REVIEW ARTICLE

Stimuli Responsive Hybrid Chitosan Nanoplatforms for Reversing Immune Exclusion in Solid Tumors: Emerging Strategies for Tumor Microenvironment Remodeling and Enhanced Cancer Immunotherapy

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Abstract

Solid tumors often develop an immunosuppressive tumor microenvironment (TME) characterized by dense deposition of extracellular matrix (ECM), aberrant vasculature, stromal barriers, and suppressive immune populations. Together, these factors promote immune exclusion and diminish the efficacy of cancer immunotherapy. Recent developments in stimuli-responsive hybrid chitosan nanoplatforms have emerged as promising options to surmount these barriers for their biocompatibility, biodegradability, mucoadhesive properties, and versatile functionalization capacity. These nanoplatforms are designed to react to either internal stimuli such as pH, redox potential, enzymes, hypoxia, and reactive oxygen species or external stimuli such as light, ultrasound, and magnetic fields to allow for regulated medication release into tumor tissues. Hybrid chitosan systems with polymers, inorganic nanoparticles, and immunomodulatory agents can remodel the TME via degradation of ECM components, normalization of tumor vasculature, repolarization of tumor-associated macrophages, reduction of immunosuppressive cytokines, and enhancement of immune cell infiltration. Moreover, these systems facilitate combination therapies, which enhance antitumor immune responses by integrating chemotherapy, phototherapy, and immune checkpoint blockade. The present work discusses the new design strategies, mechanisms of action, current challenges, and potential applications of stimuli-responsive hybrid chitosan nanoplatforms to counteract immune exclusion and improve the therapeutic outcomes of cancer immunotherapy.

Key words: Cancer immunotherapy, hybrid chitosan nanoparticles, immune exclusion, immunomodulation, nanomedicine, solid tumors, stimuli-responsive nanoplatforms, targeted drug delivery, tumor associated macrophages

INTRODUCTION

Hybrid chitosan nanoplatforms are emerging as highly adaptable systems for cancer immunotherapy as they combine the beneficial properties of chitosan with complementary materials that enhance the therapeutic performance. Hybrid systems are designed to overcome the limitations of conventional nanocarriers, including limited multifunctionality, rapid clearance, insufficient tumor accumulation, and poor stability.[29] Logical design and material integration can bring better immune modulation, enhanced responsiveness, and higher targeting efficiency to hybrid chitosan nanoplatforms. One of the most studied

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methods to improve the chitosan-based nanocarriers is the use of organic hybrid systems. To improve the efficiency of medication encapsulation, structural stability, and circulation time, polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), liposomes, and protein-based materials are combined. PEGylation improves pharmacokinetic performance and reduces rapid clearance by the reticuloendothelial system.[36,37] Liposomal hybridization allows co-delivery of several therapeutic agents and increases membrane compatibility.[38,39] Hybrid systems based on proteins improve biocompatibility and allow for controlled drug delivery.

IMMUNE EXCLUSION IN SOLID TUMORS

One of the major barriers limiting the efficacy of cancer immunotherapy in solid tumors is known to be immune exclusion. In contrast to immune-inflamed cancers in which immune cells infiltrate the tumor tissue, immune-excluded cancers are characterized by the accumulation of immune cells in the tumor periphery or stromal areas with limited infiltration into the tumor core.[11] Ultimately, this limited infiltration results in poor therapeutic responses and resistance to immunotherapeutic interventions by reducing the interactions between cytotoxic immune cells and malignant cells. Immune exclusion in the tumor microenvironment (TME) is developed and maintained through many interrelated pathways. Another major cause is the overabundance of extracellular matrix (ECM) components such as collagen, fibronectin, and hyaluronic acid that form strong physical barriers preventing the effective migration of immune cells into the tumor tissues.[11] Cancer-associated fibroblasts (CAFs) are the main regulators of these stromal structures by increasing tissue stiffness and modifying the matrix, further preventing immune cell invasion.[13] Another important element that promotes immunological exclusion is hypoxia. In cancers that have areas lacking oxygen due to rapid tumor growth and inadequate vascular development, hypoxia-inducible signaling pathways are induced.[12] Hypoxic conditions reduce the cytotoxic activity of infiltrating lymphocytes, alter the metabolism of immune cells, and increase the synthesis of immunosuppressive mediators. Moreover, aberrant metabolism of tumors leads to an acidic microenvironment that is not conducive to effective antitumor immunity and further hampers immune cell survival and function. Aberrant tumor vasculature also disrupts immune cell trafficking. Tumor blood vessels are often disorganized, leaky, and dysfunctional, resulting in an inefficient delivery of immune cells into malignant tissues.[14] Diminished arterial perfusion restricts the flow of not only nutrients and oxygen to the areas of the tumor but also the flow of immune cells and therapeutic medications. This dysregulated vascular architecture provides additional obstacles to immune exclusion. Several immune suppressive signaling pathways augment tumor resistance to immune infiltration. Transforming growth factor-beta signaling mediates stromal activation, ECM deposition, and suppression of cytotoxic immune response.[15] Furthermore, tumor-associated macrophages (TAMs), which are often M2-phenotype, secrete cytokines and inhibit T-cell activity, promoting angiogenesis, tumor growth, and immunological suppression.[16] These immunosuppressive cells create an environment that actively suppresses effective anti-cancer immune responses.

