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Topical Review

Emerging therapeutic strategies and opportunities in targeting protein pathways for breast cancer treatment: a critical review

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Abstract

Understanding breast cancer at a molecular level is essential for developing effective treatments due to its significant impact on women's mortality rates globally. Targeted medicines focus on specific proteins crucial to breast cancer progression, offering a promising treatment avenue. These proteins, often overexpressed or mutated in cancer cells, are vital for cell proliferation, division, and survival. Targeted drugs aim to inhibit these proteins, halting disease progression and sparing non-cancerous cells, which reduces side effects and improves patient quality of life. Key proteins in breast cancer treatment include HER2 (human epidermal growth factor receptor 2), ER (estrogen receptor), and PR (progesterone receptor). Drugs like Trastuzumab target HER2 to impede tumor growth in HER2-positive cancers, while hormone therapies targeting

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ER and PR improve outcomes for hormone receptor-positive cancers. Examining proteins such as EGFR, HER2/Neu, and ER reveals their roles in cancer pathways, with pathways like PI3K/Akt/mTOR (phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin) and MAPK (mitogen-activated protein kinase) being crucial targets for therapies, potentially revolutionizing breast cancer treatment.

Keywords: breast cancer, role of proteins, cancer pathway, cell cycle, signal transduction, clinical implications, current therapies

1. Introduction

Breast cancer is a complicated and varying disease that presents a notable global health hurdle. It is mainly a kind of cancer in women, with millions of newly diagnosed cases reported each year [1]. Despite some improvements in the detection and management of breast cancer, the disease remains a significant contributor to deaths caused by cancer in women [2]. Here, we will provide an in-depth overview of the instance, biological study, and current treatment options for breast cancer [3]. We will provide a base for discussing specific proteins targeted by drugs that play a role in disease processes. A complex interplay of genetic, hormonal, and environmental factors decides the incidence of breast cancer [4, 5]. Due to economic disparities worldwide, the occurrence rates of diseases, particularly cancer, show increased frequency in nations with more incredible economic wealth [6]. Breast cancer is not just a health problem. It is much more. It is a physical threat with psychological and socio-economic impacts [7]. Cancer of the breast begins at the cell level when breast cells start to grow out of control and transform into what we call tumors [8]. The distinct characteristic of malignant cancers allows them to spread throughout the body. Tissues surrounding the initial location and distant organs become invaded by cancer cells through metastasis. Multiple forms of breast cancer exist according to medical expert terminology known as subtypes. Healthcare professionals classify these subtypes based on their status regarding the ER, PR, and HER2 receptors [9].

The BReast CAncer gene 1 (BRCA1) and BReast CAncer gene 2 (BRCA2) are like naughty kids in genetic mutations. They significantly increase the risk of attracting breast cancer [10]. Molecular-level profiling has further elucidated the complex that underlies the initiation, progression, and advancement of breast cancer. Some examples are the PI3K/AKT/mTOR pathway and the RAS/RAF/MEK/ extracellular signal-regulated kinase (ERK) pathway. Let us not forget the cell cycle regulatory proteins [11]. The treatment strategies for breast cancer include surgical intervention along with radiation therapy, chemotherapy, and hormone therapy, in addition to other treatment options. Several variables determine the choice of treatment among breast cancer patients, starting with the progression of their disease and tumor molecular makeup as well as their general health condition. The healthcare industry currently adopts an increasing tendency for personalized treatment methods because doctors create therapeutic strategies using patient genetic information and tumor molecular examination results [12, 13]. Targeted drug therapies have brought about a revolution in how we treat breast cancer; the focus is on proteins involved with the growth and survival of the harmful cancer cells. For example, the drug Trastuzumab targets the HER2 protein. Aromatase inhibitors, on the other hand, target enzymes for estrogen production. Developing these smart drugs is like learning precise targeting of cancer pathways—they require a deep understanding of what gets breast cancer going [14]. However, even with recent technology advancements, there's still a long way to go to conquer breast cancer [15]. Concerns regarding the problem of drug resistance, the threat of relapse, and treatment side effects. New targets for drugs are being exposed with ongoing research, pushing the limits on making more effective yet less harmful drugs. Advancements in breast cancer treatment hinge on deeper investigation into the molecular basis of the disease and the creation of innovative, targeted drugs [16]. This review article provides a deep dive into the drug targets' proteins, providing essential insights into their function in the breast cancer pathway and their role in taking the treatment a notch higher [17]. To win the fight against breast cancer, understanding the disease's molecular details is critical. Possessing this information leads to a detailed understanding of the genetics and cell mechanisms that result in tumor formation and progression. First, it can help identify molecular targets for drug development that lead to bespoke treatments; it also helps distinguish breast cancer pieces into distinct subtypes [18]. A better understanding of breast cancer molecular science can help find biomarkers to help predict treatment response and monitor recurrence [19]. This is crucial for developing new treatments like combination therapies and, of course, immunotherapy. It opens doors to studying drug resistance mechanisms and maybe even finding ways to break these barriers and improve patient outcomes [20]. For risk assessment and preventive therapy, the molecular biology of breast cancer stresses the significance of genetic counseling and testing, especially for those people who are carrying the torch of this disease from their ancestors [21]. Breast cancer is a leading type of cancer in women, managed by an intricate network of signaling pathways that govern cell growth, survival, and metastasis. The receptor tyrosine kinases (RTKs), such as the HER2/Neu and ERs, when activated, play a critical role in response to these pathways; they trigger processes like the PI3K/Akt/mTOR and MAPK pathways [22] are shown in figure 1. Cell survival and proliferation functions of the

