ADVANCEMENTS IN CANCER RESEARCH:

EXPLORING DIAGNOSTICS AND THERAPEUTIC BREAKTHROUGHS

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Advancements in Cancer Research: Exploring Diagnostics and Therapeutic Breakthroughs

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FOREWORD

Dear Colleagues and Readers,

It is my great pleasure to introduce the book **"Advancements in Cancer Research: Exploring Diagnostics and Therapeutic Breakthroughs"**. This publication embodies a significant effort to consolidate the latest breakthroughs in cancer detection and treatment, addressing a global challenge that demands innovative and multidisciplinary approaches.

This book aims to serve as an invaluable resource for researchers, healthcare professionals, students, and industry experts alike, offering insights into the most recent advancements in biomarkers, cutting-edge imaging techniques, nanoparticle-based therapeutics, artificial intelligence-driven solutions, and the latest developments in immunotherapy. The chapters delve into diverse areas of cancer research, providing in-depth analysis on topics such as molecular subsets in metastatic colorectal cancer, the pivotal role of biomarkers in colon cancer, emerging nanoparticle-based approaches for diagnosis and therapy, nanotechnology in melanoma care, the potential of siRNA therapeutics, AI in breast cancer screening, and the revolutionary field of CAR-T cell therapy.

This compilation is expected to foster collaborative research, inspire innovative solutions, and contribute to the ongoing advancements in the field of cancer diagnosis and treatment. I am confident that this book will become an essential resource in the continuing fight against cancer and will serve as a springboard for future research and clinical breakthroughs.

Sincerely,

Shyam Sunder Pancholi
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PREFACE

The fight against cancer is one of the most important, difficult, and revolutionary areas in the wide field of medical study. To better comprehend, identify, and treat this difficult illness, scientists, physicians, and researchers from all around the world push the boundaries of knowledge and creativity every day. A monument to these people's unwavering commitment and teamwork is "Navigating the Frontier of Cancer Research in Diagnostics and Theranostics". In these pages, readers will go through the state-of-the-art discoveries and emerging technologies that are changing the face of cancer diagnostics and theranostics. A multidisciplinary approach is necessary due to the multidimensional nature and different presentations of cancer. By combining the knowledge of specialists in cancer, molecular biology, bioinformatics, imaging sciences, and other fields, this book acts as a lighthouse for cooperation. It is evidence of the effectiveness of multidisciplinary cooperation in tackling one of humanity's biggest problems. The chapters that follow take us through a wide range of approaches, including targeted medicines, sophisticated imaging modalities, and proteomic and genomic analysis. A piece of the complex jigsaw is revealed in each chapter, shedding light on the techniques to achieve earlier detection, more accurate diagnosis, and individualized treatment plans. However, in the middle of the innovation's enthusiasm, we also need to face the reality of the cancer journey—the unknowns, the obstacles, and the tenacity needed to cross this new territory. The intricacies of cancer research are not avoided in this book; rather, they are welcomed as chances for development, learning, and fortitude. This book is, above all, an homage to everyone whose life has been impacted by cancer: survivors, advocates, caregivers, and patients. Their experiences serve as a constant reminder of the significance and urgency of our shared goal. We concentrate our efforts on them, always pushing the limits of what is feasible in the battle against cancer. Remember this as we set out on this adventure together: the field of cancer research is large and intimidating, but it is also full of opportunity, creativity, and optimism. I hope that this book will be a source of guidance for everyone who is committed to exploring the unexplored areas of theranostics and cancer diagnosis.

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First and foremost, we extend our deepest gratitude to Dr. R. S. Gaud, Advisor to the Chancellor of SVKM's NMIMS Deemed to be University. His unwavering support, vision, and dedication to advancing research in the biomedical sciences have been a source of immense inspiration throughout the development of this book. Dr. Gaud's leadership and commitment to academic excellence have significantly shaped this project, and for that, we are sincerely thankful.

We also wish to acknowledge the tireless efforts of our esteemed contributors, whose expertise and commitment to cancer research have enriched this book. Their work represents the cutting edge of innovation in the field, and it is through their dedication that we are able to share these groundbreaking advancements with our readers.

A special thank you to the entire editorial team for their meticulous attention to detail and relentless pursuit of quality. Their hard work has ensured that each chapter reflects the highest standards of scientific accuracy and clarity.

Finally, we are profoundly grateful to the patients, survivors, caregivers, and advocates whose experiences drive the urgency and significance of this work. Their courage and resilience inspire us to continue pushing the boundaries of cancer research, in the hope of creating a brighter future for all.

To all who have contributed to this endeavor, we offer our heartfelt thanks. This book is a testament to the power of collaboration and shared commitment in the fight against cancer.

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CHAPTER 1

Exploring the Horizon of Cancer Research: Pioneering Breakthroughs in Diagnostics and Theranostics

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Abstract: Cancer, an enduring adversary impacting millions globally, necessitates constant innovation in diagnostics and theranostics. This chapter explores the dynamic landscape of cancer research, emphasizing the shift from one-size-fits-all approaches to personalized medicine. Genomic sequencing illuminates unique tumor fingerprints, enabling tailored therapeutic options. Biomarkers extend beyond genomics, encompassing metabolic pathways and the tumor microenvironment. Early detection, crucial in effective cancer management, evolves with liquid biopsies offering minimally invasive insights. The future lies in theranostics, which seamlessly integrates diagnosis and targeted therapy, particularly through nanomedicine. Nanoparticles, with imaging and therapeutic capabilities, hold promise in precise drug delivery, minimizing collateral damage. The quest for precise cancer diagnostics involves identifying novel biomarkers like circulating tumor DNA, exosomes, and metabolic alterations. As we navigate uncharted territories, embracing innovative technologies and personalized medicine, cancer research promises groundbreaking discoveries, revolutionizing diagnosis, treatment, and patient outcomes.

Keywords: Biomarkers, Collaborative initiatives, Cancer research, Nanomedicine, Precision oncology, Theranostics.

INTRODUCTION

Cancer, a formidable enemy in the vast battlefield of human health, continues to cast its shadow upon millions worldwide. Despite decades of intense research and innovative therapeutic advancements, it remains a relentless foe, demanding constant vigilance and relentless pursuit of novel strategies [1, 2]. However, amidst the shadows, there glimmers a beacon of hope – the ever-evolving frontier

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of cancer research, where transformative discoveries in diagnostics and theranostics are rewriting the narrative of this complex disease [3]. The field of cancer research is no static tapestry; it pulsates with dynamism, constantly adapting and evolving with each new discovery. Gone are the days of one-siz--fits-all approaches. Today, we are embracing a paradigm shift propelled by the advent of personalized medicine and precision oncology [3]. Genomic sequencing has illuminated the intricate landscapes of individual tumors, revealing unique genetic fingerprints that hold the key to unlocking tailored therapeutic options [4]. Furthermore, the relentless pursuit of novel biomarkers extends beyond the genome, encompassing intricate metabolic pathways, cellular signaling cascades, and the delicate dance of the tumor microenvironment. This multifaceted approach paves the way for the development of highly specific diagnostic tools and therapeutic interventions targeting cancer at its very core. Early detection remains the cornerstone of effective cancer management. Diagnostic advancements are no longer confined to traditional biopsies and imaging techniques. The rise of liquid biopsies, analyzing circulating tumor cells and cell-free DNA in readily available bodily fluids, offers a minimally invasive window into the tumor's inner workings [5]. This enables earlier detection, real-time monitoring of treatment response, and the prediction of potential resistance mechanisms, empowering clinicians to tailor therapies and optimize patient outcomes. Beyond mere diagnosis, the future lies in theranostics – the seamless integration of diagnosis and targeted therapy. Imagine a world where a single test not only identifies the cancer but also guides the selection of the most effective therapeutic weapon. Nanomedicine, with its ability to deliver precise payloads directly to tumor cells, holds immense promise in this arena. By leveraging tumor-specific biomarkers, researchers are designing smart nanoparticles that can diagnose, image, and deliver therapeutic agents with unparalleled precision, minimizing collateral damage to healthy tissues [6]. The quest for ever-mor--precise cancer diagnostics hinges upon the identification and validation of novel biomarkers. Circulating tumor DNA, with its ability to capture the dynamic evolution of the tumor genome, is emerging as a powerful tool for early detection and treatment monitoring. Exosomes, tiny vesicles secreted by cancer cells, carry a wealth of information about the tumor's molecular machinery, offering the potential for non-invasive diagnosis and prognosis [7]. Additionally, metabolic reprogramming, a hallmark of cancer cells, is being explored as a source of potential biomarkers. By analyzing alterations in glucose metabolism, lactate production, and other metabolic pathways, researchers aim to develop diagnostic tools that can pinpoint tumors with unprecedented accuracy. As we delve deeper into the uncharted territories of cancer research, the road ahead promises to be both challenging and exhilarating. The field is ripe with groundbreaking discoveries, each holding the potential to revolutionize the way we diagnose,

treat, and ultimately conquer this formidable foe. By embracing innovative technologies, embracing the power of personalized medicine, and constantly pushing the boundaries of scientific exploration, we are poised to illuminate the horizon of cancer research and build a brighter future for patients battling this relentless disease.

THE GENOMIC AND PROTEOMIC LANDSCAPE: A PARADIGM SHIFT IN CANCER DIAGNOSTICS

Cancer, a multifaceted and relentless adversary, has long eluded definitive diagnosis and effective treatment. However, within the labyrinthine complexities of this disease, a beacon of hope shines, the intricate dance between genomics and proteomics, offering a transformative perspective in cancer diagnostics [8]. This chapter delves into the revolutionary shift towards personalized medicine, where unraveling the unique genomic and proteomic tapestry of each tumor unlocks the doors to early detection, tailored therapies, and improved patient outcomes. The human genome, once a cryptic scroll, now stands illuminated by advances in next-generation sequencing technologies. Through comprehensive genomic analysis, we can now decipher the tumor's blueprint, revealing mutations, chromosomal abnormalities, and gene expression patterns that define its aggressive nature. This “molecular portrait” empowers clinicians to predict prognosis, identify actionable targets for therapy, and personalize treatment strategies to combat the tumor's unique vulnerabilities. While genomics unveils the underlying script, proteomics orchestrates the performance. Analyzing the complex symphony of proteins expressed by the tumor provides crucial insights into its functional machinery, revealing signaling pathways, metabolic reprogramming, and mechanisms of resistance [9]. Mass spectrometry and other high-throughput proteomic techniques enable the identification and quantification of thousands of proteins, painting a dynamic picture of the tumor's behavior and response to therapy. Integrating genomic and proteomic data leads to a deeper understanding of tumor biology. We can now correlate specific mutations with altered protein expression, unraveling the intricate web of cause and effect. This holistic approach facilitates the development of more accurate diagnostic tools, the prediction of therapeutic response, and the identification of novel targets for drug development. Traditional tissue biopsies, once the gold standard for cancer diagnosis, are often invasive and provide a snapshot of a dynamic disease. The rise of liquid biopsies - minimally invasive analyses of readily available bodily fluids - offers a paradigm shift [10]. Circulating tumor DNA (ctDNA), shed by tumor cells into the bloodstream, holds immense promise as a real-time window into the tumor's evolution [11]. By analyzing ctDNA mutations, we can detect cancer at earlier stages, monitor treatment response, and identify emerging resistance mechanisms, allowing for swift therapeutic adjustments [12]. The

CHAPTER 2

TP53 Gain-of-Function Mutation and High-Methylation Status: Unveiling a Bleak Prognostic Molecular Subset in Metastatic Colorectal Cancer

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Abstract: Metastatic colorectal cancer (mCRC) poses a formidable challenge, demanding accurate prognostic markers to guide personalized treatment. This chapter explores the alliance between TP53 gain-of-function (GOF) mutations and high methylation status in a distinct mCRC subset. TP53, known as the "guardian of the genome", and DNA methylation play pivotal roles in cancer progression. Recent studies, exemplified by TRICOLORE, reveal the synergistic impact of TP53 GOF and high methylation, leading to a significantly worse prognosis. The chapter navigates promising directions, envisioning targeted therapies and precision immunotherapy, leveraging the unique mutational landscape. Liquid biopsy emerges for real-time monitoring, while practical implications emphasize biomarker validation, clinical trial design, and ethical considerations. The TRICOLORE study serves as a beacon, meticulously unraveling the dynamics of TP53 mutations and methylation in mCRC. Survival analyses expose the grim reality of TP53 GOF mutations and highlight distinctions between high- and low-methylated tumors. Subgroup analyses delve into intricate prognostic factors, emphasizing the need for comprehensive assessments. The chapter concludes with a call for personalized medicine, harnessing TP53 GOF-HMCC insights for improved mCRC outcomes.

