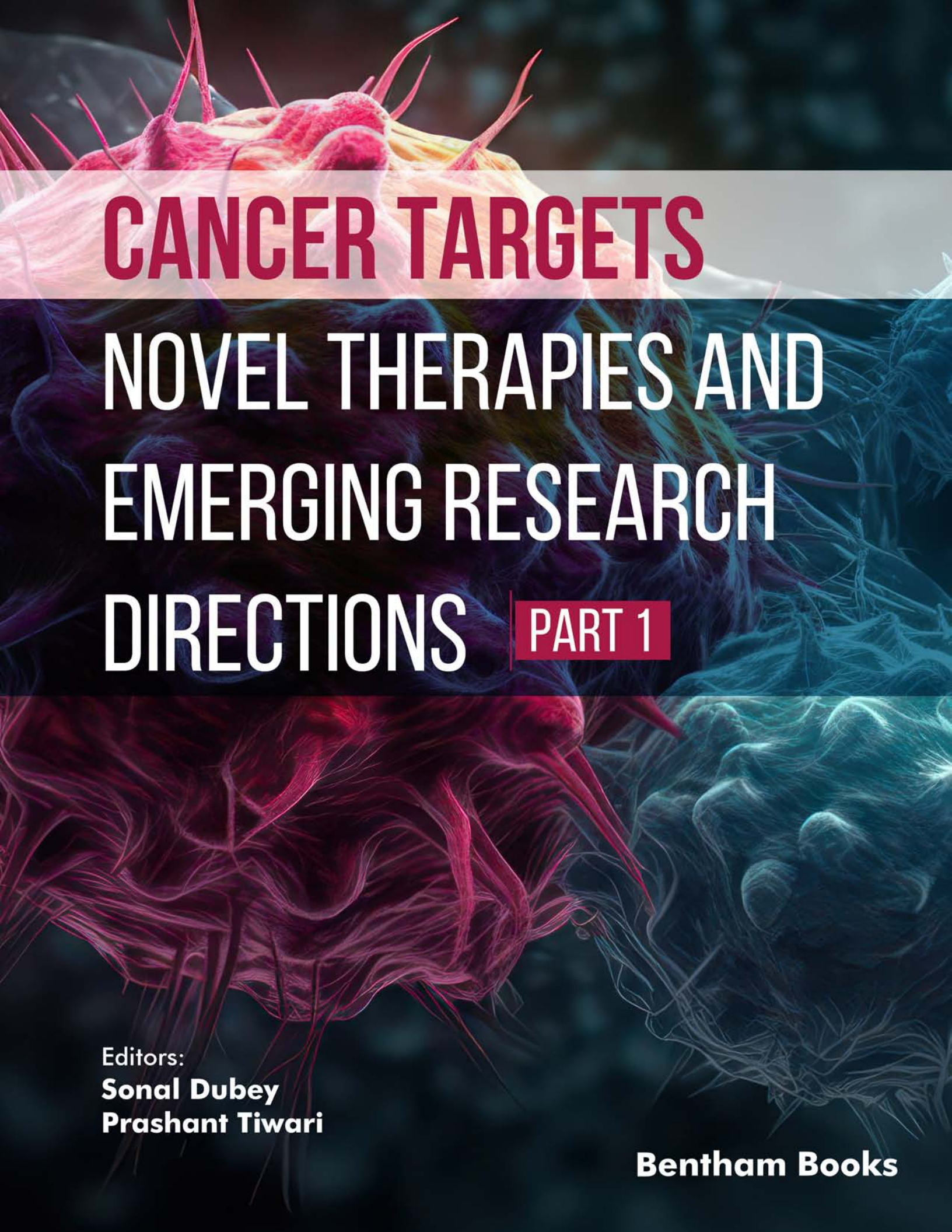

CANCER TARGETS

NOVEL THERAPIES AND EMERGING RESEARCH DIRECTIONS

PART 1

Editors:
Sonal Dubey
Prashant Tiwari

Bentham Books

Cancer Targets: Novel Therapies and Emerging Research Directions *(Part 1)*

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FOREWORD

It is with great enthusiasm that I present "Cancer Targets: Novel Therapies and Emerging Research Directions," edited by Dr. Sonal Dubey and Dr. Prashant Tiwari, and published by Bentham Science. This book represents a vital contribution to the ongoing battle against cancer, a disease that continues to challenge scientists and clinicians worldwide. With advancements in research and technology, we find ourselves at the cusp of transformative breakthroughs in cancer treatment and management.

As we know, cancer is a complex and heterogeneous group of diseases characterized by uncontrolled cell growth. Traditional therapies such as chemotherapy and radiation have long been the mainstay of treatment; however, they often come with significant limitations and side effects. The need for novel therapeutic strategies that are more effective and less toxic is more pressing than ever. This volume delves into the innovative research and emerging methodologies that are redefining our approach to cancer treatment, focusing specifically on novel therapeutic targets and mechanisms.

The chapters within this book encompass a wide array of topics, including targeted therapies, immunotherapy, and personalized medicine. Each contribution reflects the latest advancements in the understanding of cancer biology, molecular mechanisms, and potential therapeutic interventions. Dr. Dubey and Dr. Tiwari have meticulously curated a collection of expert opinions and research findings that not only highlight current trends but also provide insights into future directions for cancer therapy.

Furthermore, this book addresses the critical need for interdisciplinary collaboration in cancer research. By integrating knowledge from various fields, including molecular biology, pharmacology, and clinical medicine, we can accelerate the development of effective treatments. The insights shared in this volume will empower researchers and clinicians to explore new avenues of investigation and improve the therapeutic landscape for cancer patients.

In an era where precision medicine is gaining momentum, understanding cancer targets at a molecular level is essential. The contributions in this book pave the way for innovative approaches that could significantly improve patient outcomes and quality of life.

I am confident that "Cancer Targets: Novel Therapies and Emerging Research Directions" will serve as an invaluable resource for researchers, clinicians, and students alike. It not only informs but also inspires continued exploration in the relentless fight against cancer.

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Preface

Cancer remains one of the most complex and multifaceted diseases of our time. Despite tremendous advances in treatment modalities, such as surgery, chemotherapy, radiation, and immunotherapy, there is still a pressing need for more effective, targeted therapies that can enhance patient outcomes and reduce the collateral damage to healthy tissues. The scientific community's concerted efforts to unravel the underlying mechanisms of cancer development, progression, and resistance have paved the way for the discovery of novel molecular targets and therapeutic strategies.

This book, *Cancer Targets: Novel Therapies and Emerging Research Directions*, Volume-I aims to provide a comprehensive overview of the latest advancements in the identification of molecular targets for cancer therapy. The chapters in this volume delve into various cutting-edge research areas, from the molecular biology of cancer to the preclinical and clinical evaluation of novel agents. By focusing on the emerging directions in cancer research, the book highlights the potential of targeted therapies to transform the landscape of cancer treatment in the coming years.

We have collaborated with leading experts in the field to present a diverse range of perspectives and insights. These contributions offer a deep dive into the molecular mechanisms that drive cancer growth, metastasis, and drug resistance, while also addressing the challenges and opportunities associated with translating these discoveries into clinical practice.

This compilation will serve as a valuable resource for researchers, clinicians, and students who are keen to explore the frontier of cancer research and therapy. We believe the insights shared in this volume will inspire continued innovation in cancer treatment and foster new approaches to tackle this formidable disease.

We are grateful to all the contributors for their invaluable input and dedication to advancing cancer research. Special thanks are extended to Bentham Science for their support and for providing a platform for this important work. We hope this book will serve as a beacon for future research endeavors and as a testament to the progress being made in the fight against cancer.

