Review Article
Bulletin of Pure and Applied Sciences.
Chemistry , Vol.44 C, No.1
January-June 2025: P.66-77

http://www.bpasjournals.com/chemistry
Print version ISSN 0970 4620
Online version ISSN 2320 320X

Transforming Glioblastoma Therapy: A Study on Nanomedicine-Enhanced Radiotherapy and Tumor Microenvironment Modulation

[1]Akshata M. Girase, [2]Bhupendra M. Mahale*, [3]Narendrasing R. Girase, and [4]Dr. Ghanshyam M. Chavan

Author's Affiliations:
[1]Pharmaceutical Quality Assurance, Dr. Babasaheb Ambedkar Technological University , Lonere, SVS's Dadasaheb Rawal Pharmacy College Dondaicha, Dist- Dhule, Maharashtra 425408, India
[2]Pharmaceutics, Dr. Babasaheb Ambedkar Technological University, Lonere, SVS's Dadasaheb Rawal Pharmacy College Dondaicha, Dist- Dhule, Maharashtra 425408, India
[3]Pharmaceutical Quality Assurance, Dr. Babasaheb Ambedkar Technological University , Lonere, SVS's Dadasaheb Rawal Pharmacy College Dondaicha, Dist- Dhule, Maharashtra 425408, India
[4]Pharmacology, Dr. Babasaheb Ambedkar Technological University, Lonere, SVS's Dadasaheb Rawal Pharmacy College Dondaicha, Dist- Dhule, Maharashtra 425408, India

***Corresponding Author: Bhupendra M. Mahale,** Pharmaceutics, Dr. Babasaheb Ambedkar Technological University, Lonere, SVS's Dadasaheb Rawal Pharmacy College Dondaicha, Dist- Dhule, Maharashtra 425408, India
E-mail: bhupendramahale999@gmail.com

ABSTRACT

Glioblastoma (GBM) is still among the most common lethal primary brain tumors as a result of its heterogeneous nature and resistance to standard therapies. Recent advances in nanomedicine have introduced innovative approaches that enhance the efficacy of radiotherapy (RT) while addressing critical challenges like hypoxia, immune suppression, and redox imbalances within the tumor microenvironment (TME). The development of stimuli-responsive nanocarriers intended to cross the blood-brain barrier (BBB) is highlighted in this article and modulate the TME for improved radiosensitization. Key areas discussed include the incorporation of nanomedicine with proton and X-ray therapies, immuno-nanomedicine strategies, targeting glioblastoma stem cells, AI-guided nanoparticle development, and the use of exosomes and nanorobots for diagnosis and therapy. Collectively, these multidisciplinary innovations form the basis for adaptive and personalized GBM therapy. This review also evaluates the limitations and translational hurdles of these emerging platforms, offering a comprehensive overview of their future potential.

Keywords: Glioblastoma, Nanomedicine, Radiotherapy, Tumor Microenvironment, Immuno-nanomedicine, Adaptive Therapy

Received on 12.01.2025, Revised on 13.04.2025, Accepted on 12.05.2025

How to cite this article: Girase A.M., Mahale B.M., Girase N.R., and Chavan G.M. (2025). Transforming Glioblastoma Therapy: A Study on Nanomedicine-Enhanced Radiotherapy and Tumor Microenvironment Modulation. *Bulletin of Pure and Applied Sciences-Chemistry,* 44C (1), 66-77.

INTRODUCTION

The most aggressive and prevalent kind of glioma is glioblastoma (GBM), according to the National Cancer Institute (NCI). It is a fast-growing tumor of the central nervous system (CNS) that starts in the supporting cells called glial cells. GBM is the most aggressive of all brain tumors, classified as a grade 4 astrocytoma by the World Health Organization (WHO) [1]. The 5-year survival rate is just roughly 10%, and the median survival time is roughly six months, probably even less, despite this intensive interdisciplinary effort [2–4]. A notable change in GBM research is the emphasis on the tumor microenvironment (TME) as a key factor influencing treatment response. Resistance to conventional treatments is exacerbated by the extremely immunosuppressive terrain, hypoxia, acidic pH, increased glutathione (GSH) levels, and dysregulated metabolic pathways that define the GBM TME.

