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Exploring Recent Advancements of Nanomedicine in the Tumour Microenvironmental Tissue Engineering

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Abstract

The combination of tissue engineering and nanomedicine is transforming cancer treatment by offering creative ways to get around problems with conventional therapies. Recent developments in nanomedicine are examined in this review, with an emphasis on how they might be used to comprehend and control the tumor microenvironment (TME), a dynamic and complex environment that has a major impact on the course of cancer and the effectiveness of treatment. Targeted interactions inside the TME are made possible by emerging nanotechnologies that provide regulated release mechanisms, real-time monitoring, and precise drug administration. At the same time, tissue engineering techniques have proved crucial in developing physiologically appropriate 3D tumor models that more closely resemble in vivo circumstances than conventional 2D cultures. Deeper understanding of tumor biology, angiogenesis, immunological evasion, and treatment resistance is made possible by these engineered models. Recent advancements in stimuli-responsive nanoparticles, organ-on-chip platforms, and biomaterials have improved the ability to study and modify the TME for therapeutic advantage. When taken as a whole, these multidisciplinary developments have enormous potential for creating more potent, patient-specific cancer treatments as well as enhancing drug screening and disease modeling systems. This study emphasizes how tissue engineering and nanomedicine work together to revolutionize personalized medicine and cancer research.

Keywords: Cancer-associated fibroblasts, nanomedicine, pharmaceutical nanomedicine, tissue engineering, tumor microenvironment.

INTRODUCTION

Tumors are highly intricate and diverse entities that are pivotal in cancer's onset and advancement. Recent breakthroughs in tumor biology have greatly enhanced our comprehension of these entities, illuminating their evolution and interactions within their surroundings [1]. A tumor is generally made up of cancerous cells that multiply without restraint, resulting in neoplastic growth. These malignant cells engage in complex interactions with their surrounding environment, referred to as the tumor microenvironment (TME), which includes non-cancerous cells, signaling molecules, and the extracellular matrix (ECM) [2]. Understanding this interaction is essential for grasping tumor growth, invasion, and metastasis [2]. The TME plays a vital role in the initiation, progression, and therapeutic response of cancer. It offers biochemical and biophysical signals to tumor cells, affecting critical processes in tumor growth such as angiogenesis, metastasis, and drug resistance [3, 4]. Tissue engineering is a cutting-edge method aimed at replicating and examining the intricate interactions within a TME. This approach involves developing three-dimensional (3D) models that include cancer cells, scaffolds that imitate the extracellular matrix, and other essential components that influence the

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tumor's behavior and growth [5]. The integration of nanomedicine with tissue engineering holds considerable promise for advancing cancer treatment by specifically targeting the TME. Unlike traditional cancer treatments like chemotherapy and radiotherapy, which mainly focus on rapidly dividing tumor cells, nanomedicine provides a more targeted strategy by concentrating on modifying the TME to improve therapeutic effectiveness and address issues related to resistance and side effects. Conventional treatments often face challenges such as drug resistance and systemic toxicity, partly due to the complex nature of the TME, which comprises various cell types like fibroblasts, immune cells, and endothelial cells, all contributing to tumor growth and progression [6]. Additionally, traditional therapies can trigger a senescence-associated secretory phenotype (SASP) in cancer-associated fibroblasts (CAFs), which can worsen inflammatory responses and potentially encourage tumor progression and therapeutic resistance [7]. In contrast, nanomedicine can be tailored to target specific components of the TME. For example, nanoparticles can alter the TME by producing reactive oxygen species, changing pH levels, and depleting glutathione, which can disrupt tumor-supportive processes [8]. Nanomedicine presents transformative potential in cancer treatment by integrating with tissue engineering to overcome the limitations of conventional therapies. Its precision in targeting the TME, reduced systemic toxicity, and enhanced diagnostic capabilities represent a significant step towards more effective and personalized cancer care. Although challenges such as clinical translation persist, ongoing advancements in nanotechnology promise a more robust therapeutic arsenal against cancer [9].