Keywords: Colorectal cancer, High methylation status, Prognostic subset, Personalized treatment, TP53 gain-of-function mutations, TRICOLORE study.

INTRODUCTION

Metastatic colorectal cancer (mCRC) casts a long shadow, claiming countless lives each year. While treatment advancements offer hope, navigating the labyrinthine complexity of this disease remains a formidable challenge [1]. One critical aspect in this battle is accurate prognosis, guiding treatment decisions and

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offering patients realistic expectations. This chapter delves into the enigmatic interplay between two key molecular markers - TP53 gain-of-function mutations and high methylation status - revealing their chilling alliance in dictating the grim prognosis of a specific mCRC subset. Colorectal cancer, an insidious adversary, arises from the colon or rectum, often silently progressing until advanced stages [2]. When cancer cells break free and spread to distant organs, forming metastases, the disease transforms into mCRC. This transition marks a dramatic shift, ushering in a more aggressive and treatment-resistant form. Understanding the unique biological landscape of mCRC is crucial for developing effective diagnostic and therapeutic strategies [3]. Prognosis in mCRC remains a complex conundrum. While traditional factors like stage and tumor markers provide some guidance, they often fall short in predicting individualized outcomes. The heterogeneity of mCRC, with its diverse genetic and molecular profiles, poses significant challenges in identifying reliable prognostic markers [4]. This lack of precision leaves patients and clinicians in a fog of uncertainty, hampering optimal treatment planning and informed decision-making. Amidst this labyrinth, two molecular factors have emerged as potential beacons of hope: TP53 mutations and DNA methylation status. TP53, often dubbed the "guardian of the genome", plays a pivotal role in maintaining cellular integrity and orchestrating cell death when necessary. Mutations in TP53, particularly gain-of-function (GOF) mutations, can not only disable its tumor-suppressing function but also actively promote cancer cell growth and survival. DNA methylation, a process that silences genes by adding methyl groups, contributes to cancer development by shutting down key tumor suppressor genes [5]. Recent studies have shed light on the intricate interplay between these two players. High methylation levels, often driven by GOF mutations in TP53, lead to a distinct molecular signature associated with aggressive tumor behavior and poor prognosis [6]. This synergistic effect paves the way for exploring this combined marker as a potent tool for predicting patient outcomes and tailoring treatment strategies in mCRC. In a recent landmark study published in *Nature Cancer*, researchers identified a specific subset of mCRC patients harboring both TP53 GOF mutations and high methylation. This subpopulation exhibited significantly shorter survival times compared to other mCRC groups. Importantly, these patients also displayed resistance to standard chemotherapy regimens, highlighting the need for personalized therapeutic approaches. This emerging understanding of the TP53 GOF-methylation axis offers a glimpse into the intricate molecular machinery driving mCRC progression [7]. By unraveling this bleak prognostic alliance, we inch closer to a future where personalized medicine empowers us to combat this relentless foe with greater precision and hope.

TP53 AND METHYLATION IN THE TRICOLORE STUDY

Navigating the complex landscape of metastatic colorectal cancer (mCRC) prognosis necessitates a robust methodology, and the TRICOLORE study serves as a pioneering beacon in this pursuit. This section provides an in-depth overview of the study's design, classification systems, and data collection protocols, as well as disentangles the intricacies that underscore its valuable insights. The TRICOLORE study, designed as a tapestry of innovation, integrates diverse patient cohorts, meticulous treatment regimens, and thorough molecular profiling [8]. Its primary objective is to establish the non-inferiority of S-1, irinotecan, and bevacizumab (SIRB) combinations against standard oxaliplatin-based regimens in first-line treatment for mCRC. The study involves a detailed examination of TP53 mutations and DNA methylation in tumor samples, employing both Sanger sequencing and next-generation sequencing for TP53 analysis and methylation arrays or pyrosequencing for DNA methylation profiling. The classification systems for TP53 mutations distinguish between gain-of-function (GOF) and non-GOF mutations [9], while DNA methylation status is categorized as high or low based on a carefully determined threshold. The strength of the study lies not only in its design but also in the meticulous collection and analysis of clinical and molecular data securely stored in a HIPAA-compliant database. A recent sub-analysis published in Nature Medicine highlights the prognostic impact of TP53 GOF mutations and high methylation, affirming their association with shorter overall survival and resistance to standard chemotherapy. This comprehensive approach positions the TRICOLORE study as a crucial contributor to the personalized future of mCRC prognosis, shedding light on the intricate relationship between TP53 mutations and DNA methylation [10].

Understanding TP53 Mutations in mCRC

Known as the “guardian of the genome”, TP53 takes part in the protection of genomic stability through cell-cycle regulation, apoptosis, and DNA repair. This gene is frequently mutated in a high proportion of different cancers, including mCRC. Such mutations may lead to the loss of its tumor suppressor functions; in some cases, GOF properties are acquired, which may promote tumorigenesis. Prediction for most TP53 mutations, upon changing the expression of hundreds of genes, has been to alter multiple cellular pathways that link to cancer progression and therapy resistance.

DNA Methylation and its Role in Cancer

DNA methylation, an essential epigenetic mechanism, involves the addition of a methyl group to the DNA molecule, typically at CpG sites. This process can modulate gene expression without altering the underlying DNA sequence. In

CHAPTER 3

CD105 in the Progression and Therapy of Colon Cell Carcinoma

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Abstract: Colon cell carcinoma (CRC) poses a significant global health challenge, demanding thorough exploration. This chapter meticulously navigates the multifaceted landscape of CRC, elucidating its definition, prevalence, and established risk factors. The spotlight then shifts to CD105, an enigmatic glycoprotein intricately woven into the fabric of CRC progression. CD105 emerges as a key player in orchestrating tumor hallmarks, influencing angiogenesis, cell proliferation, invasion, and immune evasion. Discussions unfold on its clinical significance, serving as a diagnostic, prognostic, and predictive marker. Case studies illustrate CD105's pivotal role in guiding clinical decisions and reshaping the narrative of colon cancer. However, challenges in standardization and the complex interplay with other factors underscore the need for ongoing research. The chapter delves into CD105's biological functions, shedding light on its intricate role in cancer biology, particularly in angiogenesis and immune evasion. The narrative then explores CD105 expression in normal and cancerous colon tissue, deciphering its correlation with tumor progression stages. A case study approach humanizes the discussion, emphasizing CD105's diverse impact on clinical outcomes. Unveiling CD105's dual dance of angiogenesis and metastasis, the chapter presents a nuanced understanding of its influence in the complex tapestry of colon cancer progression. The ominous impact of CD105 on prognosis, angiogenesis, metastasis, and cellular reprogramming is explored, emphasizing its role as a malevolent force in colon cancer progression. The subsequent sections delve into strategies for targeting CD105 in therapy, providing a comprehensive exploration of monoclonal antibodies, small-molecule inhibitors, anti-adhesion agents, and cytoskeletal disruptors. Case studies and ongoing trials offer glimpses of the potential and challenges in silencing CD105. As the chapter concludes, it reflects on the evolving landscape of colon cancer, acknowledging CD105's potential while urging continued research to unlock its full therapeutic potential.

Keywords: Angiogenesis, Biomarker, Colon cell carcinoma, CD105, Metastasis, Therapeutic strategies.

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INTRODUCTION

Colon cell carcinoma (CRC), an insidious adversary arising from the epithelial lining of the colon and rectum, stands as a formidable challenge in the realm of global health [1]. Its prevalence spans continents, casting a looming shadow that demands meticulous exploration and profound understanding. This book chapter embarks on a comprehensive journey through the intricate landscape of CRC, delving into its definition, prevalence, and myriad risk factors that weave the complex tapestry of this malignancy. The canvas of CRC is painted with statistical revelations that underscore the urgency of unraveling its intricacies. Incidence rates, mortality figures, and geographical variations converge to emphasize the profound impact of this disease on healthcare systems worldwide [2]. As we navigate through the chapters of CRC, it becomes imperative to comprehend its pathogenesis and the key genetic and molecular alterations that set the stage for its relentless progression. The conceptual framework of cancer hallmarks, as envisioned by Hanahan and Weinberg, provides a roadmap to elucidate the multifaceted nature of CRC [3]. At the heart of this intricate narrative lies CD105, an enigmatic transmembrane glycoprotein that intricately weaves itself into the fabric of CRC [4]. CD105 transcends its role as a mere biomarker, emerging as a dynamic orchestrator influencing critical aspects of tumor progression [5]. The initial chapters unfold the biology of CD105, unraveling its structural nuances, unique composition, and the complex signaling pathways it governs. This exploration takes us beyond the conventional boundaries of basic biology, delving into CD105's profound involvement in tumor angiogenesis. The spotlight sharpens as we illuminate CD105's role in angiogenesis, a pivotal process in sustained tumor growth and metastasis [6]. Like a vascular maestro, CD105 orchestrates the construction of a dense network of blood vessels, ensuring a steady supply of nutrients and oxygen to fuel the relentless growth of the tumor. Studies, such as the TRICOLORE [7] sub-analysis published in Nature Medicine, provide compelling insights into how elevated CD105 expression correlates with increased microvessel density. These findings not only underscore CD105's role as an architect of angiogenesis but also set the stage for the exploration of its clinical implications. Moving through the chapters, the ominous undertones of CD105's influence extend into the realm of prognosis. The TARGET trial, a landmark endeavor published in JAMA Oncology, casts a shadow over the landscape, demonstrating a significant association between elevated CD105 expression and worse overall survival. A meta-analysis featured in Cancer Letters aggregates data from over 10,000 patients, further solidifying CD105 as a potent prognostic marker [8]. Case studies of individuals like Michael and Sarah provide poignant illustrations of how CD105 levels contribute to risk stratification, influencing treatment decisions and reflecting the harsh realities often associated with elevated CD105 expression. The book chapter takes a deep

dive into the macabre dance of metastasis choreographed by CD105. As a metastatic choreographer, CD105 endows cancer cells with the tools to invade and colonize distant organs, extending the reach of malignancy. Studies featured in Molecular Cancer shed light on how CD105 activates signaling pathways orchestrating cytoskeletal rearrangements [9], facilitating cancer cells' ability to traverse tissue barriers and embark on their metastatic journey. The case study of Sarah, a patient battling stage II colon cancer, underscores the nuanced layer of CD105's influence, emphasizing the importance of considering CD105 not only in tumor growth but also in its potential for dissemination. The subsequent chapters unravel the strategies for targeting CD105 in colon cancer therapy. This pursuit involves a multifaceted approach aimed at severing the tumor's lifeline constructed through angiogenesis and dismantling the macabre choreography of metastasis orchestrated by CD105. Monoclonal antibodies, small-molecule inhibitors, anti-adhesion agents, and cytoskeletal disruptors emerge as potential weapons in this war against CD105 [10]. The ongoing trials and case studies within these chapters offer glimpses into the evolving landscape of CD105-targeted therapies, showcasing both promise and challenges in the relentless pursuit of conquering CD105 in the context of colon cancer therapy. As the final act of this comprehensive exploration unfolds, the focus shifts from the ominous shadows of CD105's influence to the optimistic whispers of the future. The chapters exploring CD105 as a biomarker, its limitations, biological functions, expression in colon cancer, impact on progression, and therapeutic targeting provide a nuanced and multifaceted understanding of this enigmatic glycoprotein. The potential applications of CD105 in diagnosis, prognosis, and therapy cast a glimmer of hope in the battle against colon cancer. However, the journey toward fully harnessing CD105's potential is not devoid of challenges. The need for standardization, understanding the intricate interplay with other factors, and deciphering mechanisms of resistance underscore the importance of continued research. As the chapter concludes, a sense of cautious optimism prevails, emphasizing the ongoing pursuit of unraveling the tapestry of CD105's influence. This enigmatic glycoprotein, once an ominous force in the colon cancer narrative, now stands poised to be a beacon guiding the way towards a more nuanced and effective understanding of this formidable disease. The clarion call for further research echoes through the pages, urging the scientific community to translate promising findings into effective clinical applications, rewriting the narrative of colon cancer and offering a brighter future for those grappling with this complex and formidable adversary.