These microenvironmental features offer unique opportunities for targeted therapies, particularly when stimuli-responsive nanomedicines are created to exploit these pathological indicators for controlled and targeted drug delivery. Because GBM interacts with its surrounding stromal, vascular, and immunological components, an integrative therapy strategy that addresses tumor-host interplay is necessary [5]. Nanomedicine is the use of small molecules, usually biomolecules that range in size from 1 to 100 nm.

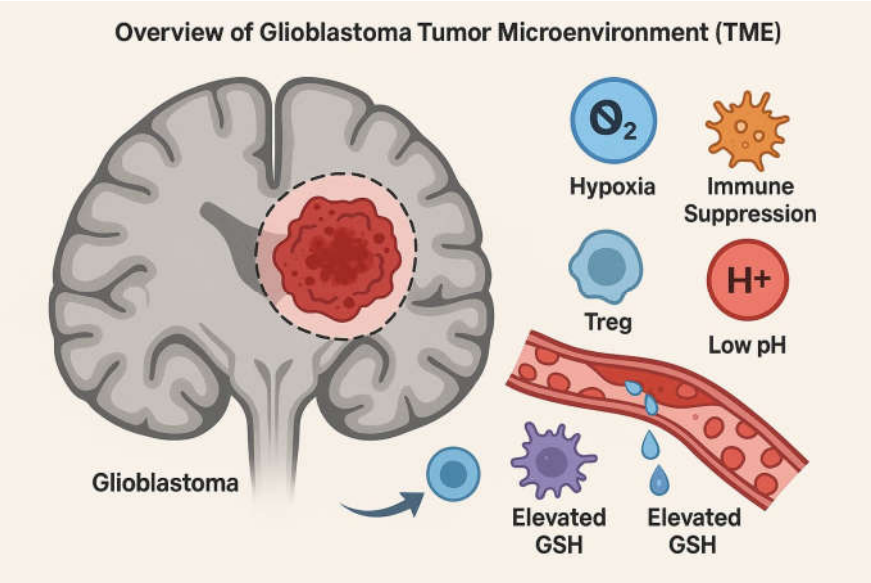

Figure 1: Overview of Glioblastoma Tumor Microenvironment (TME)

The applications of these nanoparticles in therapeutic and diagnostic medicine are growing in number. The body of research on the combined application of bulk chemotherapeutics and nanoparticles for the treatment of cancer is expanding [6]. Over 50 nanomedicines have currently been approved for use by the Food and Drug Administration [7]. They are preferable to their bulk counterparts in some circumstances due to a number of mechanical, optical, electrical, and magnetic characteristics [8]. Among many other applications, nanoparticles (NPs) are utilized in tissue engineering, genetic engineering, biosensing and biomarker detection, surgery, targeted drug delivery, artificial implants, and screening and diagnostics [9]. Two advantages of nanomedicine, which is employed in many treatment techniques, are enhanced cell specificity and sensitivity in diagnostics and better cell-specific toxicity against malignant diseases. Precision medicine and "theranostics," which combine diagnostics and treatment, have emerged as a result of these benefits [10, 11]. The application of organic nanoparticles specifically specifically made to go past the blood-brain barrier (BBB) is an intriguing

development. These consist of lipid and protein-based nanoparticles, liposomes, and micelles [12–14]. The effectiveness and safety of one type of nanotherapy are taken into consideration and weighed in previous assessments of NPs used to treat GBM [15, 16].

