between cancer cells and their dynamic microenvironment activate mechano-responses in tumor cells, leading to structural reorganization of intracellular organelles and associated genetic modifications [15]. Importantly, the TME is not static but evolves as tumors grow and develop. Stromal components, including the extracellular matrix (ECM), modulate tumor progression and metastasis by influencing cancer cell behavior [16]. In breast cancer specifically, tumor-associated macrophages (TAMs) are highly influential, secreting pro-angiogenic factors while suppressing local pro-inflammatory antitumor responses, thereby facilitating tumor cell evasion and metastasis [17, 18]. Furthermore, hypoxic conditions within the TME stimulate macrophages to produce vascular endothelial growth factor (VEGF) and suppress T-cell immune responses, further promoting metastatic progression [18].

CHALLENGES IN TARGETING THE TUMOR MICROENVIRONMENT

The complex and dynamic nature of the tumor microenvironment (TME) poses significant challenges for effective cancer therapy [19, 20]. Its heterogeneity and similarity to healthy tissue make the development of precise, tailored therapeutics difficult, increasing the risk of toxicity and off-target effects [20]. Therapeutic strategies are further complicated by the TME's ability to adapt and remodel in response to treatments [21]. Additionally, factors such as hypoxia, abnormal vasculature, and dense stromal components in solid tumors can hinder drug distribution and reduce therapeutic efficacy [22]. Despite these challenges, targeting the TME remains a promising strategy for cancer treatment. Nanomedicine offers a potential solution by enabling the engineering of nanocarriers that enhance drug delivery, selectively modify the microenvironment, and precisely target specific TME components [23].

VARIOUS NANOMEDICINE APPROACHES TO TARGETING THE TUMOR MICROENVIRONMENT VIA TISSUE ENGINEERING

Nanoparticles for Enhanced Drug Penetration

Nanomedicine approaches targeting the tumor microenvironment (TME) have shown considerable promise in improving drug efficacy and tissue penetration. Although physical and biological barriers within the TME often limit nanoparticle effectiveness, the enhanced permeability and retention (EPR) effect facilitates their accumulation in tumor tissues [24]. One promising strategy involves the use of size-shrinkable drug-delivery nanosystems, which can adapt to TME-specific conditions such as elevated enzyme activity, hypoxia, and acidic pH [25]. These nanoparticles can convert into ultrasmall particles for deeper tumor penetration after initial passive targeting via the EPR effect.

Conjugation of nanoparticles with tumor-penetrating peptides, such as iRGD, represents another approach that has demonstrated improved drug delivery and enhanced antitumor activity in breast cancer models [26]. Additionally, modification of the TME itself has emerged as a critical strategy to enhance nanomedicine delivery. Techniques such as increasing tumor perfusion, promoting nanoparticle extravasation, and enhancing interstitial transport have been employed to optimize therapeutic outcomes [27] (Figure 1).