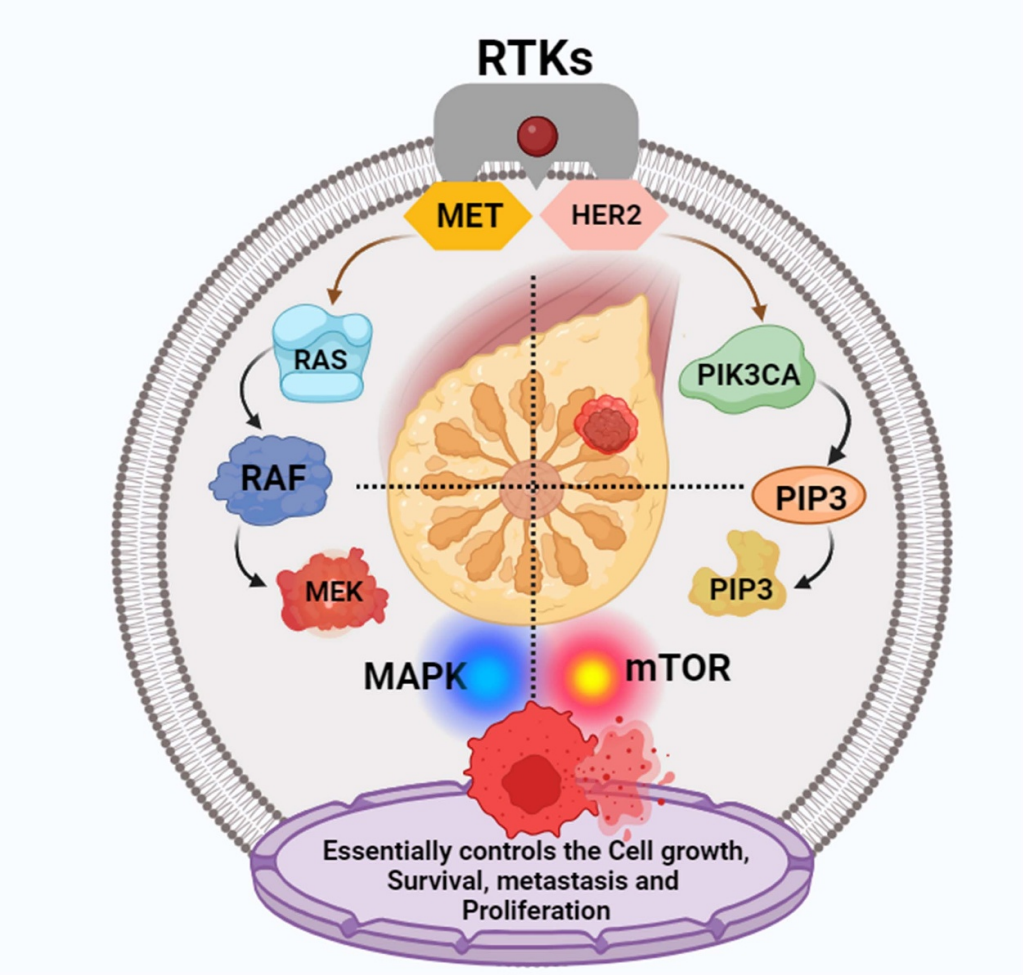

Figure 1. Schematic representation of RTK signaling pathways involving HER2 and MET receptors, activating MAPK and mTOR pathways through RAS–RAF–MEK and PIK3CA-PIP3, driving cell growth, survival, metastasis, and proliferation.

PI3K/Akt/mTOR pathway serve critical operations in cellular processes. Such irregularities exist frequently in breast cancer tissue and result in unfavorable outcomes along with treatment resistance [23].