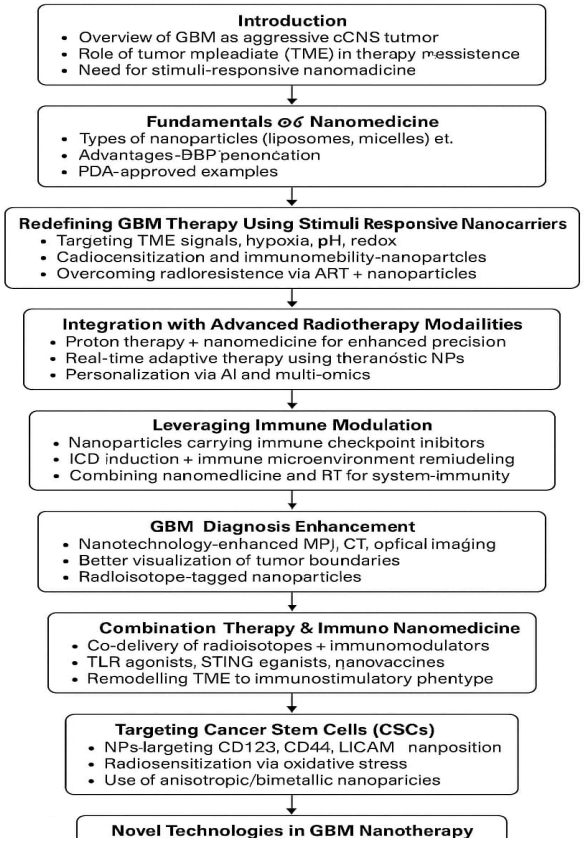

Figure 2: Schematic overview of the structure and key focus areas of this review article, outlining Using nanomedicine in conjunction with advanced radiation strategies for galioblastom treatment

Redefining Nanomedicine to Treat GBM: Theory and Method

We propose that stimuli-responsive nanocarriers, designed to interact dynamically with the TME, provide a novel strategy to treating GBM. In contrast to conventional nanotherapeutics, which use the increased effect of permeability and retention (EPR) for passive targeting, systems that respond to stimuli specifically activate in response to cues unique to tumors, such as low pH, hypoxia, or elevated GSH levels. These activatable platforms not only deliver therapeutic medications but also rewire the TME to reverse immunosuppressive signals and enhance radiosensitivity. For example, nanoparticles that are engineered to release immunomodulators in hypoxic conditions may improve radiation-induced tumor cell death and prime the immune system for a potent anti-tumor response. This dual objective is compatible with the emerging idea of combining immune checkpoint inhibitors and radiation therapy for more successful treatment results. Treatment for GBM must be diverse because to its complexity. Fractionated irradiation models suggest that GBM cells become mesenchymal, acquire stem-like traits, and fortify their DNA damage repair systems (a process called radioresistance) to endure radiation. Posttranslational protein changes, alternative splicing, and epigenetic modifications are the main drivers of this process. Given these difficulties, therapeutic paradigms may be

redefined by combining adaptive radiation therapy using nanotechnology and real-time functional imaging. With ART and nanoparticle-based radiosensitization, resistance mechanisms could be dynamically overcome by continuously tracking tumor progression and modifying treatment plans accordingly [5].

Nanomedicine presents an opportunity to reduce innate and acquired resistance to RT in GBM. One of the most significant barriers to successful RT is hypoxia, which reduces the production of radiation-induced reactive oxygen species (ROS), minimizing DNA damage and lowering therapeutic efficacy. Radiosensitivity can be restored by selectively releasing therapeutic medicines in oxygen-depleted tumor locations using stimuli-responsive nanocarriers, such as hypoxia-activated prodrugs or radiosensitizers. By enhancing radiation dose deposition in tumor tissues while limiting injury to neighboring healthy structures, gold nanoparticles (AuNPs) and other high-Z materials give extra advantages. A crucial alternative is to focus on the redox imbalance in GBM. Radiation resistance is aided by increased GSH levels within cells, which counteract ROS.When GSH levels are elevated, redox-responsive nanoparticles that can selectively release their therapeutic payload after being functionalized with disulfide bonds, causing tumor cells to experience more oxidative stress and becoming more susceptible to radiation-induced DNA damage.