COLON CELL CARCINOMA AND THE ROLE OF CD105

Colon cell carcinoma (CRC), a formidable adversary arising from the epithelial lining of the colon and rectum, stands as a global health challenge, demanding

CHAPTER 4

The Significance of N-Glycolylneuraminic Acid as a Carbohydrate Biomarker in Cancer Progression and Therapy

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Abstract: N-glycolylneuraminic acid (Neu5Gc) emerges as a pivotal player in the intricate landscape of cancer, shedding light on early detection, mechanistic intricacies, and innovative therapeutic strategies. This abstract encapsulates the captivating journey of Neu5Gc, exploring its resurgence in cancer research and its multifaceted implications. Traditionally absent in humans, Neu5Gc's reactivation on cancer cells serves as a distinctive biomarker, unveiling insights into altered cellular processes and malignant transformation. This abstract navigates through the dance of Neu5Gc, from its structural secrets to its distribution patterns on glycoproteins, offering a unique window into the enigma of cancer progression. Furthermore, Neu5Gc's diagnostic potential is showcased through compelling case studies, underlining its ability to guide cautious treatment approaches and serve as a discerning tool for early cancer detection. The chapter unfolds the mechanistic insights into Neu5Gc-mediated effects, depicting its influence on cellular adhesion dynamics, immune modulation, and resistance to therapies. A symphony of techniques for Neu5Gc detection and quantification takes center stage, exploring the power of mass spectrometry, immunoassays, and spectroscopy in decoding the whispers of this once-forgotten molecule. These analytical methods, akin to skilled musicians, contribute to Neu5Gc's characterization, promising a new era in cancer diagnosis and therapy. The narrative weaves through Neu5Gc's whispers of tumor characteristics, unraveling correlations with tumor type, grade, metastatic potential, and treatment response. This section emphasizes Neu5Gc's transcendence from a mere biomarker to a choreographer, orchestrating a vibrant prognosis of cancer's inner landscape. As Neu5Gc conducts the symphony of personalized cancer therapy, this abstract envisions a future where its unique presence becomes a spotlight for tailored interventions. From precision medicine to a symphony of therapeutic strategies, Neu5Gc emerges as a hopeful conductor, guiding cancer treatment toward a harmonious melody of healing.

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Keywords: Cancer biomarker, Detection techniques, Mechanistic insights, Neu5Gc, Personalized therapy, Tumor characteristics.

INTRODUCTION

Cancer, the insidious maestro of cellular chaos, thrives in the shadows, often concealing its malignancy until it has cast a long and devastating shadow. But within the intricate ballet of its progression, whispers of betrayal emerge, which are subtle alterations in the cellular landscape that speak volumes about the lurking disease [1]. This chapter unfolds the captivating tale of N-glycol neuraminic acid (Neu5Gc), a carbohydrate molecule emerging from the shadows as a revolutionary biomarker, poised to rewrite the script of cancer diagnosis, prognosis, and therapy. Neu5Gc, once absent in humans due to a genetic mutation millions of years ago, rears its head in cancer cells like a long-forgotten melody. Its presence on glycoproteins paints a stark picture of altered cellular processes, signaling malignant transformation and aggressive potential. This resurrection of a lost molecule carries immense significance, offering a unique window into the inner workings of cancer and its progression [2]. Traditionally, cancer diagnostics have focused on genetic mutations and protein alterations. However, these changes often lie deep within the cellular machinery, veiled from easy detection. Neu5Gc, on the other hand, dances on the cell surface, is readily accessible, and offers a tangible clue to the underlying pathology. Neu5Gc is a very complex sialic acid molecule existing mostly as terminal sugars on either glycans available in sugar chains or as single sugar residues on glycolipids and glycoproteins. Neu5Gc, however, does not exist naturally in humans due to inactivation mutations in both the CMAH gene, which codes for cytidine monophosphate---acetylneuraminic acid hydroxylase, and in the GNE gene, encoding UDP---acetylglucosamine 2-epimerase/N-acetylmannosamine kinase, responsible for Neu5Gc biosynthesis. On the contrary, the fact notwithstanding, humans can naturally make autoantibodies against Neu5Gc right from infancy because of exposure to Neu5Gc present in the animal-derived xenografts and in commensal bacteria of the human intestine and various microorganisms during life. The following review is focused on recent breakthroughs in the area of sialobiology, where autoantibodies to Neu5Gc have far-reaching consequences not only for cancer diagnosis and prognosis but also for therapeutic design based on engineering cells with an oncolytic action. Moreover, unlike genetic mutations, which can be heterogeneous within a tumor, Neu5Gc expression often exhibits remarkable uniformity, providing a reliable and representative picture of the disease. This chapter provides a compelling introduction, setting the stage for a deeper exploration of Neu5Gc's significance as a carbohydrate biomarker in cancer [3, 4].

N-GLYCOLYLNEURAMINIC ACID's DANCE WITH CANCER

N-Glycolylneuraminic acid (Neu5Gc), a carbohydrate once exiled from the human repertoire, has staged a dramatic comeback in the sinister stage of cancer. But this isn't simply a guest appearance; Neu5Gc dons a starring role, wielding its unique structure and distribution patterns to fuel tumor progression. In this chapter, we delve into the captivating enigma of Neu5Gc, exploring its structural secrets, its cellular tango with cancer, and its potential to rewrite the script of this malevolent disease. Imagine Neu5Gc as a tiny dancer adorned with a hydroxyl group and an amide moiety, setting it apart from its closest cousin, N-acetylneuraminic acid (Neu5Ac). This subtle twist, dictated by a missing enzyme in humans, imbues Neu5Gc with unique properties, influencing its interaction with other molecules and impacting cellular behavior. While absent in healthy human tissues, cancer cells reactivate their production through intricate metabolic pathways, whispering tales of their aberrant nature. Within the human body, Neu5Gc primarily paints its presence on red meat and some bacteria. In healthy cells, it remains a distant stranger [5]. However, in the warped landscape of cancer, it waltzes onto the cell surface, adorning glycoproteins with its distinct signature. This altered distribution pattern serves as a powerful biomarker, highlighting the presence of malignancy and potentially revealing the tumor's aggressiveness [6].

Case Study: Sarah, a 45-year-old diagnosed with early-stage breast cancer, exhibited elevated Neu5Gc levels in her tumor biopsy. This unusual distribution, absent in normal breast tissue, immediately raised alarms, prompting further investigation and a more cautious treatment approach. Sarah's case exemplifies how Neu5Gc's distribution can provide crucial clues for diagnosis and personalized therapy. Neu5Gc is not just a bystander in the macabre ballet of cancer; it actively influences the choreography of progression. Studies suggest it alters cell-cell adhesion, promoting tumor cell detachment and facilitating metastasis. Its presence also modulates signaling pathways, driving proliferation and enhancing resistance to therapy. These roles, woven into the fabric of cancer's spread and survival, underscore Neu5Gc's immense potential as a therapeutic target.

DECIPHERING THE Neu5Gc's CRUCIAL ROLE IN CANCER DIAGNOSIS, PROGNOSIS, AND TREATMENT STRATEGIES

In the intricate tapestry of cancer, where the malignancy often lurks beneath a façade of normalcy, the secrets of this cunning beast lie inscribed in the language of sugar. This comprehensive exploration delves into the captivating mystery of N-glycolylneuraminic acid (Neu5Gc), a carbohydrate molecule that whispers tales

CHAPTER 5

Nanoparticles for Advancing Cancer Metastases, Diagnosis, and Treatment: Current Progress and Prospective Avenues

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Abstract: In the dynamic realm of cancer research, this chapter explores the transformative potential of nanoparticles in advancing the diagnosis and treatment of metastatic cancer. Addressing the multifaceted challenges posed by metastasis, we delve into the current progress and future prospects of leveraging nanotechnology. The introductory section illuminates the complexity of metastatic cancer, emphasizing its significance in cancer-related mortality and introducing nanoparticles as revolutionary tools. Bridging the organic-inorganic spectrum, we navigate the diverse formulations of nanoparticles, emphasizing surface precision in design. The chapter unfolds to reveal precision therapeutics, controlled drug delivery systems, and the integration of imaging technologies using theranostic nanoparticles. A comprehensive exploration of liquid biopsy, exosomes, and targeted therapy paints a holistic picture of nanoparticle applications in battling metastatic cancer. The narrative further probes into the hurdles of metastasis, the biological barriers, and the strategic use of active and passive targeting in nanoparticle design. The climax introduces theranostic nanoparticles as microscopic warriors orchestrating a dual attack on diagnosis and treatment. The concluding section envisions a future where nanoparticles redefine cancer care, offering personalized therapies, early detection, and dynamic interventions.

Keywords: Biological barriers, Metastatic cancer, Nanoparticles, Nanomedicine, Precision therapy, Theranostic nanoparticles.

INTRODUCTION

In the ever-evolving landscape of cancer research, the formidable challenge posed by metastatic cancer demands innovative solutions [1]. This chapter embarks on a comprehensive exploration of "Nanoparticles for Advancing Cancer Metastases,

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Diagnosis, and Treatment", delving into the current progress and prospective avenues in leveraging nanotechnology to address the intricate dynamics of metastatic cancer. The introductory section sets the stage by unraveling the multifaceted nature of metastatic cancer, emphasizing its inherent challenges and profound significance in the context of cancer-related mortality. As we navigate through the complexities of metastasis, a spotlight is cast on the transformative potential of nanoparticles as cutting-edge tools in the field of oncology [2]. These microscopic engineers emerge as beacons of hope, offering a revolutionary approach to not only diagnose but also treat metastatic cancer [3]. The chapter unfolds with an exploration of the challenges posed by metastatic cancer, from the initiation of motility in cancer cells to their colonization of distant organs, outlining the intricate steps in this ominous dance [4]. Following this, the narrative seamlessly transitions to the role of nanoparticles as transformative tools in the oncological arsenal, promising a paradigm shift in our approach to metastatic cancer [5]. Nanoparticles are introduced as versatile agents capable of navigating the complexities of the human body with precision, offering early detection and targeted therapeutic interventions. The discussion then expands to the formulation and engineering of nanoparticles, where their unique properties, including size, shape, surface functionality, and cargo capacity, become instrumental in tailoring their interactions with specific biological structures and optimizing their therapeutic potential. This exploration paves the way for understanding how nanoparticles can be tailored to enhance their responsiveness to the tumor microenvironment and improve drug delivery efficiency [6]. As we embark on this journey, the chapter aims to unravel the untapped potential and future directions in the field of nanomedicine for metastatic cancer, pointing towards the development of smarter nanoparticles [7], overcoming biological barriers, and the promise of personalized nanomedicine. Through this comprehensive examination, the chapter seeks to offer not only a snapshot of the current progress in the field but also a roadmap for the exciting avenues that lie ahead in our quest to revolutionize the diagnosis and treatment of metastatic cancer using nanoparticles.

BRIDGING THE ORGANIC-INORGANIC SPECTRUM AND MASTERING SURFACE PRECISION

Within the expansive dominion of nanoparticle design for advancing cancer metastases, diagnosis, and treatment [8], a nuanced exploration of nanoparticle types reveals a diverse array of formulations that bridge the organic to inorganic spectrum. Organic nanoparticles, such as liposomes and polymeric nanoparticles, present themselves as versatile carriers, capable of encapsulating various therapeutic agents, including chemotherapeutics and nucleic acids, offering a biocompatible and controlled-release platform for cancer therapy [9]. On the other

end of the spectrum, inorganic nanoparticles, such as gold and magnetic nanoparticles, leverage unique physical and chemical properties for diagnostic and therapeutic applications [10]. Gold nanoparticles, for instance, exhibit exceptional optical properties that enable precise imaging, while magnetic nanoparticles provide opportunities for targeted drug delivery and hyperthermia-based therapeutic interventions [11]. The dichotomy between organic and inorganic nanoparticles highlights the need for a tailored approach, considering the specific requirements of the intended application. Surface functionalization emerges as a critical aspect in nanoparticle design, where the judicious modification of the nanoparticle's outer layer plays a pivotal role in dictating its interactions with biological entities. Strategies for surface functionalization include the attachment of ligands, antibodies, or peptides that confer targeting specificity to cancer cells, thereby enhancing the precision of diagnostic imaging and therapeutic interventions [12]. The intricate interplay between nanoparticle composition, surface properties, and targeting strategies underscores the complexity of designing nanoparticles for metastatic cancer applications, requiring a meticulous balance between biocompatibility, stability, and therapeutic efficacy. As the chapter unfolds, a detailed examination of each nanoparticle type elucidates their unique characteristics, advantages, and challenges, offering a comprehensive understanding of the diverse toolbox available for researchers and clinicians in the pursuit of enhancing cancer metastases, diagnosis, and treatment. Through this advanced exploration, the chapter aims to navigate the intricate landscape of nanoparticle design, empowering readers with a nuanced perspective on the varied approaches that contribute to the evolving field of nanomedicine in the context of metastatic cancer.