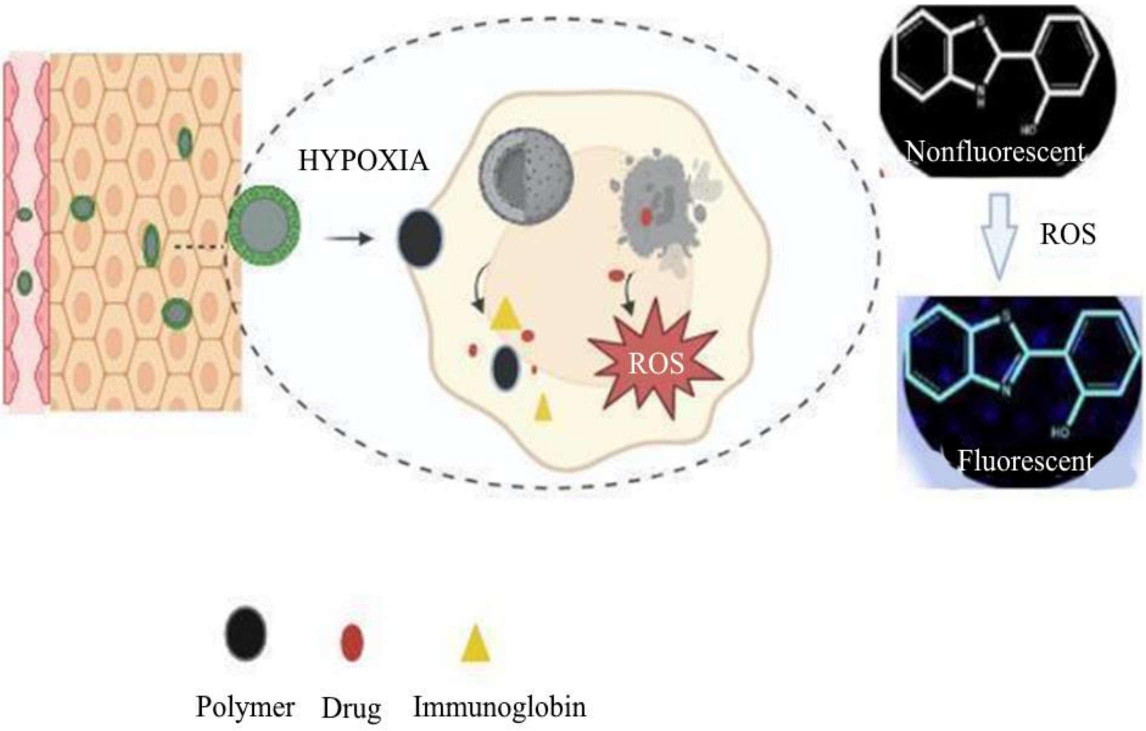

Figure 1. Illustration of the delivery route of hypoxia-responsive nanoparticles with size-shrinkable properties.

Extracellular Vesicle-Based Nanotechnology

Tissue engineering has greatly benefited from recent developments in nanomedicine, particularly the use of extracellular vesicle (EV)-based nanotechnology. Exosomes and other extracellular vesicles are nanoscale vesicles essential for intercellular communication and act as natural nanocarriers, making them promising tools for diagnosis, prevention, and therapy of various diseases [28]. A notable application is mesenchymal stem cell-derived exosomes (MSC-exosomes), which leverage inherent biological characteristics to enhance therapeutic efficacy while minimizing side effects. MSC-exosomes are under investigation for their role in tissue regeneration and as drug delivery vehicles [28]. The convergence of biotechnology and nanotechnology has further enabled regenerative applications, such as creating nanoscale environments in orthopedic surgery to support stem cell adhesion, proliferation, and controlled differentiation, highlighting EVs' potential in clinical tissue engineering [29].

Immune Modulation within the TME

The immunosuppressive and complex nature of the TME presents significant challenges for drug delivery and therapeutic efficacy. Nanomedicine contributes to tissue regeneration by modulating the immune landscape in diseased microenvironments. Immunomodulatory nanosystems integrate regenerative strategies with immune regulation, enhancing tissue repair [30]. In cancer therapy, nanomedicine can modulate the TME to improve immunotherapy outcomes by targeting immune infiltrates, tumor stroma, cytokines, and enzymes, thereby reversing immunosuppression and enhancing anti-tumor immunity [31]. Combining nanotechnology with tissue engineering and immunotherapy offers novel solutions to overcome TME-associated therapeutic barriers and develop advanced treatment strategies [32].

Nanostructured Biomaterials for Tissue Scaffolds

Nanostructured biomaterials significantly influence tissue scaffold design, improving interactions with biological systems, replicating the extracellular matrix, and guiding tissue organization for regeneration [33]. Incorporating nanoscale drug delivery systems into porous 3D scaffolds enhances cellular responses, osteogenesis, and tissue healing [34]. While materials such as chitosan and bioactive ceramics improve scaffold biocompatibility and osteogenic potential, challenges related to mechanical strength and load-bearing capacity remain [34]. Surface modifications of polymeric scaffolds—via chemical, physical, or radiation-mediated techniques—further regulate protein and cell interactions, enabling smart biomaterials to promote tissue morphogenesis in complex tissues like bone and nerves [35].