These methods demonstrate how the diseased milieu of GBM can be turned into a therapeutic target through stimuli-responsive nanomedicine. Novel strategies for getting around tumor hypoxia restrictions in radiation therapy have been made possible by recent developments in oxygen-independent radiodynamic therapy (OIRDT). OIRDT uses nanoparticles that can produce therapeutic effects regardless of oxygen levels, in contrast to traditional radiation therapy, which mostly depends on oxygen availability to produce deadly ROS. In particular, using X-ray activation processes, nanoparticles based on rare earth oxides, titanium dioxide, and hafnium oxide have shown radiosensitizing properties [17].

Integrating Nanomedicine with Emerging Radiotherapy Modalities

Another new approach to treating GBM is the combination of nanomedicine and cutting-edge RT methods like proton therapy. With its highly localized radiation delivery and low off-target effects, proton therapy complements stimuli-responsive nanocarriers' precision-targeting capabilities. By combining these modalities, the therapeutic index may be improved by increasing the radiation dose inside the tumor while protecting nearby healthy tissue. Additionally, Real-time tracking of the biodistribution and treatment of nanoparticles success is made possible by theranostic systems that integrate therapeutic delivery and diagnostic imaging, allowing for fully adaptive therapy that is customized for each patient.

The future of nanomedicine depends on patient-specific treatment approaches because of the significant intratumoral and inter-heteromoral heterogeneity shown in GBM. Artificial intelligence (AI) and multi-omics technology advancements have opened the door for customized nanocarriers that are suited to each tumor's unique characteristics. For example, drug delivery with unparalleled specificity may be achievable employing nanoparticles functionalized with ligands that target EGFRvIII, a mutation specific to GBM. Furthermore, non-invasive, real-time monitoring of disease progression and treatment response may be possible by fusing nanomedicine with liquid biopsy technologies, such as circulating tumor DNA (ctDNA) and exosomal analysis.

New Theory: Using Immune Modulation to Increase Radiosensitivity

We believe that treating GBM could be completely transformed by fusing immune-modulating techniques with nanomedicine. If nanoparticles are designed to produce cytokines or immune checkpoint inhibitors in response to radiation-induced inflammation, the typically immunosuppressive TME may become immunostimulatory. This approach links systemic immune activation and local tumor control, corroborating recent findings that RT induces immunogenic cell death (ICD).

Targeting important issues like hypoxia, immunological suppression and redox abnormalities, the combination of RT with stimuli-responsive nanomedicine constitutes a paradigm shift in the treatment of GBM. These cutting-edge platforms have the capacity to greatly increase treatment efficacy by using the pathological characteristics of GBM as therapeutic targets, opening the door to genuinely customized and adaptable oncological therapy. This review's subsequent sections will delve deeper into the workings, uses, and potential future paths of these game-changing innovations [18].

Diagnosing Glioblastoma using Nanotechnology

Making a precise diagnosis is the most crucial stage in the treatment of gliomas. Because gliomas spread invasively across the brain, it is challenging to use clinical imaging techniques to determine the exact limits of the tumor. The incapacity of surgery to completely remove the tumor is one of the primary reasons behind GBM's high recurrence and death rates. [19]. More sophisticated GBM diagnosis and treatment techniques are therefore desperately needed, and nanotechnology has demonstrated enormous promise in the detection, diagnosis, imaging, and treatment of gliomas.

The tiny particle size, magnetic properties, and photosensitivity characteristics of nanomaterials are significant benefits for obtaining a more precise diagnosis of gliomas. Furthermore, glioma visualization greatly enhances the precision of glioma diagnosis, and nanomaterials can contain a variety of radioisotopes, increasing imaging specificity and sensitivity. The most widely utilized techniques for diagnostic glioma imaging are optical imaging, computed tomography (CT), and magnetic resonance imaging (MRI). Numerous research have looked into the combined use of imaging methods and nanotechnology in recent years to diagnose gliomas [20].