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CHAPTER 1

Unveiling Cancer's Molecular Tapestry

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Abstract: Cancer is a hereditary illness that mostly results from oncogene stimulation, suppression of cancer gene dysfunction, or external factor-induced mutagenesis. Data gathered from research groups published by Springer, Elsevier, PubMed, Science Direct, and Nature will be used to write this chapter. Cancer-causing genes are proto-oncogenes that are normally necessary for proliferation, differentiation, and control, but they have been dysregulated. A proto-oncogene may become an oncogene as a result of chromosomal translocation, reorganization, or mutation brought on by viral infection, deletion, addition, or doubling of a gene. Targeting these oncogenes with drugs or the RNA interference process aims to prevent the development of cancerous cells. Numerous molecular biology techniques have been developed for the detection and treatment of cancer, including oncogene silencing, retroviral therapy, and gene modifications that decrease tumor growth. The most promising techniques for bringing about a cancer-free planet include zinc finger nucleases, RNA disruption, and CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats).

Keywords: Cancer, CRISPR, Molecular, Mutagenesis, Oncogene, Proto-oncogenes.

INTRODUCTION

Fundamentally, cancer is an illness defined by unchecked cell division and expansion that is fuelled by changes in the genes and epigenetics. Among the significant regulatory genes that are molecularly altered in cancer are oncogenes, genes involved in DNA repair, and tumor suppressor genes. Apoptosis, differentiation, and cell cycle control are among the regular biological functions

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that are disrupted by these mutations. Hanahan and Weinberg (2011) [1] state that a favorable environment for malignant transformation and tumor growth is created when oncogenes like KRAS or MYC are activated and tumor suppressors like TP53 or RB1 are inactivated. The intricacy and variety of these molecular changes have been made clear by the thorough characterization of cancer genomes made possible by recent developments in high-throughput sequencing technology [2, 3].

The earliest records of cancer research may be found in Egyptian writings, which reach back to prehistoric times. But in the 20th century, important progress was made in comprehending the illness at the molecular level. One of the turning points in the understanding that cancer is essentially a genetic illness was the discovery by Watson and Crick in 1953 that DNA is the genetic material. The discovery of a particular genetic anomaly linked to cancer came about in 1960 when the Philadelphia chromosome was found in cases of chronic myeloid leukemia [4]. In the next decades, oncogenes and tumor suppressor genes were discovered, and Knudson developed the "two-hit hypothesis" to explain the genetic basis of retinoblastoma [5]. Modern cancer genetics and tailored therapeutics have been made possible by these historical turning points [6]. The effect of these discoveries on present therapeutic techniques and continuing research orientations has been underlined by recent historical analysis [7].

It is essential to comprehend the molecular pathways driving cancer in order to create efficient prognostic, therapeutic, and diagnostic approaches. Cancer's molecular understanding has produced biomarkers that can forecast the course of the illness and how well a patient will respond to therapy. For example, EGFR gene mutations are used to select patients for tyrosine kinase antagonist therapy if they have lung cancer that is not small cell [8]. Moreover, molecular characterization of malignancies has enabled the creation of personalized healthcare, whereby a patient's medication is tailored according to the genetic composition of their specific malignancy [9]. This approach increases medicinal efficacy while reducing negative effects. In addition, understanding the molecular origins of cancer can lead to the recognition of novel treatment targets, as seen by the finding of immunological checkpoint inhibitors, which have fundamentally altered the way that cancer is addressed [10, 11].

CANCER GENOMICS

Cancer genomics primarily studies the differences in the expression of genes and the entire genome sequence of cancerous cells and normal host cells (Fig. **1**). Recent advancements in next-generation sequencing have greatly expanded our understanding of the genetic alterations and mutations that cause cancer.

Extensive genomic sequencing of malignancies has yielded novel insights into tumor variation, clonal development, and the identification of new therapeutic targets. A vital resource for personalized oncology, a database of mutations spanning a variety of cancer types has been assembled by large-scale projects like The Cancer Genome Atlas (TCGA) and the Pan-Cancer Analysis of Whole Genomes (PCAWG) [12, 13].

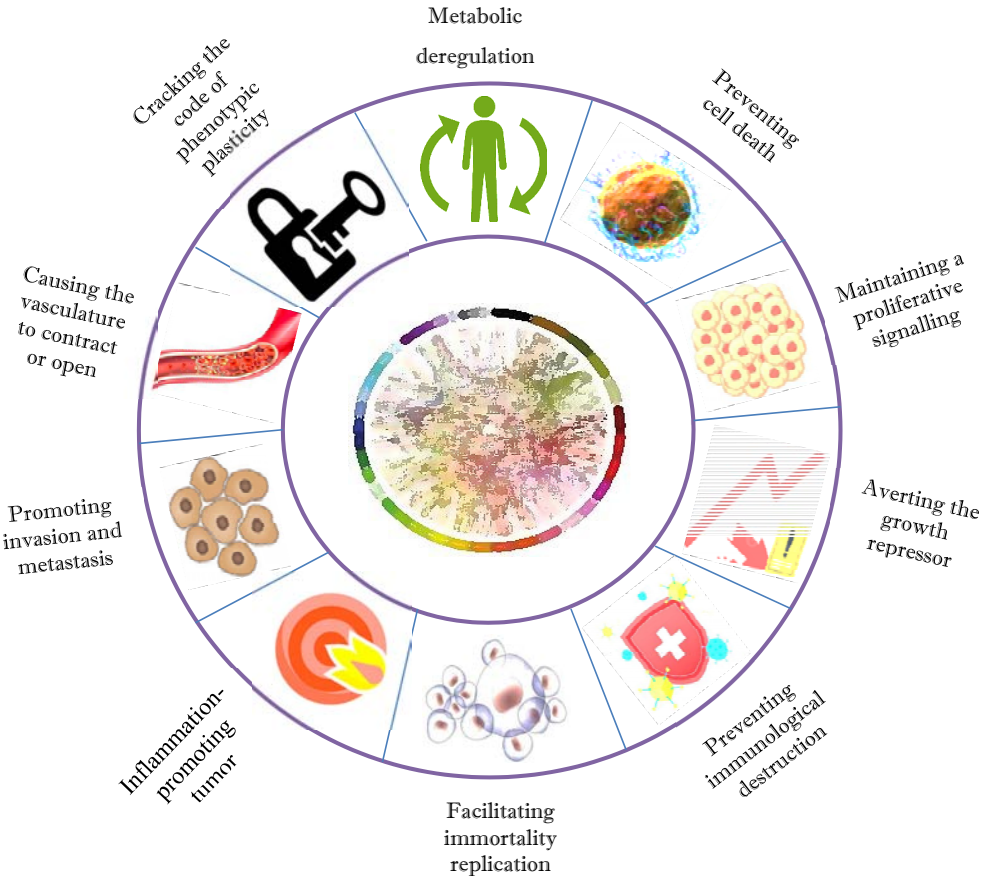

Fig. (1). A guide to cancer genomics.

The Human Genome and Cancer

The human genome's genetic code, which is prone to changes that result in cancer formation, is a crucial element in the emergence of cancer. The development of complete genome sequencing has led to the discovery of several structural alterations and mutations linked to cancer. These genetic alterations have been

CHAPTER 2

Navigating the Landscape of Cancer Genomics

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Abstract: Cancer genomics is at the cutting edge of modern oncology, altering our understanding of the complex molecular underpinnings of cancer. This chapter explores the dynamic landscape of cancer genomes, revealing their enormous impact on understanding cancer heterogeneity, progression, and treatment response. Navigating this landscape demands the expert integration of many genomic data modalities, including somatic mutations, copy number changes, and gene expression patterns. Cancer genomics not only provides critical insights into tumor biology but also provides the path for personalized therapy Strategies by unraveling the complex interaction of genetic and epigenetic modifications directing oncogenesis.