Stimuli-Responsive Nanomaterials in Cancer Therapy

Stimuli-responsive nanoparticles have revolutionized cancer therapy and tissue engineering. Advances in understanding molecular and genetic mechanisms of cancer have enabled the development of targeted therapies, including gene therapy, small molecule inhibitors, and monoclonal antibodies [36]. Lipid nanoparticles (LNPs) have significantly enhanced mRNA delivery by ensuring effective cytosolic release and cellular uptake, critical for therapeutic efficacy. However, challenges such as immunogenicity and toxicity require further optimization for clinical use [37].

Tumor Microenvironment Imaging and Monitoring

Nanomedicine has transformed TME imaging, enabling more precise diagnosis and therapy. Radiolabeled nanoparticles (e.g., technetium-99m, copper-64, lutetium-177, radium-223) improve molecular imaging and radionuclide therapy [38]. Cell membrane-coated nanoparticles enhance targeting, immune evasion, and theranostic applications [39]. Hybrid imaging systems, facilitated by multifunctional nanoparticles, support multimodal imaging (PET, SPECT, CT, MRI, optical, and ultrasound), improving tumor detection and real-time monitoring [40]. TME-responsive nanoparticles designed to react to low pH, redox conditions, or hypoxia optimize pharmacokinetics and therapeutic outcomes [41].

Nanomedicine in Modulating Hypoxia in the TME

Hypoxia in solid tumors contributes to metastasis and therapy resistance, making its modulation critical for tissue engineering and cancer treatment. Nanotechnology-based strategies, such as X-ray-induced photodynamic therapy (X-PDT) using scintillating materials, convert X-rays into visible light to activate photosensitizers in tumors, reducing side effects and improving TME modulation [42]. Controlled release and localized delivery systems enhance regenerative therapies by improving extracellular matrix remodeling and stem cell-based treatments [43]. DNA nanostructures have also been developed as imaging probes for hypoxic environments, improving stability, biocompatibility, and real-time monitoring [44].

Biodegradable and Biocompatible Nanomaterials

Biodegradable and biocompatible nanomaterials are critical for tissue engineering and regenerative medicine. Cellulose-based nanocomposites, combined with metal nanoparticles or polymers, offer mechanical strength, thermal stability, and biocompatibility, making them suitable for biomedical applications [45]. Smart nanomaterials that respond to environmental stimuli provide controlled, precise therapeutic effects, although rapid clearance and biocompatibility remain challenges [46]. Nanogels (NGs) encapsulate therapeutic drugs, offering controlled release and applications in imaging and therapy through hydrophilic and amphiphilic polymer systems [47].

Nanomedicine for Gene Therapy in Cancer

Nanomedicine has significantly advanced gene therapy and tissue engineering in cancer treatment. Nanoparticles enable precise delivery of therapeutic genes or drugs to tumor sites, improving efficacy while minimizing damage to healthy tissues [48]. This targeted approach allows selective genetic modification of tumor-initiating cells, such as in glioblastoma, offering complementary or alternative strategies to conventional therapies like surgery and chemoradiation [49] (Table 1).

Table 1. Studies on Nanoformulations for Cancer Therapy.