PRECISION THERAPEUTICS AND ILLUMINATED DIAGNOSTICS

This portion exposes the multifaceted landscape of controlled drug delivery systems, positioning them as indispensable components in the ongoing evolution of cancer therapeutics. In the monarchy of metastatic cancer, precision and controlled release of therapeutic agents become paramount, and this section unravels the intricacies of various controlled drug delivery systems leveraging nanoparticles [13]. From liposomes to polymeric nanoparticles, the discourse navigates the nuances of these carriers, elucidating their capacity to encapsulate and release a spectrum of therapeutic cargos. Emphasizing biocompatibility, stability, and sustained drug release, these controlled delivery systems emerge as potent tools in modulating drug pharmacokinetics, mitigating systemic toxicity, and enhancing therapeutic efficacy against metastatic lesions [14]. Simultaneously, the exploration extends into the empire of nanoparticles in metastases imaging, where the convergence of nanotechnology and imaging

CHAPTER 6

Recent Advances in Nanotechnology for The Diagnosis and Therapy of Melanoma Skin Cancer

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Abstract: Among the several types of cancers currently, skin cancer has emerged and risen rapidly in the last decade. The melanoma and non-melanoma typescontribute mainly to skin cancer and are considered metastatic and deadly. Extreme exposure to ultraviolet radiation (depletion of the ozone layer or industry exposure) leads to an enormous rise in cases of skin cancers. The previous therapy includes surgery, chemotherapy, and radiation,which are invasive methods and greatly associated with several adverse effects on healthy tissues. The current review aims to explore the identification of novel biomarkers (miRNA, circulating tumor DNA, S100 Family, Exosomes, Ki-67, KIT, p63, 5-S-Cysteinyldopa) and nanotechnology-based approaches for the prevention, prognosis, diagnosis, and effective therapy for all types of skin cancers. Several biomarkers are capable of recognizing the presence of melanoma thereby improving survival. The lipid-based nanocarriers (liposomes, SLN, NLC) serve as the best carrier for hydrophobic drugs and also provide biocompatibility and stability to the antitumor agents for topical delivery. Vesicular nanocarriers (niosomes, ethosomes, Transferosomes, *etc.*) are gaining significance because of nano size, higher penetration ability through stratum corneum, greater stability, and non-toxicity. The prompt recognition of melanoma or non-melanoma types through novel biomarkers significantly enhances the survival rate in many patients. Upon identification, the nanocarrier-based approaches show marked efficacy in treating several types of skin cancer.

Keywords: Ethosomes, Liposomes, Melanoma, Nanostructured lipid carrier, Niosomes, Skin cancer, Solid lipid nanoparticles.

INTRODUCTION

The largest organ of the human body is the skin. Maintaining the equilibrium of the body by regulating its temperature and moisture and protecting from the entry of any foreign content (invasion of microbes, ultraviolet rays, or any chemicals) inside the body are the most significant functions played by the skin [1]. The

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statistical data recorded with skin cancer in 2021 indicated around 115320 (68120 in males and 47200 in females) patients suffering from it, and out of these, most belonged to the melanoma category (106110). Higher mortality was observed in males (7660) than females (3880). Out of several types of cancer, melanoma skin cancer contributed around 5-6% in both sexes [2].

Types of Skin Cancer

There are 2 broad types of skin cancers, namely melanoma and non-melanoma.

Melanoma Skin Cancer (MSC)

This type of cancer is mainly initiated in the melanocytes, which are capable of generating melanin. During this condition, mutations occur primarily at the basal layer of the epidermis. The principal issue related to the MSC is the extreme contact with ultraviolet (UV) rays, which later results in the induction of melanocytes, leading to metastatic carcinoma. The chief mutations that are generally expressed in the MSC are BRAF/NRAS/MEK/MAPK pathways.

The primary therapy used during the MSC involves surgery and radiotherapy, and novel treatments are targeted therapy, immunotherapy, and a combination of both. Without metastasis, the survival rates in patients are more than 90%, and with metastasis,theyreach 10% [3].

Non-Melanoma Skin Cancer (NMSC)

This type of cancer originates in well-known pathways; hence, it seems to be easilytreated. As compared to MSC, NMSC is easy to recognize and less aggressive and therefore has a higher survival rate with a low mortality rate in the patients. There are two subtypes of NMSC, namely, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Several conditions are responsible for the induction of NMSC, such as genetic factors, excessive exposure to UV rays, tobacco use, long-term skin infections, severe inflammatory conditions, and acute use of medications and immunosuppressive agents [3, 4].

Conventional cancer therapies include chemotherapy, surgical procedures, and radiotherapy, which are associated with severe systemic toxicities. Currently, nanocarrier-based approaches are widely preferred for metastatic cancers where conventional therapy failed and showed high mortality either because of uncontrolled measures or associated toxicities. The nanocarrier-based technologies are preferred in cancer for offering targeted delivery, avoiding degradation during transport pathways, and controlling or sustaining release achieved easily [4 - 7]. Nanoparticle (NP)-based deliveries are beneficial with

respect to multidrug resistance, the potential of cell imaging, and enormous penetrability inside the tumor cells. Hence, greater therapeutic efficacy has been achieved in cancer therapy without showing any abnormal effects on the healthy tissues [8].

The Barrier to Skin Carcinoma

The skin has a surface area of about 1.8 m^2 and occupies 16% of the total body weight, being the largest organ of the body. The most suitable treatment recommended for all types of skin cancer is the topical route, which is site-specific; self-administration is also possible. Moreover, topical delivery is non-invasive and avoids the toxicities produced due to oral and parenteral medications. The therapeutic efficacy is achieved by the medicaments only after crossing the barrier, namely the stratum cornea [3, 9].

The skin is mainly made up of three distinct layers, namely epidermis (superficial), dermis (middle), and subcutaneous tissue (terminal). The epidermis is the external layer of the skin comprised of typical cells known as keratinocytes, which are responsible for the production and liberation of keratin. Keratin is an extended slim protein with a defensive function. They are also comprised of melanocytes, which protect from harmful ultravioletradiation, serving as a barrier. The epidermis in its outermost region is comprised of the stratum corneum (SC), which is the strong barrier of the skin. This barrier is formed *via* the keratinization process, which comprises 4 distinct cell layers, namely stratum basale, stratum spinosum, stratum granulosum, and stratum corneum [10, 11].

The dermis is the central layer prepared with a fibrillar structural protein called collagen and is located above the subcutaneous tissues or panniculus, enclosing tiny fatty cells known as lipocytes. Moreover, the dermis is also comprised of blood vessels, sweat glands, and pilosebaceous molecules. The innermost layer of the skin is the subcutaneous tissue, which consists of subcutaneous fat and connecting tissues [12, 13]. With the minimization of the higher risk of all types of skin cancer, there is an utmost need for advanced nanotechnology, which can be best fulfilled with nanocarriers. These nanocarriers serve as several anticancer agents that can deliver the drug at the targeted site [14].

Diagnosis of Skin Cancer

Melanoma skin cancer is metastatic, with a poor survival rate. Hence, recognizing the development of melanoma at the initial level is of utmost importance for minimizing the risk. The traditional methods involved in the diagnosis of several types of skin cancer include the examination of the skin, patient's history, dermoscopy, and surgical biopsy. Dermoscopy and biopsy are invasive methods,

CHAPTER 7

Applications of Advanced Nanocarriers in the Theranostics of Melanoma Skin Cancer

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Abstract: Among the various types of skin cancer, melanoma is the most aggressive one, and the occurrences are rising rapidly throughout the universe. The early diagnosis rate of melanoma skin cancer is around 14-15%, which hasa survival rate of less than 5 years. Conventional medicines are unable to treat it completely, resulting in the destruction of healthy cells. Similarly, radiotherapy and chemotherapy have limitations of higher toxicity, multi-drug resistance, and minimal survival rates even after the treatment. The lipid-based nanoparticles are highly effective in the therapy of melanoma skin cancer only after the prompt diagnosis. The current book chapter signifies the applications of the advanced nanocarriers utilized for the diagnosis and therapy of skin cancer. These advanced nanocarriers are classified as polymer-based approaches (micelle, dendrimer, and hydrogels) and offer additional benefits like targeted action, controlled delivery, longer circulation time, and high loading efficiency. Nanoparticle-based approaches (organic and inorganic nanoparticles) and carbon-based approaches (nanotubes, graphene oxide) are widely utilized for possessing biosensing and diagnostic properties.

Keywords: Carbon nanotubes, Dendrimers, Graphene oxide, Hydrogels, Melanoma, Nanoparticles, Nanocarriers, Polymeric micelle, Skin cancer, Theranostics.

INTRODUCTION

Melanoma skin cancer is currently very common due to a huge surge in cases worldwide. The newer cases were approximately 5 times in the last decade, comparatively with the previous one [1]. The cases arise due to excessive exposure to sunlight or UV light, genetics, depletion of ozone, alterations in the modern Western lifestyle, and immune-compromised persons [2]. Advanced melanoma hasshown a rapid proliferation rate with minimum survival rates. Hence, to control the metastatic condition, an advanced nanocarrier with imp-

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roved therapeutic efficacy is required. These nanocarriers are versatile and offer unique features of diagnosis and therapy, which are lacking by the lipid-based nanocarriers. Moreover, improved stability, prolonged retention time, and minimal resistance create a huge demand for these nanocarriers [3].

POLYMER-BASED APPROACHES

Polymeric Micelles (PMs)

Currently, PMs are very widely utilized in several drug delivery systems owing to theirversatility as nanocarriers. They are available in the size range of 10-100 nm. They offer a marked improvement in solubility and bioavailability, targeted action, and controlled release patterns [4, 5]. The incorporated therapeutic agents inside the PMs are biocompatible and have unique core-shell structures, higher stability, greater permeability, and longer retention time with minimal toxicity [6, 7].

Xu *et al.* developed a polymeric micelle incorporated with paclitaxel-loaded ibuprofen and further converted into the topical gel using Carbopol 940 for the therapy of melanoma. This gel exhibited higher penetration power through the skin and thereby showed cytotoxicity for melanoma. Comparatively, higher efficacy was achieved using PMs than using taxel derivatives alone [8]. Martin *et al.* introduced novel sonodynamic therapy (SDT), which relies on ultrasound and sonosensitizers. For the execution of SDT, zinc phthalocyanine was incorporated into the polymeric micelles. The marked improvement in the solubility and permeability was noted after loading in PMs. The profound minimization in the cell viability was observed with SDT [9]. Wei *et al.* introduced photothermal therapy (PTT) for topical tumors that rested on the aggregation-induced emission luminogen (AIEgen), which was limited due to poor solubility. To overcome the problems associated with AIEgen, a soluble microneedle system was utilized for the therapy of malignant melanoma of the skin. The PM-embedded microneedles were developed *via* nanoprecipitation and thereby showed their cytotoxic action in the single dose [10].

Odrobinska *et al.* designed and developed polyethylene glycol grafted ferulic acid for its antioxidant action. Further, it was encapsulated with arbutin and evaluated for efficacy *via* an *in vitro* diffusion study. These grafted polymeric micelles showed cytotoxicity and were found to be safe [11]. Pucelik *et al.* investigated photodynamic therapy for pigmented melanoma by incorporating redaporfin in pluronic micelles. The loading of actives in PMs showed marked cellular uptake and cytotoxicity. These modified pluronic-PMs do not show any sign of resistance with higher selectivity for tumors as well as improved reactive oxygen species [12].