The presented chapter is an exploratory overview of the current state of cancer genomics research, emphasizing significant discoveries, technological developments, and ongoing challenges. We demonstrate the critical significance of high-throughput sequencing technologies, such as (NGS) Next-Generation Sequencing, in revealing the genetic landscape of cancer with remarkable resolution. Furthermore, emphasize the transformative power of single-cell genomics and spatial transcriptomics in understanding the variability and spatial organization of tumor ecosystems.

Among a large amount of genetic data, the integration and interpretation of multi-omics datasets emerge as critical challenges. We describe the spectrum of bioinformatics tools and approaches for understanding cancer's complicated genomic architecture and generating therapeutically relevant information. Furthermore, we delve into various

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aspects of tumor heterogeneity, including both intra- and inter-tumor heterogeneity, and discuss their consequences for cancer progression, metastasis, and therapy resistance.

As precision oncology gains popularity in cancer care, look at the emerging applications of genetic profiling in patient Stratification, targeted therapy selection, and real-time monitoring of treatment response. Recognise emerging trends, such as complete molecular characterization *via* multi-omics data integration, the introduction of liquid biopsies for non-invasive tumor dynamics monitoring, and the growing field of immunogenomics for leveraging the immune system for cancer therapy.

Keywords: Somatic mutation, Heterogeneity cancer, Cancer genomics precision oncology, Gene Expression, Next-Generation Sequencing (NGS).

INTRODUCTION

Advancements in genomics and biotechnology have revolutionized our understanding of cancer, highlighting its complex, genetically driven nature. The integration of technologies such as high-throughput sequencing, single-cell sequencing, and spatial transcriptomics has provided new insights into tumor biology, enabling a more tailored approach to cancer treatment. This chapter explores the cutting-edge tools and techniques in cancer genomics, with a particular focus on single-cell sequencing, spatial transcriptomics, and their role in advancing personalized cancer therapies. A genetic disease is cancer. Any alteration to the genes governing the growth and division of cells has the potential to cause cancer. However, only a small percentage of the numerous genetic mutations that take place in a cell will result in cancer, while the vast majority will not affect the ability of the cell to survive. It is clear that identifying the genetic abnormalities that cause cancer to arise in cells is essential to understanding the origin of cancer [1].

Whole genome cancer analysis is now feasible thanks to the development of high-throughput sequence analysis during the last ten years and a hundred-fold drop in sequencing costs for analysing a single cancer genome instance, from over $100,000 to $1,000–2,000 [2]. Due to this, a vast amount of genomic data has been available: 1,457,702 distinct mutations were found in a recent whole-genome investigation of 33 cancer types [3, 4]. The oncologic scientific community faces a problem in understanding the function of mutations in cancer genesis and survival, as well as their therapeutic implications, despite the ease with which a great amount of data can be gathered. The common mutations found in human cancer, their role in carcinogenesis, the molecular pathways involved in the onset and spread of cancer, and the mechanism and cause of tumour heterogeneity have all been the subject of an astounding amount of research over

the past few decades [4, 5]. This research has altered the landscape of the cancer genome, offering a comprehensive understanding of the development and metastasis of cancer.

On the other hand, high-throughput mining of imagery characteristics from medical images can establish relationships among either quantitative or qualitative imaging results and all aspects of the cancer genome landscape, such as mutation-driven carcinogenesis, pathway-specific cancer, and metastasis development [6, 7].

For radiologists and anybody else involved in oncologic patient care, it is essential to comprehend the terrain of cancer genetics and the mechanisms behind cancer genesis [8, 9]. In clinical practice, a sizable portion of imaging investigations completed in most radiology departments are dedicated to cancer, from disease progression through diagnosis and screening. Radiologists are essential to the clinical care of cancer patients because they need to be able to understand the imaging phenotype of the disease, interpret the response to treatment with oncologic drugs, and comprehend the imaging presentation of response [10]. They can come from large academic centres or small, successful private practices.

Overview of Cancer Genomics

The structural and functional characteristics of complete genomes are studied in the interdisciplinary area of genomics. As a result, it is separated into two groups: functional genomics and structural genomics. While the latter focuses on all transcripts and encoded proteins from a particular genome, the former seeks to characterise the DNA sequences of haploid genomes. These investigations require sophisticated computational statistics and high-throughput methods that are updated frequently with new technological advancements [11]. Since cancer is a genetic disease, research on the disease involves identifying somatic and germ-line oncogenic mutations in a number of tumour suppressor genes. Regarding the prognosis of the disease and molecular therapy, some of these altered genes offer high potential [12]. With the advancement of technology for thorough genome profiling of cancers, cancer genomics has changed [13, 14].

Importance of Cancer Genomics

In contemporary oncology, cancer genetics is vital because it provides information that is critical for enhancing prevention, diagnosis, and therapy plans. Researchers can find particular molecular targets for personalised therapies—which are frequently more successful and have fewer side effects than traditional treatments—by analysing the genetic mutations and variations that drive the development of cancer. For example, knowledge of the genetic changes

CHAPTER 3

The Role of Epigenetics in Cancer Progression

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Abstract: Epigenetic mechanisms significantly influence cancer development and treatment. This chapter delves into the complex mechanisms of epigenetic regulation and their implications in oncogenesis. Initially, we explore how DNA methylation, histone modifications, non-coding RNAs, and SUMOylation contribute to cancer progression. Specifically, hypermethylation and hypomethylation of DNA, as well as histone acetylation, deacetylation, methylation, and demethylation, are examined for their roles in gene expression modulation and oncogenic transformation. The chapter also highlights the influence of microRNAs and long non-coding RNAs in tumorigenesis. We further investigate the impact of epigenetic changes on key oncogenic signaling pathways, including the EGFR, PI3K/AKT/mTOR, and RAS/RAF/MEK/ERK pathways, and their role in cell cycle regulation, invasion, and metastasis. The potential of targeting epigenetic alterations for therapeutic purposes is discussed, with an emphasis on inhibitors of epigenetic writers, readers, and erasers, as well as the combination of epigenetic and genetic therapies. Clinical applications of epigenetics in cancer diagnosis and prognosis are also covered, providing insights for developing prognostic and diagnostic biomarkers for various cancers, including breast, prostate, lung, colorectal, and liver. To highlight the potential of epigenetics to advance cancer treatment and enhance patient outcomes, the chapter concludes with a review of the present obstacles and potential paths forward in the field of epigenetic therapy.

Keywords: Cancer diagnosis, Cancer prognosis, Cancer progression, Chromatin remodelling, Combination therapies, DNA methylation, DNA methyltransferase inhibitors, Epigenetic biomarkers, Epigenetic dysregulation, Epigenetic regulators, Gene expression regulation, Gene silencing, Histone deacetylase inhibitors, Histone modifications, Metastasis, Non-coding RNAs, Oncogenes, Sumoylation, Targeted therapies, Therapeutic resistance.

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INTRODUCTION

Overview of Cancer Progression

Cancer progression is a multifaceted pathway, characterized by the transformation of normal cells into malignant ones, followed by their uncontrolled proliferation and spread throughout the body. This journey from a single aberrant cell to a complex tumor involves a series of genetic mutations and alterations, impacting various cellular pathways and mechanisms. At its core, cancer progression encompasses several key stages: initiation, promotion, and metastasis (Fig. **1a**) [1].

Cancer progression begins with initiation, where genetic mutations caused by environmental factors (such as ultraviolet radiation and carcinogens) or inherited predispositions that repress TSGs and activate oncogenes, leading to restrained cell growth. Promotion follows, characterized by the clonal expansion of mutated cells driven by growth signals and a supportive microenvironment. Angiogenesis, the development of new blood vessels, provides oxygen and nourishment to the expanding tumor, allowing it to grow into a discernible mass. When malignant cells reach the metastasis stage, they invade nearby tissues and enter the lymphatic or circulatory systems, and colonize new locations in order to spread from the initial tumor to other organs. Cancer-related deaths are caused by metastatic tumors, as they are more resistant [2]. The EMT and ECM are the two important mechanisms involved in tumor invasion and metastasis. EMT is characterized by the transition of epithelial cells into motile mesenchymal cells, enhancing cancer cell mobility and invasiveness, enabling them to spread from the primary tumor to distant sites (Fig. **1b**) [3]. ECM components provide structural support and signaling cues that influence cellular behavior, promoting cell adhesion, migration, and invasion. The cellular behaviour is influenced by the structural support and signaling cues provided by ECM, stimulating processes like migration, invasion, and cell adhesion (Fig. **1c**).

