Zodwa Dlamini *Editor*

Overcoming Breast Cancer Therapy Resistance

From Mechanisms to Precision and AI-Powered Approaches

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Preface

Breast cancer is a pervasive and complex disease that affects millions of individuals worldwide. While significant progress has been made in the field of breast cancer treatment, one formidable challenge remains—drug resistance. The ability of breast cancer cells to develop resistance to therapies poses a significant hurdle in the quest for effective treatments. This book is dedicated to addressing this critical issue and delves into the multifaceted aspects of breast cancer drug resistance, shedding light on the mechanisms behind it and the innovative strategies being developed to overcome it.

The book is organized into four distinct parts, each contributing to a comprehensive understanding of the problem and potential solutions. The arrangement follows a logical flow, starting with an introduction to breast cancer and drug resistance, then delving into various types of drug resistance in breast cancer treatment, and finally exploring innovative strategies and future directions in overcoming drug resistance. Part I provides a foundational understanding of breast cancer and drug resistance. It explores the intricate molecular mechanisms that underlie drug resistance in breast cancer, setting the stage for the subsequent discussions. Part II takes a closer look at various types of drug resistance in breast cancer treatment. It examines the potential of targeted therapies, immunotherapy, endocrine therapy, and the challenges posed by chemoresistance. These chapters offer insights into both the promising approaches and the hurdles that need to be overcome in the battle against drug resistance. Part III explores innovative strategies and future directions to combat drug resistance. It dives into the role of alternative mRNA splicing, the influence of viral infections, the potential of natural products, and the transformative power of artificial intelligence. These cutting-edge approaches hold promise in revolutionizing breast cancer treatment. The final part of the book (IV) discusses future directions and advanced treatments that promise to contribute to overcoming drug resistance. It explores the impact of the microbiome, molecular profiling, and personalized medicine. It also highlights promising new strategies, including immunotherapy, gene therapy, epigenetic modulation, nanotechnology-based drug delivery systems, and combination therapies. Furthermore, it addresses disparities in breast

cancer research and treatment, emphasizing the need for inclusivity in addressing these challenges.

Throughout the book, experts from diverse fields share their insights, research findings, and innovative approaches to tackle drug resistance in breast cancer. From the potential of natural products to the transformative impact of artificial intelligence, from the microbiome's role in treatment to the promise of personalized medicine, this book brings together a wealth of knowledge and ideas. The fight against drug resistance in breast cancer is ongoing, and it demands a multidisciplinary approach that considers all available avenues. The chapters within this book provide a glimpse into the cutting-edge research, the challenges faced, and the potential breakthroughs that lie ahead. We hope that this collection of insights and discoveries will serve as a valuable resource for researchers, clinicians, and anyone with an interest in the battle against breast cancer drug resistance. As we embark on this journey together, we remain committed to the relentless pursuit of solutions. The path may be complex, but it is illuminated by the collective expertise and determination of those dedicated to overcoming drug resistance in breast cancer. Together, we can pave the way for a brighter future in the battle against breast cancer treatment resistance.

Pretoria, South Africa Zodwa Dlamini

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About the Editor

Zodwa Dlamini is Professor of Molecular Oncology and known for her unwavering commitment to advancing precision oncology. At the core of her career is her pivotal role as the Founding Director of the Pan African Cancer Research Institute (PACRI). Additionally, as the Director of the SAMRC Precision Oncology Research Unit (PORU) and a DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), she is fully committed to advancing precision medicine in the battle against cancer. Beyond her institutional leadership, Professor Dlamini also serves as a distinguished member of the American Association for Cancer Research (AACR) Regional Advisory Committee on Sub-Saharan Africa. She additionally guides the AACR Pathology Resources in Africa Advisory Group, actively identifying strategies to address gaps in cancer pathology services across the African continent. Professor Dlamini extends her contributions to the African Organisation for Research and Training in Cancer (AORTIC), where she actively influences the organization's strategic direction and mission as a member of the Research Committee Scientific Advisory Board. Her dedication to advancing cancer research in Africa was honored with a Special Award from the Council and Executive of the African Society of Morphology and was then admitted as an "Honorary Fellow" of the West African College of Morphologists. Moreover, she is an Overseas Fellow of the Royal Society of Medicine (London), Professional Member of the New York Academy of Sciences (USA), and a member of the Academy of Science of South Africa, highlighting her contributions to the field of science. Through her multifaceted efforts, Professor Zodwa Dlamini remains steadfast in her commitment to shaping the ever-evolving landscape of cancer research, and her journey is driven by an unshakable belief that cancer can be conquered, paving the way for a healthier and more equitable world.

