NANOMATERIALS IN GLIOBLASTOMA RESEARCH, DIAGNOSIS AND THERAPY

Nura Brimo
Emir Baki Denkbas
Beyzanur Cakar

Bentham Books

Nanomaterials in Glioblastoma Research, Diagnosis and Therapy

Authored by

Nura Brimo

Emir Baki Denkbas

Beyzanur Cakar
Department of Biomedical Engineering
Başkent University, Ankara
Turkey

Nanomaterials in Glioblastoma Research, Diagnosis and Therapy

Authors: Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

ISBN (Online): 978-981-5324-18-1

ISBN (Print): 978-981-5324-19-8

ISBN (Paperback): 978-981-5324-20-4

First published in 2025.

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

FOREWORD

It gives me immense pleasure to introduce to you the groundbreaking book, "Nanomaterials in Glioblastoma Research, Diagnosis and Therapy." This comprehensive work delves into the transformative potential of nanotechnology in addressing the challenges of glioblastoma, a highly aggressive form of brain cancer that continues to pose significant obstacles to researchers and medical practitioners.

Despite advancements in conventional therapies, the prognosis for glioblastoma patients remains bleak. However, the advent of nanomaterials has ushered in a new era of hope and possibility for both diagnosis and treatment. Within the pages of this meticulously crafted volume, leading experts and researchers in the field have collaborated to explore the remarkable potential of nanomaterials in eradicating glioblastoma.

Covering a wide array of topics, including the synthesis and characterization of nanomaterials, their applications in targeted drug delivery, imaging techniques, and emerging nanotherapeutic strategies, this book offers a comprehensive overview of the latest advancements in the field.

Nanomaterials provide a multifaceted approach that holds promise for personalized medicine in glioblastoma treatment. By precisely tailoring nanoparticles to deliver therapeutic agents with spatial and temporal control, nanotechnology is revolutionizing the fight against this devastating disease. Furthermore, the use of nanomaterials enables novel diagnostic techniques, facilitating early detection and more accurate monitoring of disease progression.

As you embark on this enlightening journey through the pages of "Nanomaterials in Glioblastoma Research, Diagnosis and Therapy," you will witness how the convergence of nanotechnology and neuro-oncology has the potential to reshape the future of glioblastoma management. The authors' expertise and dedication shine through in their compelling narratives, presenting cutting-edge research findings and visionary predictions.

This volume aims not only to inform researchers, clinicians, and students in the field but also to inspire interdisciplinary collaborations, fostering the translation of scientific discoveries into impactful clinical applications. By fostering a deeper understanding and appreciation for the immense possibilities offered by nanotechnology, we aim to expedite the development of more effective and safer therapies, ultimately leading to improved outcomes and a brighter future for glioblastoma patients worldwide.

I express my deepest gratitude to all the esteemed contributors who have shared their knowledge and insights, driving the advancement of nanomaterials in glioblastoma research. My heartfelt appreciation also goes to the dedicated teams working tirelessly in laboratories and hospitals, united by the common goal of finding a cure for this formidable disease.

May this landmark publication serve as a guiding light, paving the way for transformative advancements and opening new avenues for hope and healing in the battle against glioblastoma.

Büşra Akay Hacan
University of Health Sciences, Ankara
Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital
Ankara, Turkey

PREFACE

Welcome to "Nanomaterials in Glioblastoma Research, Diagnosis and Therapy"! In this groundbreaking book, we explore the unprecedented potential of nanotechnology in revolutionizing the field of glioblastoma research, diagnosis, and therapy. Glioblastoma, the most aggressive form of brain cancer, has posed significant challenges to clinicians, researchers, and patients alike for decades. Current treatment options often fall short of providing effective and long-lasting solutions. However, with the advent of nanotechnology, a new era of possibilities has dawned upon us.

The integration of nanomaterials into glioblastoma research has allowed for remarkable advancements in detection, imaging, drug delivery, and therapy. Nanotechnology offers precise control over the targeted delivery of therapeutics, enabling the enhancement of treatment efficacy while minimizing side effects. Moreover, nanomaterials possess unique physicochemical properties that can be harnessed for improved diagnostics and monitoring of glioblastoma progression. This book brings together leading experts in the field, who have made significant contributions to the development and application of nanomaterials in glioblastoma research and therapy. Each chapter explores the latest discoveries, methodologies, and breakthroughs, providing a comprehensive overview of the current state of the art in nanotechnology for glioblastoma.

We begin by delving into the fundamental principles of nanomaterials, their synthesis, and characterization techniques. Subsequently, we delve into the utilization of nanomaterials for imaging glioblastoma, from traditional imaging modalities to cutting-edge molecular imaging and theranostics approaches. The subsequent sections delve into the innovative applications of nanomaterials in targeted drug delivery, gene therapy, immunotherapy, and hyperthermia. Each chapter uncovers the immense potential of nanotechnology in enhancing the efficacy of therapeutic interventions while minimizing the adverse effects on healthy brain tissue.

Finally, we explore emerging trends and future directions in nanomaterials research, highlighting the ongoing efforts to translate these advancements from the laboratory bench to the clinical setting. We also address the challenges and ethical considerations surrounding the use of nanomaterials in glioblastoma research and therapy. "Nanomaterials in Glioblastoma Research, Diagnosis and Therapy" aims to serve as a comprehensive resource for scientists, clinicians, and students interested in the intersection of nanotechnology and glioblastoma. We hope that the knowledge shared within these pages will spark curiosity, drive innovation, and ultimately contribute to the development of effective treatments for this devastating disease. We would like to express our gratitude to the contributing authors for their invaluable insights and expertise, as well as the diligent efforts of the editorial team in bringing this book to fruition. May this collective endeavor pave the way toward a brighter future for glioblastoma patients through the power of nanomaterials.

Nura Brimo

Emir Baki Denkbas

Beyzanur Cakar
Department of Biomedical Engineering
Başkent University, Ankara
Turkey

ACKNOWLEDGEMENTS

We would like to express our deepest gratitude and appreciation to all those who have contributed to the completion of this book, "Nanomaterials in Glioblastoma Research, Diagnosis and Therapy".

First and foremost, we are immensely thankful to the researchers, scientists, and experts in the field of nanomaterials and glioblastoma who have tirelessly dedicated their time, efforts, and knowledge to share their invaluable insights and advancements. Your expertise has undeniably enriched the content of this book and shed light on the intricate relationship between nanomaterials and glioblastoma. We extend our sincere appreciation to the individuals who have supported and encouraged us throughout this journey. To our colleagues, mentors, and friends who have provided guidance, constructive feedback, and encouragement, we are indebted to your unwavering belief in our work.

We offer our heartfelt gratitude to the editorial team who has worked tirelessly to shape this book into its final form. Your meticulous attention to detail and commitment to excellence have immensely contributed to the quality and coherence of this work. We would also like to thank the reviewers and experts who critically evaluated the manuscript, offering valuable suggestions and observations that have undoubtedly improved its overall quality.

Finally, we express our deepest gratitude to our families for their unwavering love, support, and understanding throughout the course of this project. Your patience and encouragement have been invaluable, and we are forever grateful.

This book would not have been possible without the collective efforts of these individuals. We humbly acknowledge and appreciate the contributions of all those who have played a part, however big or small, in bringing this book to fruition.

Thank you

CHAPTER 1

Molecular Genetics of Glioblastoma (GBM)

Abstract: Glioblastoma (GBM) is a highly malignant brain tumor with complex genetic alterations. This chapter provides an overview of the molecular genetics of GBM, including the genetic alterations that contribute to its pathogenesis, the molecular subtypes of GBM, and potential therapeutic targets for GBM treatment. The genetic alterations in GBM involve multiple signaling pathways, including the receptor tyrosine kinase (RTK) pathway, the p53 pathway, the RB pathway, and the PI3K/AKT/mTOR pathway. GBM is also characterized by molecular subtypes that have distinct genetic alterations and clinical features. Potential therapeutic targets for GBM treatment include RTK inhibitors, PI3K/AKT/mTOR inhibitors, and histone deacetylase inhibitors. However, the development of effective therapies for GBM is challenging due to its genetic heterogeneity and the presence of the blood-brain barrier. Understanding the molecular genetics of GBM is crucial for the development of effective therapies and improving patient outcomes.