Nanoformulation	Gene Type	Type of Cancer	Particle Size	Zeta Potential	In Vitro / In Vivo	Therapeutic Outcome	References
Lipid nanoparticle (LNP)	siRNA	Hepatocellular carcinoma (HCC)	80–120 nm	−10 to −20 mV	In vitro (HepG2) / In vivo (BALB/c mice)	Tumor growth inhibition, oncogene silencing	[50]
Polymeric nanoparticle	CRISPR/Cas9	Lung cancer (NSCLC)	100–200 nm	+20 to +40 mV	In vivo (Nude mice)	Enhanced apoptosis, chemo-sensitization	[51]
Gold nanoparticle	ShRNA	Breast cancer	30–60 nm	~−20 mV	In vitro (MCF-7) / In vivo (SCID mice)	Gene silencing, reduced tumor size	[52]
Micellar nanoparticle	iGRD	Pancreatic cancer	–	–	In vitro (pancreatic cell lines) / In vivo (orthotopic KPC mouse model)	Tumor growth suppression	[53]
ROS-responsive polymeric nanoparticle	Cancer stem cells	Breast cancer	–	–	In vitro (4T1 CSCs) / In vivo (TNBC tumor-bearing mice)	Suppression of tumor growth, recurrence, and metastasis	[54]
Multimodal theranostic platform (DMCH)	miRNA-122, miRNA-222	Hepatocellular cancer	–	–	In vitro (HCC cell lines) / In vivo (mice)	Tumor growth suppression, reduced drug resistance, minimized systemic toxicity	[55]
Nanomedicine with scFv ligands	siRNA	NSCLC	100–200 nm	−10 to −30 mV	In vitro (NSCLC cell line)	Downregulation of Bcl-xL, enhanced apoptosis, synergistic with cisplatin, improved chemo-sensitivity	[56]
Nanoplatforms	ATP7A	Colorectal cancer	80–150 nm	–	In vitro (CRC cell lines) / In vivo	Enhanced tumor apoptosis, improved suppression, reduced systemic toxicity	[57]

Anti-EGFR aptamer-coupled cationic lipid nanocarriers	Bcl-2, PKC-ι	Breast cancer	~172 nm	−2.7 ± 0.6 mV	In vitro (TNBC cell line) / In vivo (Mouse xenograft)	Gene silencing	[58]
Various (liposomes, dendrimers, polymeric NPs, gold NPs)	siRNA, miRNA, gene augmentation	Breast cancer	50–200 nm	−10 to −30 mV	In vitro (MCF-7, MDA-MB-231, BT-474, T47D) / In vivo (BALB/c or nude mice)	Enhanced gene silencing (Bcl-2, HER2), increased apoptosis, reduced tumor growth, better targeting, reduced toxicity	[59]
Hyaluronic acid-decorated phenylboronic dendrimer (HAPD)	CRISPR-Cas9 RNP (APC & KRAS)	Colorectal cancer	130–150 nm	–	In vitro (CRC cell lines) / In vivo (xenograft & orthotopic models)	Tumor growth inhibition, prevention of metastasis, dual gene editing efficacy (Wnt/β-catenin & RAS/ERK)	[60]
Nanogel	siRNA (unspecified)	Solid tumors (general)	–	–	In vitro / In vivo (tumor-bearing mice)	Combined immunotherapy, gene therapy, photodynamic therapy; improved ROS, drug release, and targeting	[61]
DNA nanostructure (nanokite)	p53 tumor suppressor	Multidrug-resistant breast cancer (MCF-7R)	100–150 nm	–	In vitro (MCF-7R) / In vivo (mouse xenograft)	Co-delivery of p53 and DOX, tumor growth inhibition, low systemic toxicity, enhanced uptake and synergy	[62]
Lipid-based nanoparticles (RNA lipoplexes)	mRNA	Melanoma	80–200 nm	–	In vivo (patients) / In vitro	Immune activation (IFNα-dependent), enhanced tumor rejection, strong T-cell response	[63]
Iron oxide & gold core nanoparticles	siRNA	Multiple cancers	<100 nm	–	In vitro / In vivo	Efficient gene silencing, improved uptake, reduced degradation, biodistribution tracking, suitable for combination therapies	[63]
Lipid-based nanoparticles	Tumor suppressor genes (RB1, p53), siRNA	Retinoblastoma	<200 nm	–	In vitro (RB cell lines) / In vivo (ocular tumor models)	Improved transfection, controlled gene expression, potential tumor size reduction	[64]
Polymeric nanoparticles (PLGA, PEI, chitosan)	siRNA, pDNA, shRNA	Retinoblastoma	100–250 nm	–	In vitro (Y79, WERI-Rb1) / In vivo (xenograft/orthotopic models)	Enhanced gene delivery, low cytotoxicity, prolonged circulation, tumor gene silencing	[64]
Gold nanoparticles (AuNPs)	siRNA, antisense oligonucleotides	Retinoblastoma	20–100 nm	–	In vitro / in vivo	Effective gene knockdown, photothermal combination benefits, minimal ocular toxicity	[64]