COMPONENTS OF TUMOUR MICROENVIRONMENT

Development, progression, and metastasis of cancer are significantly influenced by the complex ecosystem known as the TME, comprising both cellular and non-cellular components. Adipocytes, fibroblasts, endothelial cells, neoplastic cells, pericytes, stem, and progenitor cells, extracellular matrix (ECM) components, and various immune cells are all found in the TME [10]. Through complex ways, these components interact to influence tumor behavior and treatment outcomes. Notably, the TME is dynamic, with its constituents performing a variety of functions that, depending on systemic and local circumstances, can either stimulate or impede the growth of tumors [11]. Immune cells like dendritic cells, lymphocytes, macrophages, and myeloid-derived suppressor cells, for instance, can have both pro- and anti-tumorigenic effects in gastric cancer [12]. Cell behavior and tumor progression are also greatly influenced by the biomechanical forces produced within the TME, such as growth-induced solid stresses, increased matrix stiffness, and altered interstitial flow [13].

TUMOUR MICROENVIRONMENT ROLE IN CANCER PROGRESSION AND METASTASIS

The TME plays a crucial role in progression and metastasis across various cancer types. In breast cancer, the TME significantly influences development, progression, and metastasis, with diverse immune cell populations contributing to both anti-tumor and pro-tumor activities [14]. The biophysical interactions between cancer cells and their dynamic microenvironment activate cancer mechano-responses, triggering structural reorganization of intracellular organelles and associated genetic modifications [15]. Interestingly, the TME is not static but changes as tumors grow and develop. Stromal components, including extracellular matrix (ECM), contribute to tumor progression and metastasis by affecting cancer cell function [16]. In breast cancer, tumor-associated macrophages (TAMs) are particularly influential, secreting proangiogenic factors and suppressing local pro-inflammatory antitumor responses, thus enhancing tumor cell evasion and metastasis [17]. Additionally, hypoxia in the TME stimulates macrophages to produce VEGF and suppress T-cell immune responses, further promoting metastasis [18].

CHALLENGES IN TARGETING THE TUMOUR MICROENVIRONMENT

The complex and dynamic nature of the TME makes it difficult to target cancer [19, 20]. It is challenging to create efficient tailored medicines because of this intricacy. Targeting the TME is difficult due to its heterogeneity and resemblance to healthy tissue, which can result in toxicity and off-target consequences [20]. Therapeutic approaches are further complicated by the TME's capacity to

change and adapt in response to therapies [21]. Drug distribution and efficacy may be hampered by solid tumors' hypoxic environments, aberrant vascular, and thick stroma [22]. Targeting the TME in cancer treatment is still a potential strategy in spite of these obstacles. One promising way to get beyond some of these challenges is through nanomedicine. Nanocarriers can be engineered to enhance drug delivery, modify the microenvironment, and target TME components selectively [23].

VARIOUS NANOMEDICINE APPROACHES TO TARGETING THE TUMOUR MICROENVIRONMENT VIA TISSUE ENGINEERING

Nanoparticles for Enhanced Drug Penetration

Targeting the TME with specific nanomedicine techniques has demonstrated very significant promise for improving medication efficacy and penetration. Although barriers in the TME frequently reduce the effectiveness of nanoparticles, the enhanced permeability and retention (EPR) effect permits them to accumulate in tumor tissues [24]. Utilizing size-shrinkable drug-delivery nanosystems is one promising strategy that can adapt to the particular features of the TME, including elevated enzyme levels, hypoxia, and acidic pH [25]. These nanoparticles can become ultrasmall particles for deep tumor penetration after first using the EPR effect for passive targeting. Conjugating nanoparticles with tumor-penetrating peptides, such as iRGD, is a further tactic that has demonstrated improved drug delivery and increased antitumor activity in breast tumor cells [26]. TME modification has become a key tactic to enhance the delivery of nanomedicines. Increasing tumor perfusion, promoting nanoparticle extravasation, and boosting interstitial transport are among strategies [27] (Figure 1).