Keywords: Glioblastoma, Inhibitors, Pathogenesis, Signaling pathways.

INTRODUCTION

Glioblastoma (GBM) represents one of the most aggressive and lethal types of brain tumors, characterized by an extremely poor prognosis. This malignancy is defined by complex genetic alterations, encompassing a wide range of mutations, amplifications, deletions, and chromosomal rearrangements. The intricate molecular genetics underlying GBM are essential for informing the development of more effective therapeutic interventions against this formidable disease. Key genetic alterations in GBM are seen across multiple signaling pathways, notably the receptor tyrosine kinase (RTK) pathway, the p53 pathway, the RB pathway, and the PI3K/AKT/mTOR pathway, all of which play crucial roles in regulating cell proliferation, survival, and differentiation. Disruptions in these pathways significantly contribute to the pathogenesis and progression of GBM [1]. Furthermore, GBM encompasses several molecular subtypes, including the classical, mesenchymal, proneural, and neural variants. Each subtype exhibits unique genetic profiles and clinical characteristics, presenting distinct challenges and opportunities for targeted therapeutic strategies. Potential treatment options for GBM focus on inhibiting critical pathways and molecular targets, such as

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

RTK inhibitors, PI3K/AKT/mTOR inhibitors, and histone deacetylase inhibitors. Nevertheless, developing effective therapies remains a substantial challenge due to the genetic heterogeneity of GBM and the protective barrier posed by the blood-brain interface, which restricts drug delivery to the tumor site [2, 3].

This chapter aims to provide a comprehensive overview of the molecular genetics of GBM, focusing on the genetic alterations that drive its pathogenesis, the defining characteristics of its molecular subtypes, and the potential therapeutic targets under investigation. Additionally, we will explore the ongoing challenges in creating effective treatments for GBM and outline prospective research directions that may yield new insights and advancements in the fight against this devastating disease.

GENETIC ALTERATIONS IN GLIOBLASTOMA

Glioblastoma (GBM) is distinguished by its complex genetic landscape, which includes a variety of mutations, amplifications, deletions, and chromosomal rearrangements. These genetic changes affect several critical signaling pathways, such as the receptor tyrosine kinase (RTK) pathway, the p53 pathway, the RB pathway, and the PI3K/AKT/mTOR pathway. The dysregulation of these pathways plays a fundamental role in GBM pathogenesis, fostering tumor growth and resistance to apoptosis.

One of the most frequently altered pathways in GBM is the RTK pathway, with mutations in the epidermal growth factor receptor (EGFR) gene being among the most common genetic modifications observed. These EGFR mutations can result in the constant activation of the RTK pathway, thereby enhancing cell proliferation and survival. Beyond EGFR, other RTKs, such as the platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR), also exhibit genetic alterations, including gene amplification, which further drives the dysregulation of this pathway [4].

The p53 pathway is another key pathway frequently disrupted in GBM. The p53 protein acts as a tumor suppressor, regulating cell proliferation and DNA repair mechanisms. Mutations in the TP53 gene, leading to a loss of p53 function, are common in GBM and contribute to uncontrolled cell growth and diminished DNA repair. Additional alterations within the p53 pathway include the amplification of the MDM2 gene, which negatively modulates p53 activity, and mutations in the CDKN2A gene, which encodes p16^INK4a, a crucial negative regulator of the RB pathway [5]. Similarly, the RB pathway is commonly disrupted in GBM, with mutations in the RB1 gene frequently observed. Loss of RB function promotes unchecked cell proliferation and impairs cellular differentiation. Other genetic changes in this pathway include the amplification of the CDK4 gene, which

encodes cyclin-dependent kinase 4, a positive regulator of the RB pathway, further contributing to GBM pathogenesis [6].

The PI3K/AKT/mTOR pathway, essential for regulating cell growth, metabolism, and survival, is also frequently altered in GBM. Mutations in genes such as PIK3CA and PTEN are prevalent in this pathway. Dysregulation within this pathway drives increased cell proliferation and survival while inhibiting apoptosis. Additional genetic changes in the PI3K/AKT/mTOR pathway include amplification of the AKT3 gene and mutations in TSC1 and TSC2, which act as negative regulators of mTOR signaling.

In summary, genetic alterations in key pathways—including the RTK, p53, RB, and PI3K/AKT/mTOR pathways—are integral to the development and progression of GBM. A deeper understanding of these genetic changes is essential for the development of targeted therapies that may more effectively combat this aggressive form of cancer.

Receptor Tyrosine Kinase (RTK) Pathway

The receptor tyrosine kinase (RTK) pathway plays a crucial role in cellular processes, and its dysregulation is frequently observed in glioblastoma (GBM), a highly aggressive brain tumor characterized by its rapid proliferation and resistance to therapy. RTKs are transmembrane proteins that facilitate cellular communication by binding to specific extracellular ligands, which trigger the activation of downstream intracellular signaling cascades. These cascades regulate fundamental cellular processes, including proliferation, survival, and differentiation, which are critical for maintaining normal cellular function. However, when the RTK pathway is dysregulated, as is often the case in GBM, it can drive uncontrolled cell growth and invasive behavior typical of this malignancy. The aberrant activation of the RTK pathway in GBM not only contributes to tumorigenesis but also complicates therapeutic intervention strategies [5].

Among the various alterations within the RTK pathway, mutations or amplification of the epidermal growth factor receptor (EGFR) gene stands out as some of the most prevalent and impactful in GBM. Mutations in EGFR can lead to its constitutive activation, meaning that the RTK pathway remains persistently active even in the absence of external ligand binding. This constitutive activation results in the continuous promotion of cellular proliferation and enhanced cell survival, fostering an environment conducive to tumor growth and progression. Additionally, gene amplification—where multiple copies of the EGFR gene lead to overexpression of the EGFR protein—can further exacerbate RTK pathway activation. The net effect of these genetic modifications is an intensified signaling

CHAPTER 2

Epigenetic Mechanisms of Glioblastoma

Abstract: Transferable modifications that occur without any mutations in the DNA and can change gene profiling are explained by epigenetics. Epigenetic changes can occur directly on DNA, as well as through histone proteins or non-coding RNAs. Thanks to this, many mechanisms can be reorganized in the organism. As a result of changing the expression levels of genes, the development of many diseases, including cancer, can be promoted. Epigenetic mechanisms such as DNA methylation, Histone Modifications, and non-coding RNA are particularly associated with the formation and development of GBM. It is important to investigate the relevant epigenetic regulation patterns for early diagnosis, treatment, and prevention of poor prognosis of GBM. In this section, the mechanisms of epigenetic modification, which are often observed in GBM, a highly aggressive brain tumor, are introduced. In this way, although the gene base sequence does not change, it is explained how gene profiles change and how they support the development of GBM.

Keywords: DNMT, Epigenetic, HAT, Modifications, RNA, Regulations.

INTRODUCTION

Glioblastoma (GBM) is a highly malignant and aggressive brain tumor, characterized by complex molecular and cellular heterogeneity that poses significant challenges in treatment. Recent research into GBM has uncovered a critical role of epigenetic mechanisms in driving the disease's development and progression. Epigenetics refers to changes in gene expression that occur without alterations to the underlying DNA sequence. These changes are heritable and can be induced by modifications directly on DNA, through histone proteins, or *via* non-coding RNAs. Epigenetic mechanisms allow for the dynamic regulation of gene activity, enabling cells with the same genetic material to adopt distinct phenotypes, a process that is especially important during development and in response to environmental stimuli [1 - 12].