Yang *et al.* developed α-mangostin nanomicelles for their anti-melanoma activity. The α-mangostin action was restricted due to its hydrophobic nature and resolved by embedding in the form of nanomicelles. An outcome of this approach was that the developed nanomicelles generated apoptosis, and suppressed proliferative action was achieved [13]. Lin *et al.* experimented with combating metastatic melanoma of the skin. They tested a polymeric prodrug loaded with sulfur dioxide and grafted with glutathione with DOX. The grafted polymer was incorporated in the PM, which comprised of potent agent DOX. Marked suppressive action with less proliferation against subcutaneous melanoma was achieved [14].

Tokarska *et al.* utilized combination therapy comprised of photosensitizer (IR-768) and anti-tumor agent daunorubicin for the treatment of melanoma. Both these agents were delivered *via* PMs, and synergistic action was reported, which increased with higher concentration. These PMs were rapidly uptaken by mitochondria and generated high oxygen capacity inside the A375 cells. Significant chemo-photodynamic therapy was also reported with this synergistic combination [15]. Lamch *et al.* utilized targeted drug delivery for the therapy of melanoma as it offers several benefits. In this approach, zinc and phthalocyanine were encapsulated with folate-functionalized micelles. The zinc-loaded micelles indicated high chemical and physical stability. These micelles were evaluated, and significant phototoxicity was observed in Me45 and SKOV-3 cells, thereby serving the potential nanocarriers for several anticancer agents. Moreover, ROS was also generated, and it was found to be useful in melanoma therapy [16].

Imiquimod (IQM) is used for the therapy of keratosis and warts and for BCC. Poor aqueous solubility and permeability are the rate-limiting steps for IQM. To overcome this drawback, Ghezzi *et al.* enhanced the solubility and dissolution rate of imiquimod (IQM) using polymeric micelle. The polymeric micelle was prepared using d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) obtained from vitamin E, which served as a carrier for the micelle. The evaluation parameters indicated an enormous rise in the solubility of IQM. For topical delivery, the polymeric micelle of IQM was converted into hydrogel [17].

Dendrimers

These are alternatively known as cascade polymers, which are hyperbranched or considered tree-like arms. They possess unique architecture, 3-D monodispersed macromolecules consisting of a central core and multiple units linked with the nucleus [18 - 20]. Several groups of polymers contributed significantly as promising nanocarriers, including polyamidoamine (PAMAM), poly (propylene imine) (PPI), Poly-L-lysine, melanin, poly (ether hydroxylamine) (PEHAM), *etc.* Special attention is given to dendrimers for their unique structure and also for

CHAPTER 8

Recent Advances in Immunotherapy-Based Approaches for the Therapy of Melanoma Skin Cancer

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Abstract: Melanoma is one of the most violent forms of skin cancer that has become a major global health concern in recent years. Despite the efforts made to understand the pathogenesis of this cancer, its incidence has continued to rise over time. In response, various new therapeutic approaches have been developed over the past decade, including immunotherapy. Immunotherapy involves inspiring defense mechanisms to identify and attack tumor cells. The immunotherapies consist of immune checkpoint blockade (TRC blockade, MHC blockade, B7 blockade, T-VEC blockade, IDO blockade), adoptive T-cell transfer, cytokines (IL-1, IL-12, IL-6, IL-15, GM-CSF, IFN-γ, TNF-α), vaccines, (Gp-100 vaccine, IDO-Peptide Vaccine, 6-melanoma helper peptide vaccine), and oncolytic viruses ((T-VEC) Talimogene Laherparepvec, JX-594/ Pexa Vec,(CVA21) Coxsackievirus A21 / Cavatak, (Reolysin®) Pelareorep). Immune checkpoint blockade is an immunotherapy that works by hindering precise proteins known as immune checkpoints that control the immune response. These checkpoints are present on the exterior of immune cells and show a serious character in modifiable immune response, averting over-instigation and autoimmunity. The tumor cells have evolved ways to achieve these checkpoints to escape the immune response, leading to decreased immunity against cancer cells. Immune checkpoint blockade works by targeting these checkpoints and blocking their activity. By blocking the activity of these checkpoints, immune checkpoint blockade therapy can enrich the immune response contrary to the tumor cells. This approach showspromising outcomes in the cure of melanoma with several molecules permitted by the US FDA.

Keywords: Adoptive T-cell transfer, Cytokines, Cancer vaccines, Immunotherapy, Skin cancer, Immune checkpoint inhibitors.

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INTRODUCTION

Immunotherapy

A novel kind of therapy introduced for the tumor that triggers the immune mechanism is known as immunotherapy (IMT). This therapy works significantly in melanoma skin cancer (MSC) by triggering the defense mechanism, thereby destroying the tumor cells and also prohibiting their proliferation [1]. Several kinds of treatment are included under immunotherapy, and out of them, the worthiest mechanism is immune checkpoint suppressors (ICS). The ICS obstructs the action of proteins that rely on the exterior of immune cells, which mimic the immune response, hence termed immune checkpoint proteins (ICP). Moreover, adoptive T cell transfer, CAR-T, and TCR-engineered T cell therapy are widely employed in the therapy of MSC [2]. These therapies encompass eradicating T-lymphocytes from plasma and transforming them to target cancer cells in the form of modified T-lymphocytes. Thus, significant destructive action on the tumor cells was observed, and proliferation was restricted [3]. Another kind of IMT thatenables the stimulation of immune mechanisms by the cytokines that destroy the tumor cells is termed cytokine-based immunotherapy [4, 5]. Recently, the introduction of vaccines for cancer therapy has been in huge demand for the management and cure of tumors. Oncolytic virus therapy is a novel concept that incorporatesa virus that infects the infected tissue and further damagesit. Further, immune cells elicit a defense mechanism in contrast to the tumor cells [6, 7].

Immune Checkpoint Inhibitors (ICIs)

A new paradigm in the cure of metastatic melanoma is the ICIs. ICIs denote the mechanism by delaying precise proteins known as immune checkpoints that control the immune response. These are present on the surface of immune cells and contribute a significant part in adapting the immune response, averting over-activation and autoimmunity [8]. Tumor cells have advanced behaviors to exploit these checkpoints to escape the immune response, foremost to diminished immunity in contradiction of tumor cells. ICIs direct these checkpoints and hinder their movement, hence, improving the immune reflection counter to the tumor [9]. These are recognized as monoclonal antibodies (MCA), which target the programmed death cell protein 1(PD-1), the programmed death cell-ligand protein 1(PDL-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which are the prerequisite for evading the immune response. The marked suppression of T-lymphocyte action was observed by the triggering of PD1 and CTLA-4 [10]. The researchers achieved success in 2011 after the invention of the first ICI, namely ipilimumab, for the therapy of metastatic melanoma. A noteworthy rise in the existence of infected patients was recognized after the induction of ipilimumab

[11]. Hence, a new ray of hope emerged, and research was initiated in the same direction with greater potency and efficacy. This therapy was far better compared with chemotherapy, radiotherapy, and surgery. After a couple of years, researchers worked and introduced anti-PD1 and PDL1 agents for metastatic melanoma. A synergistic combination of Nivolumab and Ipilimumab was also displayed for metastatic melanoma. Swelling and toxic effects on the immune system were reported by the patients after this combination. Hence, more careful design and combination strategies were proposed for combating metastatic MSC [12]. The approved agents for metastatic melanoma are displayed in Table **1** [13, 14].

Table 1. List of ICIs for the advanced melanoma.

Sr. No	Name of Drug	Category	Approved Year
1	Ipilimumab	Anti-CTLA-4	2011
2	Toripalimab	Anti-PD-1	2018
3	Pembrolizumab	Anti-PD-1	2014
4	Nivolumab	Anti-PD-1	2014
5	Cemiplimab	Anti-PD-1	2018
6	Dostarlimab	Anti-PD-1	2021
7	Prolgolimab	Anti-PD-1	2020
8	Atezolizumab	Anti-PD-L1	2016
9	Durvalumab	Anti-PD-L1	2017
10	Avelumab	Anti-PD-L1	2017
11	Relatlimab	Anti-LAG-3/anti-PD-1	2017

TCR Blockade

ICIs bind the command on the immune system to combat the tumor. The prime constituent of this approach is the targeting of the T cell receptors (TCRs), which contribute significantly to modifying the movement of the immune system. TCR blockade comprises the disbursement of drugs that restrict the usual working of TCRs and, therefore, aid in discharging the brakes on the immune system and boosting its capability to prevent the outbreak of tumor cells [15]. Recently, TCR blockade has become a favorable part of the investigation in immunotherapy for melanoma. The practice of TCR-engineered T cells, which are modified to target specific tumor antigens, has shown potential in the early phase of the clinical trials. For example, those patients who were formerly unsuccessful in curing tumor conditions became happy after the invention of TCR-engineered T-cell blocking agents in 2020. Moreover, the chimeric antigen receptor T (CAR-T)

CHAPTER 9

Update on Applications of Nanotheranostics for the Management of Cancer

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Abstract: This book chapter is a scientific compilation with an emphasis on recent applications of nanotheranostics for the management of cancer. We will start with a brief background of nanotheranostics for the management of cancer. Applications of nanotheranostics in the diagnosis and treatment of cancer will be discussed in this book chapter. Challenges and future perspectives will also be discussed.

Keywords: Cancer research, Nanotheranostic, Photodynamic therapy, Photothermal therapy.

INTRODUCTION

Even today, cancer is one of the prime causes of death across the world, with lung cancer leading the chart in men and breast cancer in women. It was estimated that there would be approximately 1.9 million new cases of cancer in 2022, with cases projected to increase by 12.5% at the close of 2025. Despite the fact that treatment for cancer has improved considerably in recent years, it still has one major challenge, especially associated with RT and CT, involving problems relating to its efficacy and the general condition of patients [1].

It is in this context that nanomedicine opens new avenues toward solving the limitations of conventional chemotherapy, more particularly in the domains of drug delivery, distribution, and compatibility. Theranostics, an approach that combines diagnosis and therapy into the precision targeting of tumors for treatment with medication, has a place in nanomedicine. It can also be defined as a new, potential technique of treatment for cancer derived from the simultaneous integration of diagnostic and therapeutic functions [2].

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Nanomedicine applies nanotechnology to diagnose, treat, and prevent diseases at the nanoscale and molecular levels. This has further contributed to the development of theranostics candidates that bring together therapy and diagnosis. Nanotheranostics relies on colloidal nanoparticles normally between 10-1000 nm (1 μm) to facilitate better and more effective delivery of treatment. Several nanocarriers, like liposomes, dendrimers, polymer conjugates, carbon nanotubes, metal and inorganic nanoparticles, micelles, and biodegradable polymer nanoparticles, have been engineered for the co-delivery of diagnostic and therapeutic agents in a targeted, controlled, and sustained manner so as to improve theranostic effects while reducing adverse side effects [3, 4].

Advanced theranostic nanomedicine, by virtue of being multifunctional, makes an exact diagnosis and targeted delivery of therapies to the exact pathological cells possible, thereby allowing huge scope in the efficacy of cancer treatment [5].

This book chapter discusses the potential of nanotheranostics to change the face of cancer diagnosis and treatment. We delve into molecular mechanisms, synthesis techniques, and the most current research in this area, together with clinical trials that are most likely to shed light on the real-world efficacy of these cutting-edge therapies. Against the broad canvas of progress in the field of nanotheranostics, the present paper tries to underline the transformative potential of this technology toward better cancer management and improving patient outcomes.

APPLICATIONS OF NANOTHERANOSTICS FOR THE DIAGNOSIS OF CANCER

X-ray CT Imaging

By staking the cross-sectional images, CT imaging extends traditional X-ray technology into three dimensions and provides a more lucid image. Since the tissues do not naturally contrast with one another, a contrast agent must be utilized. Because of its higher-resolution imaging and deeper tissue penetration, it is highly helpful. Typically, contrast agents for CT imaging include tungsten, barium, and iodine [6].

Gold nanoparticles (AuNPs), gold nanorods (GNRs), and nanoscale metal-organic frameworks (NMOFs) are examples of nanoparticulate contrast agents that are used. These are superior to traditional contrast agents because they allow for a significant reduction in the doses that must be used [7].