Physical barriers, metabolic imbalance, vascular abnormalities, and immunosuppressive cellular interactions in the TME result in immune exclusion. A deep understanding of these pathways is required for the design of advanced therapeutic strategies such as stimuli-responsive hybrid chitosan nanoplatforms that aim to modulate the TME and re-establish effective immune infiltration.

CHITOSAN AS A NANOMEDICINE PLATFORM

Chitosan is derived from chitin by deacetylation and has many properties useful for nanomedicine: Biocompatibility,[17] Biodegradability,[18] Positive surface charge,[19] Mucoadhesion,[20] Capability of functional modification.[21]

The chemical modifications are: Carboxymethyl Chitosan, Trimethyl chitosan, Chitosan-thiol, Chitosan-PEGylated, Chitosan-glycol. Such derivatives enhance stability, targeting, and responsiveness.[22]

STIMULI-RESPONSIVE MECHANISMS IN HYBRID CHITOSAN NANOPLATFORMS

Much attention has been paid to stimuli-responsive hybrid chitosan nanoplatforms due to the possibility of controlled and site-specific therapeutic release in tumor tissues.[23] This will reduce systemic toxicity and improve the efficacy of the treatment. The systems are designed to deliver therapeutic payloads in response to endogenous or foreign triggers that are specifically found in the TME. The incorporation of some response mechanisms also improves the therapeutic precision and immunological regulation of chitosan-based nanocarriers. Most of the research has been done on pH-responsive devices, since solid tumors are acidic. In tumor tissues, the extracellular space typically has a pH of 6.5–6.8, whereas the normal physiological pH is about 7.4. In an acidic environment, the chitosan molecules become protonated, and the nanoparticles expand and become unstable, releasing the encapsulated drugs.[23] Chitosan nanoplatforms conjugated with acid-sensitive chemical linkages such as hydrazone bonds, Schiff base bonds, and acetal linkages have been used for the selective release into acidic tumor compartments.[24] These systems increase the efficacy of the treatment and reduce the side effects