In the context of GBM, epigenetic alterations such as DNA methylation, histone modifications, and the expression of non-coding RNAs play an essential role in tumor formation, growth, and resistance to therapy. Understanding these epigenetic processes is crucial for unraveling the complexity of GBM, as they not

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

only contribute to tumor initiation and progression but also have a significant impact on treatment response and patient outcomes [13 - 19].

Epigenetic Modifications and their Role in Gene Expression

Epigenetic changes influence gene expression without altering the DNA sequence itself. This regulation allows for the activation or suppression of genes in a reversible manner, which can be inherited by daughter cells (Fig. **1**). DNA methylation, one of the most studied epigenetic mechanisms, involves the addition of a methyl group to the cytosine base within CpG islands in gene promoters. This methylation is catalyzed by a family of enzymes known as DNA methyltransferases (DNMTs). In mammals, five DNMTs exist: DNMT1, DNMT3A, DNMT3B, DNMT3L, and DNMT2 (Fig. **2**). DNMT1 maintains methylation patterns during DNA replication, ensuring the inheritance of epigenetic marks, while DNMT3A and DNMT3B are involved in establishing new methylation patterns during early development [20 - 22].

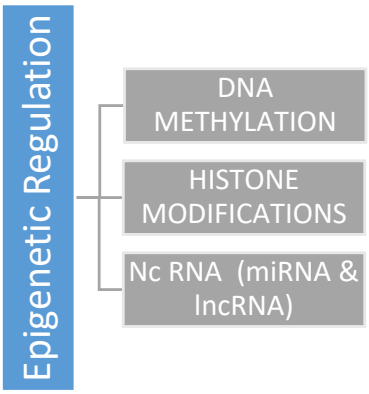


Fig. (1). Summary of the epigenetic mechanisms.

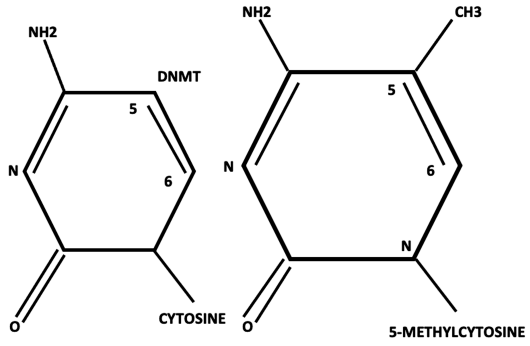


Fig. (2). DNA methylation.

DNA methylation plays a key role in GBM and is observed at aberrant levels in tumor cells. This process helps silence tumor suppressor genes and activate oncogenes, contributing to tumorigenesis. Hypermethylation in GBM is commonly observed in CpG islands within promoter regions of tumor suppressor genes, leading to gene silencing, while hypomethylation may activate oncogenes. This dynamic regulation of methylation affects gene expression profiles, creating conditions favorable for GBM progression [23 - 28].

Histone modifications are another crucial aspect of epigenetic regulation. Histones are positively charged proteins around which DNA is wrapped, forming nucleosomes. Modifications such as acetylation, methylation, phosphorylation, and ubiquitination on the N-terminal tails of histone proteins alter chromatin structure, thus influencing gene accessibility and transcriptional activity. Acetylation, for instance, is typically associated with gene activation, while deacetylation results in gene repression. Enzymes such as acetyltransferases, deacetylases, methyltransferases, and demethylases mediate these modifications, determining the chromatin state and subsequent gene expression patterns [29].

In GBM, aberrant histone modifications play a significant role in modifying gene expression and driving tumor behavior. Dysregulation of histone-modifying enzymes, such as histone deacetylases (HDACs), is frequently observed in GBM and has been associated with the repression of tumor suppressor genes and the promotion of oncogenic pathways. Targeting these enzymes with HDAC inhibitors and other modulators of histone modifications has shown promise in preclinical studies as a potential therapeutic approach for GBM, as these inhibitors may reverse abnormal gene silencing and restore normal cellular function.

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), represent a third category of epigenetic regulators. These RNA molecules do not code for proteins but play a crucial role in regulating gene expression at both transcriptional and post-transcriptional levels. miRNAs can function as oncogenes or tumor suppressors, depending on their target genes. In GBM, dysregulation of specific miRNAs has been linked to the promotion of cell proliferation, invasion, and resistance to therapy. Similarly, lncRNAs are involved in gene regulation through diverse mechanisms, such as chromatin remodeling and the modulation of transcription factors. The abnormal expression of ncRNAs in GBM is associated with the tumor’s invasive and therapy-resistant nature, highlighting their potential as diagnostic biomarkers and therapeutic targets.

CHAPTER 3

Methods for Targeting DNA Damage Response in Glioblastoma

Abstract: Currently, GBM is treated with chemotherapy, radiotherapy, and surgical-based approaches. However, these treatments often fail due to the development of resistance mechanisms. The goal of these treatments is to induce DNA damage in tumor cells. If the induced single-strand or double-strand DNA break cannot be repaired, it leads to dangerous lesions and triggers apoptosis in the cell. In contrast, mammals have multiple DNA damage repair mechanisms that utilize different enzymes and pathways. These repair mechanisms are more developed in cancer cells and contribute to their resistance to chemotherapy and radiation therapy. Resistance mechanisms are commonly observed in the treatment of GBM, which is an aggressive type of cancer. This section explains the mechanisms of resistance that develop in response to DNA damage in GBM, their causes, and various strategies for inhibiting resistance.

Keywords: Chemotherapy, DDR, DNA damage, GBM, Radiotherapy, Resistance.

INTRODUCTION

Glioblastoma multiforme (GBM) is recognized as one of the most aggressive and lethal forms of brain tumors, distinguished by its high degree of malignancy and typically poor prognosis in affected individuals [1]. Classified as a Grade IV astrocytoma, GBM is both common and notorious for its rapid progression and resistance to treatment [2]. The incidence of GBM is notably higher in men than in women, and its prevalence correlates strongly with advancing age. Globally, the impact of this disease is profound, with an estimated 100,000 people succumbing to GBM each year [3, 4]. Despite advances in early detection, the average survival period following a GBM diagnosis remains dishearteningly short, typically around 14 months even with prompt intervention [5].

Current therapeutic approaches for GBM primarily include surgical resection, chemotherapy (CT), radiotherapy (RT), and immunotherapy. However, the complexity of GBM, coupled with its unpredictable response to these treatments, poses a significant challenge in identifying an optimal treatment regimen. The

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

tumor cells in GBM frequently exhibit resilience against CT and RT, largely due to robust DNA damage repair (DDR) pathways that enable them to counteract therapeutic damage. Moreover, the tumor's location within the brain complicates surgical intervention, as its invasive growth pattern and proximity to critical functional areas reduce the feasibility and safety of extensive resection. Consequently, while chemotherapeutic and radiotherapeutic interventions remain prominent, their efficacy is limited by challenges such as non-specific side effects, dose-dependent toxicity, and the protective barrier of the blood-brain barrier (BBB).

The primary objective of CT and RT in GBM treatment is to halt tumor growth, induce cellular destruction, and prevent metastasis by damaging the tumor cells' genetic material. Yet, GBM cells often continue to survive and adapt, utilizing DDR mechanisms and associated enzymes to repair therapy-induced DNA damage. Through these mechanisms, treatment-resistant GBM cells can assume stem-like properties, effectively supporting the tumor's progression and spread. This intrinsic resistance renders GBM treatment a multifaceted challenge, necessitating ongoing research efforts aimed at elucidating these resistance mechanisms. Researchers are striving to improve survival rates by exploring combination therapies that integrate multiple treatment modalities to counteract GBM's adaptive defenses.