Drug Delivery and Penetration of the Blood–Brain Barrier (BBB)

The blood–brain barrier (BBB) remains one of the most difficult obstacles in the treatment of GBM because it is a tightly regulated gatekeeper that severely limits the penetration of medications into the brain parenchyma. The BBB's permeability varies widely, with intact portions preventing medicine transport and reducing the efficacy of systemic treatments, despite the fact that high-grade gliomas often destroy the BBB.[21]. The development of novel drug delivery methods is necessary since traditional small molecule chemotherapies, despite their restricted capacity to cross the blood-brain barrier, usually fail to achieve therapeutic concentrations in the tumor core and infiltrative margins. Recent advances in receptor-mediated transcytosis (RMT) have made it possible for nanoparticles to traverse the blood-brain barrier using endogenous transport systems.

In preclinical GBM models, functionalizing nanoparticles with ligands that target low-density lipoprotein receptors (LDLR), insulin receptors (IR), or transferrin receptors (TfR) has shown enhanced BBB penetration [22]. Focused ultrasound (FUS) combined with microbubble cavitation is another new technique that momentarily breaks down the blood-brain barrier to improve nanoparticle penetration and retention in GBM tissues [23]. But there are still concerns with the safety and reproducibility of FUS-mediated BBB modulation, hence more clinical study is required [24]. Moreover, peptide-functionalized nanoparticles containing BBB-penetrating moieties, such as TAT or Angiopep-2 peptides, have been shown to potentially improve drug transport via endothelial cells [24].

Utilizing receptor-ligand interactions, these designed nanocarriers minimize systemic toxicity while promoting transcytosis. Future iterations of BBB-targeted nanomedicines may integrate multiple targeting components through multi-ligand functionalization to optimize specificity and efficiency [25]. When it comes to GBM clinical translation of nanomedicines, safety, toxicity, and long-term biocompatibility pose significant obstacles beyond BBB penetration. Nanoparticles have longer

circulation durations and better cellular absorption than small-molecule medications, which can result in systemic toxicity and off-target accumulation [26]. Specifically, in vivo inflammatory reactions, complement system activation, and oxidative stress have all been linked to metal-based nanoparticles, including gold and silver nanostructures [26, 27]. These worries have prompted a move toward biodegradable and bioinspired nanocarriers, such as formulations generated from lipids, polymers, and exosomes, which provide better clearance profiles and lower long-term toxicity [27].

Combination Therapy

Combination Therapies Using Immuno-Nanomedicine

Advances in immuno-nanomedicine are revolutionizing the treatment of GBM by fusing immunotherapeutic methods with nanotechnology to modify the tumor microenvironment and enhance radiation therapy. If nanoparticles are engineered to generate immune checkpoint inhibitors, cytokines, or tumor vaccines in response to stimuli unique to a tumor, radiation therapy could turn into an immunostimulatory technique. The immunosuppressive nature of the GBM microenvironment, which is driven by regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), is a major barrier to effective immune activation. Nanocarriers functionalized with PD-1/PD-L1 inhibitors can disrupt these pathways, lowering systemic harm and reviving the immune response against malignancies [28].

One especially intriguing tactic is the co-delivery of immunomodulators and radioisotopes within nanoparticle formulations. Alpha-emitting radioisotopes such as astatine-211 and actinium-225 have demonstrated considerable promise in promoting immunogenic cell death (ICD), which raises dendritic cell activation and promotes long-term tumor immunity, as well as localized tumor removal [29]. These strategies utilize the concept of in situ vaccination, which involves converting the tumor microenvironment into an area rich in antigens that may elicit systemic immune responses. Stimuli-responsive nanoparticles designed for the spatiotemporal release of immunotherapies further expand the possibilities of nanomedicine in GBM. By employing hypoxia- or pH-sensitive carriers, immunostimulatory medications such as IL-12, GM-CSF, or STING agonists can be precisely delivered within the TME, ensuring optimal immune activation while safeguarding healthy tissues [30].