Zhao *et al.* (2021) formulated and investigated stable bismuth nanoparticles. In the *in vitro* and *in vivo* x-ray computed tomography study, the author found that

Bi nanocomposites have the potential to be a superior CT contrast medium due to the great X-ray attenuation capabilities of Bi, which is element 83 on the periodic table. CT imaging *in vivo* was carried out. Prior to the intratumoural injection of Bi@mSiO2@MnO2 NCs, there were no CT signals. Twelve hours later, a sizable CT signal was seen at the site of the tumor. As a result, Bi@mSiO2@MnO2 NCs are a potential CT contrast media [8].

Zhou *et al.* (2021) constructed and investigated smart nanothernostic Bi-Ag @PVP NPs. The authors performed *in vivo* X-ray CT imaging on HepG2-bearing mice. Intratumourally, 100μL of Bi-Ag@PVP suspension (1 mg/kg) was administered to the HepG2-bearing mice. Prior to injection, there was no apparent CT signal intensity at the tumor site. CT signals at the tumor site were found to be enhanced significantly post-administration. Results showed that Bi-Ag@PVP NPs are potential candidates for contrast agents for the diagnosis of tumors [9].

Magnetic Resonance Imaging

A non-invasive imaging technique that combines radio waves and magnetic fields is called magnetic resonance imaging (MRI). For imaging soft tissues, it is very helpful as it provides cross-sectional images. Nonetheless, contrast media must be used to improve its signals because of its longer time and low sensitivity to obtain the images. Either ferromagnetic or paramagnetic contrast agents are possible. MRI contrast agents primarily consist of gadolinium and superparamagnetic iron oxide nanoparticles (SPIONs) [10, 11].

In a study by Wang *et al.* (2021), the author investigated *in vivo* DPPB-Gd-I NPs' efficacy as MR agents to diagnose tumors. Following IV administration, the tumor region's MR signal progressively increased. The MR signal at the tumor site was approximately 1.7-fold after 24 hours of injection, compared to pre-injection. NPs demonstrated dual-modal NIR-II/MR imaging capabilities of the tumor, which has enormous potential for tumor diagnosis with respect to superior spatial sensitivity and deep tissue penetration [12].

Zhu *et al.* (2021) demonstrated the efficacy of MONs@PDA-ICG as a tumor microenvironment-responsive nanotheranostic agent for the diagnosis of liver cancer. They found that when MONs@PDA is added to the normal physiological environment (pH 7.4), the MR signals remain unchanged. However, when MONs@PDA is added to the tumor microenvironment (pH 6.5 and 2 mM H2O2), the MR signals become stronger. According to the findings, MONs@PDA may serve as a tumor microenvironment-responsive magnetic resonance imaging contrast for the very accurate and targeted detection of liver cancer [13].

CHAPTER 10

Biomaterials for Bone Tumor: Present and Future Trends in Control and Treatment Strategy

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Abstract: Tumors associated with the osseous system have been a major challenge in recent decades. There is a tremendous attempt to design and develop biomaterials that inherit the capabilities to regenerate osteocytes in bone defects induced by surgical resection and elimination of the residual tumor cells. A biomaterial-based scaffold should mimic the normal bone tissue during the restoration of bone defects in regard to hierarchical structure, chemical composition, and biomechanical properties. However, a considerable number of biomaterials have been developed for bone tissue targeting with osteogenic, osteoinductive, and osteoconductive properties. Bone tissue-related research has progressed towards combinatorial therapy such as photothermal therapy, chemotherapy, and magnetic therapy in orientation with biomaterials which will elevate the efficacy of bone tumor therapy. New combinatorial approaches with bio-imaging and efficient tumor eradication exhibit significant potential for the synergistic treatment of osteosarcoma. Currently, in the arena of bone tissue engineering, the focus is on the incorporation of antitumor and pro-bone forming drugs into scaffold matrix using modified techniques in biomaterials. With the help of these techniques, a therapeutic material could be unloaded onto a target site precisely which can help in enhancing the therapeutic outcome and stop the potentially harmful effects on healthy cells. Multifunctional biomaterials have been proposed for the treatment of bone tumor cells with a better understanding of biomaterial design and development. To fabricate a biomaterial-based scaffold more precisely, powerful tools like 3D printing technology have evolved in the recent past, which can guide the development of scaffolds that imitate the structural and functional composition of bone which could be helpful in the treatment of bone tumours and promote osteogenesis. There is a need for the development of effective targeted drug delivery in corroboration with profound binding with a suitable biomaterial that can effectively treat bone tumors without any adverse effect on human physiology. Future research should be in line with combining various therapies for improved bone tumor treatment and precise control of antineoplastic drug-oriented treatment oriented with stimuli-responsive systems.

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Keywords: Bone tumors, Multifunctional biomaterials, Osteosarcoma, Osseous system, Scaffolds, Tumor cells.

INTRODUCTION

Tumors in bone are associated with bone and its associated tissues like bone marrow, blood vessels, nerves, *etc*., and are characterized by immense pain and destruction of bone [1]. Bone tumors can be broadly divided into sarcomas or primary bone tumors, metastases, or secondary bone tumors. Primary bone tumors occur in all age groups and are mostly uncommon as they comprise 0.2% of malignant tumors. These tumors are heterogeneous and include osteosarcomas, chondrosarcomas, and Ewing sarcomas. They are most commonly diagnosed in childhood and adolescence and 1/3rd of the patients do not survive beyond 5 years due to poor response to treatment. Metastatic bone tumors have a 10% survival rate due to poor prognosis with a high incidence of complications in breast cancer and prostate cancer [2, 3].

Current treatment modalities are based on chemotherapy, radiotherapy, and surgical interventions. However, the chances of failure of surgical procedures are high as they cannot remove the tumor cells completely, which may cause recurrence and metastasis of cancer. Chemotherapy and radiotherapy-oriented treatment of cancer are associated with severe adverse effects and side effects like liver dysfunction, toxicity to the cardiovascular system, and normal tissue damage. Bone tumors like osteosarcoma are resistant toward chemotherapy and radiotherapy [4]. Given the challenges associated with the current treatment approaches for bone tumors, the recent research focus is on deriving biomaterials capable of extending application in bone tumor therapy and bone tissue regeneration [5].

Bone-tissue engineering has been a prominent field of research with emerging fields like biomaterial science, molecular science, and nanotechnology. In the last decade, research related to this field has progressed to innovation in new biomaterials, scaffold design, and newer fabrication techniques with its applications. Eliminating the tumor cells and promoting bone regeneration are the two major challenges in bone tumor therapy. Therapy related to biomaterial scaffolds can promote bone tissue repair by activating bioactive molecules as it can demonstrate a suitable environment for the cells to proliferate, grow, and differentiate in the *in vivo* environment (Fig. **1**). Therefore, biomaterials for bone tissue healing and engineering are an innovative strategy in the field of tissue engineering [6, 7].

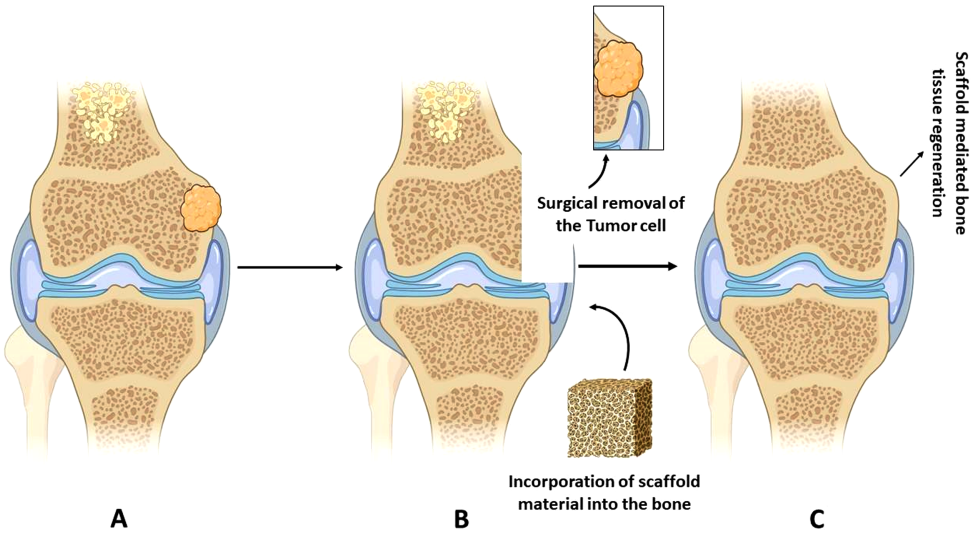

Fig. (1). Advent of biomaterials and their applications in promoting bone tissue regeneration after eliminating tumor cells. **A**) Occurrence of tumor on bone cell. **B**) Surgical intervention for the removal of tumor cells and implantation of the scaffold material in the surgically removed part of the osseous tissue. **C**) Successful regeneration of bone cells mediated by scaffold and composite material.

The common malignant primary tumors that account for 70% of bone-related malignancies are osteosarcoma, chondrosarcoma, and Ewing sarcoma. Cancer in the bone originates in the mesenchymal stem cells (MSC), which are both ontogenic progenitor tumor cells and stromal cells and participate in tumor development [8, 9]. The formation of tumor-supporting stroma in bone occurs by osteoblasts, which are bone-forming cells derived from MSC, osteoclasts that are responsible for the resorption of osteocytes, immune and endothelial cells, and MSCs. Osteoclasts adheres to the surface of the bone and the different factors responsible for their activation depend on the type of tumor. Tumor-induced osteoblasts and tumor cells can metabolically activate osteoclasts to form tumor supporting stroma [10, 11]. The presence of osteoclasts in the microenvironment in cases of osteosarcoma may aggravate the osteoblastic behavior of tumor cells and this could be a negative prognostic factor [12]. In the cases of bone metastasis, the disruption between bone deposition and bone resorption leads to the formation of the pathogenic process [13]. With respect to other carcinomas, the control and treatment approach of bone tumors have undergone a consistent slowdown due to their complexity and heterogeneity. Many challenges hinder the study of bone cancers that vary from difficulties in manipulating bone as a tissue, the rarity of occurrence of bone cancer, difficulties associated with locating bone metastasis in human patients, and the limited number of models mimicking

CHAPTER 11

Nanoparticle-Mediated Delivery of RNA-Based Therapeutics for Colon Cancer: Current Status and Future Prospects

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Abstract: Colon cancer is a leading cause of cancer-related mortality globally, and the available treatment options are often limited in their effectiveness. RNA-based therapeutics hold promise as a novel approach for treating colon cancer. However, the delivery of these therapeutics to cancer cells poses significant challenges. Nanoparticles have emerged as a potential solution for the targeted delivery of RNA-based therapeutics to colon cancer cells. This chapter provides a comprehensive review of the development of nanoparticles specifically designed for the delivery of RNA-based therapeutics in the context of colon cancer. The chapter highlights the advantages offered by nanoparticle-based delivery systems, such as improved stability, protection against degradation, and extended circulation time. Various types of nanoparticles utilized for RNA delivery are discussed, including lipid-based nanoparticles, polymeric nanoparticles, and inorganic nanoparticles. The challenges associated with nanoparticle-based delivery, such as potential immunogenicity and toxicity, are also addressed, emphasizing the need for further refinement and optimization. In conclusion, the development of nanoparticle-based delivery systems holds significant promise in overcoming the challenges associated with the delivery of RNA-based therapeutics for colon cancer. This chapter provides a comprehensive overview of the current state of research in this field and offers insights into future directions for advancing nanoparticle-based delivery strategies in colon cancer therapy.

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Sankha Bhattacharya, Mayank Sharma, Amit B. Page, Dhrubojyoti Mukherjee and Abhishek Kanugo (Eds.)

Keywords: Colon cancer, Nanoparticles, Nanomedicine, RNA-based therapeutics, Targeted delivery.