Part I
Understanding Breast Cancer and Drug Resistance

Introduction to Breast Cancer and Drug Resistance

Rodney Hull, Zukile Mbita, and Zodwa Dlamini

Abstract Breast cancer is the most prevalent cancer in women, worldwide. Thus, it has attained the number one spot as the most diagnosed cancer in most regions across the world. It is also the cancer with the highest mortality rates for women, worldwide. The soaring incidence, mortality, and recurrence rates can be partly attributed to late diagnosis and resistance to the current treatment strategies. These treatment regimens include chemotherapy, targeted therapy, immunotherapy, endocrine therapy, radiotherapy, and surgery. However, common mechanisms have evolved in cancers to counteract these treatments, resulting in cancer drug resistance. Resistance to treatment results in higher recurrence rates and increased mortality. These mechanisms can be targeted to reverse this resistance. Moreover, multiple treatments can be employed in order to bypass resistance. In addition to this, biomarkers for the development of resistance can be employed to detect the development of resistance at the early stages, allowing for treatments to be altered or supplemented with other drugs or treatments. There are also revolutionary treatments being developed to counteract resistance. These include the use of natural products to target novel pathways in cancer and be used to supplement other treatments. Nanomedicine and nanoparticles have been developed to assist in drug delivery. The more refined and precise delivery of drugs offered by nanotechnology can ensure efficient drug uptake and minimize efflux. Lastly, the development of personalized medicine, which is made possible using artificial intelligence and machine learning to analyze large omics databases, means that more precise customized treatments can be applied specifically to suit a single patient which may lower the chance of the development or resistance. Personalized medicine will allow the

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detection of gene expression or pathway changes that will increase the chance of resistance development, which would allow for more appropriate therapies to be selected.

Keywords Low-to-middle income countries · Breast cancer subtypes · Resistance mechanisms · Novel targeted therapies · Novel immunotherapy · Personalized medicine · Targeted therapy

Introduction

Medical historians have traced the first mention of breast cancer to ancient Egypt where cases were documented. These historical writings also show that misunderstandings and misconceptions were rife in breast cancer. There are many reasons for the development of new treatments to replace existing ones. These reasons include the side effects of current treatments (Akram et al., 2017) and the development of resistance (Cleator et al., 2007). Drug resistance in breast cancer is a leading cause of mortality, forcing changes in treatments to try and ensure a long-term cure. As resistance develops, patients and oncologists are forced to change therapeutic strategies, which in turn could also result in the development of further resistance. Drug resistance also leads to disease recurrence. More accurate and timely diagnosis has resulted in an increase in breast cancer incidence by 0.5%, annually in the last four decades. These advances are not only the result of early detection but better public awareness. At the same time, modern treatment strategies have resulted in a dramatic decline in mortality (Giaquinto et al., 2022). Despite these advances, the ability to predict outcomes remains inconsistent. This situation is particularly true in younger and socially disadvantaged women, which suggests that there may be other factors involved.

Epidemiology and Classification of Breast Cancer

Worldwide, breast cancer is the leading cause of cancer-related deaths among women. As such, breast cancer is a major source of global concern. This concern is increased as both the incidence and mortality rates of breast cancer are on the rise (Bray et al., 2018; World Health Organisation, 2023). The incidence rate of breast cancer makes it the leading cancer in women, regardless of age. The disease is, however, more prevalent in women of a more advanced age; thus, age should be viewed as a risk factor increasing the chance of developing breast cancer. According to the WHO fact sheet on breast cancer, there were 2,300,000 new cases of breast cancer recorded in 2020 with 685,000 deaths attributed to it. In the last 5 years, the

WHO reported that 7.8 million women had been diagnosed with breast cancer (World Health Organisation, 2023). The prevalence of breast cancer has increased to such an extent that it has surpassed lung cancer as the most prevalent cancer (Sung et al., 2021). Statistics from the International Association of Cancer Registries (IACR) show that the highest prevalence of breast cancer is found in those countries that have a high human development index (HDI) or those considered to be High Income Countries (HIC). Consequently, this means that these countries are located in North America, Europe, and Oceania (Australia and New Zealand), and these continents have the highest incidence rates of breast cancer. However, these same continents and high-income countries with high HDIs have a comparatively low mortality rates compared to their high incidence rates. This is in stark contrast to Africa, which has the highest mortality rate of any continent (Fig. 1). This can be best described using the ratio of mortality to incidence. For North America and Europe this ratio is 0.16 and 0.2, respectively. While the ratio for Africa is 0.47. This means that nearly half of all diagnosed cases in Africa result in fatality compared to only a fifth of cases in Europe. One of the factors contributing to this is the frequency of the different subtypes of breast cancer found in the populations in these countries, with the more lethal and difficult-to-treat breast cancer subtypes being found more frequently in African populations.

There are five molecular subtypes of breast cancer (Table 1). This molecular classification is largely dependent on the presence of hormone receptors and other proteins specific to each type. The most common subtype is named luminal A or HR+/HER2– (ER-positive/HER2-negative). This subtype is defined by the presence of estrogen and progesterone receptors, while being negative for HER2 and low