In recent years, promising advancements have emerged from research focusing on DDR inhibitors as a means to counteract the tumor's resilience. Studies indicate that these inhibitors, when used in conjunction with other therapeutic strategies, hold potential for enhancing the efficacy of GBM treatment. Additionally, innovative drug delivery systems are being developed to circumvent obstacles that typically hinder chemotherapeutic agents, such as BBB permeability, adverse side effects, and the limitations associated with high-dose requirements. Nanoparticle-based drug delivery systems have gained considerable attention as they offer a more targeted approach to drug release, minimizing systemic toxicity while improving drug accumulation at the tumor site. These advancements underscore a growing understanding within the scientific community that tackling GBM's resistance mechanisms and delivery challenges may pave the way toward more effective treatments.

Present Clinical Therapy Protocol of GBM

In the treatment landscape for glioblastoma multiforme (GBM), a range of therapeutic strategies, including chemotherapy (CT), radiotherapy (RT), and surgical resection, are routinely employed to manage this aggressive malignancy [6]. However, due to the highly invasive nature of GBM, complete tumor removal

through surgical intervention is an exceedingly challenging and high-risk procedure. Research has demonstrated that combination therapy, integrating multiple treatment approaches, tends to yield improved survival outcomes for patients compared to the use of RT or CT alone [5, 7]. Consequently, in clinical settings, a treatment protocol involving chemotherapy and radiotherapy centered around temozolomide (TMZ) has been established as the standard therapeutic regimen.

Despite the limited efficacy of surgery alone, TMZ is administered in conjunction with radiotherapy, typically at a dose of 75 mg/m^2 daily over a six-week period following surgical intervention. Based on the patient's response and overall health status, the daily dosage of TMZ may be escalated to 150 mg/m^2. As a pivotal chemotherapeutic agent for GBM, TMZ functions as a DNA-alkylating agent and is administered orally, which facilitates patient compliance and ease of delivery [8]. Notably, TMZ is capable of traversing the blood-brain barrier (BBB), allowing it to access and exert its effects directly within the brain tissue. Upon crossing the BBB, TMZ undergoes hydrolysis and converts into an active metabolite, 5-(3-methyl triazen-1-yl) imidazole-4-carboxamide (MTIC), which is instrumental in initiating DNA damage within tumor cells [8].

TMZ induces over ten types of DNA lesions by adding electrophilic alkyl groups to the DNA structure. For example, it frequently forms N-7 methylguanine (N7MeG) lesions by methylating guanine at the N7 position or generates N-3 methyladenine (N3MeA) lesions through methylation of adenine at the N3 position. Although these types of damage can generally be repaired through cellular repair mechanisms, TMZ is also capable of creating O6 methylguanine lesions, a relatively rare but highly cytotoxic form of DNA damage [9]. When TMZ-induced DNA damage occurs, the tumor cell's cycle is disrupted as part of an initial cellular response. Repair mechanisms are subsequently activated, with specific proteins recruited to manage DNA repair processes, as summarized in Table **1**. If these repair attempts fail, the tumor cell is directed towards programmed cell death, receiving signals for apoptosis or necrosis, ultimately leading to its elimination [10].

The effectiveness of TMZ as part of the GBM treatment protocol underscores its status as the gold standard in the chemotherapeutic management of this challenging disease. However, the recurrence and resistance frequently observed in GBM highlight the need for ongoing research to optimize combination therapies and explore adjunctive strategies to enhance the therapeutic impact of TMZ and improve patient outcomes.

CHAPTER 4

Biomaterials to Improve the Efficiency of Immunotherapy of Glioblastoma Treatment

Abstract: Glioblastoma is a highly aggressive and difficult-to-treat brain cancer that has a poor prognosis. Immunotherapy has emerged as a promising approach for the treatment of glioblastoma, as it harnesses the power of the immune system to target and kill cancer cells. However, the efficacy of immunotherapy is limited by several factors, including the immunosuppressive microenvironment of the brain and the lack of effective drug delivery systems. Biomaterials have the potential to improve the efficiency of immunotherapy of glioblastoma treatment by enhancing drug delivery, modulating the immune response, and overcoming the immunosuppressive microenvironment of the brain. This chapter summarizes recent advances in biomaterials for the treatment of glioblastoma, with a focus on their potential to improve the efficiency of immunotherapy. The chapter highlights the potential of biomaterials to enhance drug delivery, modulate the immune response, and overcome the immunosuppressive microenvironment of the brain, providing more effective and targeted therapies for patients with glioblastoma. Further research is needed to optimize the design and performance of biomaterial-based immunotherapies and to evaluate their safety and efficacy in humans.

Keywords: Biomaterial, DDS, Immunotherapy, Therapy.

INTRODUCTION

The treatment of glioblastoma, an extremely aggressive form of brain cancer, poses substantial challenges, primarily due to the complexities of delivering effective drug concentrations to the brain and the immunosuppressive nature of the tumor microenvironment. Immunotherapy, a strategy that leverages the body's immune system to recognize and attack cancer cells, has shown potential in treating glioblastoma. However, its therapeutic efficacy is frequently compromised by the tumor’s ability to create an immunosuppressive environment that restricts immune activity against cancer cells. In response to these obstacles, biomaterials have emerged as a promising solution to enhance the effectiveness of immunotherapy for glioblastoma treatment, addressing issues related to drug delivery and immune evasion mechanisms [1].

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

This chapter on "Biomaterials to Improve the Efficiency of Immunotherapy of Glioblastoma Treatment" offers a detailed review of recent advances in biomaterial applications for glioblastoma immunotherapy. The use of biomaterials in this context presents a novel approach, facilitating the targeted delivery of immunotherapeutic agents directly to the tumor site. By doing so, these materials help to mitigate the immunosuppressive effects of the tumor microenvironment and significantly enhance the potency of immunotherapy treatments [2]. Various types of biomaterials, including hydrogels, nanoparticles, and scaffolds, are explored in this chapter, each offering unique advantages for use in immunotherapy. These materials can be engineered to release immunotherapeutic agents in a controlled manner, optimizing both the safety and efficacy of the delivered drugs [3].

The authors also emphasize the critical role of targeting specific immune cells, such as T-cells and dendritic cells, to improve immunotherapy outcomes. By functionalizing biomaterials with specific ligands, they can be designed to target and recruit these immune cells more effectively to the tumor site, thereby enhancing immune response within the tumor and increasing the likelihood of successful treatment. This targeting capability represents a crucial advancement in the strategic application of immunotherapy, as it allows for precise modulation of the immune system in a way that directly counters the tumor's defense mechanisms.

In addition to enhancing immune-targeting capabilities, the chapter discusses the potential benefits of combination therapies that integrate immunotherapy with other treatments, such as chemotherapy or radiotherapy, to improve the overall management of glioblastoma. Biomaterials can serve as delivery vehicles for multiple therapeutic agents, facilitating controlled release and enabling synergistic interactions between therapies to maximize therapeutic impact [4]. This approach of using biomaterials for combined therapy offers a multifaceted advantage, addressing both the need for effective drug delivery and the challenge of overcoming the tumor's protective environment.

Overall, this chapter provides a valuable resource for researchers and clinicians focused on advancing glioblastoma treatment through biomaterials. By improving drug delivery and countering the immunosuppressive properties of the tumor microenvironment, these biomaterial-based solutions show considerable promise in addressing the limitations of current glioblastoma therapies. As research progresses, biomaterials hold the potential to significantly improve patient outcomes in this challenging field, offering hope for more effective and sustained treatment options against this devastating disease.