Importance of Epigenetic Regulation in Cancer

Although genetic mutations have long been understood to be crucial for the development of cancer, it is becoming more and more clear that epigenetic regulation is just as important. “Epigenetics is the study of heritable variations in gene expression that do not involve alterations to the underlying DNA sequence”. Histone modifications, ncRNA molecules, and DNA methylation are some of the processes that mediate these alterations.

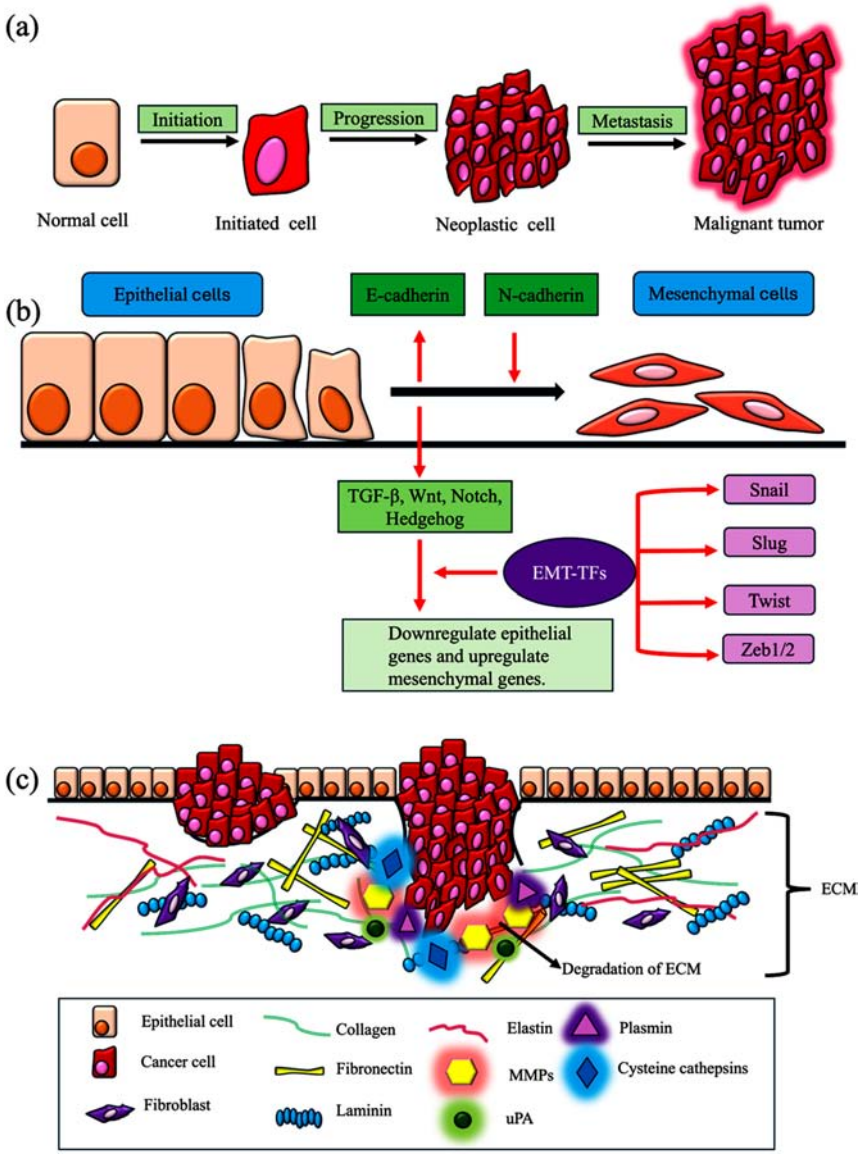

Fig. (1). Schematic representation of the key processes in cancer progression. (a) The figure illustrates the three stages of cancer progression, where a normal cell undergoes genetic mutations leading to the formation of cancer cells. (b) EMT is the transition of endothelial cells to acquire a mesenchymal phenotype. (c) ECM degradation is the process facilitated by MMPs and other proteases, such as serine proteases (uPA and plasmin) and cysteine cathepsins, leading to invasion and metastasis of cancer., Copyright 2018, MDPI. The diagram was made using Microsoft® PowerPoint® Version 16.86 (24060916) Build 16.0.16924.20054 (Microsoft®, Redmond, WA, USA).

CHAPTER 4

Immunotherapy: Harnessing the Power of the Immune System

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Abstract: Immunotherapy is an advanced technique in modern medicine that employs the body's natural defenses against diseases, including cancer. Unlike traditional medicines, immunotherapy doesn't target cancer cells immediately. Instead, it strengthens the immune system's ability to recognize and destroy cancerous cells. The immune system is essential to this procedure and holds the power to entirely alter how diseases are handled by offering customized and efficient treatments.

This work offers an in-depth overview of the basic concepts and procedures that support immunotherapy. It includes an array of methods, like immunological checkpoint agonists, cytokine therapy, inhibitors of checkpoints, and oncolytic viral treatment. These strategies work efficiently to activate, control, and redirect the immune system's attack on cancerous cells. Bispecific T-cell engagers, Adoptive cell transfer, and monoclonal antibodies are examples of targeted immunotherapy methods that stimulate the immune system to fight malignancies. Prospective improvements in immunotherapy concentrate on customized techniques, combination therapies, and the development of novel targets and techniques. While there are still challenges to be addressed, like managing immune-related side effects and combating resistance, the immune system's transformative potential offers enormous potential for the discipline of medicine in the coming years. When immunotherapy is coupled with complementary medicines, patients' general well-being and therapeutic outcomes may be strengthened.

Keywords: Adoptive T-cell therapy, Cancer cells, Checkpoint inhibitors, Cancer vaccines, Immune system, Immunotherapy, Immunoregulatory systems, Personalized medici.

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INTRODUCTION

The application of immunotherapy, an approach that targets and attacks diseases by activating the immune system, has transformed the medical management of cancer, along with various diseases. Unlike conventional methods such as radiation and chemotherapy, which attack cancer cells directly, immunotherapy fights cancer by utilizing the body's natural defenses [1, 2]. This technique provides a less harmful and more targeted approach by prolonging the immune system's capacity to recognize and eradicate cancerous cells. The word "immunotherapy" refers to an expansive group of medical procedures designed to strengthen the immune system's defenses against cancer as well as additional diseases [3, 4].

Although the idea of employing the immune system for fighting illness is hardly novel, there are significant modifications regarding the way it is utilized in contemporary healthcare. Considered the " founding father of immunotherapy," Dr. William Coley treated individuals with ineffective malignancies employing bacterial toxins in the latter part of the nineteenth century, with mixed results in cancer remission. It represented the earliest phase of immunotherapy as we understand it nowadays [4, 5]. This significant result opened the path for additional studies into the immune system and its possible application in cancer therapy.

The latter half of the 20th century saw the development of immune-mediated checkpoints like CTLA-4 and PD-1, which led to the creation of checkpoint inhibitors, and the early 1900s saw the development of monoclonal antibodies like rituximab, indicating a paradigm shift in the scientific community [6]. Modern medicine has generated revolutionary therapies, which have significantly boosted the effectiveness of immunotherapy in the management of cancer and made it a cornerstone of cancer care. As an important force in the fight against cancer, immunotherapy is now established due to its creative techniques and potential applications. To safeguard the body against harmful germs, toxins, and cancer, the immune system is a system made from a complex structure of cells, tissues, and organs. The immune system could target harmful infections while avoiding healthy cells by discriminating between the person's cells and foreign particles. The immune system is alert and responsive to dangers, which makes it a potent weapon in fighting against cancer and other illnesses [7 - 9].