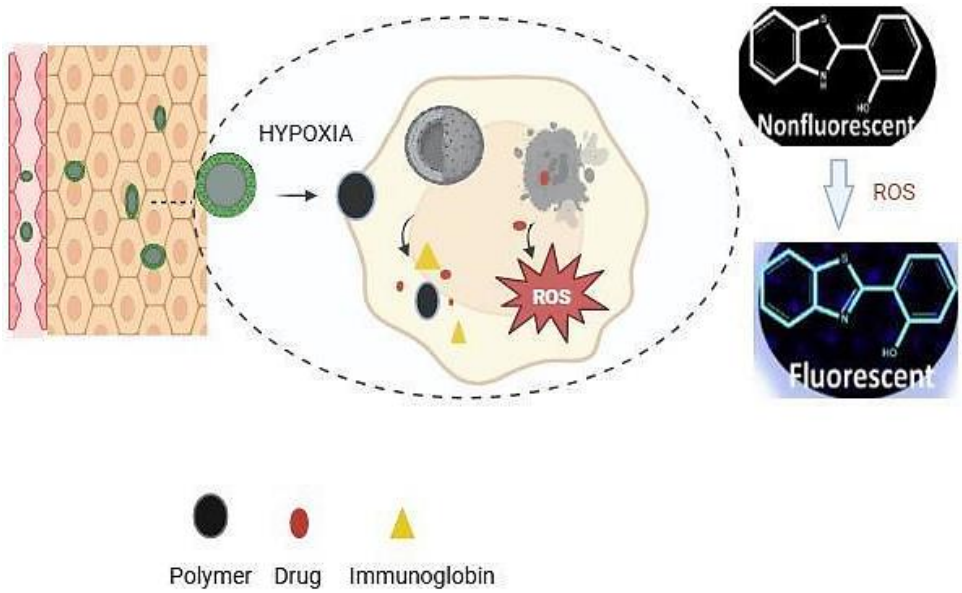

Figure 1. Schematic illustration of Transport path for the hypoxia-responsive size-shrinkable nanoparticle.

Extracellular Vesicle-Based Nanotechnology

Tissue engineering has greatly benefited from recent developments in nanomedicine, especially the use of extracellular vesicle (EV)-based nanotechnology. Exosomes and other extracellular vesicles are nanoscale vesicles that are essential for intercellular communication. Because they can act as natural nanocarriers, these vesicles have become promising instruments in nanomedicine for the detection, prevention, and therapy of a variety of disorders [28]. The application of mesenchymal stem cell-derived exosomes (MSC-exosomes) for tissue engineering is one significant development. These exosomes' inherent biological characteristics and functioning make them superior to artificial nanoparticles. MSC-exosomes have the potential to improve efficacy and decrease negative effects by acting as nanocarriers for medication administration and are being investigated for their involvement in tissue regeneration [28]. Additionally, the application of exosomes in regenerative medicine has been

made possible by the convergence of biotechnology and nanotechnology. For example, nanotechnology has been used in orthopedic surgery to develop nanoscale environments that support stem cell adhesion, proliferation, and controlled differentiation – all of which are essential for tissue engineering. This method highlights the revolutionary potential of EVs in clinical applications by promoting the regeneration of tissues like bone, cartilage, and nerves [29].

Immune Modulation within the TME

TME's intricacy and immunosuppressive characteristics provide special difficulties for medication distribution and therapeutic effectiveness. By altering the immunological landscape in diseased microenvironments, nanomedicine also contributes significantly to tissue regeneration. By addressing the local immunological milieu and its critical role in tissue repair, immunomodulatory nanosystems have demonstrated promise in promoting tissue regeneration. These systems use nanotechnology to combine regenerative techniques with immune regulation, offering new ways to improve tissue regeneration [30].

Nanomedicine has shown promise in modulating the immunosuppressive TME in the context of cancer immunotherapy. To increase the effectiveness of immunotherapies, this entails focusing on different immunological components, such as immune cells that infiltrate tumors. To improve the body's immune response against cancers, nano-enabled tactics involve reversing the immunosuppressive environment by modifying immune cells, tumor stroma, cytokines, and enzymes [31]. All things considered, a possible approach to getting over the TME's drawbacks is the incorporation of nanotechnology into tissue engineering and immunotherapy. In addition to addressing current therapeutic challenges, nanomedicine's capacity to improve drug delivery within the TME and modulate immune responses creates new opportunities for the development of cutting-edge treatment plans, especially in the fields of cancer therapy and regenerative medicine [32].

Nanostructured Biomaterials for Tissue Scaffolds

The construction of tissue scaffolds is one area in which nanostructured biomaterials have a major influence on tissue engineering. They improve interactions with biological systems, improve scaffold properties, and replicate the extracellular matrix found in nature. By directing tissue organization and development, these substances promote regeneration [33]. Nanoscaled drug delivery systems in porous 3D scaffolds improve the regenerative potential of biomaterials by encouraging cellular responses and tissue healing, boosting osteogenesis, and creating a structurally supportive environment [34]. Although the osteogenic potential and biocompatibility of scaffolds are improved by the addition of materials like chitosan and bioactive ceramics, issues with mechanical strength and load-bearing capacity persist [34]. The relevance of surface modifications in regulating protein and cell interactions is highlighted by developments in polymeric scaffolds. Techniques such as chemical, physical, and radiation-mediated alterations are used to improve biocompatibility and functional performance (Katti et al., 2008). By interacting with cells and forming dynamic scaffolding for enhanced tissue regeneration, smart biomaterials facilitate innovative tissue morphogenesis, particularly in complicated tissues like bone and nerves [35].