Microenvironment of Glioblastoma

The microenvironment of glioblastoma (GBM) consists of a complex network of cells, extracellular matrix (ECM), and signaling molecules that not only surround but actively support the growth and persistence of GBM tumors. This microenvironment is essential to the development and progression of GBM, as it supplies vital nutrients and growth factors to tumor cells and establishes an immunosuppressive setting that promotes tumor expansion [2]. A defining aspect of the GBM microenvironment is its cellular diversity, which includes various cell types such as cancer cells, astrocytes, microglia, and endothelial cells. Each of these cell types contributes to the tumor's progression by secreting signaling molecules like cytokines and growth factors, thereby fostering tumor growth and enhancing its invasive potential.

One significant factor in this network is the secretion of vascular endothelial growth factor (VEGF) by GBM cells, which stimulates the formation of new blood vessels, ensuring a steady supply of nutrients to the tumor cells. Astrocytes, a type of glial cell in the brain, also play a crucial role by releasing factors that promote the survival and proliferation of GBM cells. Additionally, microglia, which are immune cells within the brain, inadvertently support GBM progression by secreting factors that both suppress immune responses and encourage angiogenesis [2, 5]. These interactions illustrate how the cellular components of the microenvironment work collectively to sustain and protect the tumor.

The ECM, which forms the structural scaffold of the tumor, also holds significant sway over GBM behavior. Composed of various proteins and molecules, the ECM directly influences how tumor cells adhere to, migrate, and interact with their surroundings. For instance, ECM proteins like laminin and fibronectin facilitate the adhesion and migration of GBM cells, enhancing their ability to invade adjacent tissues. Moreover, the ECM impacts the tumor's response to chemotherapy and radiotherapy, with certain ECM components contributing to GBM's resistance to these treatments [6, 7].

A further characteristic of the GBM microenvironment is its hypoxic, or low-oxygen, state, a condition driven by the rapid proliferation and high metabolic demands of GBM cells. This hypoxia not only promotes tumor growth and invasiveness but also contributes to resistance against therapeutic interventions. Hypoxia-inducible factor 1 (HIF-1), a key transcription factor activated in low-oxygen conditions, drives the expression of genes involved in angiogenesis, metabolism, and cell survival. Research has underscored HIF-1's pivotal role in the advancement and resilience of GBM, as it enables tumor cells to adapt and thrive under hypoxic conditions [2, 6].

CHAPTER 5

Glioblastoma Diagnosis by 2-D Nanomaterials-Based Electrochemical Biosensors

Abstract: This book chapter focuses on the development of electrochemical biosensors based on 2-D nanomaterials for the diagnosis of glioblastoma, a highly aggressive and malignant form of brain cancer. 2-D nanomaterials, such as graphene and transition metal dichalcogenides, have unique electronic, optical, and mechanical properties that make them ideal candidates for the development of biosensors. These materials can be functionalized with biological molecules to selectively detect biomarkers associated with glioblastoma. Electrochemical biosensors based on 2-D nanomaterials work by detecting changes in the electrical properties of the material in response to the presence of a target biomarker. This chapter highlights recent advances in the development of 2-D nanomaterial-based electrochemical biosensors for the diagnosis of glioblastoma. These biosensors have the potential to revolutionize the way glioblastoma is diagnosed and treated and to significantly improve patient outcomes. The chapter also discusses the challenges and future directions of this field, including the need for further optimization and validation of these biosensors for clinical use.

Keywords: 2D material, Biosensor, Diagnosis, Glioblastoma, Nanomaterials.

INTRODUCTION

Glioblastoma is an exceptionally aggressive and malignant brain cancer, often associated with poor prognosis and high mortality rates. Timely and accurate diagnosis is essential for initiating effective treatment and improving patient outcomes. However, existing diagnostic methods for glioblastoma, such as imaging and biopsy, are often invasive, costly, and time-intensive, which can limit their practical application in clinical settings. Consequently, there has been a growing interest in developing electrochemical biosensors based on two-dimensional (2-D) nanomaterials for glioblastoma diagnosis. These biosensors provide several advantages over conventional diagnostic techniques, including high sensitivity, specificity, and accuracy. Furthermore, they enable non-invasive and cost-effective biomarker detection, offering an appealing alternative to current methods.

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

Two-dimensional nanomaterials—such as graphene, transition metal dichalcogenides (TMDs), and black phosphorus—possess unique electronic, optical, and mechanical properties that make them ideal for biosensor applications. These materials can be easily functionalized with biological molecules, including antibodies and aptamers, which enables the selective detection of glioblastoma-associated biomarkers. By attaching these specific biological molecules to the nanomaterial surface, biosensors can achieve high specificity in identifying molecular targets associated with glioblastoma, such as proteins, nucleic acids, or other biomarkers present in bodily fluids.

Electrochemical biosensors based on 2-D nanomaterials operate by detecting changes in the electrical properties of the material upon interaction with a target biomarker. This detection can occur through various mechanisms, including electrochemical impedance spectroscopy, cyclic voltammetry, and amperometry. These techniques enable sensitive measurement of biomarker presence by monitoring alterations in the current, resistance, or potential of the biosensor surface in response to the biomarker's binding. Although research in this field is still in its early stages, significant progress has been made. For example, graphene-based biosensors have demonstrated the capability to detect glioblastoma-specific biomarkers in blood and cerebrospinal fluid samples with impressive sensitivity and specificity, highlighting their potential for practical clinical applications.

The development of electrochemical biosensors using 2-D nanomaterials shows immense potential for transforming glioblastoma diagnostics. These biosensors could enable earlier and more accurate detection of glioblastoma, which is crucial for effective intervention and improved patient prognosis. As research advances, these innovative diagnostic tools have the potential to revolutionize glioblastoma diagnosis and treatment approaches, ultimately contributing to better patient outcomes and reduced healthcare costs [1].

Definition of 2-D Nanomaterials

Two-dimensional (2-D) nanomaterials are an innovative class of materials characterized by their extremely thin structure—just a few nanometers thick—yet capable of covering extensive areas in two dimensions. Their unique structural form imparts exceptional electronic, optical, and mechanical properties, making them highly versatile and attractive for numerous applications, including biosensing, electronics, and energy storage. Notable examples of 2-D nanomaterials include graphene, transition metal dichalcogenides (TMDs), and black phosphorus. These materials exhibit a high surface area-to-volume ratio, rendering them highly responsive to environmental changes. Additionally, their

electronic properties, such as high electron mobility and tunable band gaps, make them ideal candidates for electronic and optoelectronic devices [2].

Beyond their impressive electronic and optical characteristics, 2-D nanomaterials are also flexible and mechanically robust, lending themselves well to applications in flexible electronics and devices where mechanical flexibility is essential. Another advantageous feature of 2-D nanomaterials is their capacity for functionalization with biological molecules like antibodies or aptamers. This functionalization enables the selective detection of biomarkers associated with various diseases, including cancer, enhancing their utility in biosensing applications [3].

Overall, the distinctive properties of 2-D nanomaterials position them as valuable assets across diverse fields such as biosensing, electronics, and energy storage. As research in this area progresses, the potential applications of 2-D nanomaterials are anticipated to expand, opening new possibilities and innovations for these materials in technology and healthcare [4].

2-D Nanomaterials-based Electrochemical Biosensors

Two-dimensional (2-D) nanomaterials-based electrochemical biosensors represent a cutting-edge approach to disease detection and diagnosis, with promising applications in identifying cancers and other serious conditions. These biosensors operate by detecting shifts in the electrical properties of 2-D nanomaterials in response to a specific target biomarker. Various electrochemical techniques can facilitate this detection, including electrochemical impedance spectroscopy, cyclic voltammetry, and amperometry. Utilizing 2-D nanomaterials in biosensors offers several advantages over traditional diagnostic methods. Due to their high surface area-to-volume ratio, these materials are exceptionally sensitive to environmental changes. Additionally, their unique electronic properties, such as high electron mobility and tunable band gaps, make them highly suitable for use in electronic and optoelectronic devices.