The immune system's ability to recognize and eliminate recently formed tumor cells is critical in the case of cancer. On the contrary, cancer cells frequently create defenses against the immune system [10, 11] This can be done by creating checkpoint proteins, which decrease immune responses, or by creating a tumor

microenvironment that hinders the immune system. Immunotherapy treats these issues by boosting the immune system's innate barriers against cancer, restarting immunological responses against cancer cells, and carefully observing the immune system to avoid a return to cancer [12, 13] It is crucial to appreciate the purpose and function of the immune system to properly understand the process behind immunotherapy. Several signaling molecules and both the innate and adaptive immune systems engage extensively in this network. Through improvement or rerouting of these immune parts, immunotherapy offers an opportunity to transform the management of cancer and diseases, leading to improved outcomes and specific therapies [14].

TYPES OF IMMUNOTHERAPY

Immunotherapy is an innovative cancer therapy that improves the immune system's defenses against illness. This therapy method comprises multiple approaches, all geared toward eliminating cancer cells through different immune system processes [15, 16]. As indicated in Table **1**, this offers an in-depth overview of the main categories of immunotherapy as well as its underlying processes and therapeutic uses.

Table 1. Overview of Cancer Immunotherapies: Mechanisms, Applications, and Benefits

S. No.	Type	Mechanism	Applications	Benefits	Reference
1.	**Checkpoint Inhibitors**	PD-1, PD-L1, and CTLA-4 are examples of proteins that may be suppressed to stop T-cells from operating correctly, enabling T-cells to recognize and suppress cancer cells.	• Melanoma • Lung cancer • Bladder cancer	• Enhances immune response • Effective in various cancers • Can cause immune-related side effects	[17, 18]
2.	**Adoptive Cell Transfer (ACT)**	Extract, enhance, or modify T-cells outside the body and reinfuse them to fight cancer.	• B-cell acute lymphoblastic leukemia • Metastatic melanoma	• Personalized approach • Effective in certain blood cancers • High cost and potentially severe side effects	[19, 20]

CHAPTER 5

Cancer Stem Cells: Insights Into Tumor Heterogeneity

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Abstract: Background: New insights into the development and evolution of tumors are provided by the idea of Cancer Stem Cells (CSC), which was introduced recently. A ubiquitous feature of both in vitro and in vivo mammalian cells is heterogeneity. It has recently been discovered that, even in optimal culture circumstances, human and mouse embryonic stem cells are heterogeneous, containing both partially committed and pluripotent cells. Adult organ somatic stem cells are also diverse, with numerous subpopulations of self-renewing cells with unique capacities for regeneration. New insights into the development and evolution of tumors are provided by the idea of Cancer Stem Cells (CSC), which has emerged recently. It is hypothesized that CSC self-renewal, replication, and differentiation within the microenvironment result in a hierarchy of cells that make up the tumor mass.

Aims and Objectives: This work demonstrates that the Cancer Stem Cells (CSC) concept's hierarchical structure of malignant clones has important ramifications for tumor biology. The growth of tumors driven by CSCs is intrinsically coordinated concerning invasion, influences clone selection, and has fundamental implications for the development of efficient cancer treatments.

Methodology: It involved reviewing literature on organic farming, cover cropping, and precision agriculture. A comparative analytical study about the heterogeneity between normal stem cells, such as HSC, and cancer stem cells was carried out. A review of Examining Cancer Stem Cells in Depth and the Mosaic of Tumor Heterogeneity was also done. Electronic searches were carried out using the databases, *viz*. Google, Google Scholar, and PubMed for the study.

Result: It is likely that "Cancer Stem Cells: Insights into Tumor Heterogeneity" provides a thorough examination of how Cancer Stem Cells (CSCs) contribute to the heterogeneous composition of tumors. It investigates how CSCs' capacity to produce diverse cell types and genetic modifications affects tumor heterogeneity. Offering

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important insights into the creation of new treatments and the course of cancer, the paper addresses implications for tumor invasion, clonal selection, and response to medicines. Modifications affect tumor heterogeneity. Offering important insights into the creation of new treatments and the course of cancer, the paper addresses implications for tumor invasion, clonal selection, and response to medicines.

Conclusion: The newly found variability in CSCs and plasticity in non-CSCs has generated some confusion and led some researchers to dispute the validity of the CSC concept as well as the existence of CSCs. Before these discoveries, CSCs were thought to be a stable and fixed population of unique cells.

Keywords: Biomarkers, Clonal evolution, Drug resistance, Epithelial-mesenchymal transition, Genetic mutations, Heterogeneity, Microenvironment, Metastasis, Oncogenic signalling pathways, Plasticity, Self-renewal, Single-cell analysis, Stemness, Tumor-initiating cells, Tumor microenvironment, Tumor progression, Tumor recurrence, Tumor-initiating capacity, Therapy resistance, Tumorigenesis.

INTRODUCTION

Tumour heterogeneity presents a significant problem in the complex field of cancer biology, hindering the development of effective treatments and a cure. Previously believed to be single-celled masses, tumours are now understood to be dynamic ecosystems made up of several cell populations displaying a range of molecular, phenotypic, and functional traits [1]. The interesting subset of cells known as Cancer Stem Cells (CSCs), whose special qualities have recently attracted a lot of attention, sits at the centre of this intricacy. The finding that tumors, like normal tissues, contain a hierarchical organization resembling stem cell systems gave rise to the notion of CSCs [2, 3]. These uncommon, self-renewing cells may sustain their own population while producing children with a variety of phenotypes. CSCs are thought to induce treatment resistance, promote carcinogenesis, and coordinate the spread of metastatic disease within the tumor microenvironment, making them an important target for therapeutic intervention. Recognizing the complexity of these entities and their significant consequences for cancer biology and clinical management is crucial as we continue our investigation into the world of CSCs and tumor heterogeneity [4]. The primary objective of this inaugural chapter is to provide a comprehensive introduction to the concepts of Cancer Stem Cells (CSCs) and tumor heterogeneity, elucidating their historical evolution, defining characteristics, regulatory mechanisms, and practical implications. Commencing with an exploration of the historical underpinnings of CSC investigation, the narrative traces its trajectory from initial scepticism to widespread recognition as a cornerstone of modern cancer biology. We will examine the ground-breaking findings and paradigm shifts that have

influenced our understanding of CSCs to date, emphasizing the important studies and theoretical models that have advanced this field. Characterizing CSCs and the unique characteristics that differentiate them from bulk tumor cells is central to our discussion. The analysis will encompass the molecular signatures, functional assays, and phenotypic markers utilized for the identification and isolation of CSC populations across various cancer types [5, 6]. Additionally, scrutiny will extend to the dynamic phenomenon of CSC plasticity, delineating the cells' capacity to transition between differentiated and stem-like states in response to endogenous and exogenous cues within the tumor microenvironment. In parallel, exploration will delve into the intricate landscape of tumor heterogeneity, characterized by temporal and spatial fluctuations in genetic composition, cellular diversity, and functional attributes, evident in both intra- and inter-metastatic sites [7]. The examination will encompass the diverse origins of heterogeneity that contribute to the complex array of cellular diversity observed within tumors, including clonal evolution, epigenetic alterations, genetic mutations, and microenvironmental influences. The goal is to elucidate the underlying strata of tumor heterogeneity and discern its implications for cancer advancement, therapeutic efficacy, and clinical outcomes. To accomplish this objective, contemporary advancements in single-cell methodologies, multi-omics profiling, and computational modelling will be harnessed [8]. We will also look at how CSCs interact with the tumor microenvironment, including how they exchange information with immune cells, stromal cells, and extracellular matrix elements that influence the structure and function of tumors. Navigating through the intricate interactions between Cancer Stem Cells (CSCs) and tumor heterogeneity unveils significant clinical implications for cancer diagnosis, prognosis, and treatment. Addressing these phenomena entails a meticulous examination of the challenges posed by intertumoral heterogeneity [9]. Precision medicine strategies encounter hurdles in effectively targeting CSCs amidst this diversity, complicating the identification of underlying factors driving treatment resistance and relapse. To sum up, this first chapter provides an overview of CSCs and tumor heterogeneity and lays the groundwork for further chapters that will focus on certain facets of this emerging topic. The objective is to foster a holistic comprehension of Cancer Stem Cells (CSCs) and tumor heterogeneity by elucidating the intricate facets of cancer biology. This endeavor aims to catalyze groundbreaking discoveries and novel therapeutic modalities in the perpetual combat against cancer [10].