Stimuli-Responsive Nanomaterials in Cancer Therapy

Nanomedicine has created stimuli-responsive nanoparticles that have transformed cancer treatment and tissue engineering. Improved knowledge of the molecular and genetic causes of cancer has led to the development of targeted medicines, including gene therapies, small molecule inhibitors, and monoclonal antibodies [36]. Lipid nanoparticles (LNPs) have also transformed the transport of mRNA. These nanoparticles are made to guarantee effective cytosolic release and cellular absorption, both of which are essential for cancer treatments. However, issues including immunogenicity and toxicity still exist, requiring more study to maximize their use in mRNA therapies [37].

Tumor Microenvironment Imaging and Monitoring

Tissue engineering and TME imaging have been transformed by nanomedicine, allowing for more accurate and effective treatments. Theranostic systems and customized cancer treatments are improved by the use of radiolabeled nanoparticles such as technetium-99m, copper-64, lutetium-177, and radium-

223 in radionuclide therapy and molecular imaging [38]. Theranostics for cancer shows promise with cell membrane-coated nanoparticles, which help target tumor tissue, avoid immune system surveillance and sequestration, and open the door for further advancements in biomimetic nanomedicine [39]. The creation of hybrid imaging systems, which enable complementing data collection from many imaging modalities with a single contrast agent injection, has also been made possible by nanotechnology. In these systems, multifunctional nanoparticles facilitate multimodal imaging methods like PET, SPECT, CT, MRI, optical imaging, and ultrasound imaging, enhancing the data available for accurate tumor diagnosis and tracking [40]. TME-responsive nanoparticles enhance pharmacokinetics and therapeutic efficacy in solid tumors by altering the TME. They are made to react to low pH, redox conditions, and hypoxia [41].

Nanomedicine in Modulating Hypoxia in the TME

Effective tissue engineering and cancer treatment depend on the control of hypoxia in the TME, which has been greatly altered by nanomedicine. Solid tumors frequently exhibit hypoxia, a state marked by low oxygen levels that aids in the spread of cancer and treatment resistance. Nanotechnology provides creative ways to deal with TME hypoxia. The application of penetrating X-rays as sources for deep-seated tumor treatment, known as X-ray-induced photodynamic therapy (X-PDT), is one potential strategy. Through the inventive use of scintillating materials, this approach transforms X-rays into visible light, which triggers photosensitizers inside the tumor. X-PDT is a promising cancer treatment option since it decreases side effects and enhances the TME by employing low-dose X-ray radiation [42]. Exploring new tissue engineering frontiers has also been made possible by advancements in medication delivery methods. The accuracy and effectiveness of treatments have increased as a result of the incorporation of controlled release systems and localized delivery methods into regenerative medicine. Nanotechnology addresses hypoxic conditions in the TME and promotes the regeneration of soft and hard tissues by improving the extracellular matrix and using stem cell-based therapies [43]. Furthermore, DNA nanotechnology has played a key role in the creation of imaging probes for hypoxic environments. Researchers have increased the stability of these probes and improved their performance in physiological settings by creating DNA nanostructures that are both programmable and biocompatible. These developments provide focused interventions by assisting in the real-time monitoring of hypoxic zones [44].

Biodegradable and Biocompatible Nanomaterials

Biodegradable and biocompatible nanomaterials have demonstrated great promise for tissue engineering, especially in the creation of smart nanomaterials and nanocomposites. These developments take advantage of the special qualities of nanomaterials to tackle regenerative medicine's problems. Cellulose nanocomposites, which are becoming more and more popular because of their affordability, biodegradability, and biocompatibility, are one noteworthy breakthrough. Because of its excellent mechanical and thermal durability, cellulose nanomaterials can be mixed with other substances, such as metal nanoparticles and organic polymers, to form composites that preserve the cellulose's inherent mechanical, optical, and thermal characteristics. Because of their adaptability and the latest developments in preparation technology, these composites have great promise for use in engineering and environmental applications [45]. By reacting to environmental stimuli and improving accuracy and regulated responses, smart nanomaterials are transforming biomedical applications. However, issues like quick excretion from the body and biocompatibility necessitate more research and development for next-generation smart nanomaterials [46]. Therapeutic drugs are encapsulated in nanogels (NGs), which are sophisticated drug delivery devices with controlled release. Applications in biological imaging and therapy are expanded through synthesis employing hydrophilic and amphiphilic polymers [47].