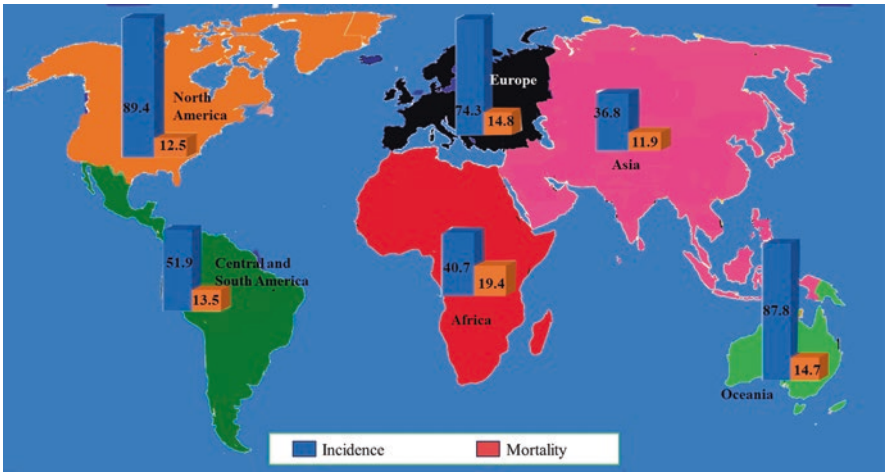

Fig. 1 Breast cancer incidence and mortality age-standardized rate by continent. North America and Oceania (Australia, New Zealand, Polynesia, and Micronesia) have the highest incidence rates. Asia and Africa have the lowest age-standardized rate (ASR) per 100,000 individuals. Despite this, Africa has higher mortality rates than North America, Oceania, and Europe. This implies that treatment outcomes in Africa are less favorable

Table 1 Breast cancer classification (Adapted from Eliyatkın et al. (2015))

Subtype	Estrogen receptor	HER2	Ki-67	Progesterone receptor	Growth	Prognosis
Luminal A	Positive	Negative	Low	Positive	Slow	Good
Luminal B	Positive	Negative	High or normal	Negative if KI-67 is normal	Fast	Worse
Luminal B like	Positive	Positive	Any level	Positive or negative	Fast	Worse
HER2 enriched	Negative	Positive	–	Negative	Faster	Bad but treatable
Triple-negative	Negative	Negative	–	Negative	Most aggressive	Worst

levels of proliferation promoting Ki-67 protein. These low levels of Ki-67 are one of the reasons for the luminal A cancers to progress slowly and have a better prognosis than most cancers. Luminal B breast cancers are also known as ER+/HER2+. These cancers are defined by the expression of the estrogen receptor but are HER2 negative. They can either express high levels of Ki-67 or lack the expression of progesterone receptors. Luminal B-like breast cancers are those that express both estrogen receptor and HER2 and both luminal B and luminal B-like are characterized by fast growth and have a worse prognosis than luminal A. The HER2-enriched breast cancer subtype expresses HER2 but niether the estrogen receptor nor the progesterone receptor. They grow faster than the previous three types and have a worse prognosis than the previous three types. However, this subtype is susceptible to treatment with therapies that target HER2. Finally, basal or triple-negative breast cancer (TNBC) does not express estrogen receptor, progesterone receptor, or HER2, It is the most aggressive and hardest to treat, and as such, generally, it has a poor prognosis. This type is more common in individuals with a BRCA1 mutation. It is also more common in individuals with African ancestry and can be found in younger women than in the other subtypes (Anders & Carey, 2009). This classification system allows for the selection of the most appropriate treatment as well as the development of therapies targeting each specific type based on the expression of the specific receptors (Sharma et al., 2010).

Despite the fact that breast cancer is the most commonly diagnosed cancer in women throughout the entire world and it is the second most common cause of cancer-related death among women, the incidence and death rates of breast cancer differ according to ethnicity. Studies on the variation between different ethnic groups show that the incidence rates for breast cancer are highest in those of European ancestry when it comes to HEER2+, in women of African ancestry with regard to TNBC and other breast cancer subtypes (Kong et al., 2020). The differences in the level of drug and xenobiotic metabolizing enzymes differ in different ethnicities, and this is only one of the factors that contribute to differences in drug resistance in different population groups. Other differences arise due to differences in socioeconomic status and lifestyle (Gerend & Pai, 2008; Harper et al., 2009; Echeverría et al., 2009).

Common Treatments and Resistance to these Therapies

Breast cancers are treated with a wide range of different therapeutic approaches (Table 2 and Fig. 2). These include surgery, chemotherapy, hormonal therapy, biological therapy, immunotherapy, and radiation therapy (Control et al., 2018). The choice of treatment depends on many factors. Some of these include the size and stage of cancer, the location of the tumor, histopathology, whether the tumor has already spread to the lymph nodes, the metastatic potential of the tumor, the age and health of the patient, the hormonal status of the patient and finally its molecular subtype (Cardoso et al., 2019). Endocrine therapy is used to treat breast cancers that express multiple hormone receptors on the surface of breast cancer cells, such as luminal A and B breast cancers. This is supplemented through the use of chemotherapy to supplement these treatments. HER 2-positive tumors (luminal B and HER2+) are most often treated with monoclonal antibodies (Tai et al., 2010; Harbeck et al., 2019; Waks & Winer, 2019). More recent treatment strategies that have been applied to breast cancer include immunotherapy, cyclin-dependent kinase inhibitors, tyrosine kinase inhibitors, microRNAs (miRNAs), use of repurposed drugs, nanomedicine, and electrochemotherapy (ECT).