A key benefit of 2-D nanomaterials is their ease of functionalization with biological molecules, like antibodies or aptamers, allowing for selective detection of disease-associated biomarkers. This functionalization enables highly specific and sensitive detection, even at extremely low biomarker concentrations, enhancing the precision and reliability of disease diagnosis. Specifically, in the diagnosis of glioblastoma, electrochemical biosensors based on 2-D nanomaterials offer a non-invasive, cost-effective approach for early and accurate detection. These biosensors are capable of identifying glioblastoma-specific biomarkers in blood and cerebrospinal fluid samples with high sensitivity and specificity, which could facilitate earlier diagnosis and ultimately improve patient outcomes.

CHAPTER 6

Gold Nanoparticles and Cold Plasma for GBM Therapy

Abstract: Glioblastoma (GBM) is a highly aggressive and malignant form of brain cancer that is difficult to treat due to the blood-brain barrier (BBB) and drug resistance. Gold nanoparticles (AuNPs) and cold plasma have emerged as promising approaches for GBM therapy due to their unique physical and chemical properties. AuNPs can be engineered to selectively target cancer cells and deliver therapeutic agents, while cold plasma can induce apoptosis and inhibit tumor growth. This book chapter reviews the recent advances in the use of AuNPs and cold plasma for GBM therapy. The chapter discusses the mechanisms of action of AuNPs and cold plasma, as well as the challenges and opportunities for their clinical translation. The chapter also highlights the potential of combining AuNPs and cold plasma for synergistic GBM therapy. Overall, this book chapter provides a comprehensive overview of the current state of the art in the use of AuNPs and cold plasma for GBM therapy.

Keywords: Cold plasma, Drug resistance, Gold nanoparticles.

INTRODUCTION

Glioblastoma (GBM) represents one of the most aggressive and malignant types of brain cancer, notorious for its resistance to treatment and challenging prognosis. This resistance is primarily due to the presence of the blood-brain barrier (BBB), which restricts the passage of many therapeutic agents, and the cancer cells' inherent ability to develop drug resistance. Although conventional treatment modalities, including surgery, radiation, and chemotherapy, have been advanced and widely utilized, the survival outcomes for GBM patients remain discouraging. Given these limitations, there is an urgent need for innovative and more effective therapeutic strategies that can overcome these obstacles. Among the promising approaches that have emerged for GBM therapy are gold nanoparticles (AuNPs) and cold plasma technology, each offering distinct physical and chemical properties that can be harnessed for targeted cancer treatment.

Gold nanoparticles (AuNPs) have attracted significant attention in cancer therapy due to their ability to be engineered for targeted delivery. AuNPs can be func-

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

tionalized to selectively recognize and bind to cancer cells, allowing them to deliver therapeutic agents directly to the tumor site, thereby minimizing damage to surrounding healthy tissue. This targeted approach enhances the efficacy of the treatment while reducing systemic toxicity. On the other hand, cold plasma, a partially ionized gas composed of ions, radicals, and electrons at room temperature, has shown the potential to induce apoptosis, or programmed cell death, in cancer cells. Additionally, cold plasma possesses tumor-inhibitory effects, making it a valuable tool in disrupting GBM cell growth and proliferation. The combination of AuNPs and cold plasma may yield a synergistic effect, amplifying the therapeutic benefits against GBM by simultaneously targeting cancer cells through multiple mechanisms [1].

This chapter aims to provide an exhaustive analysis of the latest advancements in employing AuNPs and cold plasma for GBM therapy. The discussion will begin with an introduction to GBM, detailing its biological characteristics and the significant challenges it poses in the treatment. This section will set the context for understanding why new therapies are critical for improving patient outcomes. Following this, the chapter will delve into the unique properties of AuNPs and cold plasma that make them suitable for GBM therapy. This will include a comprehensive examination of the mechanisms through which AuNPs can selectively target cancer cells and the ways cold plasma can initiate cancer cell apoptosis and inhibit tumor growth.

Subsequent sections will review recent *in vitro* (laboratory-based) and *in vivo* (animal model-based) studies that demonstrate the efficacy of AuNPs and cold plasma in treating GBM. These studies highlight the therapeutic potential of each approach individually and explore how their combined use might enhance treatment outcomes. Specifically, the review will examine the synergistic interactions between AuNPs and cold plasma, as well as the underlying mechanisms that contribute to their enhanced effectiveness when used in conjunction. The chapter will then shift focus to the challenges and opportunities associated with the clinical translation of these technologies. This includes addressing regulatory hurdles, safety concerns, and the technical requirements necessary to bring AuNPs and cold plasma from experimental research into practical, patient-oriented therapies [2 - 4].

Overall, this book chapter seeks to encapsulate the current state of research and development in the application of AuNPs and cold plasma for GBM therapy. It will serve as a valuable resource for researchers, clinicians, and students who are engaged in cancer research and are interested in exploring innovative therapeutic modalities for GBM. By providing an in-depth overview of the potential of AuNPs and cold plasma, along with the challenges in their clinical adoption, this

chapter aims to contribute to the growing body of knowledge in cancer treatment and inspire further research into novel, multi-faceted therapeutic approaches that could one day improve outcomes for patients suffering from this devastating disease.

Properties and Applications of Gold Nanoparticles (AuNPs) and Cold Plasma for GBM Therapy

Gold nanoparticles (AuNPs) and cold plasma possess unique physical and chemical characteristics that render them highly promising in the treatment of glioblastoma (GBM), an exceptionally aggressive and challenging brain cancer. The therapeutic potential of AuNPs and cold plasma lies in their complementary mechanisms of action, which could provide a synergistic approach to GBM therapy. Specifically, AuNPs can be precisely engineered to selectively target cancer cells, serving as vehicles for delivering therapeutic agents directly to the tumor site. Meanwhile, cold plasma, due to its ability to induce apoptosis and inhibit tumor growth, introduces another layer of efficacy by directly attacking cancer cells and creating an environment unfavorable to tumor survival and proliferation. Together, these modalities hold the potential to enhance GBM treatment effectiveness when used in combination.

Several properties make AuNPs particularly attractive for GBM therapy. AuNPs have a high surface area-to-volume ratio, a characteristic that allows for efficient loading and delivery of therapeutic agents. Additionally, AuNPs can be functionalized with various targeting moieties, such as antibodies or peptides, to improve selectivity for cancer cells. This functionalization enables AuNPs to bind specifically to GBM cells, facilitating the targeted delivery of drugs or other therapeutic agents, thereby minimizing off-target effects. Beyond their role in therapy, AuNPs also offer significant potential in imaging and diagnostic applications due to their unique optical and magnetic properties, which enable enhanced visualization of tumor sites during imaging procedures.

Cold plasma, also known as non-thermal atmospheric pressure plasma, is a partially ionized gas comprising a mix of reactive oxygen and nitrogen species. It has shown remarkable potential in cancer treatment due to its ability to induce apoptosis and inhibit tumor growth through mechanisms such as DNA damage, oxidative stress, and alterations in cellular signaling pathways. Cold plasma not only directly impacts cancer cells by triggering cell death but also enhances the efficacy of existing treatments like chemotherapy and radiation therapy. By sensitizing cancer cells to these conventional treatments, cold plasma can potentially lower the required doses, thereby reducing systemic toxicity and enhancing the overall treatment response.