Recent research has shown that Toll-like receptor (TLR) agonist-loaded polymeric nanoparticles efficiently change The transformation of TAMs from an M2 immunosuppressive to an M1 pro-inflammatory phenotype, improving RT effectiveness and reversing immune evasion mechanisms in GBM [31]. Another novel approach is provided by nanoparticle-based cancer vaccines, in which syn thetic carriers encapsulate immunological adjuvants and tumor-associated antigens to elicit cytotoxic T cell responses. Lipid-based nanovaccines that provide neoantigens in combination with radiotherapy (RT) have shown remarkable preclinical efficacy in GBM models, leading to enhanced tumor shrinkage and prolonged survival. Personalized nanovaccine methods using patient-derived tumor antigens are currently being studied in clinical settings to generate tailored anti-tumor immunity [32].

Despite the great potential of these immuno-nanomedicine strategies, a number of translational issues need to be resolved. Because GBM is heterogeneous, it is challenging to find universal antigenic targets, which calls for more investigation into immunological markers unique to each patient. The optimal mix of RT, nanomedicine, and immunotherapy must also be determined in order to optimize synergy and reduce immune-related toxicities [33].

Nanoparticle-Assisted Reprogramming of Cancer Stem Cells (CSCs)

Within GBM, cancer stem cells (CSCs) constitute a extremely combative and resistant to treatment subpopulation that plays a role in treatment failure and tumor recurrence. Because of their plasticity and capacity for self-renewal, these

cells can adjust to environmental stresses including radiation therapy and chemotherapy. Because of their modest rates of proliferation, improved DNA repair mechanisms, and location within protected tumor niches, CSCs are not eliminated by conventional therapy. By facilitating the targeted modification of CSC biology, stimuli-responsive nanomedicine presents a viable approach to overcoming these obstacles [34]. The development of nanocarriers functionalized with ligands that bind selectively to CSC surface markers including CD133, CD44, and L1CAM is one tactic to ensure precise drug delivery while maintaining healthy brain stem cells.

These nanoparticles can be engineered to release epigenetic modulators, such as DNAmethyltransferase inhibitors or histone deacetylase inhibitors, in response to tumor-specific stimuli like hypoxia or acidic pH. These nanotherapeutics can cause differentiation by interfering with CSC epigenetic plasticity, making the cells more vulnerable to conventional therapies [35]. Additionally, nanoparticles designed for the regulated release of substances that induce differentiation, including retinoic acid or bone morphogenetic proteins, have been successfully used to promote CSC differentiation, hence reducing the tumorigenic potential of these cells. When paired with radiosensitizers or chemotherapeutics in multifunctional nanocarriers, these strategies have demonstrated synergistic advantages, effectively eradicating both CSCs and the bulk tumor cell population. Preclinical models have shown that CSC-targeted nanomedicine significantly reduces tumor proliferation and improves survival when compared to standard treatment alone [35, 36].

Integrating Nanomedicine with Proton Therapy

Proton therapy has emerged as a viable treatment option for GBM due to its superior dose distribution profile and Bragg peak effect, which permits maximal energy deposition at a precisely defined tumor depth while sparing surrounding healthy tissues. Proton treatment's therapeutic success is still limited by the hypoxic nature of the tumor microenvironment and the radioresistance of GBM cells, necessitating the development of innovative tactics to boost its effectiveness. In order to overcome these limitations, a rapidly expanding area of research involves integrating nanomedicine—specifically, gold nanoparticles, or AuNPs—into proton therapy [37].

Gold nanoparticles have been extensively studied as radiosensitizers because of their high atomic number and potent interaction with ionizing radiation. In preclinical models, they have been shown to promote local energy deposition when exposed to proton radiation. The impact of nanoparticle size, shape, and functionalization on radiosensitization has been investigated recently. Because of their larger surface area and improved cellular absorption, anisotropic AuNPs—like gold nanopeanuts—have demonstrated better radiosensitizing qualities than their spherical counterparts [38].