It is estimated that the resistance of cancers to various drugs is responsible for up to 90% of cancer-related deaths (Łukasiewicz et al., 2021). Multidrug resistance (MDR) can reduce the effectiveness of chemotherapy which can lead to relapse or metastasis. Drug resistance can be classified as either innate or acquired resistance (Wang et al., 2019b). Intrinsic resistance that occurs before treatment, involving genetic mutations, pre-existing resistant sub-populations of cells, and increased activation of drug detoxifying enzyme pathways (Holohan et al., 2013). Acquired resistance, which results due to the exposure to the drug is the result of the activation of proto-oncogenes, altered epigenetic modifications, and mutations that lead to altered gene expression as well as changes in the tumor microenvironment (Holohan et al., 2013). Some of these resistance mechanisms include increased efflux of drugs, upregulated DNA repair, senescence escape, epigenetic modifications, tumor heterogeneity, TME, and epithelial-to-mesenchymal transition (EMT) (Holohan et al., 2013; Cosentino et al., 2021; He et al., 2021).

Cancers apart from TNBC can be targeted by targeting the hormone receptor, resulting in proliferation (Nilsson et al., 2001). For instance, activation of the estrogen receptor and the subsequent estrogen signaling pathway lead to the expression of genes such as *MYC* and *CCND1*, resulting in cell cycle progression (Prall et al., 1998) and increased growth factor, and transcription, leading to increased proliferation (Bocchinfuso & Korach, 1997). Endocrine therapies include selective ER modulators (SERMs), selective ER downregulators (SERDs), and aromatase inhibitors (AIs) (Aggelis & Johnston, 2019). These therapies are able to substantially reduce the recurrence rates of breast cancer as well as lowering the mortality rates (Lin & Winer, 2008). However, ER^+ metastatic breast cancer is known to develop resistance to endocrine therapy with the loss of ER expression only accounting for a small number of the cases where resistance develops (Shiino et al., 2016). The predominant

Table 2 Common drugs used to treat various types of breast cancer and the mechanisms underlying resistance to these drugs

Treatment	Drug resistance	Resistance mechanism	References
Aromatase inhibitors	Relapse after initial treatment	Exemestane (false aromatase enzyme substrate) alongside everolimus (an mTOR inhibitor)	(Carlini et al., 2007; Chin et al., 2007)
ER+			
Tamoxifen	Mutations in estrogen receptor	Fulvestrant-ER downregulatory	(Kang et al., 2005)
	CYP2D6 polymorphisms		(Li et al., 1997; Zakharchenko et al., 2011)
	cAMP/PKA 2 PI3K and MAPK pathways upregulated leading to transcription changes		
	PTEN mutations		(Razavi et al., 2018)
PI3K inhibitors	Increased toxicity	Everolimus (Afinitor) with the CDK4/6 inhibitor	(Hurvitz & Peddi, 2013)
Pictilisib and buparlisib	Increased toxicity		(Krop et al., 2016) (Dhakal et al., 2020)
ER+/PR+/HER2-			
ER downregulators	*PIK3CA* mutations	Piqray (PI3K inhibitor)	(Thorpe et al., 2015)
ER+/HER2			
CDK4/6 inhibitors	Increased toxicity	Combination of CDK4/6 inhibitors with FUL	(Turner et al., 2018; Killock, 2019)
HER2+			
Trastuzumab, pertuzumab, and 19H6-Hu	*PIK3CA* mutations	19H6-Hu (anti-HER2 antibody)	(Christianson et al., 1998)
	Truncated form of HER2 (P95HER2)	Pertuzumab is a monoclonal antibody that binds to the extracellular dimerization domain of HER2	(Warmerdam et al., 1991)
TNBC			
Chemotherapy by alkylating agents, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, TKIs, and mitotic inhibitors	Epigenetic alterations	Epigenetic therapies	(Verweij et al., 1994)
	Enzyme system deactivation of drugs	Taxanes along with anthracyclines	(Miklavčič et al., 2014)
	TWIST overexpression due to NF-κB	Immunotherapy	(Loibl & Furlanetto, 2015)

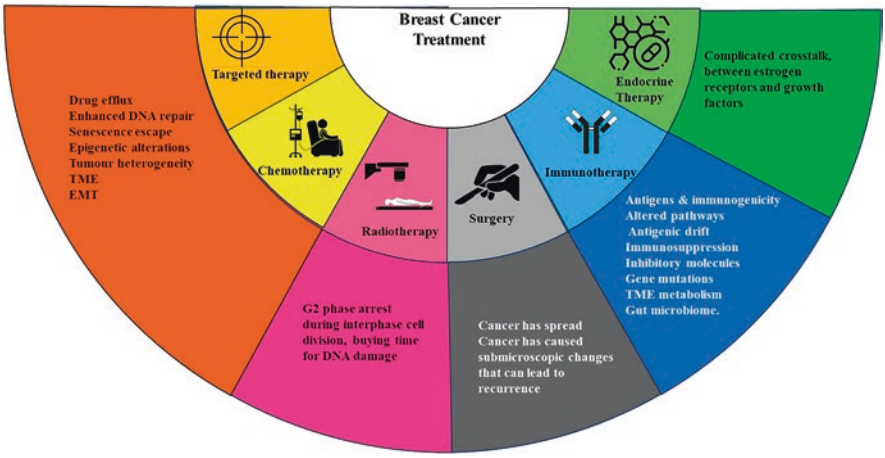

Fig. 2 Breast cancer treatment strategies and the mechanisms of resistance to these treatments. Breast cancers can be treated with multiple strategies (the middle circle), including targeted therapies, chemotherapy, radiation therapy, surgery, immunotherapy, and endocrine therapy. The outer circle shows the mechanisms developed by breast cancer cells to overcome these treatments