Nanomedicine for Gene Therapy in Cancer

Gene therapy and tissue engineering, especially in the treatment of cancer, have been greatly influenced by nanomedicine. Utilizing the special qualities of nanoparticles, nanomedicine enhances targeted medication delivery, diagnostics, and the creation of individualized treatment regimens. Nanotechnology has made it possible to create and use nanoparticles for more effective drug delivery systems in the field of cancer therapy. By employing both passive and active targeting mechanisms,

these nanoparticles can be designed to deliver medications or gene treatments precisely to tumor locations. In addition to improving treatment effectiveness, this focused strategy reduces harm to healthy tissues, which is a typical disadvantage of conventional chemotherapy [48]. More precise genetic changes to fight cancer are made possible by the more accurate delivery of genes to target cells through the use of nanoparticles. For example, nanotechnology has made it possible to deliver therapeutic genes that selectively target tumor-initiating cells in the treatment of brain tumors like glioblastoma. This offers an alternative or supplement to conventional therapies like surgery and chemoradiation [49] (Table 1).

Table 1. Studies on nanoformulation 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	-10 to -20	*In vitro* (HepG2 cell lines) / *In vivo* (BALB/c mice)	Tumor growth inhibition, silencing of oncogene	[50]
Polymeric nanoparticle	CRISPR/Cas9	Lung cancer (NSCLC)	100–200	+20 to +40	*In vivo* (Nude mice)	Enhanced apoptosis, chemo sensitization	[51]
Gold nanoparticle	ShRNA	breast cancer	30–60	~-20	*In vitro* (MCF-7) / *in vivo* (SCID mice)	Gene silencing, reduced tumour size	[52]
Micellar nanoparticle	iGRD	Pancreatic cancer	-	-	*In vitro* (pancreatic cell lines) / *In vivo* (orthotopic KPC mouse model)	Suppression of tumour growth	[53]
ROS-responsive polymeric nanoparticle	Cancer stem cells	Breast cancer	-	-	*In vitro* (4T1 Cancer Stem Cells) /*in vivo* (TNBC tumor-bearing mice)	suppressing tumor growth, recurrence, and metastasis.	[54]
Multimodal theranostic platform (DMCH)	miRNA-122 miRNA-222	Hepatocellular cancer	-	-	*In vitro* (HCC cell lines) / *in vivo* (mice)	Suppressed tumor growth, reduced drug resistance, and minimized systemic toxicity	[55]
Nanomedicine with scFv ligands	Small interfering RNA (siRNA)	Non-small cell lung cancer (NSCLC)	100–200 nm	−10 mV to −30 mV	*In vitro* (NSCLC cell line)	Downregulation of Bcl-xL at transcriptional and translational levels, Enhanced apoptosis in NSCLC cells ,Synergistic activity with cisplatin ,Improved cell sensitivity to chemotherapy	[56]
nanoplatforms	ATP7A	Colorectal cancer	80-150nm	-	*In vitro* (CRC cell lines) / *In vivo*	Enhanced tumor cell apoptosis Improved tumor suppression efficacy with reduced systemic toxicity	[57]
Anti-EGFR aptamer-coupled cationic	Bcl-2 and PKC-ι genes	Breast cancer	~172 nm	−2.7 ± 0.6 mV	*In vitro* (TNBC cell line) / *In vivo* (Mouse xenograft model)	Gene silencing	[58]

