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Nanotechnology-Enabled Reprogramming of the Tumor Microenvironment: Targeting Cancer-Associated Fibroblasts and Immune Suppression

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ABSTRACT

The tumor microenvironment (TME) is a dynamic and complex ecosystem composed of malignant cells, stromal components, immune cells, extracellular matrix, and soluble mediators that collectively drive tumor progression, metastasis, and therapeutic resistance. Among its non-malignant constituents, cancer-associated fibroblasts (CAFs) and immunosuppressive immune populations play central roles in shaping a tumor-permissive niche. Conventional anticancer therapies largely target cancer cells directly, often neglecting the stromal and immune context that enables tumor survival and immune evasion. Nanotechnology has emerged as a transformative strategy to overcome these limitations by enabling precise, spatiotemporally controlled modulation of the TME. Nanoparticle-based platforms can selectively deliver drugs, nucleic acids, and immunomodulators to CAFs and immune cells, reprogramming their phenotypes toward tumor-restraining functions. This review critically examines recent advances in nanotechnology-enabled targeting of CAFs and immune suppression within the TME. We discuss the biological rationale for TME reprogramming, design principles of functional nanomaterials, and therapeutic strategies aimed at normalizing fibroblast activity and restoring antitumor immunity. Current challenges, safety considerations, and translational prospects are also highlighted. Collectively, nanotechnology-driven TME modulation represents a promising paradigm shift toward more durable and effective cancer therapies.

INTRODUCTION

Cancer progression is no longer viewed as a cell-autonomous process driven solely by genetic alterations within malignant cells[1, 2]. Instead, tumors are increasingly recognized as complex tissues whose growth, survival, and metastatic potential are critically dependent on interactions with the surrounding tumor microenvironment (TME)[3–5]. The TME consists of stromal cells, immune cells, blood and lymphatic vessels, extracellular matrix (ECM), and a diverse array of cytokines, chemokines, and growth factors. These components engage in reciprocal signaling with cancer cells, shaping tumor evolution and influencing therapeutic outcomes[3, 4].

One of the most striking features of the TME is its ability to promote immune evasion and resistance to therapy. Immunosuppressive networks, including regulatory T cells, myeloid-derived suppressor cells, tumor-associated macrophages, and dysfunctional dendritic cells, actively inhibit effective antitumor immune responses. In parallel, stromal elements such as cancer-associated fibroblasts (CAFs) remodel the ECM, secrete pro-tumorigenic factors, and establish physical and biochemical barriers that limit drug penetration and immune cell infiltration[6–8].

Despite remarkable advances in molecularly targeted therapies and immune checkpoint inhibitors, clinical responses remain heterogeneous and often transient. Resistance frequently arises not only from cancer cell adaptation but also from TME-mediated protective mechanisms[9–11]. Consequently, therapeutic strategies that fail to address the TME are inherently limited in their long-term efficacy. This realization has prompted growing interest in approaches that directly modulate the tumor ecosystem rather than targeting malignant cells alone[11].

Nanotechnology offers a unique and powerful toolkit to address the complexity of the TME. Engineered nanomaterials can be designed with precise control over size, shape, surface chemistry, and functional payloads, enabling selective accumulation within tumors and specific cellular compartments[12–14]. Through passive targeting mechanisms such as the enhanced permeability and retention (EPR) effect, as well as active targeting via ligand-receptor interactions, nanoparticles can preferentially localize to the TME while sparing healthy tissues.

Importantly, nanotechnology enables multifunctional therapeutic strategies that integrate drug delivery, imaging, and microenvironmental modulation within a single platform. Nanoparticles can carry chemotherapeutic agents, small-molecule inhibitors, nucleic acids, proteins, or immune modulators, releasing them in response to specific stimuli such as pH, redox potential, or enzymatic activity characteristic of the TME[15–17]. This capability allows for spatiotemporally controlled reprogramming of stromal and immune components.