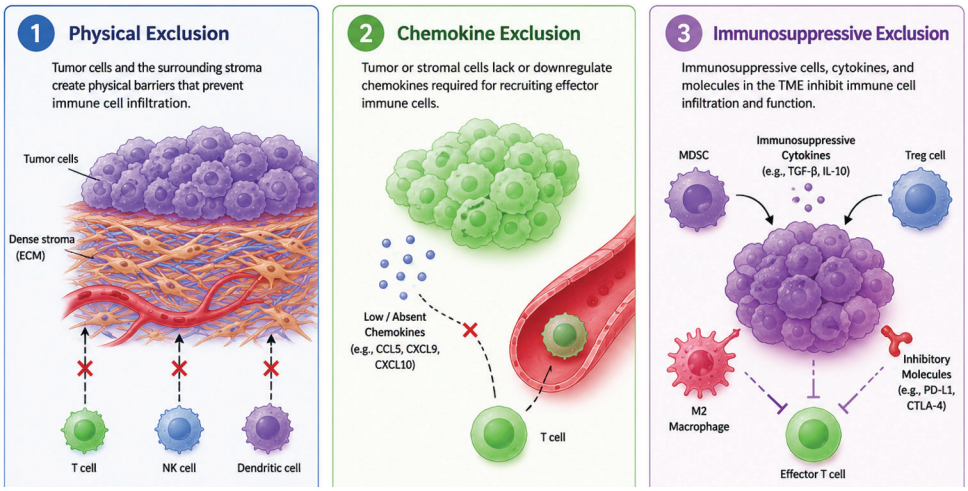

Figure 1: Mechanisms of immune exclusion

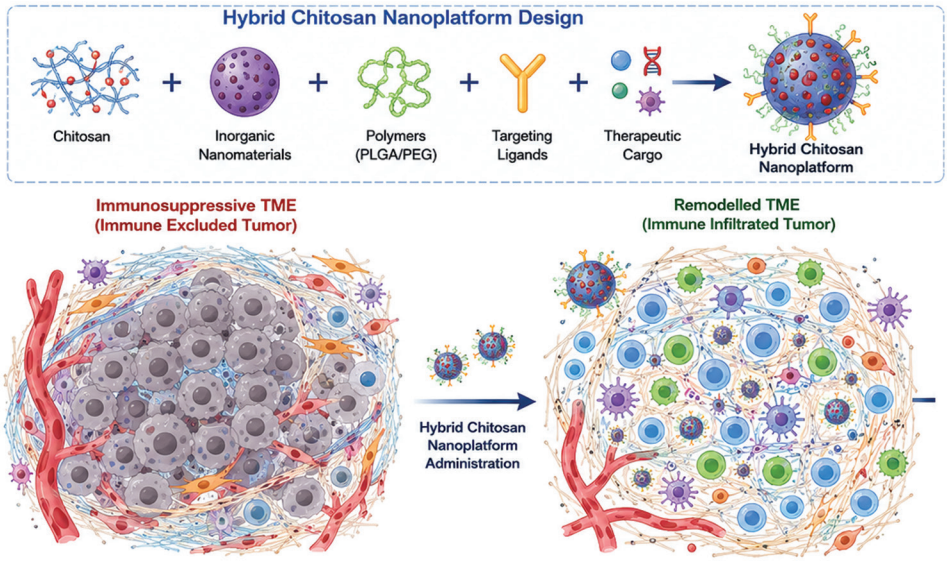

Figure 2: Hybrid chitosan nanoplatform-mediated tumor microenvironment remodeling

Table 1: Stimuli-responsive chitosan nanoplatforms

Stimulus	Trigger source	Mechanism	Therapeutic benefit
pH	Tumor acidity	Bond cleavage	Controlled release
Redox	High GSH	Disulfide reduction	Intracellular delivery
Enzyme	MMPs	Matrix degradation	Tumor specificity
Light	NIR irradiation	Heat generation	Combined therapy
Magnetic	External field	Targeting	Deep penetration

GSH: Glutathione, NIR: Near-infrared, MMPs: Matrix metalloproteinases

by enhancing the intracellular absorption and endosomal escape. Redox-responsive chitosan nanoplatforms exploit the higher intracellular glutathione (GSH) levels in immune cells and tumor tissues. The intracellular level of GSH in malignant tissues can be sometimes many times higher than that in normal tissues, allowing for selective intracellular drug release.[25] Disulfide-containing linkers are often added to chitosan nanoparticles as they cleave in reductive environments and release the payload only in tumor cells. These approaches reduce the early leakage of drugs during systemic circulation and greatly improve the efficacy of cytoplasmic delivery. Another important class of stimuli-responsive nanoplatforms is enzyme-responsive systems. The TME contains enzymes actively involved in tumor growth and ECM remodeling, such as matrix metalloproteinases, hyaluronidases, and cathepsins.[26]

Table 2: Applications of hybrid chitosan systems in immunotherapy

Strategy	Payload	Target	Outcome
Checkpoint blockade	Anti-PD-L1	T cells	Increased infiltration
Vaccine delivery	Tumor antigens	APCs	Strong immunity
Photothermal therapy	Gold NP	Tumor cells	ICD induction
Macrophage modulation	TLR agonists	TAMs	M1 polarization
Gene delivery	siRNA	TME genes	Immune activation

TLR: Toll-like receptor, ICD: Implantable cardioverter-defibrillator, APCs: Antigen-presenting cells, TAMs: Tumor-associated macrophages

Chitosan nanoparticles are designed with enzyme-cleavable substrates that fall apart when encountering these enzymes to release therapeutics in a targeted manner. Moreover, this selective activation not only enhances tumor specificity but also increases penetration through thick stromal barriers that promote immune exclusion [Figure 1 and Table 1].