mechanism for the development of resistance is the ligand-independent ER reactivation (Miller et al., 2011). This can occur through multiple mechanisms which include gain-of-function mutations in ER, alterations in the interactions between ER and coactivators or corepressors, development of compensatory crosstalk between ER and growth factor receptors and finally, increased oncogenic signaling (Ma et al., 2015). For example, in 2018 Razavi and colleagues performed whole-exome sequencing on 1918 breast cancer patients to identify genetic alterations in various breast cancer types including those resistant to endocrine therapy. They identified mutations in ERBB2, which increased the activity of the protein and increased downstream signaling. They also identified loss-of-function mutations within the tumor suppressor gene Neurofibromin1 (NF1) (Razavi et al., 2018). These mutations were also commonly accompanied by alterations in MAPK genes and genes that regulate the transcription of Estrogen receptors (Razavi et al., 2018). Another approach is to prevent the recurrence of endocrine-resistant breast cancer, is to target dormant ER^+ breast cancer cells (Gawrzak et al., 2018; Zhang et al., 1997).

The Prevalence of Resistance in Breast Cancer

The development of chemoresistance has become a major problem in the control and management of breast cancer. Treatment resistance is exacerbated by relapses in the tumors that responded well to treatment in the early phases of the disease as well as resistance to multiple agents and strategies (Perez, 2009). The development of resistance can be caused by multiple changes at the molecular level, in the tumor

microenvironment, through interaction with other cancer cells as well as the modification of the interaction between immune cells and cancer cells. Apart from this, there are other factors that can contribute to the development of resistance. These include the pH of cells, hypoxia and paracrine signaling (Mansoori et al., 2017; Nikolaou et al., 2018). Multidrug resistance (MDR) can arise due to the activity of multiple drug-resistance genes that act to transport drugs from the cell. The complex interplay between these factors contributing to resistance and the multiple mechanisms of resistance means that it is difficult to develop successful strategies to overcome resistance to treatments in breast cancer (Wind & Holen, 2011). The complexity and heterogeneity of breast cancer are in contrast to the relatively minor changes in gene expression, simple mutations in one or more genes (Organization, 2019). In addition to this the contribution of the differences between individual patients or tumors, regardless of their classification, means that patients respond differently to the same treatment. As such, the chances of a patient developing resistance cannot easily be predicted (Luque-Bolivar et al., 2020). The complexity and heterogeneity of breast cancer are in contrast to the relatively minor changes in gene expression, simple mutations are one or more genes (Organization, 2019).

Overcoming Resistance to Common Therapies

The primary strategy to counter the development of drug resistance has been to use a variety of drugs in different combinations. This strategy can be further complicated by multidrug resistant disease (Waks & Winer, 2019). Targeted therapy depends on the selection of a therapy based on the subtype of breast cancer and the stage at diagnosis (Kinnel et al., 2023). Targeted therapies have advanced in their specificity and effectiveness due to an increased understanding of the molecular changes that promote breast cancer development and progression. Potential molecular targets that have been investigated or used to overcome resistance include the Aryl hydrocarbon receptor (AhR), linked to increased drug efflux (Powell et al., 2013), nitric oxide synthase (NOS), linked to cisplatin resistance (Jin et al., 2015), Phosphoinositide 3 kinase (PI3K), involved in endocrine, HER-2, and cytotoxic therapy resistance (Paplomata & O'Regan, 2014), the Wnt/β-Catenin Pathway, which regulates cancer cell stemness (Zhong & Virshup, 2020) and Protein tyrosine kinase 6 (PTK6), which regulates anoikis resistance (Irie et al., 2010). Additional targets include those whose increased expression negates the effectiveness of drugs which act to inhibit them. These include epidermal growth factor receptor (EGFR (Ali & Wendt, 2017), Cyclin-Dependent Kinase 4/6 (CDK4/6) (Yang et al., 2017), Poly (ADP-Ribose) Polymerases (PARP) (O'Connor, 2015). Finally, human epidermal growth factor (HER-2) where antiHER2 therapy effectiveness is decreased due to decreased drug binding, lack of HER-2 downregulation, and alterations in apoptotic and cell cycle pathways (Zhang, 2021).

Studies have shown that immunotherapy can successfully be used to treat early-stage breast cancer patients with high levels of tumor-infiltrating lymphocytes

(TILs) even without accompanying chemotherapy treatment (Park et al., 2019). For non-responders, the improved understanding of tumor-immune interactions and the contribution of the TME, notably with the help of the latest technologies such as single-cell analyses and spatial transcriptomics, may provide new drug targets and strategies to overcome resistance (Aldea et al., 2021; Morad et al., 2021). For instance, single-cell transcriptome analysis was used to monitor HER2+ breast cancer patients undergoing a combination of CDK4/6 inhibitors. This analysis revealed an immunosuppressive population of immature myeloid cells that infiltrate resistant tumors. This study also showed that these cells can be targeted with cabozantinib, a tyrosine kinase inhibitor, used in combination with compounds that enhance immune checkpoint blockade (Wang et al., 2019a).