lipid nanocarriers							
Various (e.g., liposomes, dendrimers, polymeric NPs, gold NPs)	siRNA, miRNA, gene augmentation	Breast Cancer (BC)	Varies (-10 to -30 mV, typically)	~50–200 nm (range depending on system)	*In vitro* (MCF-7, MDA-MB-231, BT-474, T47D cells) / *In vivo* (BALB/c or nude mice xenograft models)	Enhanced gene silencing (e.g., Bcl-2, HER2), increased apoptosis, reduced tumor growth, better targeting and uptake, reduced systemic toxicity	[59]
Hyaluronic acid-decorated phenylboronic dendrimer (HAPD)	CRISPR-Cas9 RNP targeting *APC* and *KRAS* mutations	Colorectal cancer (CRC)	-	~130–150 nm	*In vitro* (CRC cell lines) / *In vivo* (CRC xenograft and orthotopic mouse models)	Significant tumor growth inhibition, prevention of *liver* and *lung metastasis*, dual gene editing demonstrated efficacy in Wnt/β-catenin and RAS/ERK pathways	[60]
Nanogel	siRNA (exact target gene not specified)	Solid tumors (general)	-	-	*In vitro* cancer cell lines / *In vivo* tumor-bearing animal models (likely mice)	Combined *immunotherapy, gene therapy*, and *photodynamic therapy* led to significant tumor cell killing, improved ROS generation, enhanced drug release, and tumor-targeting specificity	[61]
DNA nanostructure (nanokite) for co-delivery of gene and drug	*p53 tumor suppressor gene*	*Multidrug-resistant breast cancer (MCF-7R)*	-	~100–150 nm (typical for DNA nanostructures)	*In vitro* (MCF-7R cell line) / *In vivo* (Mouse xenograft tumor models)	Effective co-delivery of p53 and DOX, significant tumor growth inhibition, low systemic toxicity, enhanced cellular uptake and therapeutic synergy	[62]
Lipid-based nanoparticles (RNA lipoplexes)	mRNA	*Melanoma*	-	80–200 nm for lipoplexes	*In vivo* (Human melanoma patients) / *In vitro*	Lipoplex mRNA delivery triggered immune activation (IFNα-dependent), enhanced tumor rejection, strong T-cell response, improved targeting of oncogenes and tumor suppressors	

Iron oxide & gold core nanoparticles	siRNA	Multiple cancer types	-	< *100 nm*	*in vitro* / *in vivo*	- Efficient gene silencing through RNAi - Improved cellular uptake and reduced degradation - Tracked biodistribution via imaging - Reduced immunogenicity - Suitable for *combination therapies* (e.g., RNAi + chemo/PTT/immune/radiotherapy)	[63]
Lipid-based nanoparticles	Tumor suppressor genes (e.g., RB1, p53), siRNA	Retinoblastoma (RB)	-	< 200 nm	*In vitro* (RB cell lines) / *In vivo* (animal eye tumor models)	Improved transfection efficiency in ocular tissues; controlled gene expression; potential tumor size reduction	[64]
Polymeric nanoparticles (e.g., PLGA, PEI, chitosan)	siRNA, pDNA, shRNA	Retinoblastoma (RB)	-	100–250 nm	*In vitro* (Y79, WERI-Rb1) / *In vivo* (xenograft or orthotopic models)	Enhanced gene delivery with low cytotoxicity; prolonged circulation; tumor gene silencing	[64]
Gold nanoparticles (AuNPs)	siRNA, antisense oligonucleotides	Retinoblastoma (RB)	-	~20–100 nm	*In vitro* / animal models (e.g., rabbit or mouse	Effective gene knockdown; photothermal combinational benefits; minimal ocular toxicity	[64]

3D Bioprinting with Nanocomposites

In 3D bioprinting with nanocomposites, tissue engineering techniques that integrate nanomedicine have become a viable method for creating intricate tissue structures. In order to improve scaffold performance, control the cellular microenvironment, and enhance the mechanical and biological characteristics of bioinks, nanobiomaterials are essential [65]. Exact control over scaffold geometry, microstructure, and cellular behavior is made possible by the incorporation of nanoparticles into 3D printed structures [65]. It is interesting to remark that the fusion of nanotechnology and 3D bioprinting has created unanticipated biofabrication prospects. By directing cell fate and development toward particular tissues, nano-composite bioinks can be directly printed with cells or create scaffolds that train cells [65]. Furthermore, control via external physical stimuli is made possible by the presence of nanoparticles, which adds another tool for healthcare applications [65]. As rheological and mechanical reinforcements in bioinks, clays – both natural and synthetic – have shown special utility in boosting cellular proliferation, adhesion, differentiation, and alignment as well as printability and build resistance [66]. Significant promise for tissue engineering applications, such as bone, nerve, blood vessel, tendon, and internal organ regeneration, is presented by the combination of 3D bioprinting with nanotechnology [67]. The application of nanostructured biomaterials, like nanofibrous polymeric scaffolds and nanocrystalline bioceramics, improves tissue regeneration results by offering a closer similarity to natural extracellular matrix [68] (Figure 2).