Moreover, light-responsive hybrid chitosan systems have exhibited great potential in cancer immunotherapy. The advantage of near-infrared irradiation is its minimal invasiveness and its ability to penetrate deep into tissue. The incorporation of photothermal agents, such as gold nanoparticles or photosensitizers, into chitosan matrices allows for the external activation of therapeutic reactions, such as heat generation, reactive oxygen species production, and controlled drug release.[27] In addition to direct tumor cell killing, these pathways induce anticancer immune activation via immunogenic cell death. Recently, multi-stimuli responsive systems, in which multiple activation pathways are integrated into a single nanocarrier, have emerged as sophisticated therapeutic platforms. These multifunctional devices provide greater selectivity and better spatiotemporal control of therapeutic release by combining pH, redox, enzyme, magnetic, or light responsiveness.[28] Therefore, multi-responsive hybrid chitosan nanoplatforms are promising approaches for next-generation immunotherapeutic approaches to improve immunotherapeutic outcomes, tune the TME, and reverse immunological exclusion.

DESIGN STRATEGIES OF HYBRID CHITOSAN NANOPLATFORMS

Hybrid chitosan nanoplatforms are versatile systems in cancer immunotherapy, combining useful properties of chitosan with complementary materials to enhance therapeutic performance. The development of hybrid systems aims to overcome the drawbacks of traditional nanocarriers, such as limited multifunctionality, rapid clearance, low accumulation in tumors, and poor stability.[29] Through the logical design and material integration, the hybrid chitosan nanoplatforms can achieve better immune modulation, responsiveness, and targeting efficiency. Association with organic hybrid systems is one of the most investigated strategies to improve chitosan-based nanocarriers. Polymers such as PLGA, PEG, liposomes, and protein-based materials are combined to improve the encapsulation efficiency, structural stability, and circulation time of the medication. PEGylation improves the pharmacokinetic behavior and reduces the rapid elimination by the reticuloendothelial system. Liposomal hybridization improves membrane compatibility and allows co-administration of many therapeutic. Protein-based hybrid systems also help to improve biocompatibility and to control drug release. Inorganic hybridization has also attracted great attention due to the special physical and chemical properties of inorganic materials, which are difficult to be achieved by polymers alone. Iron oxide nanoparticles are magnetically responsive and can be used for imaging, while gold nanoparticles embedded in chitosan matrices can convert light to heat and provide controlled light-responsive therapy. Mesoporous silica nanoparticles have large surface areas, an improved drug-loading capacity, and can provide prolonged therapeutic release. Furthermore, quantum dots and other nanoscale inorganic materials are used in imaging-guided therapy and theranostics. Incorporation of these inorganic elements significantly extends the functionality of chitosan nanoplatforms and improves their therapeutic selectivity.

Biomimetic hybrid nanoplatforms have emerged as a novel strategy to improve tumor targeting and immune evasion. Exosome-inspired carriers, cell membrane-coated nanoparticles, and hybrid vesicular systems mimic natural biological architecture, which results in better circulation and less recognition by the immune clearance mechanism. Furthermore, these systems may take advantage of homotypic targeting mechanisms that guarantee preferential accumulation into tumor tissues. Biomimetic strategies are very promising for improving intratumoral distribution and overcoming the biological barriers of immune-excluded tumors. The therapeutic benefits of combining organic, inorganic, and biomimetic components into hybrid chitosan systems include improved stability, enhanced pharmacokinetic profile, increased tumor accumulation, controlled responsiveness, and improved immunogenic potential.[29] With the development of multifunctional therapeutic systems, hybrid chitosan nanoplatforms are expected to play a greater role in remodeling the TME and improving the outcomes of cancer immunotherapy.

STRATEGIES TO RESHAPE THE TME

Reprogramming the TME is an emerging important strategy to enhance the response to cancer immunotherapy and overcome immune exclusion. The TME is characterized by dense extracellular matrices, aberrant vasculature, immunosuppressive cells, hypoxia, and metabolic dysregulation, which results in limited immune cell infiltration and tumor growth.[30] Stimuli-responsive hybrid chitosan nanoplatforms have shown considerable promise in redesigning these barriers by the localized administration of therapeutic drugs and the simultaneous manipulation of several immunosuppressive pathways. Excess ECM components are a major barrier to effective immune infiltration in malignancies. A thick stroma of collagen, hyaluronic acid, fibronectin, and active fibroblasts physically blocks immune cells and drugs from reaching the cancer cells. Therefore, ECM degradation has become a major therapeutic target for TME remodeling. Hybrid chitosan nanoplatforms have been loaded with matrix-degrading enzymes such as collagenase and hyaluronidase and delivered to the tumor sites to increase matrix degradation and improve nanoparticle penetration.[30]

Moreover, the inhibition of CAFs decreases the mechanical barriers and stromal deposition, leading to improved infiltration of cytotoxic T lymphocytes into tumor tissues.