INTRODUCTION

Colorectal cancer (CC), affecting the colon (large intestine), ranks as one of the most prevalent cancers globally, posing significant risks to health and life. It remains a formidable public health challenge, standing as the third most common cancer and the second leading cause of cancer-related mortality worldwide [1, 2]. In 2020 alone, there were over 1.9 million newly diagnosed cases of colorectal cancer, with more than 930,000 deaths attributed to the disease. Projections indicate a worrisome trend, with estimates suggesting a staggering increase to 3.2 million new cases and 1.6 million deaths annually by 2040, underscoring the urgent need for innovative therapeutic approaches [3]. The World Health Organization (WHO) reports colorectal cancer as the third most prevalent cancer globally, comprising approximately 10% of all cancer diagnoses. Notably, the burden of colorectal cancer predominantly affects older individuals, with a significant proportion of cases occurring in those aged 50 and above [4, 5]. Lifestyle factors, including a diet high in processed meats and low in fruits and vegetables, sedentary habits, obesity, smoking, and excessive alcohol consumption, significantly contribute to its incidence and progression [6].

Despite advances in early detection and treatment modalities, the prognosis for patients with advanced-stage colon cancer remains poor, emphasizing the need for a novel therapeutic approach. In recent years, RNA-based therapeutics have emerged as promising candidates for the treatment of colon cancer, offering the potential to modulate gene expression, inhibit oncogenic pathways, and induce selective cytotoxicity in cancer cells [7, 8]. However, the clinical translation of RNA drugs faces numerous challenges, including poor stability, rapid degradation, limited cellular uptake, and off-target effects [9].

To address these challenges and unlock the full therapeutic potential of RNA-based drugs, innovative delivery systems are being developed, with nanoparticles serving as versatile carriers for RNA molecules [10]. Nanoparticles offer several advantages for drug delivery, including their small size, large surface area-to-volume ratio, tunable physicochemical properties, and ability to encapsulate and protect RNA payloads from degradation [11]. By exploiting these unique characteristics, researchers aim to optimize the pharmacokinetics, biodistribution, and intracellular uptake of RNA drugs, thereby enhancing their efficacy and minimizing adverse effects [8].

RNA-based therapeutics, including messenger RNA (mRNA), small interfering RNA (siRNA), and microRNA (miRNA), hold immense promise for CC treatment by targeting specific genes or pathways involved in cancer initiation and progression [12, 13]. However, a major hurdle in exploiting their potential lies in their inherent instability and inability to efficiently reach target colon cancer cells [14]. Nanoparticles have emerged as powerful tools to overcome these limitations, offering a safe and effective approach for enhanced delivery of RNA-based therapeutics in CC therapy (Fig. **1**) [15, 16].

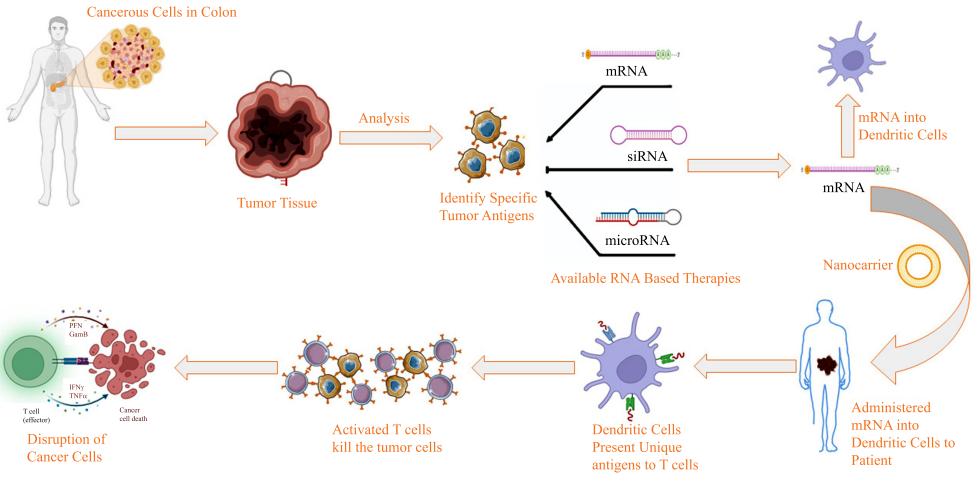

Fig. (1). Schematic representation of colon cancer treatment by RNA-based nanocarriers.

The chapter explores the potential of nanoparticles to overcome challenges in delivering RNA drugs and enhance their efficacy in colon cancer therapy. It delves into the diverse range of nanocarriers used for RNA delivery, highlighting their unique properties and functionalities. Additionally, it offers a comprehensive overview of the current state-of-the-art nanoparticle-mediated delivery of RNA-based therapeutics for colon cancer. Through examination of recent advancements and ongoing research, the chapter aims to provide insights into future directions for advancing nanoparticle-based delivery strategies in colon cancer therapy.

Current Treatment Options for Colon Cancer

Therapies Using Medication

Colon cancer treatment has indeed witnessed significant advancements, with medication playing a crucial role alongside surgery and radiation therapy. Therapies using medication for colon cancer encompass a wide range of options tailored to the individual's disease stage, molecular profile, and overall health

CHAPTER 12

Polymeric Nanocarriers for Advanced Cancer Therapy: Current Developments and Future Prospects

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Abstract: Cancer remains a formidable challenge in modern medicine, characterized by the uncontrolled growth and proliferation of abnormal cells that form tumors, which can infiltrate and damage healthy tissues. Metastasis, the spread of cancerous cells, exacerbates the condition, affecting immune function and organ health. Various factors contribute to cancer development, including lifestyle choices, genetics, and environmental exposures. At the cellular level, cancer progression involves mutations, survival mechanisms, invasion, and metastasis. Effective cancer treatment requires targeted delivery of therapeutic agents to tumor sites while minimizing damage to healthy tissues. Nanotechnology-based drug delivery systems offer promising solutions to this challenge, leveraging the unique characteristics of nanoparticles to enhance drug solubility, specificity, and efficacy. This abstract reviews the challenges in tumor targeting and the rationale behind it, emphasizing the importance of understanding the tumor microenvironment (TME) for developing effective strategies. The TME, comprising various cellular and non-cellular components, influences tumor progression, metastasis, and response to treatment. The enhanced permeation and retention (EPR) effect exploits the abnormal vascular architecture of tumors, allowing passive accumulation of nanocarriers in tumor tissues. Active targeting strategies involve surface modifications of nanoparticles to enhance specificity for cancer cells, improving drug delivery and reducing off-target effects. Polymeric nanocarriers offer several advantages, including tumor targeting, enhanced bioavailability, and reduced side effects, making them valuable tools in cancer therapy. Nanotechnology-based drug delivery systems hold great promise for targeted cancer treatment by overcoming the limitations of conventional therapies. Understanding tumor biology and exploiting the unique features of nanoparticles can lead to innovative approaches for combating cancer while minimizing adverse effects on healthy tissues.

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Keywords: Cancer, Drug delivery, Metastasis, Nanotechnology, Tumor targeting, Therapeutic efficacy.

INTRODUCTION

Cancer is a multifaceted disease that involves the abnormal growth of cells and their uncontrollable proliferation in the body. Cancerous cells form lumps of tissue called tumors. The cells from the cancerous tissue may damage other healthy tissue and invade the tissues of different body parts, wherein they would again start to grow out of control [1]. Metastasis refers to the spreading of cancerous cells through the circulatory or lymphatic system. This condition causes damage to the immune system and malfunction of various body organs. The causes of cancer growth are diverse and complex. The most common factors involve diet, sedentary lifestyle, diseased conditions, alcohol, obesity, *etc.* A number of internal factors can also contribute to cancer, such as hormones, genetic mutations, genetic disorders, or the immune system [2]. It is believed that certain carcinogenic factors like smoking, radiation, bacteria, or viruses penetrate the cytoplasm of cells and cause genetic mutations by disrupting the function of the nucleus. At the cellular level, the development of cancer involves steps like (i) mutations, (ii) progression, (iii) survival, (iv) invasion, and (v) metastasis [3].

Cancer involves the abnormal growth of various cells in the body. Depending upon the type of cell proliferation, different types of cancer exist and require a distinct treatment strategy. The tumors may be further classified as benign (not spreadable) and malignant (able to spread). Benign tumors are harmless to healthy tissues as they do not invade and spread. On the contrary, malignant tumors prove lethal and life-threatening as they are capable of metastasis. Benign tumors can be treated or removed by surgery. Malignant tumors are comprised of cancerous cells with tumor heterogeneity and invasion capability to the various sites in the body. On the basis of the tissue affected, cancer can be classified as (i) Carcinomas (epithelial cells), (ii) Sarcomas (connective tissue), (iii) Leukaemia and Lymphoma (blood-forming cells), and (iv) Adenomas (benign tumors of epithelial tissue). Most of the cancers in humans involve carcinomas *i.e.*, malignancies associated with epithelial cells [4].

Cancer is the second most common cause of death globally and in countries with a high or very high human development index (HDI). In 2023, it was projected that new cancer cases would rise up to 1,958,310, with an increased number of cancer deaths up to 609,820 in the United States. In India, it is estimated that one person in nine suffers from cancer. The approximate number of cancer cases in India in 2022 was estimated to be 14,61,427. Among the various cancers, breast

and lung cancers are the most common types found in women and men, respectively [5].

Cancer refers to a group of diseases resulting from abnormal cell growth that interferes with normal body functioning and the immune system, becoming a life-threatening malignancy [6]. A wide range of methods is available for cancer treatment, including chemotherapy, radiation therapy, and surgery. However, these methods are associated with a large number of side effects due to the lack of solubility, non-specific targeting, low therapeutic index, low bioavailability, and development of multi-drug resistance [7]. Thus, there is a prerequisite to developing such a drug delivery system that is safe, with specificity for cancerous cells and high therapeutic efficiency. The structure and the microenvironment surrounding tumors enable us to target specifically cancerous tissues without harming the healthy ones. Nanotechnology-based drug delivery systems like nanoparticles, dendrimers, polymerosomes, etc., possess the potential to release their payload specifically to the targeted site in various types of cancers. Nanotechnology-based drug delivery systems have emerged as a promising field in the targeted treatment of cancer [8, 9].

CHALLENGES IN TUMOR TARGETING

Though a number of nanocarriers have been successfully developed, their effectiveness is concomitant with their interaction with biological conditions surrounding the tumor, properties of the nanocarriers (size, shape, and composition), and route of administration [10]. It is convenient to administer the anticancer drug into the systemic circulation and is compatible with patients. However, the limitation of systemic administration is the circulation of anti-cancer drugs throughout the body, which risks the healthy tissues at the same time. Systemic delivery also allows anti-cancer drugs to be trapped in the periphery of the tumors, resulting in tumor recurrence. Thus, the invasive localized delivery of anti-cancer agents is difficult to perform (peritumoral or intratumoral) but possesses potential benefits like improved retention time, increased efficacy, and subduing tumor recurrence [11]. The perfusion heterogeneity of tumors, which involves non-directional blood flow along with the altered vascular permeability within the vessels of the same tumor, limits the delivery of anti-cancer agents to tumor cells. The tumor's extracellular matrix becomes denser, stiffer, and leaky. This collapses the normal diffusion of oxygen in the tumor and presents a barrier to entry of anti-cancer agents, resulting in treatment failure. As a consequence of the abnormal extracellular matrix, a high tumor interstitial fluid pressure (TIFP) develops inside the tumor, which also restricts the passage and uniform distribution of anticancer agents into tumor tissues [12].

CHAPTER 13

Unravelling the Melanoma Maze: Biomarkers, Diagnosis, and Future Perspectives in Skin Cancer Management

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Abstract: The present chapter gives an overview of the critical role of melanoma biomarkers with regard to the improvement of diagnosis and treatment of melanoma in the context of oncology. Melanoma is a very aggressive type of skin cancer that is gaining growing incidence rates worldwide and hence requires an early diagnosis and effective treatment. The background information provided in the introduction covers almost everything concerning melanoma, its pathophysiology, and more importantly, the dire need for reliable biomarkers for early diagnosis of melanoma, prognostication, and monitoring therapeutic responses. The chapter presents a systematic overview of melanoma biomarkers, classifying them in relation to their utility in different clinical settings. Under genetic mutation biomarkers, it covers BRAF and NRAS, two genes of importance for explaining the molecular mechanisms of melanoma progression. Protein-based biomarkers include S100B and LDH, which are discussed in the context of prognosis, especially at the advanced stages of the disease. Discussion focuses on their incorporation into clinical practice in view of their role in advancing the development of personalized medicine approaches, targeted therapies, and immunotherapies for these diseases. This chapter is closed by a critical review of the emerging biomarkers and future directions in melanoma research, underscoring that new findings may radically alter the landscape of patient outcomes.