The potential of AuNPs in conjunction with proton therapy to alter the GBM tumor microenvironment has been investigated in addition to physical dose enhancement. Functionalized AuNPs can be designed to transport immune-stimulatory molecules, hypoxia-activated prodrugs, or radiosensitizing compounds, changing the typically ra dioresistant GBM phenotype into one that is more sensitive. Recent studies, for example, have shown that AuNPs coupled with redox-modulating drugs can interfere with The antioxidant defense mechanisms of the tumor, making cells GBM more vulnerable to oxidative stress brought on by proton irradiation [39].

Combining X-ray radio therapy with nanomedicine

The majority of popular treatment for GBM is still X-ray radiotherapy radiation resistance, tumor hypoxia, and collateral harm to healthy brain tissue frequently reduce its effectiveness. By taking use of the special interactions among ionizing radiation and high-Z nanoparticles, the incorporation of Combining X-ray radiation with nanomedicine has been studied to improve effectiveness of treatment. X-ray photons mainly Engage with materials through the photoelectric and Compton processes, which increase dosage by Auger cascades and secondary electron production, in contrast to energy deposition in proton therapy, where it is extremely confined

through the Bragg peak [40]. Because of their high atomic number, gold nanoparticles (AuNPs) effectively absorb X-rays and produce an effect of localized dosage amplification. AuNPs enhance the generation of secondary electrons, such as those with low energy that cause oxidative stress and double-strand breaks in DNA in tumor cells,when exposed to kilovoltage or megavoltage X-ray radiation.

This phenomenon preserves nearby normal tissues while increasing tumor cytotoxicity. AuNPs' size, concentration, and intracellular location all affect how well they radiosensitize. AuNPs in the 1–5 nm range have been found to have the best absorption and DNA proximity, which maximizes their radiosensitizing effects [41]. Functionalized AuNPs conjugated with radiosensitizers, like cisplatin or PARP inhibitors, have been investigated in recent nanomedicine developments to further intensify DNA damage. Furthermore, when compared to monometallic formulations, bimetallic nanoparticles—such as those based on hafnium and gold-silver—have shown better radio-enhancing qualities. When paired with fractionated X-ray radiation, these nanoparticles dramatically improve tumor control, according to preclinical research [42].

To increase tumor selectivity and reduce systemic toxicity, research is being done on improving the surface chemistry, composition, and administration methods of nanoparticles. The accuracy and security of using nanomedicine boosted by X-rays to treat GBM may be improved by using sophisticated Simulations using Monte Carlo to enhance nanoparticle-based radiation procedures [43].

Novel Nanomedicine Applications in GBM Therapy

Many new nanomaterials are still being created and researched for use in glioma therapy as nanotechnology research advances and intersects with medical research. Exosomes are tiny extracellular vesicles (sEVs) that are produced by cells and are about 100 nanometers in size. They carry certain chemicals to their intended cells [44] Packed with carbohydrates, lipids, proteins, DNA, and RNA,, exosomes control the extracellular matrix and communicate with other cells, impacting every aspect of cell life [45]. Because exosomes can pass the blood-brain barrier, they may be used as glioma diagnostic and therapeutic agents [46, 47]. Glioma patients have had their serum exosomal EGFRvIII mRNA examined, and it might offer enough diagnostic details [48].

Traditional nanoparticles, such as metal particles or liposomes, offer few advantages and are comparatively poor in terms of bioactivity, compatibility, and tumor selectivity [49].

Exosomes, on the other hand, are a unique nanomedicine delivery technique that can effectively induce antiglioma immune responses and may be prospective carriers due to their low toxicity, enhanced biocompatibility, and appropriate stability [49]. sEVs with dual-targeting functionalization of TAT and angiopep-2 were created by Zhu et al. and used in glioma therapy research [50]. The low-density lipoprotein receptor (LRP-1), which is extensively expressed on the surface of glioma cells and cerebrovascular endothelial cells, can be precisely targeted by angiopep-2 peptide [51].