Another important strategy to overcome tumor-associated immunosuppression is the reprogramming of macrophages. Most TAMs have an M2 phenotype that promotes angiogenesis, immune suppression, and tumor progression. These macrophages can be switched to the proinflammatory M1 phenotype, which greatly enhances antitumor immunity.[31] Stimuli-responsive chitosan nanocarriers have been applied to deliver toll-like receptor agonists, cytokines, and small interfering RNA molecules capable of changing polarization states of macrophages. Reprogramming of macrophages enhances cytokine production, improves antigen presentation, and promotes recruitment of cytotoxic immune cells into immune-excluded tumors. A further defining feature of solid tumors is hypoxia, which strongly contributes to immunosuppression and resistance to therapy. Tumors are characterized by rapid cell division and poor vascularization, resulting in oxygen-deficient environments that activate hypoxia-inducible signaling pathways, which enhances tumor survival and dampens immunological activity.[32] To solve this difficulty, hybrid chitosan nanoplatforms have included oxygen-generating materials like catalase enzymes, manganese dioxide nanoparticles, and peroxide-based systems to increase the local oxygen concentration. Reduced hypoxia increases drug sensitivity and the survival of immune cells, and improves checkpoint blockade therapy. Irregular tumor vasculature plays a major role in immunological exclusion, by limiting immune cell trafficking and creating irregular blood flow. Disorganized vascular networks lead to poor oxygen delivery, high interstitial pressure, and poor drug distribution.[33] The aim of nanoplatform-mediated vascular normalization strategies is to enhance perfusion and allow efficient immune cells and nanoparticles delivery into tumor tissues through restoring more functional blood artery architecture. Ultimately, improved vascular function translates into enhanced immune responses to malignancies and enhanced therapeutic accumulation. In summary, these remodeling approaches suggest that effective treatment of immune-excluded tumors will require simultaneous alteration of multiple TME components. Stimuli-responsive hybrid chitosan nanoplatforms provide a flexible platform to incorporate these tactics into multifunctional therapeutic platforms that can break through stromal barriers, reduce immunosuppression, and improve the outcomes of cancer immunotherapy.

COMBINATION WITH IMMUNOTHERAPY IN CANCER

A very promising strategy to overcome immune suppression and improve treatment outcomes in solid tumors is the combination of current cancer immunotherapy with stimuli-responsive hybrid chitosan nanoplatforms.[1-10] These multifunctional devices modify the TME and precisely deliver immunomodulatory drugs to enhance immune cell infiltration and activation. They have attracted special interest for combination immunotherapy treatments as they can be administered in a controlled and site-specific manner.[34] One of their most promising applications is in combination with immune checkpoint blockade therapies. Immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated protein-4, programmed cell death protein-1 (PD-1), and ligand-1 (PD-L1) have revolutionized cancer therapy. However, immune exclusion and poor immune infiltration have caused resistance in many solid malignancies.[34] Chitosan nanoplatforms can improve checkpoint therapy by increasing the number of immune cells in tumors, reducing systemic toxicity, and improving the localized distribution of antibodies. Controlled release methods further optimize the therapeutic exposure and the treatment efficacy.

Another important area of application with great promise for hybrid chitosan systems is cancer vaccines. These nanoplatforms provide effective encapsulation and protection of tumor antigens, neoantigens, nucleic acids, and adjuvants from degradation and allow customized delivery to antigen-presenting cells (APCs).[35] This leads to improved dendritic cell activation and antigen presentation and consequently to greater cytotoxic T-cell responses and stronger and more durable antitumor immunity. Moreover, the mucoadhesive and immunostimulatory properties enhance the effectiveness of the vaccination. Nanotechnology-assisted modification of the TME also benefits adoptive cell therapies, including natural killer cell-based strategies and chimeric antigen receptor T-cell therapy. Immune-excluded solid tumors are often impenetrable and inhospitable to transplanted immune cells. Hybrid chitosan nanoplatforms can improve

these treatments[36] by delivering cytokines, chemokines, or stromal-modulating drugs that promote the migration of immune cells and the survival of tumor cells. Such strategies may be useful to overcome existing limitations of adoptive cell therapy efficacy against solid tumors. It can also activate the stimulator of interferon genes (STING) signaling pathway that plays an important role in antigen presentation and innate immune activation. The combination of STING activation with checkpoint inhibitors or immunization techniques may increase the efficacy of treatment [Figure 2 and Table 2].