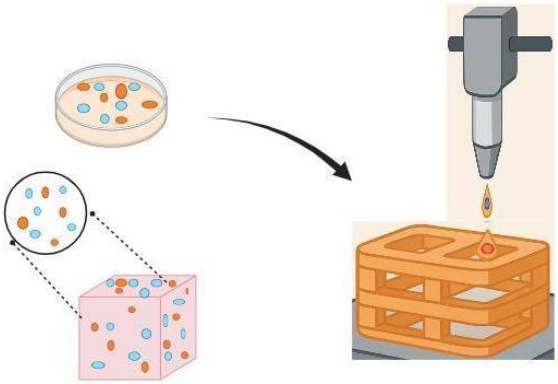

Figure 2. Schematic illustration of nanocomposite bioinks.

Nano-Based Approaches for Vascularization

The challenge of vascularization, which is essential to the survival and operation of designed tissues, has led to an increased integration of nanomedicine into tissue engineering. Utilizing nanoparticles to promote angiogenesis – the process by which new blood vessels are formed from preexisting vasculature – is one promising tactic. Angiogenesis is crucial for providing oxygen and nutrients to modified tissues [69]. By enhancing regenerative therapies for a variety of tissue types, nanotechnology makes a substantial contribution to the area of tissue engineering. By fostering conditions that are conducive to cell proliferation and differentiation, nanostructured materials have demonstrated significant promise in fostering tissue regeneration [70]. In particular, the addition of metals and nanostructured polymers has improved vascularization and increased biocompatibility [70]. A number of nanotechnology-based approaches have been developed to support vascularization in tissue engineering. For instance, europium hydroxide nanorods (EHNs) embedded in electrospun polycaprolactone (PCL) scaffolds have shown strong pro-angiogenic effects. As shown in both in vitro and in vivo models, these scaffolds dramatically increase endothelial cell proliferation and vascularization, possibly via pathways such as the VEGFR2/Akt signaling pathway [71]. To encourage quick and stable neovascularization, other nanomedicine techniques involve delivering growth factors and cells inside scaffolds utilizing nanoparticles. In the early stages following implantation, these methods aid in overcoming the sluggish process of spontaneous angiogenesis and avert ischemia and cell death in larger tissue constructs [72]. Additionally, nanotechnology makes it easier to develop and optimize scaffold architecture, which is essential for successful vascularization. Scaffolds' pore architecture is crucial because open macropores facilitate improved cell motility, nutrition distribution, and oxygen diffusion, all of which support the development of new tissue and vascularization [73].

Integration of Nanomaterials in Organoid Models

Nanomedicine's incorporation into tissue engineering techniques, especially using organoid models, offers encouraging developments in regenerative medicine. The field of nanomedicine, which applies nanotechnology to medicinal applications, presents intriguing opportunities to improve organoid models, which are three-dimensional structures made from stem cells that replicate the structure and function of actual organs [74]. Within this context, the use of nanotechnology in drug delivery is one of its major benefits. Because of their enormous surface area and compact size, nanostructured materials are very good at accurately delivering therapeutic chemicals to certain tissues [75]. Mesoporous silica nanoparticles (MSNs) have also become powerful nanocarriers that can identify stem cells, distribute bioactive substances, and improve tissue engineering scaffolds [76]. These nanoparticles' shape, pore size, and surface chemistry can all be precisely adjusted to maximize their usage in bone tissue engineering and other tissue-engineering applications. Additionally, it is becoming easier to create bioengineered structures that replicate the self-organizing characteristics of natural tissues by integrating nanotechnology into organoid models. This multidisciplinary field aims to expedite the clinical translation of organoids for customized tissue healing and biofunction rebuilding by integrating engineering ideas into biomedicine [62]. In addition to providing structural support, nanostructured

materials – like magnetic nanoparticles, or MNPs – are also employed to enhance medication delivery and regulate biological reactions in tissue engineering scaffolds [77].