Furthermore, bionic nanorobots will be crucial to the field of future of medicine. Deng and associates created NK cell-mimicking AIE nanorobots (NK@AIE dots) by wrapping Aggregation-induced luminescence (AIE) organic semiconductor skeletal materials combined with natural killer (NK) cell membranes that have Two-region fluorescence properties within the near-infrared. They then assessed how well these nanorobots performed in glioma diagnosis and therapy [52].

AI-Powered Nanomedicine for the Treatment of GBM

By speeding up the development of new formulations of nanoparticles and improving how they engage with the tumor TME, artificial intelligence is revolutionizing nanomedicine. To determine the best nanoparticle compositions for tumor targeting, immunological modulation, and radiosensitization, the AI-driven algorithms examine enormous datasets. AI helps create nanoparticles that preferentially aggregate

within hypoxic tumor regions, activate the immune system, or change metabolic pathways to improve therapeutic results by mimicking in vivo interactions [53]. By combining multi-omics information to forecast Immunogenicity particular to a patient, AI is also involved in a critical part in comprehending resistant responses brought on by nanomedicine. Machine learning methods evaluate the effects of nanoparticles on immune cell infiltration, antigen presentation, and cytokine release within the TME. These discoveries facilitate the creation of immuno-nanomedicine strategies that work in concert with radiation therapy to produce long-lasting anti-tumor effects [54].

AI improves accuracy in adaptive RT by combining real-time tumor response evaluations with imaging data boosted by nanoparticles. By examining ra diosensitization effects, hypoxia state, and nanoparticle biodistribution, AI-driven algorithms improve dose adaption tactics. With the help of this dynamic technique, RT is continuously modified to maximize therapeutic efficacy and minimize harm to healthy tissues [55, 56]. One of the biggest obstacles to the clinical deployment of AI is still regulatory approval. By rigorously evaluating AI-designed nanocarriers for immunointeractions, current experimental research aims to validate AI-driven nanoparticle proposals. These nanoparticles are initially verified in vitro to evaluate their therapeutic efficacy, biocompatibility, and aimed at effectiveness following computational modification for immune evasion and tumor-specific binding. Successful candidates should then undergo in vivo studies to evaluate biodistribution, clearance, and tumor response in physiological circumstances. This methodical process guarantees that the designs of AI-generated nanoparticles are in line with biological facts, enhancing their ability to translate theoretical models into clinically applicable medicines. Standardized procedures for the validation of AI-driven nanoparticles must be developed in order to hasten their clinical integration and regulatory certification. Even if AI models excel at analyzing vast amounts of data, identifying trends, and predicting outcomes, they still lack the ethical judgment, contextual flexibility, and sophisticated comprehension that human scientists and doctors provide [57].

CONCLUSION

The fusion of nanomedicine with advanced radiotherapy offers a transformative strategy for glioblastoma treatment. By leveraging the unique features of the tumor microenvironment, including elevated glutathione levels and hypoxia, and immune suppression, stimuli-responsive nanoparticles have demonstrated the ability to improve radiosensitization, enhance drug delivery across the BBB, and reprogram cancer stem cells. Innovations such as immune-modulating nanocarriers, AI-driven nanodesign, and the integration of proton and X-ray therapies further enhance the therapeutic window while minimizing systemic toxicity. Despite promising preclinical outcomes, clinical translation remains limited due to challenges in scalability, long-term safety, and regulatory hurdles. Overcoming these obstacles should be the main goal of future studie, optimizing patient-specific therapies through liquid biopsies and omics integration, and validating AI-generated nanocarrier models. These next-generation nanotechnologies hold the potential to redefine glioblastoma management through personalized, targeted, and adaptive oncologic care.

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