PRECLINICAL DATA

Preclinical studies have amply demonstrated the effectiveness of stimuli-responsive hybrid chitosan nanoplatforms to overcome immunological exclusion and to improve the outcomes of cancer immunotherapy. These multi-purpose systems have been shown in several in vitro and *in vivo* studies to be able to enhance therapeutic accumulation in tumors, modulate the TME, and induce stronger anti-cancer immune responses. Therefore, they are promising candidates for next-generation cancer therapeutic strategies due to their capacity to integrate immunomodulation, controlled release, and targeted delivery.[38] There are a number of pre-clinical studies documenting the increased infiltration of cytotoxic immune cells following treatment with hybrid chitosan nanoplatforms. Remodeling of the TME and reduction of stromal barrier have been shown to improve recruitment and penetration of CD8+ T cells into tumor tissues.[38] Immunological exclusion is one of the major limitations of the immunotherapeutic strategies employed today. Improving T-cell infiltration is of particular importance to overcome this. The nanoplatforms enable immune cells to reach the tumor core, which then promotes stronger and longer-lasting anticancer responses. Hybrid chitosan systems have been shown to enhance dendritic cell maturation and antigen presentation and promote T-cell infiltration. More efficient activation of APCs increases cytotoxic immune activity against tumor cells and more often triggers adaptive immune responses.[39] Several nanoparticle formulations have been shown to enhance cytokine production and co-stimulatory molecule expression that improves communication between innate and adaptive immune compartments. Many experimental tumor models have also shown longer survival and inhibition of tumor development. In animal models, nanoplatforms have been used to deliver immunotherapeutic drugs, photothermal materials, nucleic acids, and cytokines, and have significantly reduced tumor volume and delayed disease progression.[40] Combinatorial therapies involving phototherapy, immune checkpoint inhibitors, or macrophage reprogramming strategies have demonstrated enhanced survival and synergistic therapeutic advantages.[41] Importantly, stimuli-responsive systems often outperform traditional nanocarriers by being able to achieve precise spatiotemporal control of therapeutic release. Sensitive to tumor-specific stimuli such as acidic pH, elevated GSH levels, enzymatic activities, and external stimuli, allowing selective activation in tumor tissues with reduced systemic exposure.

CHALLENGES IN CLINICAL TRANSLATION

Although stimuli-responsive hybrid chitosan nanoplatforms show promising pre-clinical performance, several scientific, manufacturing, regulatory, and safety challenges limit successful clinical translation. These multifunctional systems have great potential to improve cancer immunotherapy and TME remodeling, but the translation from laboratory research to clinical application will face great challenges in long-term safety evaluation, large-scale production, and reproducibility.[42] Major problems are manufacturing reproducibility and batch-to-batch uniformity. Hybrid chitosan nanoplatforms are often characterized by complex architectures such as targeting ligands, polymers, inorganic materials, and therapeutic payloads. Small modifications during synthesis can significantly affect nanoparticle size, surface charge, drug loading efficiency and release behavior, and in turn cause inconsistency in therapeutic efficacy.[42]

Standardized production techniques must be used to produce repeatable clinical-grade materials. Further challenges involve scale-up and industrial manufacturing. Many methods of producing nanoparticles on a laboratory scale are difficult to replicate in industrial settings due to increased process complexity and quality control requirements.[43] The characteristics of the particles have to be controlled very strictly, to make large-scale production possible, that is, both economically viable and compatible with the requirements of pharmaceutical manufacturing. These challenges may prevent widespread clinical use and delay commercialization. The regulatory approval pathways of multifunctional nanomedicines are complicated by the fact that hybrid nanoplatforms often exhibit characteristics of pharmaceuticals, biologics, and medical devices.[44] The regulatory bodies require detailed evaluation of pharmacokinetics, biodistribution, toxicity, biodegradation, and immunogenicity before approval is given. The absence of internationally standardized regulatory frameworks for the development of complex nanomedicines hinders clinical translation and prolongs development timelines. Another great challenge is the interaction of nanoparticles with biological systems after systemic distribution. The development of a protein corona around the surfaces of nanoparticles can alter the targeting ability, biodistribution, immunological recognition, and therapeutic efficacy.[45] Such interactions may decrease the efficacy of treatment by reducing tumor formation or increasing non-specific clearance by the mononuclear phagocyte system. Therefore, methods to modulate surface chemistry and improve nanoparticle stability are needed to optimize clinical performance. Another issue with natural polymers such as