CHALLENGES AND FUTURE DIRECTIONS

Overcoming Biological Barriers

Biological barriers, such as tissue matrices, cellular membranes, and protein corona can make it difficult for drugs to be delivered effectively in therapeutic applications like tumor control and tailored cancer nanomedicine [78]. Delivering biological medications, like as siRNA and mAbs, via intracellular domain barriers is a difficulty in tailored cancer nanomedicine. In order to ensure therapeutic reach, nanotechnology offers promising options by targeting the protein corona, improving tumor penetration, and overcoming cellular membranes [78]. Biomedical micro- and nanomotors (MNMs) are emerging as promising tools to tackle these barriers due to their small size and autonomous navigation capabilities [79]. Gene therapy also faces significant barriers, such as extracellular degradation and inefficient cellular uptake. Both viral and nonviral vectors show potential for overcoming these challenges [80]. Physiological obstacles make small-molecule medications bioavailable, and novel approaches like nanotechnology and stimuli-responsive delivery systems are being investigated to address this problem [81]. Engineering more intelligent nanosystems and particles that can overcome every obstacle that arises in vivo is one of the future directions. This will require applying comprehensive design principles and utilizing developments in various nanomedicine strategies [82].

Improving Nanoparticle Specificity and Efficacy

Several strategies and technologies are being used to improve the specificity and efficacy of nanoparticles in drug delivery systems, as well as to open the door for further developments. Targeting nanoparticles precisely to particular tissues or cell types is difficult and frequently calls for active techniques involving ligands or antibodies [83]. Multifunctional nanoparticles and cell-mediated delivery systems are being investigated for better circulation times and targeting accuracy. Nanoparticles must be made to evade immune system clearance [84]. Despite their ability to circumvent efflux pumps, nanoparticles in clinical applications raise important safety and regulatory issues, and further research and development are needed to overcome multidrug resistance in cancer treatment [85]. Through the simulation and prediction of nanoparticle behavior in biological contexts, artificial intelligence (AI) is improving the design and optimization of nanoparticle systems, facilitating the development of personalized medicine [86]. Multifunctional nanoparticles and creative ligand designs are being used to improve the targeting and stability of nanoparticles through the development of new materials and surface modification techniques [84]. It is crucial to bridge the gap between laboratory research and clinical application through clinical translation and interdisciplinary collaboration. Nanoparticle designs must be optimized for scalability, reproducibility, and regulatory compliance, which calls for interdisciplinary cooperation [87].

Translating Nanomedicine Approaches to Clinical Applications

Circulation time, effectiveness, and industrial acceptability are some of the issues facing nanomedicine. In order to overcome these challenges, multifunctional nanoparticles – such as protein-based and cell-mediated nanoparticles – are being created [88]. It is essential to comprehend pathophysiological heterogeneity and biological barriers in nanomedicine tumor targeting to develop successful therapeutic applications, identifying bottlenecks that go beyond problems with materials and production [89]. Significant technological and application obstacles must be overcome by nanomedicine formulations in order to be accepted by industry and to align efforts with market opportunities and clinical trial designs. End-user perspectives must also be taken into account [90]. Personalized nanomedicine, which can increase treatment effectiveness by tailoring medications for certain patient populations, has difficulties with safety and quality requirements set by the market and regulations [91, 92].

CONCLUSION

The combination of tissue engineering and nanomedicine has opened up exciting new avenues for understanding and treating cancer. Recent advancements in these fields have yielded previously

unheard-of insights into the complex interactions within the TME and novel approaches to molecular cancer treatment. Emphasize the important developments in developing medication delivery methods based on nanoparticles that can precisely target tumor cells while minimizing damage to healthy tissues. Stress how improved knowledge of how the TME affects cancer development and resistance to therapy has resulted in more potent treatment approaches. Talk about the potential for more accurate drug screening and individualized treatment plans made possible by engineered 3D tissue models that more closely resemble the TME. Bring up the encouraging results of combining immunotherapy and nanomedicine to strengthen the body's defenses against cancer. Recognize the ongoing difficulties, such as creating more sophisticated in vitro models of the TME and improving nanoparticle design for increased biocompatibility. Emphasize how this research is interdisciplinary and how crucial it is for oncologists, tissue engineers, nanoscientists, and other experts to continue working together. Consider potential future paths, such as using machine learning and artificial intelligence to expedite drug discovery and improve therapeutic approaches. Emphasize how these developments could improve the quality of life and results for cancer patients.

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