A 2018 global study estimated that 13% of cancers globally can be attributed to microbial infections, both bacterial and viral. The main causes of these infections were *H. pylori*, Human papilloma virus, Hepatitis B virus (HBV), and Hepatitis C virus (HCV) (de Martel et al., 2020). However, there are a vast number of microbes living within the human body. The microbiota is thought to play an important role in determining the severity and mortality of breast cancer. This is largely due to the generation of secondary metabolites with biological activity by these microbes, which can increase or decrease the risk of developing breast cancer, by changing energy intake and utilization or through the regulation of circulating steroid hormone levels. Breast tissue has a distinct microbial community which changes following the development of breast cancer (Parida & Sharma, 2019a, 2019b; Urbaniak et al., 2014; Smith et al., 2019). Additionally, this microbiota differs depending on the malignancy and type of breast cancer. The gut microbiota is known to play an important role in the development of breast cancer (Parida & Sharma, 2019a) and is expected to influence the effectiveness of endocrine therapy in the treatment of breast cancer due to the significant role played by the gut microbiota in estrogen metabolism (Brooks, 1984; Jerry, 2007; Truin et al., 2017). The gut microbiota achieves this by secreting the enzyme β-glucuronidase, which acts to deconjugate estrogens into their active forms (Parida & Sharma, 2019a).

Individual variations in the makeup of the gut microbiome depend on factors such as the individual's ethnicity, nutrition, BMI, use of antibiotics, and any current infections (Parida & Sharma, 2019a). Dysbiosis of the gut microbiota leads to a decline in the levels of circulating estrogens, a condition that is linked to many kinds of cancer (Helmink et al., 2019). Both the immune system and inflammatory response, both of which play a role in cancer development, can be regulated by the microbiota. The microbiota can also influence the effectiveness of immunotherapy such as checkpoint inhibitors (ICIs) and CTLA-4 (Li et al., 2019). The efficacy of many drugs that function to block immune-related molecules such as CTLA (Vétizou et al., 2015) or anti-PD-1 therapy (Gopalakrishnan et al., 2018; Sivan et al., 2015; Killock, 2018) are dependent on the presence of specific species of bacteria within the microbiome. The microbiome also regulates the response of tumors to radiation therapy (Shiao et al., 2021). The microbiota can also alter the metabolism of anticancer drugs. These include irinotecan, fluorouracil, and leucovorin (Bailly, 2019; Kang et al., 2015).

Chimeric antigen receptor cells are immune cells that have been modified to express molecules that are a combination of different cancer antigens, allowing them to recognize multiple cancer cells. These CAR-T or CAR-NK cells are a new immunotherapy that allows cancer cells to be specifically targeted using synthetic receptors that are specific to tumor cells expressed on their surface. There are promising breast cancer-specific targets for CAR cell therapy (Vitorino et al., 2021; Tóth et al., 2020; Szőőr et al., 2020).

Revolutionary Approaches to Reverse Resistance in Breast Cancer

Apart from adapting or improving existing therapies to overcome resistance, there are new revolutionary treatments that take advantage of new technologies such as the use of artificial intelligence to analyze large datasets. This would allow for the identification of new drug targets, active compounds, and biomarkers (Fig. 3). One exciting source of new drug targets are cancer promoting or specific protein isoforms or components of the alternative splicing machinery. Alternative splicing is the process where pre-mRNA is spliced to give rise to multiple mRNAs, which code for different protein isoforms. These isoforms may have completely different functions from each other, or they may share common functions (Abou Faycal et al., 2016). Alternative splicing is known to be dysregulated in cancers, including breast cancer. This can give rise to cancer promoting isoforms or isoforms which assist in promoting drug resistance. This includes isoforms of HER2, the estrogen receptor, caspase 9, and certain growth factor receptors (Gahete et al., 2022). Altered expression of spliceosome components and splicing regulators can also lead to a drastic change in the splicing pattern within a cancer cell that could promote drug resistance. These splicing factors may themselves be spliced to give rise to isoforms that promote the splicing of pro-oncogenic isoforms of other proteins (Gahete et al., 2022). As such, these splicing factors and proteasome components are viable targets to overcome drug resistance. Small molecule inhibitors of these spliceosome components and splicing regulators have been developed. In addition to this splice switching oligonucleotides have been developed that are complementary to splice sites or splice silencing sites on the target mRNA. By binding to these sites, they can stop the formation of pro-oncogenic or resistance promoting isoforms (Grollman, 1968; Havens & Hastings, 2016).