CHAPTER 6

Targets and Therapies in Hematologic Malignancies

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Abstract: A recent and significant advancement in the handling of hematological hostilities is molecular target therapy. The utilization of tyrosine kinase inhibitors in the management of chronic myeloid leukemia has exhibited noteworthy efficacy in augmenting both overall survival rates and enhancing the quality of life for affected individuals. Furthermore, the advent of Janus kinase inhibitors, exemplified by ruxolitinib, presents a potential proportional benefit in the treatment of myeloproliferative disorders, encompassing polycythemia vera, main myelofibrosis, and chief thrombocythemia. The therapeutic landscape has expanded to encompass various other potent targeted therapeutic modalities, including but not limited to FLT3 inhibitors, histone deacetylase inhibitors, farnesyl transferase inhibitors, novel antibodies directed against surface antigens, small molecule inhibitors targeting tumor suppressors and oncogenic signaling pathways, inhibitors of immune checkpoints, and chimeric antigen receptor T-cells. These advancements have swiftly developed and hold promise in the realm of precision medicine for hematological malignancies. While patients with lymphoma have responded quite well to treatment with these targeted medicines, side effects should be taken into consideration. More research is necessary to determine the best combinations, dosages, and most appropriate candidates. The advancements in embattled treatment for malignant lymphoma were logically defined in this review, offering a justification for mechanism-based handling.

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Keywords: Chronic Myeloid Leukemia, Check-point inhibitors, Farnesyl transferase inhibitors, FLT3 inhibitors, Histone deacetylase inhibitors, Janus kinase inhibitors, Myelofibrosis, Myeloproliferative disorders, Molecular target therapy, Novel antibodies, Oncogenic signaling pathways, Polycythemia vera, Ruxolitinib, Surface antigens, Small molecule inhibitors, Thrombocythemia, Tyrosine kinase inhibitors, Tumor suppressors.

INTRODUCTION

Hematologic malignancies encompass a spectrum of neoplastic conditions impacting the hematopoietic system, including blood, bone marrow, and lymphatic tissues. They comprise various types such as leukemia, lymphoma, and multiple myeloma. Treatment strategies for hematologic malignancies rely on the specific category of tumor, its phase, and the age of the patient.

Overview/Understanding Hematologic Malignancies/Cancers

Hematologic cancers, encompassing a diverse array of malignancies originating from the blood and lymphatic systems, represent a complex and clinically challenging group of diseases. These cancers arise from aberrant propagation and dysregulation of forerunner cells, leading to the overproduction of abnormal blood cells [1]. Leukemias, lymphomas, and myelomas are the most common hematologic malignancies, each characterized by distinct clinical, pathological, and molecular features. Leukemias, including acute and chronic lymphocytic leukemia (AML and CLL), are categorized by the accumulation of immature or dysfunctional WBC within the bone marrow and peripheral blood [2]. Lymphomas, such as Hodgkin and non-Hodgkin lymphoma, arise from malignant transformation of lymphocytes within lymphoid tissues, manifesting as lymph node enlargement, organ infiltration, and systemic symptoms. Multiple myeloma, a neoplasm, is typified by clonal propagation of abnormal plasma cells within bone marrow, creating osteolytic lesions, hypercalcemia, renal dysfunction, and immunodeficiency. The pathogenesis of hematologic cancers is multi-factorial, involving genetic, epigenetic, and microenvironmental factors. Chromosomal translocations, gene mutations, and dysregulated signalling pathways split oncogenesis and disease progression, often leading to the activation of pro-survival pathways, evasion of apoptosis, and immune evasion [3]. Advances in genomic knowledge, like next-generation sequencing, have facilitated the comprehensive molecular characterization of hematologic malignancies, enabling the detection of persistent genetic modifications, driver mutations, and therapeutic targets. Furthermore, the intricate milieu of tumors made up of stromal cells, immune cells, and extracellular matrix constituents exerts a crucial influence on the pathophysiology of the disease and the efficacy of therapeutic interventions

[4]. Immune dysregulation, inflammatory cytokine signaling, and immune evasion mechanisms contribute to tumor growth, immune escape, and treatment resistance. Comprehending the nuanced interactions between tumor cells and microenvironments is imperative for advancement in innovative healing approaches, including immunotherapies and targeted agents. Despite significant evolution in the diagnosis and treatment of hematologic cancers, challenges such as disease heterogeneity, therapy resistance, and treatment-related toxicities remain formidable obstacles. Moreover, Disparities in healthcare access, influenced by socioeconomic variables and the adequacy of healthcare infrastructure, present supplementary hurdles to achieving optimal patient outcomes [5]. Therefore, a multidisciplinary approach, integrating genomic profiling, molecular diagnostics, and personalized therapeutics, is essential for improving prognosis and the well-being and overall satisfaction with life experienced by individuals diagnosed with hematologic malignancies.

Importance of Targeted Therapies

Targeted therapies have revolutionized the treatment landscape for hematologic malignancies, offering more precise and effective options compared to conventional chemotherapy. These therapies exploit specific molecular targets or pathways crucial for cancer cell survival and proliferation, thereby minimizing collateral damage to healthy tissues [6]. By elucidating the genetic and molecular aberrations driving hematologic cancers, researchers have identified a plethora of druggable targets, ranging from mutated kinases to dysregulated signaling cascades and immune checkpoints [7]. The advent of small molecule inhibitors, monoclonal antibodies, and immunotherapies has led to significantly better outcomes and quality of life for patients with diseases such as leukemia, lymphoma, and multiple myeloma [8 - 10]. Notably, targeted therapies have demonstrated remarkable efficacy even in cases refractory to traditional treatments, providing hope for those previously considered incurable. Persisting challenges, such as acquired resistance and adverse effects associated with treatment, highlight the necessity for continuous research and development endeavors. The high cost and accessibility of targeted agents remain significant barriers to equitable care [11]. Despite these challenges, the importance of targeted therapies in hematologic malignancies cannot be overstated, as they continue to redefine standards of care and offer new avenues for personalized medicine.

CHAPTER 7

The Microbiome and Cancer: Exploring the Gut Connection

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Abstract: The intricate relationship between the microbiome and cancer has emerged as a significant research focus, revealing that the human microbiome can support and hinder cancer development. The human microbiome consists of a diverse collection of microbial communities that interact across different body sites within the host. Dysbiosis of this commensal microbiota has emerged as a critical factor directly linked to cancer development. Notably, certain microbial species such as *Escherichia coli*, *Fusobacterium nucleatum*, *Helicobacter pylori*, and *Bacteroides fragilis* have been shown to promote tumorigenesis. Conversely, specific microbial communities exhibit tumor-suppressive properties through mechanisms such as influencing apoptosis, immunomodulation, and inhibition of angiogenesis. Additionally, members of the fungome and virome contribute substantially to the burden of cancer malignancy. The microbiome influence extends to cancer treatment outcomes, affecting chemotherapy, radiotherapy, and immunotherapy responses. Exciting developments in microbiome-based diagnostics and bacteria-based cancer therapies may offer promising avenues for personalized cancer treatment. Moreover, dietary interventions, fecal microbial transplantation, and probiotic therapies present novel strategies to manipulate the microbiome for therapeutic benefit. This chapter highlights the microbiome-cancer axis's importance in shaping cancer development, treatment response, and future therapeutic approaches.