Targeting CAFs and immune suppression represents a particularly promising avenue for nanotechnology-enabled TME reprogramming. CAFs are abundant in many solid tumors and are key orchestrators of tumor-supportive signaling networks. Meanwhile, immunosuppressive pathways within the TME blunt the effectiveness of immunotherapy[18–20]. Nanoparticle-based interventions that normalize fibroblast function and restore immune competence may therefore synergize with existing therapies to produce more durable clinical responses. This review focuses on recent progress in nanotechnology-driven strategies aimed at reprogramming the TME, with particular emphasis on CAF targeting and immune modulation. We explore the biological roles of CAFs and immune suppression, the design principles of nanotherapeutic systems, and emerging preclinical and translational evidence supporting this approach.

2 Cancer-Associated Fibroblasts: Origins and Pro-Tumorigenic Functions

Cancer-associated fibroblasts represent a heterogeneous population of activated stromal cells that play multifaceted roles in tumor progression. Unlike normal fibroblasts, CAFs exhibit persistent activation characterized by enhanced proliferation, altered metabolic states, and increased secretion of ECM components and soluble mediators[21]. Their origins are diverse, arising from resident fibroblasts, mesenchymal stem cells, epithelial-to-mesenchymal transition of cancer cells, endothelial-to-mesenchymal transition, and recruitment of bone marrow–derived precursors.

Functionally, CAFs contribute to tumor growth through several interconnected mechanisms. They remodel the ECM by depositing collagen, fibronectin, and hyaluronan, leading to increased tissue stiffness and elevated interstitial pressure[22]. This altered ECM architecture not only facilitates cancer cell invasion and metastasis but also impedes the delivery of therapeutic agents and infiltration of cytotoxic immune cells.

CAFs secrete a wide range of growth factors and cytokines, including transforming growth factor-β (TGF-β), hepatocyte growth factor, fibroblast growth factors, and vascular endothelial growth factor[23]. These factors promote cancer cell proliferation, angiogenesis, epithelial-to-mesenchymal transition, and resistance to apoptosis. In addition, CAF-derived chemokines recruit immunosuppressive immune cells and skew immune responses toward tolerance rather than tumor elimination[23].

Metabolic crosstalk between CAFs and cancer cells further enhances tumor survival. CAFs can undergo metabolic reprogramming, producing lactate, amino acids, and lipids that fuel cancer cell metabolism under nutrient-limited conditions[24]. This metabolic symbiosis contributes to therapy resistance and aggressive tumor behavior. Given their central role in shaping the TME, CAFs are increasingly viewed as attractive therapeutic targets. However, complete ablation of fibroblasts has been associated with adverse outcomes in some models, underscoring the need for strategies that reprogram rather than eliminate CAFs[25]. Nanotechnology provides a means to selectively modulate CAF activity, normalize ECM deposition, and disrupt pro-tumorigenic signaling without compromising tissue integrity.

3 Immune Suppression within the Tumor Microenvironment

Immune suppression is a defining hallmark of the TME and a major barrier to effective antitumor immunity. Tumors exploit multiple mechanisms to evade immune surveillance, resulting in dysfunctional immune cell infiltration and impaired cytotoxic activity[26]. Central to this process is the accumulation of immunosuppressive cell populations, including regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages with M2-like phenotypes[26].

These cells secrete inhibitory cytokines such as interleukin-10 and TGF-β, express immune checkpoint ligands, and deplete essential metabolites required for T-cell activation. Additionally, metabolic constraints within the TME, including hypoxia, acidosis, and nutrient deprivation, further suppress immune effector functions[26]. Collectively, these factors create an environment that favors tumor tolerance and progression. Immune checkpoint blockade therapies have revolutionized cancer treatment, yet their efficacy is limited to a subset of patients. Resistance often arises from inadequate immune cell infiltration, persistent stromal barriers, and compensatory immunosuppressive pathways. Therefore, strategies that remodel the immunosuppressive TME are essential to enhance the responsiveness to immunotherapy[27].

Nanotechnology offers innovative solutions to overcome immune suppression by enabling targeted delivery of immunomodulatory agents directly to immune cells within the TME[28, 29]. Nanoparticles can deliver

cytokines, immune checkpoint inhibitors, or nucleic acids that reprogram immune cell phenotypes and enhance antitumor responses while minimizing systemic toxicity.