Precision medicine is the tailoring of treatments, detection, and monitoring of breast cancers based on individual variations, environment, genes, and lifestyles. Precision medicine offers great potential to improve the management of breast cancer (Collins & Varmus, 2015). The application of precision medicine has only become an option due to the development of new high throughput methods to study the “omics,” such as genomics, transcriptomics, proteomics, epigenomics, metabolomics, and microbiomics (Naito & Urasaki, 2018). These omics technologies allow

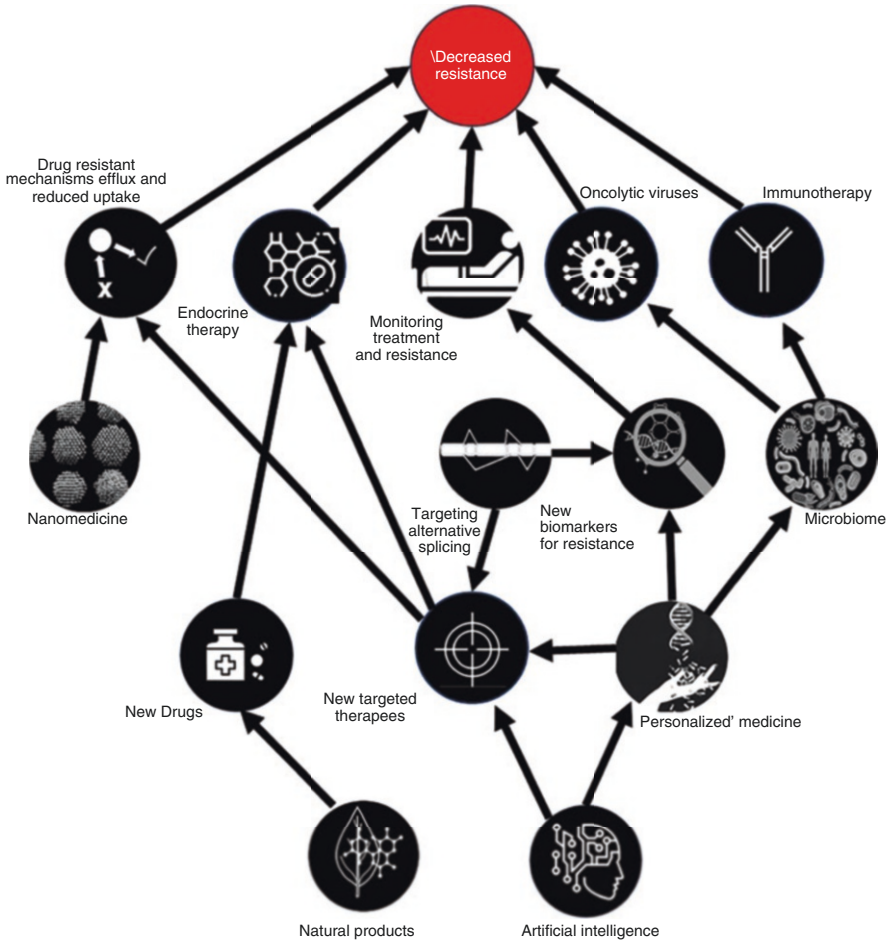

Fig. 3 Strategies for overcoming resistance to treatment in breast cancer. Artificial intelligence serves as the basis for the analysis of large amounts of omics data ranging from genomics to microbiomics. This data can be used to develop a personalized approach to medicine and will allow for the identification of biomarkers for the development of resistance. This in turn would allow for the modification of the treatment being used to overcome resistance. The microbiome analysis would allow for the identification of dysbiosis, which could result in suppression of the immune system or altered immune signaling. Rectifying this matter restores sensitivity to immunotherapy. Personalized medicine will also aid in the development of new targeted therapies. This will be aided by the identification of new processes to target, such as alternative splicing or a new source of potential drugs such as natural compounds

for the development of new biomarkers for improved prognosis and diagnosis. These predictive biomarkers would also help in the selection of the correct therapy and could be used to either predict the potential for resistance to develop or monitor treatment to detect the onset of treatment resistance (Lainetti et al., 2020).

Almost all current chemotherapy drugs originate from natural sources. These natural products are also the source of new drugs that are being developed. Research is centered on identifying highly active natural compounds, such as phytochemicals, that have anticancer activity and are suitable for modification to create synthetic compounds with improved pharmacokinetics. (Sharifi-Rad et al., 2019). One such compound is curcumin (Xiang et al., 2020) and has been modified to create curcumin analogs that effectively inhibit P-glycoprotein-mediated resistance in drug-resistant breast cancer (Gao et al., 2020). These synthetic analogs have reduced toxicity and increased solubility, making them far more appropriate and viable drugs (Liao et al., 2020). Other natural compounds that have been used as the basis for the design of synthetic derivatives include epigallocatechin and catechin. Both these compounds also inhibit P-glycoprotein (P-gp) activity preventing MDR as a result of drug efflux (Wong et al., 2021). Other natural products target drug resistance that results from apoptosis-resistance, metastatic processes, inflammation, necroptosis, autophagy, and proliferation.

Other advancements include the use of nanomedicine to improve drug delivery and targeting. Nanostructures can be used to overcome drug resistance by overcoming drug efflux, removal, and detoxification through this improved delivery or by shielding the drug (Lainetti et al., 2020). These nanoparticles can also be used to deliver drugs that are poorly soluble thereby improving drug uptake (Lainetti et al., 2020). Nanoparticles can also help to reduce side effects on normal tissue as the drug can be delivered specifically to the tumor cells (Cao et al., 2021).