Keywords: Colorectal cancer, Fecal microbiota transplantation, Dysbiosis, Microbiota, Intratumoral, Probiotic, Tumor microenvironment.

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INTRODUCTION

Microbiome

The human body is a complex ecosystem hosting various microorganisms, including bacteria, fungi, yeast, protozoa, archaea, and viruses. Collectively, these microorganisms constitute the commensal microbiota. The genetic repertoire of this community, known as the microbiome, is significantly more extensive than that of humans. Studying the microbiome has become crucial in understanding human health, as it is affected by factors such as age, nutrition, lifestyle, genetics, and underlying health conditions [1].

A balanced microbiota, particularly in the gut, is essential for overall health, as it produces metabolites that impact local and systemic well-being [2]. For example, microorganisms within the microbiota support anti-tumor immunity and produce essential metabolites such as hormones and vitamins [3]. The gut, the primary site of host-microbe interactions, exhibits vast species diversity among individuals, making it challenging to identify a core microbiome. However, metabolic gene abundance can be a potential metric for defining a healthy core. A 'healthy' microbiota is characterized by diversity, beneficial microbes, and resilience to stress, while disease-associated microbiota exhibit lower diversity and may harbor pathogenic species [4, 5]. The gut microbiomes of healthy individuals predominantly feature Bacteroidetes and Firmicutes bacteria, although each person's microbiome is unique and more diverse than previously thought [4, 6].

Recent estimates suggest that microbial genes significantly outnumber human genes, highlighting the significance of the microbiome [7]. Understanding the composition and function of the microbiome is crucial for comprehending well-being and disease.

Cancer

Many factors, including lifestyle, genetic, and environmental factors, cause the complex disease known as cancer [8]. The host's genetic makeup and external environmental factors influence the variability in the abundance and composition of bacteria within tumors. This variability leads to differences in tumor appearance and physiological characteristics, ultimately impacting treatment [9]. The tumor microenvironment (TME) is pivotal in the development and progression of cancer. It consists of the ecosystem around the tumor, including nearby blood vessels, various signaling molecules, bone marrow-derived inflammatory cells, immune cells, fibroblasts, and the extracellular matrix (ECM) [10]. Intracellular microbiota exists within the cancer cells and host immune cells in the TME. The tumor microbiota can alter the TME, prompting tumor cells to

recruit and activate immune cells and related matrix components. This influence significantly impacts cancer development, prognosis, and treatment [11].

The gut and intratumoral microbiome's involvement in metastatic processes impacts cancer development and the effectiveness of anti-cancer therapies by altering microbial diversity in the gastrointestinal tract and associated metabolites. Disrupted gut mucosal thickness can lead to bacterial translocation and bloodstream infections. Gastrointestinal dysbiosis-induced inflammation may facilitate cancer cell spread through altered immune responses. Additionally, research indicates a link between intratumoral bacteria and metastasis, which suggests increased resistance to mechanical stress [12].

Current research focuses on understanding what drives unfavorable microbes to impact tumor progression. Therefore, ongoing extensive research in numerous clinical trials may uncover prognostic microbial markers that predict treatment outcomes in metastatic disease. Identifying microbial biomarkers will be vital in understanding the microbiome's role in cancer progression.

CANCER-PROMOTING MICROBIOME

In the early 2000s, researchers started systematically studying the connection between microbiomes and cancer, led by the International Agency for Research on Cancer (IARC) identifying seven viruses (Kaposi sarcoma herpesvirus, Epstein–Barr virus, human papillomaviruses, human T-cell lymphotropic virus Type 1, hepatitis B virus, hepatitis C virus, human immunodeficiency virus-1), three parasites (*Clonorchis sinensis, Opisthorchis viverrini, Schistosoma haematobium*), one bacterium (*Helicobacter pylori*), and certain fungi (such as *Aspergillus flavus*) as human carcinogens [13], while acknowledging that an increasing number of microbes are identified as promoters, rather than inducers, of cancer.

Cancer-promoting Microbes

Fusobacterium Nucleatum

F. nucleatum is a Gram-negative anaerobic bacterium found in the oral microbiota. It can spread to different body parts and is linked to several types of cancer, including Head and Neck Squamous Cell Carcinoma (HNSCC), esophageal, pancreatic, gastric, and colorectal cancers [14]. High levels of *F. nucleatum* are particularly noted in colorectal cancer (CRC) compared to healthy tissues. This microbe promotes cancer *via* virulence factors such as Fibroblast activation protein 2 (Fap2), Fusobacterium adhesion A (FadA), and radiation D (RadD) [15]. FadA, a cell surface protein, binds to E-cadherin, resulting in E-

CHAPTER 8

Recent Advancements in Chemotherapy for Targeted Therapeutic Strategy

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Abstract: The advancement of targeted drug delivery systems using nanocarriers such as liposomes, dendrimers, nanoparticles, micelles, and nanotubes has changed chemotherapy through recent biomedical research and biotechnology developments. To reduce systemic toxicity and enhance treatment efficacy, these systems facilitate the targeted delivery of chemotherapeutic drugs to certain tissues, cells, and intracellular organelles. Combination therapies involve the synergistic integration of drugs to improve the effectiveness of chemotherapy and reduce the development of drug resistance. Drug antibody conjugates selectively transport cytotoxic drugs to cancer cells, thereby minimizing systemic toxicity. Multi-target therapies are capable of simultaneously targeting numerous cancer pathways, which is significant in the treatment of breast, colorectal, prostate, and lung cancers. These approaches are designed to decrease the minimum therapeutic doses and avoid the impact of side effects on healthy tissues. This chapter discusses the mechanisms and advantages of targeted drug delivery systems in improving chemotherapy and emphasizes their crucial role in delivering drugs *via* nanocarriers to specific compartments of the body for various types of cancer.

Keywords: Breast cancer, Colorectal cancer, Immunotherapy, Lung cancer, Prostate cancer, Targeted drug delivery.

INTRODUCTION

Cancer is a complex and progressive group of disease conditions characterized by a loss of control over cell growth. For several decades, the available cancer treatment choices were limited to surgery, radiation therapy, and chemotherapy, either as standalone treatments or in combination [1 - 3]. However, there has been a significant improvement in the various pathways that play a role in the progression of cancer and how they might be specifically targeted. This advan-

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cement has been achieved through the use of combinatorial methods, which involve the simultaneous use of multiple targeted therapies or conventional chemotherapeutics [4]. Chemotherapy for cancer treatment utilizes a range of anticancer drugs that employ multiple routes of action, including inhibiting cell division, inducing apoptosis, and specifically targeting cancer cells [5 - 8]. Chemotherapy typically functions by inhibiting the proliferation and division of cancer cells. Cancer cells typically undergo rapid division and growth, beyond the normal rate of cell proliferation. Additionally, they exhibit a high level of inherent physiological stress. As a result, drugs can rapidly and effectively destroy them in comparison to neighboring cells. Many inhibitor therapies have shown promise in the treatment of solid cancers, such as angiogenesis inhibitors, polyadenosine diphosphate-ribose polymerase inhibitors, p53/ Mouse double minute 2 homolog (MDM2) inhibitors, inhibitors of the hedgehog pathway, tyrosine kinase inhibitors, proteasome inhibitors, Histone deacetylase (HDAC) inhibitors, *etc* [9, 10]. Chemo-preventive medications or combinations of drugs are frequently selected based on the nature and stage of cancer, with the primary goal of neutralizing malignant cells and reducing the stress produced by tumour growth.