chitosan is variability from batch to batch. The behavior of nanoparticles and the reproducibility of studies can all be affected by the molecular weight, degree of deacetylation, purity, and source material.[46] The variability in the raw material and characterization technique could be reduced by standardization, and this would improve the reliability of the manufacturing process. Finally, the long-term biosafety of many multifunctional hybrid nanoplatforms remains largely unknown. Widespread clinical adoption will require careful assessment of biodegradation products, long-term tissue accumulation, immunological reactions, and chronic toxicity. To accelerate the translation of stimuli-responsive hybrid chitosan nanoplatforms from experimental systems to approved therapeutics, future research should emphasize scalable manufacturing, consistent quality control, rigorous safety evaluation, and clinically relevant validation models.

FUTURE PERSPECTIVES

Emerging pathways are: AI-assisted nanoplatform optimization, Tailored nanomedicine, Immune biomimicry engineering, Multiple response systems, Clinical quality production.[47-49] A promising future direction is hybrid chitosan systems, which can simultaneously sense, modify, and activate the immune system.[50] To sum up Stimuli-responsive hybrid chitosan nanoplatforms are promising tools for reversing immunological exclusion via targeted therapeutic administration and TME modification. Current resistance to treatment may be overcome with current immunotherapy, and clinical results may be improved. Multifunctionality, safety, and translational scalability optimization should continue.

CONCLUSION

Stimuli-responsive hybrid chitosan nanoplatforms have great promise in reversing immunological exclusion through targeted therapeutic administration and TME modification. Their combination with current immunotherapy might overcome current treatment resistance and improve clinical results. Multifunctionality, safety, and translational scalability should continue to be optimized.

REFERENCES

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5.
2. Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56-61.
3. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017;541:321-30.
4. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, *et al*. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018;24:541-50.
5. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015;348:74-80.
6. Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Int J Mol Sci 2019;20:4557-66.
7. Gao S, Yang X, Xu J, Qiu N, Zhai G. Nanotechnology for boosting cancer immunotherapy and remodeling tumor microenvironment: The horizons in cancer treatment. ACS Nano 2021;15:12567-603.
8. Fathi M, Barar J, Aghanejad A, Omidi Y. Hydrogels for biomedical applications. BioImpacts 2017;7:269-77.
9. Yan Y, Ding H. pH-responsive nanoparticles for cancer immunotherapy: A brief review. Nanomaterials 2020;10:1613.
10. Lu Q, Kou D, Lou S, Ashrafizadeh M, Aref AR, Canadas I, *et al*. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. J Hematol Oncol 2024;17:16.
11. Mpekris F, Voutouri C, Baish JW, Duda DG, Munn LL, Stylianopoulos T, *et al*. Combining microenvironment normalization strategies to improve cancer immunotherapy. Proc Natl Acad Sci U S A 2020;117:3728-37.
12. Rankin EB, Giaccia AJ. Hypoxic control of metastasis. Science 2016;352:175-80.
13. Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer 2016;16:582-98.
14. Jain RK. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. Science 2005;307:58-62.
15. Batlle E, Massagué J. Transforming growth factor-β signaling in immunity and cancer. Immunity 2019;50:924-40.
16. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumor-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017;14:399-416.
17. Dash M, Chiellini F, Ottenbrite RM, Chiellini E. Chitosan-a versatile semi-synthetic polymer in biomedical applications. Prog Polym Sci 2011;36:981-1014.
18. Rinaudo M. Chitin and chitosan: Properties and applications. Prog Polym Sci 2006;31:603-32.
19. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. Eur J Pharm Biopharm 2012;81:463-9.
20. Kean T, Thanou M. Biodegradation, biodistribution and toxicity of chitosan. Adv Drug Deliv Rev 2010;62:3-11.
21. Muxika A, Etxabide A, Uranga J, Guerrero P, De La Caba K. Chitosan as a bioactive polymer: Processing, properties and applications. Int J Biol Macromol 2017;105:1358-68.
22. Mohammed MA, Syeda JT, Wasan KM, Wasan EK. Chitosan nanoparticles overview. Int J Nanomedicine 2017;12:765-82.
23. Bae YH, Park K. Targeted drug delivery to tumors:

Myths, reality and possibility J Control Release 2011;153:198-205.
24. Li HJ, Du JZ, Du XJ, Xu CF, Sun CY, Wang HX, *et al*. Stimuli-responsive clustered nanoparticles for improved tumor penetration and therapeutic efficacy. Proc Natl Acad Sci U S A 2016;113:4164-9.
25. Liu J, Huang Y, Kumar A, *et al*. Redox-responsive systems in nanomedicine. Biotechnol Adv 2014;32:693-710.
26. Hu Q, Sun W, Wang C, Gu Z. Enzyme-responsive systems. Chem Soc Rev 2016;45:5165-87.
27. Lucky SS, Soo KC, Zhang Y. Nanoparticles in photodynamic therapy. Chem Rev 2015;115:1990-2042.
28. Cheng Y, He C, Ding J, Xiao C, Zhuang X, Chen X. Thermosensitive hydrogels and nanomaterials for cancer immunotherapy. Adv Mater 2019;31:e1808100.
29. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: Progress, challenges and opportunities. Nat Rev Cancer 2017;17:20-37.
30. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21:418-29.
31. Cassetta L, Pollard JW. Targeting macrophages: Therapeutic approaches in cancer. Nat Rev Drug Discov 2018;17:887-904.
32. Song G, Ji C, Liang C, *et al*. Tumor hypoxia modulation. Nano Lett 2017;17:4317-24.
33. Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res 2013;73:2943-8.
34. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: Progress, challenges and opportunities. Nat Rev Cancer 2017;17:20-37.
35. Gao S, Yang X, Xu J, Qiu N, Zhai G. Nanotechnology for boosting cancer immunotherapy and remodeling tumor microenvironment: The horizons in cancer treatment. ACS Nano 2021;15:12567-603.
36. Yang Y, Sun B, Zuo S, Li X, Zhou S. Engineered nanomaterials for reprogramming tumor-associated macrophages in cancer immunotherapy. Adv Funct Mater 2022;32:2109905.
37. Wang Y, Tiruthani K, Li S, *et al*. mRNA delivery nanoplatforms for cancer immunotherapy. Adv Drug Deliv Rev 2022;182:114113.
38. Li X, Lovell JF, Yoon J, Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. Nat Rev Clin Oncol 2020;17:657-74.
39. Hu Q, Li H, Wang L, Gu H, Fan C. DNA nanotechnology-enabled cancer immunotherapy. Adv Mater 2019;31:e1900185.
40. Liu Y, Crawford BM, Vo-Dinh T. Gold nanoparticles-mediated photothermal therapy and immune activation. ACS Nano 2018;12:12173-89.
41. Cheng Y, He C, Ding J, Xiao C, Zhuang X, Chen X. Thermosensitive hydrogels and nanomaterials for cancer immunotherapy. Adv Mater 2019;31:e1808100.
42. Zhang F, Stephan SB, Ene CI, Smith TT, Holland EC, Stephan MT. Nanoparticles that reshape the tumor milieu create a therapeutic window for effective T-cell therapy in solid malignancies. Nat Nanotechnol 2018;13:152-61.
43. Raju G.S.R., Pavitra E., Varaprasad G.L., Bandaru S.S., Nagaraju G.P., Farran B, *et al*. Nanoparticles mediated tumor microenvironment modulation: Current advances and applications. J Nanobiotechnol 2022;20:274.
44. Zhou Y, Yuan J, Xu K, Li S, Liu Y. Nanotechnology reprogramming metabolism for enhanced tumor immunotherapy. ACS Nano 2024;18:1846-64.
45. Zhao X, Yang K, Zhao R, Ji T, Wang X. Multifunctional nanoplatforms for tumor immune microenvironment regulation. Bioact Mater 2023;24:356-81.
46. Yu H, Yang C, Jian L, Gu Z. Bio-inspired hybrid nanomaterials for immune remodeling. Acta Biomater 2022;146:1-20.
47. Wang C, Sun W, Wright G, Wang A, Gu Z. Inflammation-triggered cancer immunotherapy by programmed delivery of CpG and anti-PD1 antibody. Advanced materials (Deerfield Beach, Fla.). 2016 Aug 25;28(40):8912.
48. Li J, Wang Y, Zhu Y, Oupicky D. Recent advances in delivery systems based on chitosan derivatives. J Control Release 2019;307:77-88.
49. Zhang X, Cui H, Zhang W, Li Z, Gao J. Engineered tumor-cell derived vaccine systems for enhanced antitumor immunity. Bioact Mater 2023;22:491-507.
50. Zheng P, He J, Fu Y, Yang Y, Li S, Duan B, *et al*. Engineered bacterial biomimetic vesicles reprogram tumor-associated macrophages and remodel tumor microenvironment to promote innate and adaptive antitumor immune responses. ACS Nano 2024;18:6863-86.

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