3D Bioprinting with Nanocomposites

The integration of nanomedicine with 3D bioprinting has emerged as a powerful strategy in tissue engineering for fabricating complex tissue structures. Nanobiomaterials play a critical role in enhancing scaffold performance, modulating the cellular microenvironment, and improving the mechanical and biological properties of bioinks [65]. Incorporation of nanoparticles into 3D-printed constructs allows precise control over scaffold geometry, microstructure, and cellular behavior, enabling tailored tissue formation [65]. The synergy between nanotechnology and 3D bioprinting has expanded biofabrication possibilities by guiding cell fate and tissue development. Nano-composite bioinks can either be printed directly with living cells or used to create scaffolds that instruct cell behavior [65]. Moreover, the presence of nanoparticles enables modulation via external physical stimuli, adding another dimension for biomedical applications [65]. Clays, both natural and synthetic, serve as rheological and mechanical reinforcements in bioinks, enhancing printability, structural integrity, and promoting cellular proliferation, adhesion, differentiation, and alignment [66]. The combination of 3D bioprinting and nanotechnology shows significant potential in regenerating tissues such as bone, nerve, blood vessels, tendon, and internal organs [67]. Nanostructured biomaterials, including nanofibrous polymeric scaffolds and nanocrystalline bioceramics, further improve tissue regeneration by closely mimicking the native extracellular matrix [68–73] (Figure 2).

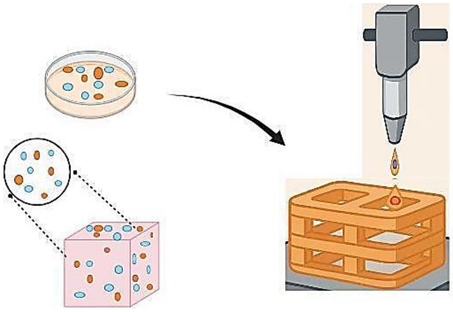

Figure 2. Illustration depicting the structure and composition of nanocomposite bioinks. L. Integration of Nanomaterials in Organoid Models.

Nanomedicine integration into tissue engineering, particularly in organoid models, represents a promising advancement for regenerative medicine. Organoids—3D stem cell-derived structures that replicate organ function—benefit significantly from nanostructured materials, which enable precise drug delivery due to their high surface area and nanoscale size [74, 75]. Mesoporous silica nanoparticles (MSNs) act as efficient nanocarriers for stem cell targeting, bioactive molecule delivery, and scaffold enhancement in tissue engineering applications [76].

The tunable properties of nanoparticles, such as shape, pore size, and surface chemistry, allow for optimized functionality in bone tissue engineering and other regenerative applications. Incorporating nanotechnology into organoid models enhances the self-organizing characteristics of natural tissues, promoting bioengineered structures that mimic native tissue architecture. This multidisciplinary approach accelerates the clinical translation of organoids for personalized tissue regeneration and functional restoration [62]. Additionally, nanostructured materials like magnetic nanoparticles (MNPs) are utilized to improve drug delivery and regulate biological responses within tissue engineering scaffolds, further expanding their therapeutic potential [77].