Keywords: Biomarkers, Diagnosis, Immunotherapies, Melanoma, Skin cancer.

INTRODUCTION

Melanoma, a type of skin cancer arising from melanocytes, poses a significant public health concern due to its aggressive nature and potential for metastasis. Early detection and accurate prognosis are critical factors influencing treatment outcomes in melanoma patients. Biomarkers, molecular indicators reflecting the

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presence or progression of the disease, have emerged as invaluable tools in advancing our understanding of melanoma biology and refining clinical management strategies [1 - 3]. The identification and characterization of specific biomarkers associated with melanoma provide insights into the molecular mechanisms underlying its initiation, progression, and response to therapy [4]. Biomarkers can be diverse, encompassing genetic mutations, gene expression profiles, protein markers, and epigenetic alterations. The integration of these biomarkers into clinical practice holds the promise of enhancing diagnostic precision, prognostic accuracy, and treatment tailoring [5].

This introduction explores the evolving landscape of biomarkers in melanoma skin cancer, emphasizing their role in early detection, risk stratification, and the development of targeted therapies. By elucidating the intricate molecular signatures associated with melanoma, biomarkers offer a personalized approach to patient care, paving the way for more effective interventions and improved outcomes in the challenging landscape of melanoma management [6]. As we delve into the intricate world of melanoma biomarkers, it becomes apparent that these molecular signatures hold the key to unlocking new dimensions in diagnosis, prognosis, and therapeutic advancements for this formidable skin cancer [7].

MELANOMA DIAGNOSIS AND DISEASE PROGRESSION BIOMARKERS

Diagnosis Biomarkers

BRAF mutation used for the detection of mutations in the BRAF gene, particularly the V600E mutation, is a critical diagnostic biomarker. This mutation is present in a significant percentage of melanoma cases, guiding targeted therapy decisions [8]. Melan-A (MART-1) and S100 Protein: Immunohistochemical analysis of melanoma-specific markers like Melan-A and S100 protein aids in confirming the diagnosis, especially in distinguishing melanoma from other skin lesions [9]. MITF (Microphthalmia-Associated Transcription Factor) is a transcription factor crucial for melanocyte development and differentiation. Aberrant MITF expression is observed in melanoma and can serve as a diagnostic marker [10]. Molecular Profiling is a genome-wide molecular profiling technique, such as gene expression profiling or next-generation sequencing, which can reveal unique molecular signatures associated with melanoma, contributing to accurate diagnosis [11]. Different biomarkers are represented in Fig. (**1**).

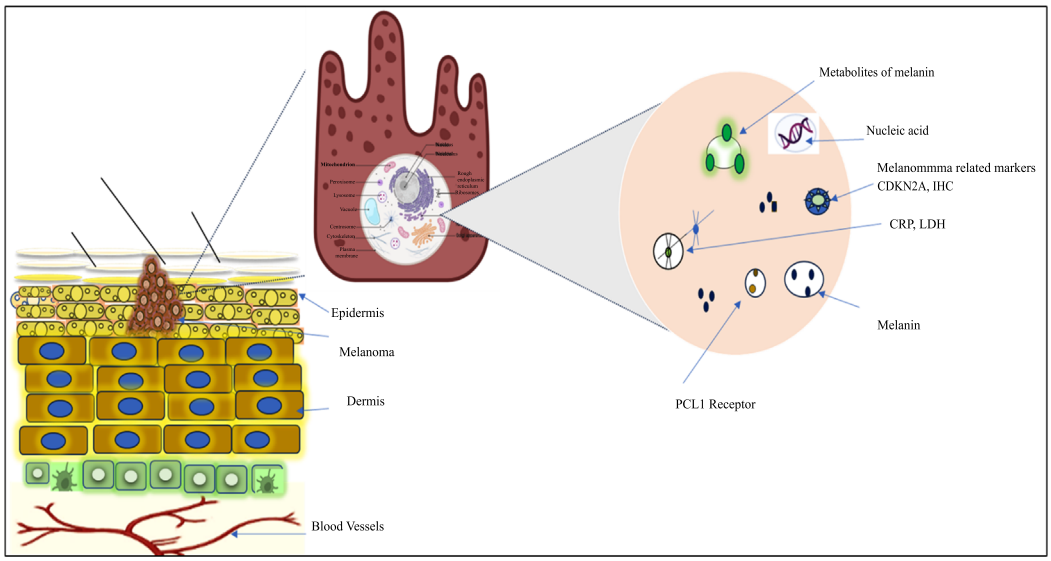

Fig. (1). Melanoma alongside some of its related markers and products resulting from tumorigenesis.

ENHANCED ROLE OF IMMUNOHISTOCHEMISTRY (IHC) IN MELANOMA DIAGNOSIS

Our section on immunohistochemistry is greatly improved, with a much more in-depth discussion of major protein markers used for confirming the diagnosis and distinguishing melanoma from other skin lesions. Specifically, this increased discussion will dwell on the S100 family of proteins, HMB-45, and Melan-A, which play such a big role in the IHC diagnostic process and their important clinical roles. Amongst the S100 family of proteins, S100B is very useful in IHC due to its increased sensitivity for melanocytic lesions. S100 proteins are calcium-binding proteins involved in various intracellular and extracellular functions that include cell growth, motility, and differentiation. In melanoma, S100B becomes overexpressed and represents a highly useful marker for identifying primary and metastatic melanomas. The chapter details how S100B staining is performed in IHC and illustrates its wide application in clinical practice. However, the section also mentioned the limited efficacy of S100B due to lack of specificity a phenomenon that may occur in other cell types, thus requiring complementary markers to allow definitive diagnosis. Another key marker discussed in this section is HMB-45, an antibody directed against a glycoprotein associated with melanosomes. The high specificity of HMB-45 to melanocytic lesions results from the fact that it can identify the existence of immature melanosomes within melanoma cells. The paper represents data on the diagnostic value of HMB-45 and places particular emphasis on its role in the differential diagnosis of melanoma from benign nevi and non-melanocytic lesions. Some examples of the

CHAPTER 14

Targeting Transforming Growth Factor-beta Receptor (TGF-βR) with Transethosomes: Novel Strategies for Targeted Skin Cancer Treatment

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Abstract: Transforming growth factor (TGF) is a multifunctional cytokine that plays a key role in proliferation, metastasis, and several other critical malignancy-related activities. Pharmaceutical firms have investigated TGF- inhibitors as cancer therapies, and several of these are now undergoing clinical trials. For many years, nanotechnology has substantially influenced a range of treatments. A variety of medications may now be delivered more safely and effectively because of developments in materials and formulation. Targeted administration guarantees a particular impact and minimizes systemic negative effects. Delivery methods based on transethosomes are also highly promising for cancer immunotherapy. The adaptability and specificity of nanoparticle-based delivery methods offer the possibility of simultaneously addressing the immune system to trigger a powerful immune response and the tumor tissue to alter the tumor microenvironment locally. Regardless of the presence or stage of malignancies, a powerful systemic immune response was induced by a transethosome-based nanocarrier. Transethosomes that specifically silence TGF- expression in the tumor microenvironment improved the transethosomal formulation's effectiveness in treating an advanced animal model of melanoma . The combination of these two medications offers a versatile and potent platform for the development of immunotherapeutic approaches as well as mechanistic research. The TGF-signaling system, its functions in cancer development and fibrotic disorders, and developments in TGF- antibodies and small-molecule inhibitors are all covered in this review.

Keywords: Nanotechnology, Skin cancer, Transforming growth factor-beta receptor (TGF-βR), Transethosome.

INTRODUCTION

Skin cancer, the most common type of cancer, originates in skin cells and is primarily triggered by exposure to ultraviolet (UV) radiation from the sun or

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artificial sources like tanning beds. The three main types are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Basal cell carcinoma, prevalent and slow-growing, typically occurs on sun-exposed areas, while squamous cell carcinoma, the second most common, may develop on sun-exposed skin or arise from pre-existing conditions [1]. Melanoma, though less frequent, is the most aggressive, originating in melanocytes and having a higher propensity to metastasize. Risk factors include UV exposure, fair skin, the presence of unusual moles, family history, and a weakened immune system. Prevention involves sun protection measures and regular skin checks [2]. Early detection through self-examinations and professional checks is crucial, enabling timely treatment and improved outcomes in managing skin cancer. Dermatologists recommend routine skin examinations, especially for those with risk factors, to identify any abnormalities at an early stage [3].

The treatment of skin cancer faces several current challenges, reflecting the complexity of the disease and the need for more effective therapeutic strategies [4]. One significant challenge is the increasing incidence of skin cancer cases globally, placing a growing burden on healthcare systems. The rise in ultraviolet (UV) radiation exposure, changes in lifestyle, and an aging population contribute to this escalating challenge [5]. Another notable challenge is the diversity of skin cancer types, each requiring a tailored approach. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma demand different treatment modalities, making it essential to develop versatile and targeted interventions. Melanoma, in particular, poses a challenge due to its potential for aggressive behavior and metastasis [6]. Early detection remains a critical issue. While routine skin examinations and screenings are effective, there is a need for improved diagnostic tools that can accurately identify skin cancer at its earliest stages. Enhancing public awareness and encouraging regular skin checks can contribute to early detection, but barriers such as accessibility to healthcare resources and education persist. Treatment side effects and impacts on quality of life constitute another challenge [7]. Current treatment options, including surgery, radiation therapy, and systemic therapies, may lead to adverse effects, emphasizing the importance of balancing efficacy with minimizing patient discomfort and long-term consequences. Resistance to therapies is a growing concern, particularly in advanced cases of skin cancer [8]. As with many cancers, resistance can develop against targeted therapies and immunotherapies, necessitating ongoing research into novel treatment approaches and combination therapies to overcome or prevent resistance. Finally, the economic burden associated with skin cancer treatment is a significant challenge. The cost of advanced treatments, ongoing surveillance, and management of potential complications can strain healthcare systems and place financial burdens on patients [9]. Addressing these challenges requires a comprehensive and interdisciplinary approach, incorporating

advancements in research, technology, and public health initiatives to improve prevention, early detection, and treatment outcomes for individuals affected by skin cancer [10].

The significance of the role of transethosomes in the context of skin cancer treatment lies in their potential as an advanced and targeted drug delivery system. Transethosomes offer several advantages that make them promising for addressing challenges in skin cancer therapy [11] Transethosomes are designed to improve drug penetration through the skin. In the treatment of skin cancer, this property is crucial for ensuring that therapeutic agents reach the targeted cancerous cells effectively. By enhancing skin permeability, transethosomes can facilitate the delivery of anti-cancer drugs to the desired skin layers, optimizing treatment outcomes [12]. The specific targeting of drugs to cancer cells while minimizing exposure to healthy tissues is a key goal in cancer treatment. Transethosomes can be engineered to carry therapeutic agents directly to the site of skin cancer, improving drug concentration at the tumor site and reducing the risk of side effects associated with systemic drug distribution [13]. The formulation of transethosomes can be optimized for various factors, including size, deformability, and entrapment efficiency. This flexibility allows researchers to tailor the transethosome composition for specific drugs and therapeutic needs, ensuring an efficient and customized delivery system [14]. Skin cancer treatments often involve potent drugs that, if systemically absorbed, may lead to adverse effects. Transethosomes can help minimize systemic absorption, allowing for higher drug concentrations at the tumor site while reducing the risk of systemic side effects. This is particularly relevant in case of skin cancer treatments where localized drug delivery is desirable [15]. Transethosomes can protect bioactive compounds from degradation and maintain their stability during delivery. This is crucial for preserving the efficacy of therapeutic agents, especially in the challenging environment of the skin. Therapeutic Efficacy: The use of transethosomes can potentially enhance the therapeutic efficacy of anti-cancer drugs by ensuring their efficient delivery to the targeted skin cancer cells. This may lead to improved treatment outcomes, better patient responses, and potentially reduced resistance to therapy [16]. Overall, the significance of transethosomes in skin cancer treatment lies in their ability to overcome challenges associated with drug delivery, offering a targeted and effective approach that may enhance the overall success of skin cancer therapies. The development and utilization of transethosomes represent a promising avenue for advancing the field of skin cancer treatment [17, 18].

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