4. Nanotechnology Platforms for Tumor Microenvironment Targeting

A diverse array of nanotechnology platforms has been developed to specifically target and modulate the tumor microenvironment (TME), recognizing its central role in tumor progression, metastasis, and therapeutic resistance[30]. Among the most widely explored systems are liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles, and biomimetic nanocarriers, each offering unique physicochemical and functional advantages. Liposomes, for example, are biocompatible and capable of encapsulating both hydrophilic and hydrophobic agents, making them suitable for co-delivery strategies[31, 32]. Polymeric nanoparticles provide high structural versatility, controlled drug release profiles, and tunable degradation kinetics, while dendrimers offer precise molecular architecture and high surface functionality for ligand attachment. Inorganic nanoparticles, such as gold, silica, and iron oxide nanoparticles, introduce additional functionalities including imaging contrast, photothermal effects, and magnetic guidance[33, 34]. Biomimetic platforms, including cell membrane–coated nanoparticles and exosome-inspired systems, leverage natural homing abilities and immune evasion properties to improve tumor accumulation.

A defining feature of TME-targeted nanotechnology is surface functionalization with ligands that enable selective interaction with specific cellular components of the microenvironment[12, 13]. Peptides, antibodies, aptamers, and small molecules have been conjugated to nanoparticle surfaces to target cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), endothelial cells, and immune checkpoints. This active targeting complements passive accumulation via the enhanced permeability and retention (EPR) effect and improves therapeutic specificity while minimizing off-target toxicity.

Stimuli-responsive nanoplatforms further enhance precision by exploiting the unique biochemical and biophysical features of the TME[35, 36]. Acidic pH, elevated reactive oxygen species (ROS), hypoxia, and overexpression of proteolytic enzymes such as matrix metalloproteinases are commonly used triggers for controlled drug release. These smart systems remain relatively inert in circulation but undergo structural or chemical changes within the tumor milieu, ensuring spatially confined therapeutic action[35].

Importantly, multifunctional nanotechnology platforms enable simultaneous modulation of multiple TME components. A single nanoparticle system can be engineered to deliver antifibrotic agents to CAFs, immunostimulatory molecules to dendritic cells or T cells, and chemotherapeutics to cancer cells[37]. Such combinatorial designs allow coordinated reprogramming of the TME, addressing both physical barriers, such as dense extracellular matrix (ECM), and immunological barriers, such as immune suppression[37]. Collectively, these advanced nanotechnology platforms provide a versatile and powerful toolkit for TME-focused cancer therapy, moving beyond tumor cell–centric approaches toward holistic microenvironmental intervention.

5. Nanoparticle-Based Targeting and Reprogramming of Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) are a dominant stromal population within the TME and play a critical role in tumor growth, invasion, immune evasion, and resistance to therapy[38]. Nanoparticle-based strategies targeting CAFs aim either to suppress their pro-tumorigenic functions or to reprogram them toward a quiescent or tumor-restraining phenotype. These approaches have gained increasing attention as conventional therapies largely fail to address the stromal compartment. Nanoparticles have been employed to deliver small-molecule inhibitors that block key CAF-activating pathways, particularly transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and hedgehog signaling[39]. Inhibition of these pathways reduces CAF activation, limits ECM deposition, and alleviates mechanical stiffness within tumors. Additionally, RNA-based nanotherapeutics, including siRNA and miRNA mimics, have been designed to silence CAF-specific genes involved in fibrosis, cytokine secretion, and metabolic support of cancer cells[39].

Targeting specificity is enhanced through ligand-mediated delivery strategies. Fibroblast activation protein (FAP), a surface marker highly expressed on CAFs but minimally present in normal tissues, has emerged as a prominent targeting ligand[40]. Nanoparticles functionalized with FAP-binding peptides or antibodies exhibit preferential uptake by CAFs, resulting in localized therapeutic effects. Other targeting moieties include integrin-binding peptides and ECM-recognizing ligands that exploit the CAF-rich stromal niche[40].

Preclinical studies demonstrate that CAF-targeted nanoparticles effectively reduce desmoplasia, normalize ECM architecture, and improve intratumoral drug penetration. By decompressing tumor vasculature and reducing physical barriers, these systems enhance the efficacy of co-administered chemotherapeutics and immunotherapies[41]. Furthermore, CAF reprogramming has been shown to indirectly promote immune cell infiltration and restore antitumor immunity, highlighting the interconnected nature of stromal and immune compartments.