TARGETED THERAPIES USING NOVEL DRUG DELIVERY SYSTEMS

Over the past decades, oncology has focused on precisely targeting cancer cells to lower the serious adverse reactions that patients endure and combat treatment resistance. Targeted therapy aims to address specific proteins while avoiding undesirable effects selectively. Researchers have developed nanocarrier organic platforms to transport drugs *via* encapsulation or conjugation.

Nanocarriers

Liposomes (LP)

The LP is the initial recognized transporter with the capability to serve as a vehicle for delivering both hydrophilic and hydrophobic molecules [11]. LPs are sphere-shaped structures consisting of a central aqueous core surrounded by successive lipid and aqueous layers. These successive layers are made up of bipolar molecules that have both non-polar lipid chains and polar ends [12]. Their size might range from 20 nanometres to several micrometres. Liposomes are crucial because they can encapsulate medications and carry them throughout the body. LPs provide a notable advantage as their envelope can be altered through ligands to selectively target distribution sites or enhance the shelf life and ADMET profile of the formulation [13]. For example, the insertion of ssDNA/ssRNA to the exterior of LPs enables accurate and specific delivery of small biomolecules, peptides, or entire cells. Systematic Evolution of Ligands by Exponential Enrichment (SELEX) is a method for selecting aptamers that

involves screening an arbitrary oligonucleotide collection. Multiple aptameric molecules that specifically bind to prognostic markers have demonstrated efficacy in treating both solid tumors and blood cancers (Fig. **1**) (Medina *et al*., 2004).

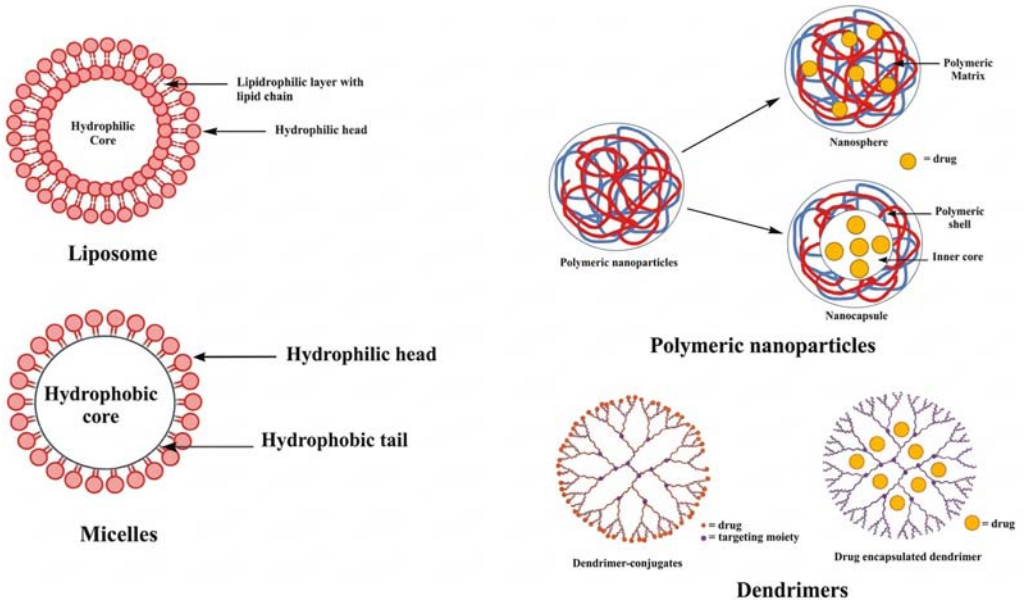

Fig. (1). Schematic representations of targeted therapies using novel drug delivery systems.

As per the reports, there have been clinical approvals for 14 LP carriers as well. In 1995, the first drug called Caelyx was introduced. Caelyx is a type of pegylated LP doxorubicin and is used to treat ovarian cancer, followed by DaunoXome, a daunorubicin formulation for Kaposi's sarcoma, in 1996 [15, 16]. Arikayce, an amikacin LP inhalation solution, has obtained the latest license for the treatment of lung disease in Europe since 2020. Liposomal carriers can be delivered by several methods, including IV infusion, IM and IT injection, spinal, and local infiltration. Most of these tiny carriers are unilamellar vesicles, ranging in size from approximately 30 to 100 nanometers. Licenced carriers mostly comprise glycerol phospholipids, sphingomyelin, and cholesterol. LPs can exist in two forms: charged or neutral, depending on the chemical makeup of their environment. This property enables them to either target specific areas or prevent clumping together due to a powerful repulsive force known as Coulombic repulsion. An example of such LPs is the daunorubicin/cytarabine LP injection developed by Vyxeos [17].

An additional characteristic of the LP carriers is their capacity to transport multiple drugs, providing a practical option for MDR. In 2012, Isacchi *et al*.

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Sonal Dubey

Dr. Sonal Dubey is an eminent academician and researcher in pharmaceutical education and scientific inquiry. She brings a wealth of expertise shaped by 23 years of teaching and 25 years of dedicated research experience. A former CSIR fellow, Dr. Dubey earned her doctorate from the University Institute of Pharmaceutical Sciences (UIPS), Panjab University—one of India's premier institutions in pharmaceutical education. Her scholarly contributions include four patents and six major research grants awarded by prestigious bodies such as DST, AICTE, and RGUHS, as well as DSU, where she has served as both Principal Investigator and Co-Principal Investigator. She has authored several book chapters, one book, and more than 60 research publications.

Dr. Dubey has mentored number of postgraduate and doctoral scholars, fostering innovation and academic excellence. Her research interests span a broad spectrum of therapeutic areas, including anticancer, antimicrobial, antitubercular, anti-HIV, and neurodegenerative disorders. She is particularly recognized for her expertise in computational drug design, integrating advanced modelling techniques to accelerate drug discovery and development.

With a career marked by academic leadership, impactful research, and a commitment to nurturing future scientists, Dr. Sonal Dubey continues to be a driving force in the field of pharmaceutical sciences.

Prashant Tiwari

Dr. Prashant Tiwari is a distinguished academician and researcher in pharmaceutical sciences with over 15 years of teaching and research experience across reputed institutions in India. Previously, he served as an Assistant Professor at Arka Jain University, Jamshedpur; Royal College of Pharmacy, Raipur; and the School of Pharmacy, CEC, Bilaspur. He also held a prestigious Senior Research Fellowship (SRF) under the Indian Council of Medical Research (ICMR) at Siksha O Anusandhan University, Bhubaneswar, where he conducted advanced research in neuropharmacology and drug development.

Dr. Tiwari's innovative research is reflected in multiple national and international patents. These include the microencapsulation of celecoxib to improve solubility for Alzheimer's therapy, AI-driven strategies for cancer drug analysis, and a smart IV fluid controller with advanced locking mechanisms. He has received research grants from the Department of Biotechnology (DBT), Government of India, along with seed project funding from DSU.

He has authored and edited more than 30 scholarly books and book chapters with leading publishers such as Springer, CRC Press, Cambridge Scholars, De Gruyter, Bentham Science, Taylor & Francis, and Nirali Prakashan. Notable works include The 3R's Approach in Preclinical Pharmacology (2025), Enzymatic Targets for Drug Discovery Against Alzheimer's Disease (2024), and Brain Tumor Drug Development (2024). Dr. Tiwari has organized national conferences, delivered lectures, and chaired sessions at international forums. His achievements have earned him prestigious honors, including the SPSR Excellence Award (2025), Dr. P. D. Patil National Award (2022), Young Scientist Award (2023), IPES Fellowship (2021), and the ICMR Senior Research Fellowship (2016–2019). His research interests include neurodegenerative diseases, drug interactions, pharmacokinetics/pharmacodynamics, and metabolic disorders.