CHAPTER 7

Combinational Nanomedicine Approaches in Brain Cancer

Abstract: Brain cancer is a complex and challenging disease to treat due to its location and the blood-brain barrier (BBB), which makes it difficult for therapeutic agents to reach the tumor site. Resonance imaging and therapy have emerged as promising approaches for the diagnosis and treatment of brain cancer. Resonance imaging techniques, such as magnetic resonance imaging (MRI), can be used to detect brain tumors and monitor their growth. Resonance therapy, such as chemotherapy, radiation therapy, and immunotherapy, can be used to destroy cancer cells. Combinational nanomedicine approaches that combine resonance imaging and therapy can be used to guide the delivery of therapeutic agents to brain tumors. Nanoparticles can be used as contrast agents and drug delivery vehicles, which can be functionalized with targeting moieties to selectively target brain tumor cells. Resonance imaging can then be used to monitor the accumulation and distribution of these nanoparticles in the brain, as well as the response of brain tumors to therapy. Therapeutic agents can also be delivered to brain tumors using resonance therapy. Chemotherapy and radiation therapy can be combined with immunotherapy to enhance the efficacy of treatment. The combination of resonance imaging and therapy as a combinational nanomedicine approach offers several advantages for the diagnosis and treatment of brain cancer. Resonance imaging provides high-resolution images of the brain, allowing for the precise targeting of brain tumors. Resonance therapy offers a non-invasive and targeted approach to the treatment of brain tumors. Combinational nanomedicine approaches can also enhance the efficacy and specificity of therapeutic agents for brain cancer. Overall, the combination of resonance imaging and therapy as a combinational nanomedicine approach offers a promising strategy for the diagnosis and treatment of brain cancer. Further research is needed to optimize and personalize this approach for each patient's tumor, as well as to evaluate its safety and efficacy in clinical trials.

Keywords: Nanomedicine, Resonance, Radiation therapy.

INTRODUCTION

Brain cancer presents a significant therapeutic challenge due to its complex and heterogeneous nature, as well as its difficult-to-access location and the presence of the blood-brain barrier (BBB), which limits the efficacy of many therapeutic agents. Additionally, cancer cells in the brain often develop resistance to conventional treatments, complicating efforts to achieve effective outcomes.

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

Recently, resonance imaging and therapy have emerged as promising approaches to enhance both the diagnosis and treatment of brain cancer. Resonance imaging techniques, particularly magnetic resonance imaging (MRI), are widely used for detecting brain tumors and monitoring their growth over time. Resonance therapy, which includes chemotherapy, radiation therapy, and immunotherapy, aims to eliminate cancer cells while sparing healthy brain tissue.

In combinational nanomedicine approaches, resonance imaging serves a dual purpose: it guides the delivery of therapeutic agents to brain tumors and monitors the treatment response. For example, nanoparticles can act as both contrast agents for imaging and vehicles for drug delivery. These nanoparticles can be functionalized with targeting moieties, such as antibodies or peptides, to selectively bind to brain tumor cells. Through this targeting mechanism, resonance imaging can track the accumulation and distribution of nanoparticles in the brain, providing real-time feedback on the delivery process and therapeutic response of brain tumors [1]. By enhancing the precision and effectiveness of treatment, this approach holds promise for improving outcomes in brain cancer therapy.

Furthermore, therapeutic agents can be administered directly to brain tumors using resonance-based techniques. Chemotherapy and radiation therapy, when used in combination with immunotherapy, can enhance the overall effectiveness of treatment by leveraging multiple mechanisms to attack cancer cells. The integration of resonance therapy with resonance imaging enables clinicians to precisely target brain tumors while simultaneously monitoring the delivery and therapeutic efficacy of these agents in real time. This combinational nanomedicine approach offers a range of benefits, as it combines high-resolution imaging with targeted treatment, thereby optimizing the precision of brain cancer therapies [2, 3].

In summary, the combination of resonance imaging and therapy within the framework of combinational nanomedicine provides a promising strategy for the diagnosis and treatment of brain cancer. Resonance imaging offers detailed, high-resolution images that allow for the accurate localization of brain tumors, while resonance therapy provides a targeted, non-invasive approach to treating brain cancer. Further research is essential to optimize and personalize this approach to each patient's unique tumor profile, as well as to validate its safety and effectiveness in clinical trials. The continued development of this combinational nanomedicine strategy holds the potential to transform the treatment landscape for brain cancer, offering hope for more effective, personalized therapeutic options in the future.

Magnetic Resonance Imaging & Therapy

Magnetic resonance imaging (MRI) and associated therapeutic techniques have shown potential as a combinational nanomedicine approach for the diagnosis and treatment of brain cancer. MRI is a non-invasive imaging modality that uses magnetic fields and radiofrequency waves to generate detailed images of brain tissue. In brain cancer diagnosis and treatment, MRI serves as a critical tool for detecting brain tumors, monitoring their growth, and evaluating their response to therapies. Within the framework of combinational nanomedicine, MRI can guide the targeted delivery of therapeutic agents to brain tumors, thus enhancing the precision and efficacy of treatment strategies.

One example of this approach involves using superparamagnetic iron oxide nanoparticles (SPIONs), which serve dual purposes as MRI contrast agents and drug delivery vehicles. SPIONs can be functionalized with specific targeting moieties, such as antibodies or peptides, enabling them to selectively bind to brain tumor cells. Once targeted, MRI can track the accumulation and spatial distribution of SPIONs within the brain, offering real-time monitoring of nanoparticle delivery and providing critical insights into the tumor's response to therapy [4 - 7].

Additionally, therapeutic agents can be delivered to brain tumors using MRI-guided focused ultrasound (FUS). Focused ultrasound employs high-frequency sound waves to heat and ablate cancerous cells, selectively destroying tumor cells while sparing the surrounding healthy tissue. When combined with MRI, FUS can precisely target brain tumors, allowing clinicians to monitor both the delivery and therapeutic response of treatment agents in real-time. This integration of MRI and FUS enhances the precision of treatment and optimizes the effectiveness of therapeutic interventions for brain cancer.

The combination of MRI with therapeutic modalities, such as FUS and nanomedicine, offers several advantages for brain cancer diagnosis and treatment. MRI provides high-resolution images of brain structures, enabling precise localization and targeting of brain tumors. It also facilitates continuous monitoring of the tumor's response to therapy, allowing for individualized and optimized treatment regimens tailored to each patient's specific needs. Therapeutic agents delivered *via* MRI-guided FUS present a non-invasive, targeted approach for treating brain tumors, which may reduce collateral damage to healthy brain tissue. The use of SPIONs as drug delivery vehicles further enhances the specificity and efficacy of therapeutic agents, ensuring that treatments are more concentrated within tumor tissues [8, 9].

CHAPTER 8

Oral Delivery Nanostructures for Brain Cancer Treatment

Abstract: Brain cancer is a highly aggressive and malignant disease that is difficult to treat due to the blood-brain barrier (BBB), which limits the delivery of therapeutic agents to the tumor site. Oral delivery nanostructures offer a promising approach for the treatment of brain cancer. Nanostructures such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, and dendrimers can be used as drug-delivery vehicles, allowing for the targeted and controlled release of therapeutic agents. However, there are several challenges associated with the oral delivery of nanostructures to the brain, including the BBB. Strategies for overcoming the BBB, such as functionalization with targeting moieties and the use of BBB-disrupting agents, have been developed to improve drug delivery to the brain. There is growing research on the use of oral delivery nanostructures for brain cancer treatment. Liposomes, solid lipid nanoparticles, and polymeric nanoparticles have been investigated for their ability to deliver therapeutic agents to brain tumors. These nanostructures offer advantages such as improved drug stability, prolonged circulation time, and targeted drug delivery to the brain. The development of strategies for overcoming the BBB and the use of targeted drug delivery systems can improve the efficacy and safety of brain cancer treatment.

Keywords: Liposomes, Nanomaterials, Polymeric nanostructures.

INTRODUCTION

Brain cancer remains one of the most formidable challenges in oncology due to its aggressive nature, complex tumor microenvironment, and location within the central nervous system. Compounding the challenge is the presence of the blood-brain barrier (BBB), a selective and protective layer that restricts the delivery of therapeutic agents to brain tissues, limiting the effectiveness of traditional treatments. Existing treatment options for brain cancer, including surgery, chemotherapy, and radiation therapy, are often associated with limited efficacy, as well as significant side effects that can affect patients' quality of life. These limitations underscore the pressing need for the development of new, more effective treatments that can overcome these barriers and provide targeted therapy for brain tumors [1].