Overall, nanoparticle-based CAF targeting represents a promising strategy to dismantle the supportive tumor stroma, sensitize tumors to therapy, and improve long-term treatment outcomes. Continued refinement of targeting ligands and reprogramming agents will be essential for successful clinical translation.

6. Nanotechnology-Driven Modulation of Immune Suppression

Immune suppression within the TME is a major obstacle to effective cancer immunotherapy, characterized by dysfunctional cytotoxic T cells, expansion of regulatory T cells, and accumulation of immunosuppressive

myeloid populations[42]. Nanotechnology has emerged as a powerful approach to locally modulate immune responses, enabling precise delivery of immunotherapeutic agents while minimizing systemic toxicity.

Nanoparticles have been widely used to deliver immune checkpoint inhibitors, cytokines, tumor antigens, and genetic materials such as mRNA and siRNA[43, 44]. Encapsulation of checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4 enhances their stability and promotes sustained release within tumors. Similarly, nanoparticle-mediated delivery of cytokines such as interleukin-2 or interferon-γ can activate effector immune cells without inducing severe systemic inflammation.

Beyond direct immune activation, nanotechnology enables reprogramming of suppressive immune populations. For instance, nanoparticles delivering agents that shift TAMs from an M2-like immunosuppressive phenotype to an M1-like pro-inflammatory phenotype have demonstrated significant antitumor effects[45]. Genetic nanomedicines targeting immunosuppressive signaling pathways further amplify immune responses within the TME. Combination strategies that integrate immune modulation with stromal targeting are particularly compelling. CAF depletion or normalization reduces immune exclusion and enhances nanoparticle penetration, thereby synergizing with immunotherapeutic payloads. Preclinical models consistently show that dual targeting of stromal and immune components results in superior tumor regression compared to monotherapies[45].

Collectively, nanotechnology-driven immune modulation offers a versatile platform for overcoming immune suppression, revitalizing antitumor immunity, and enhancing the durability of immunotherapeutic responses.

7. Challenges, Translational Considerations, and Future Perspectives

Despite substantial advances, several challenges hinder the clinical translation of nanotechnology-enabled TME reprogramming strategies. One major limitation is nanoparticle heterogeneity, including variability in size, surface chemistry, and drug loading, which can affect reproducibility and therapeutic consistency[46]. Manufacturing scalability and quality control remain critical hurdles for regulatory approval and widespread clinical adoption.

Safety concerns also persist, particularly regarding long-term biodistribution, accumulation in off-target organs, and potential immunogenicity[47]. While many nanomaterials demonstrate favorable short-term safety profiles, comprehensive long-term toxicity studies are essential. Additionally, interpatient heterogeneity in TME composition poses a significant challenge, as stromal density, immune infiltration, and molecular signaling vary widely across tumor types and individuals.

To address these challenges, future research should prioritize improved TME characterization and patient stratification strategies. Advances in single-cell sequencing, spatial transcriptomics, and imaging technologies will facilitate the identification of TME subtypes and guide personalized nanotherapeutic design. Integration of artificial intelligence and computational modeling may further optimize nanoparticle formulation and targeting strategies.

Looking ahead, the convergence of nanotechnology, immunotherapy, and precision oncology holds immense promise. Rationally designed, multifunctional nanoplatforms capable of adaptive and patient-specific TME modulation are likely to define the next generation of cancer therapeutics, ultimately improving clinical outcomes and survival.

CONCLUSION

Nanotechnology-enabled reprogramming of the tumor microenvironment represents a paradigm shift in cancer therapy. By targeting cancer-associated fibroblasts and alleviating immune suppression, nanoparticle-based strategies address fundamental mechanisms of tumor progression and therapeutic resistance. Rather than focusing solely on malignant cells, this approach leverages precise, multifunctional nanoplatforms to normalize stromal architecture and restore effective antitumor immunity. While challenges related to safety, scalability, and patient heterogeneity remain, continued advances in nanomaterial design and TME biology are rapidly narrowing the gap between preclinical success and clinical translation. Ultimately, integrating nanotechnology-driven TME modulation with existing treatment modalities holds strong promise for achieving more durable and broadly effective cancer therapies.

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