Limitations to the Development in Implementation of Novel Strategies to Overcome Resistance in Breast Cancer

The limitations for the implementation of these new strategies to combat drug resistance in breast cancer are primarily due to limitations in current knowledge and technology combined with financial constraints. Other disadvantages involve ensuring the safety and efficacy of these new or modified treatments. An example of the limitations of current technology is the use of circulating tumor DNA (ctDNA) to identify genes that play a role in drug resistance and could be used as targets for the development of new drugs to counteract resistance. CtDNA could also serve as the source for the detection of biomarkers to monitor treatment and identify the development of resistance. However, in order for ctDNA to play a role in screening and the detection of resistance it must be able to detect a low burden of disease (Bettegowda et al., 2014). This may be a problem for current sequencing technologies, that cannot be overcome by increasing the intensity of sequencing or by using error correction techniques (Vasan et al., 2019).

Many of these new treatments and therapies are not guaranteed to be safe or have low toxicity. Many of the natural products isolated to serve as new drugs will need synthetic versions to be developed to overcome toxicity due to poor solubility or the

compounds may have an innate cytotoxic effect that is not easily overcome or suitable for use as a treatment option. Drugs that inhibit components of the spliceosome may inhibit splicing to such a universal extent that they may disrupt proper cell function (Rymond, 2007).

Finally, when it comes to the cost of developing or putting these new therapies in place, and one of the most pressing issues is that the countries with increasing breast cancer burden and a disproportionately large mortality rate are the same countries that can ill afford the financial costs associated with implementing these new strategies. In addition, many of these new strategies involve the use of artificial intelligence to analyze data concerning genomics, transcriptomics, etc. However, these datasets are currently mostly generated in wealthier countries, and as such the genomic or transcriptomic patterns are characteristic of the population within these countries and not of those individuals in lower-income countries. This can only be rectified by ensuring that these individuals are more represented in any large datasets (Yamamoto et al., 2022).

Conclusion

This book aims to discuss the effect of the development of breast cancer on various therapies, the mechanism behind the development of this resistance, and the strategies being developed to overcome this resistance. The book is divided into four parts that follow a logical flow, starting with an introduction to breast cancer and drug resistance. Apart from this introductory chapter, this section also contains a chapter providing a detailed discussion of the mechanisms underlying drug resistance in breast cancer in order to shed light on how these complex and intricate molecular mechanisms hinder effective treatment. Part two of the book delves into various types of drug resistance in breast cancer treatment. The first chapter of this section will discuss the potential use of targeted therapies to overcome or counteract drug resistance and improve treatment outcomes in breast cancer. This will be followed by a chapter discussing the use of immunotherapy as a treatment for breast cancer and describing the mechanisms underlying the development of resistance to these treatments. In a similar manner, the following chapter will examine the use of endocrine therapy as a treatment for breast cancer and examine the mechanisms employed by breast cancers that contribute to the development of resistance to this therapeutic approach. The final chapter in part two will examine the mechanisms underlying chemoresistance in breast cancers.

Part three of the book will explore innovative strategies and future directions in overcoming drug resistance and will be initiated by a chapter discussing the contribution of alternative mRNA splicing to the development of drug resistance. It will then explore strategies based on correcting or changing these splicing events to restore treatment sensitivity. This will be followed by a chapter reviewing the relationship between viral infections and drug resistance in breast cancer, and how viral infections can contribute to the development of drug resistance.

The chapter will explore research into the development of effective strategies to overcome drug resistance by exploiting viral vulnerabilities for therapeutic intervention. The potential of natural products as a valuable resource in the battle against drug resistance will be explored in the following chapter. The chapter will describe the mechanisms by which this diverse range of bioactive compounds exert their anticancer effects. The final chapter in part three will discuss the potential of artificial intelligence to transform the way we approach overcoming drug resistance in breast cancer. It will discuss how the use of AI to analyze large sets of biological data collected from an individual in conjunction with machine learning can be used to develop personalized treatment and identify novel therapeutic targets.

The final part of the book discusses the future directions and advanced treatments that promise to contribute to overcoming drug resistance. The first chapter in this section will explore the application of research on the microbiome to the problem of drug resistance and reversing treatment outcomes in breast cancer. The chapter will delve into the relationship between the microbiome and breast cancer cells. It will then discuss the potential for microbiome-based interventions to reverse drug resistance. This will be followed by a chapter that focuses on the utilization of molecular profiling techniques and personalized medicine to manage drug resistance in breast cancer. This includes the use of biomarkers and the molecular alterations associated with drug resistance to develop personalized medicine strategies. The following two chapters will highlight promising new strategies to tackle drug resistance in breast cancer. The first of these will explore innovative therapeutic approaches such as immunotherapy, gene therapy, epigenetic modulation, nanotechnology-based drug delivery systems, and combination therapies that have the potential to overcome resistance to therapy in breast cancer. This will be followed by a chapter that will discuss the role played by effective drug delivery and how new advanced drug delivery systems can be used to overcome drug resistance in breast cancer. The final chapter in this section concerns not the development of a new technology or method to treat breast cancer, but rather addresses the disparities in breast cancer research and treatment regarding drug resistance. These include disparities in the ability to access healthcare, differences in the quality of care, and skewed representation in clinical trials leading to differential outcomes in breast cancer patients. It is imperative that these disparities must be addressed, and the chapter will discuss the various means this can be accomplished including inclusive research efforts, community engagement, and tailored interventions to overcome these disparities. This section of the book and the entire book will be closed off by a concluding chapter summarizing the book and discussing the way forward.

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