Nura Brimo, Emir Baki Denkbas & Beyzanur Cakar

In recent years, oral delivery nanostructures have emerged as a promising approach to address some of these challenges in brain cancer treatment. These nanostructures, which include liposomes, solid lipid nanoparticles, polymeric nanoparticles, and dendrimers, function as sophisticated drug delivery vehicles. They are capable of carrying therapeutic agents directly to tumor sites in a controlled manner, thus offering both targeted and sustained release of drugs. The oral administration of these nanostructures presents an attractive alternative to invasive delivery methods, potentially enhancing patient compliance and improving the bioavailability of therapeutics by providing a non-invasive route [2].

Despite the advantages of nanostructured delivery systems, several obstacles remain, particularly regarding the efficient transport of therapeutic agents across the BBB. The BBB is a highly selective membrane that prevents most drugs, especially large or hydrophilic molecules, from entering the brain. To circumvent this, researchers have developed strategies to functionalize nanostructures with targeting moieties, such as antibodies or peptides, which can recognize and bind to specific receptors on the BBB, facilitating translocation into the brain. Additionally, BBB-disrupting agents have been employed to temporarily open the barrier, allowing for greater permeability and enhancing drug delivery. These strategies are critical for improving the effectiveness of nanostructure-based brain cancer therapies and highlight the importance of designing delivery systems that can bypass the natural defense mechanisms of the brain [3, 4].

There is a growing body of research dedicated to exploring the potential of oral delivery nanostructures for brain cancer therapy. Liposomes, solid lipid nanoparticles, and polymeric nanoparticles, in particular, have garnered attention for their capacity to encapsulate and transport therapeutic agents across the BBB to target brain tumors. These nanostructures offer multiple advantages, including enhanced stability of encapsulated drugs, extended circulation time within the body, and the ability to target specific brain regions, thereby minimizing off-target effects. Additionally, some nanostructures are designed to release their payload in a controlled manner, reducing the frequency of dosing and potentially lessening the adverse effects associated with traditional cancer treatments [5, 6].

In conclusion, oral delivery nanostructures represent a promising frontier in brain cancer therapy, offering innovative solutions to overcome the limitations posed by the BBB and traditional drug delivery systems. By enhancing targeted delivery and reducing systemic toxicity, these nanostructures could improve both the safety and efficacy of brain cancer treatments. However, further research is essential to refine the design and functionality of these delivery systems to ensure optimal bioavailability, stability, and targeting accuracy. Clinical trials are crucial

to assessing the safety and therapeutic potential of these nanostructures in a real-world setting, and their outcomes will play a pivotal role in determining the future landscape of brain cancer treatment [7].

Oral Delivery Nanostructures

Oral delivery nanostructures represent a transformative approach to the treatment of brain cancer, offering the potential to enhance the delivery, stability, and efficacy of therapeutic agents targeting brain tumors. These nanostructures are meticulously engineered to protect drugs from degradation in the gastrointestinal tract, optimize their bioavailability, and enable precise targeting of tumor cells in the brain. The functionalization of these nanostructures with specific targeting moieties, such as antibodies or peptides, allows for the selective recognition of brain tumor cells, while their size and surface properties are finely tuned to ensure prolonged stability and circulation time in the bloodstream. These factors collectively contribute to improving the pharmacokinetics and biodistribution of therapeutic agents within the body, which is particularly critical in the context of brain cancer treatment.

A variety of nanostructures have been explored for their capacity to deliver therapeutic agents directly to brain tumors. Liposomes, solid lipid nanoparticles, polymeric nanoparticles, and dendrimers are among the most studied. Liposomes are spherical vesicles with a lipid bilayer structure capable of encapsulating both hydrophilic and hydrophobic drugs, making them highly versatile for drug delivery. Their composition is particularly advantageous, as the lipid bilayer can merge with cell membranes, facilitating the release of the encapsulated drug directly into the brain tumor cells. Solid lipid nanoparticles, on the other hand, are made from solid lipids stabilized by surfactants. These nanoparticles provide a matrix structure suitable for encapsulating hydrophobic drugs, offering enhanced stability and controlled release properties that are beneficial for sustained drug delivery to the brain. Polymeric nanoparticles, constructed from biodegradable polymers, can accommodate both hydrophilic and hydrophobic drugs, providing flexibility in drug formulation. Finally, dendrimers are highly branched, tree-like polymers that can be functionalized extensively with various targeting agents, enabling multivalent interactions with brain tumor cells. Their unique architecture allows for the encapsulation or attachment of therapeutic agents in a controlled manner, enhancing targeted delivery and reducing potential side effects [1, 8].

One of the greatest challenges in treating brain cancer is overcoming the blood-brain barrier (BBB), a highly selective barrier that restricts the entry of most therapeutic agents into the brain. The BBB is composed of endothelial cells connected by tight junctions, astrocytes, and pericytes, forming a regulatory

SUBJECT INDEX

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

V

Nura Brimo

Nura Brimo is a Ph.D. candidate in Mechanical Engineering and Materials Science at Duke University, with certifications in Nanoscience and Innovation & Entrepreneurship. She holds an MSc in Entrepreneurship from Bartın University and an MPhil in Biomedical Engineering from Başkent University, where she graduated in the top 1% of her class.

With 12 publications, 99 citations, and an H-index of 4, her research spans DNA-nanoparticle interactions, nanofiber drug delivery systems, and regenerative therapies, leading to patents and book chapters with Springer and Bentham.

Her work has earned multiple accolades, including Gold Medals for Best Invention at ARCA and ISIF and a Silver Medal at ISIF'23. She has also led humanitarian projects, securing international funding for innovations like drone-based UXO detection and sterile operating room kits.

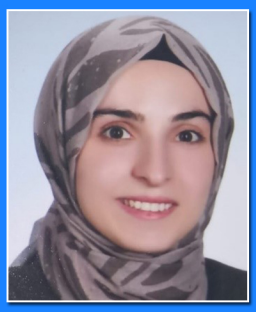
Emir Baki Denkbas

Prof. Denkbaş completed his doctoral studies at Hacettepe University, Bioengineering Division, and has over 29 years of academic experience. He is currently a full-time faculty member at Başkent University, Department of Biomedical Engineering.

He has received prestigious awards, including the TÜBİTAK Incentive Award and Hacettepe University Science Incentive Award. His research focuses on drug carrier systems, targeted therapies, tissue engineering, and biosensors. As an academic supervisor, he has guided 19 Ph.D. and 45 M.Sc. theses.

Prof. Denkbaş has published 143 SCI-indexed articles with 3,791 citations (h-index: 34) and has presented his work at over 170 national and international meetings, including 50 invited talks. He serves on the editorial boards of leading journals and has contributed to 20 book chapters.

He has participated in 30+ research projects funded by organizations like TÜBİTAK and the EU and holds one international and one national patent. Prof. Denkbaş is a founding member of the Controlled Release Systems Association of Turkey.



Beyzanur Cakar

Beyzanur Çakar is a Biomedical Engineer who completed a double major in Molecular Biology and Genetics. As part of her master's thesis, she worked on gene silencing technologies using nanoparticle-based approaches in breast cancer. Her thesis was funded by TÜBİTAK, and she received the second-best oral presentation award at the BIO Turkey International Biotechnology Congress for her paper published as part of the thesis. She has conducted research on the production, coating, and modification of various nanoparticle formulations.

Çakar won first place in a national competition for her project in the field of Health and Medical Technologies, Biomaterials, Pharmaceuticals, and Cosmetics. She served as the principal investigator in an industry-oriented R&D project funded by TÜBİTAK. Later, she worked as a research assistant at a university. She is currently pursuing a Ph.D. in Biomedical Engineering and working at TÜBİTAK.