CHALLENGES AND FUTURE DIRECTIONS

Overcoming Biological Barriers

Biological barriers, including tissue matrices, cellular membranes, and protein corona formation, pose significant challenges for effective drug delivery in therapeutic applications such as tumor targeting and personalized cancer nanomedicine [76]. Delivering biological therapeutics, such as siRNA and monoclonal antibodies (mAbs), across intracellular barriers remains a critical limitation.

Nanotechnology offers promising solutions by modulating the protein corona, enhancing tumor penetration, and overcoming cellular membrane barriers [76]. Emerging biomedical micro- and nanomotors (MNMs) show potential due to their small size and autonomous navigation capabilities [79]. Gene therapy also faces obstacles, including extracellular degradation and inefficient cellular uptake, with both viral and nonviral vectors providing potential solutions [80]. Physiological barriers limit the bioavailability of small-molecule drugs, prompting investigations into nanotechnology-based and stimuli-responsive delivery systems [81]. Future directions involve engineering intelligent nanosystems capable of overcoming multiple in vivo barriers through integrated design principles and advances in nanomedicine strategies [82].

Improving Nanoparticle Specificity and Efficacy

Enhancing the specificity and efficacy of nanoparticles in drug delivery remains a key focus to enable further therapeutic developments. Precisely targeting nanoparticles to specific tissues or cell types often requires active targeting strategies using ligands or antibodies [83]. Multifunctional nanoparticles and cell-mediated delivery systems are being explored to improve circulation time, targeting accuracy, and immune evasion [84]. While nanoparticles can circumvent efflux pumps, they introduce safety and regulatory challenges, emphasizing the need for further research to overcome multidrug resistance in cancer therapy [85]. Artificial intelligence (AI) is increasingly applied to simulate and predict nanoparticle behavior in biological systems, supporting the design and optimization of personalized nanomedicine [86]. Advanced material development, surface modification, and multifunctional ligand design are being employed to improve nanoparticle stability and targeting [84]. Bridging the gap between laboratory research and clinical application requires clinical translation and interdisciplinary collaboration, ensuring nanoparticle designs meet scalability, reproducibility, and regulatory standards [87].

Translating Nanomedicine Approaches to Clinical Applications

Clinical translation of nanomedicine faces challenges related to circulation time, therapeutic efficacy, and industrial feasibility. Multifunctional nanoparticles, including protein-based and cell-mediated systems, are being developed to address these issues [88]. Understanding pathophysiological heterogeneity and biological barriers in tumor targeting is crucial to identify bottlenecks beyond material and manufacturing limitations [89]. Nanomedicine formulations must overcome technological and practical hurdles to gain industrial acceptance, align with market needs, and meet clinical trial requirements, while considering end-user perspectives [90]. Personalized nanomedicine, which can enhance therapeutic outcomes by tailoring treatments to specific patient populations, also faces regulatory and quality control challenges [91, 78].

CONCLUSION

The integration of tissue engineering and nanomedicine has opened exciting new avenues for understanding and treating cancer. Recent advances in these fields have provided unprecedented insights into the complex interactions within the tumor microenvironment (TME) and have led to innovative strategies for molecularly targeted cancer therapy. Notably, the development of nanoparticle-based drug delivery systems enables precise targeting of tumor cells while minimizing damage to healthy tissues. Enhanced understanding of the TME's role in tumor progression and therapy resistance has facilitated the design of more effective treatment approaches. Engineered 3D tissue models that closely mimic the TME offer improved platforms for drug screening and the development of personalized therapies. Furthermore, combining nanomedicine with immunotherapy has shown promising potential in augmenting the body's natural defenses against cancer. Despite these advances, challenges remain, including the creation of more physiologically accurate in vitro TME models and the design of nanoparticles with optimized biocompatibility and therapeutic efficiency. The interdisciplinary nature of this research underscores the importance of continued collaboration among oncologists, tissue engineers, nanoscientists, and other experts. Future directions may involve integrating machine learning and artificial intelligence to accelerate drug discovery and optimize therapeutic strategies. Collectively, these innovations hold the potential to significantly improve clinical outcomes and quality of life for cancer patients.

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