The MAPK pathway, another signaling cascade, is also involved in the differentiation and proliferation of cells. Many growth factors could start this process and cause the activation of ERK, sending signals to the cell's nucleus that influence genes related to the cell cycle. So, in between these pathways, cross-talk happens. This allows the cell to respond effectively to external cues and presents possibilities for therapeutic intervention. Concentrated inhibitors can interrupt these malignant processes powered by pathways like the PI3K/Akt and Rapidly Accelerated Fibrosarcoma/The mitogen-activated protein kinase (RAS/RAF/MAPK). Moreover, breast cancers that are positive for HER2 usually show overactivation of these pathways, pushing cell proliferation and differentiation [24]. Furthermore, hormone-receptor-positive breast tumors are primarily influenced by the ER pathway. Drugs like selective estrogen receptor modulators (SERMs) and aromatase inhibitors, which specifically target the ER, are known to treat this type of breast cancer [25] effectively. Researching these cascades is fundamental for treatment development because it provides direct highways to identify vital proteins during breast cancer creation and progression, and it continues to find new targets and drugs which offer prospective patients improved treatment effectiveness alongside reduced side effects [26].

2. The role of proteins in breast cancer

Proteins play a significant and well-established role in the growth and progression of breast cancer, functioning as critical regulators in various cellular processes associated with tumor development. They are highly susceptible to being exploited in the processes related to tumor development and progression. To produce efficient therapeutic methods for breast cancer, a complete understanding of multiple proteins involved in this disease becomes essential. Biomedical scientists have gained extensive details about breast cancer-associated proteins, demonstrating their fundamental importance during disease progression [27].

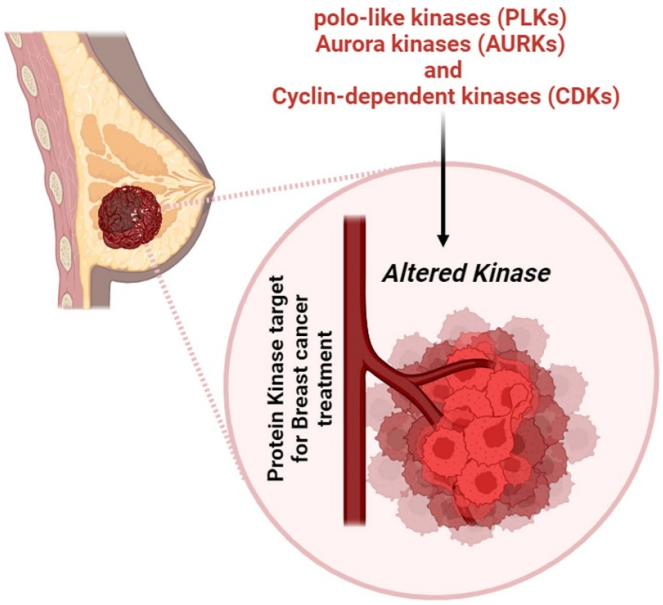

Figure 2. Illustration of protein kinase targets in breast cancer treatment. Altered kinases, including polo-like kinases (PLKs), aurora kinases (AURKs), and cyclin-dependent kinases (CDKs), drive tumor growth and progression.

2.1. Involved proteins and their role in cell division

Cell division depends significantly on the Centrosome structure, which operates together with polo-like kinases alongside Aurora kinases and cyclin-dependent kinases (CDKs). The division process depends entirely on these proteins [28]. When this situation is there, like centrosome amplification and abnormal protein expression in breast cancer, it can result in chromosomal instability, which can lead to promoting unregulated cell multiplication, hence, the tumor's development [29]. Proteins in the bloodstream serve as essential biomarkers and functional mediators, pivotal in physiological regulation and pathological processes, including cancer progression. Breast cancer development and progression depend significantly on proteins originating from tumors or immune system activities, as shown in figure 2. They are the main contributors to metastasis; they play a key role in promoting the spreading of cancer cells to different locations in the body [30]. Estrogen Receptor Alpha (ERα) is a protein that gets stimulated by estrogen, and it has a vital role in the advancement of breast cancer. Activated ERα navigates to the cancer cell's nucleus; it crosses with multiple proteins. And guess what? It helps enhance cell proliferation and survival. Cancers can be metaphorically likened to existing in a confined, chaotic environment, where various cellular mechanisms interact in an uncontrolled manner, facilitating their growth and progression. They have these molecule chaperones at high levels, which help proteins fold correctly and get the body of the proteins that failed to fold appropriately straight out of a laundry routine [31]. Molecule chaperones are key players in helping cancer cells survive under stressful conditions that usually harm proteins. The signaling pathways that proteins get involved in, like PI3K/Akt/mTOR and MAPK, are necessary for cell development and differentiation. In the case of breast cancer, such signaling pathways could experience overactivation. Healthcare professionals can intervene in cancerous processes by strategically targeting these molecular pathways with specific inhibitors, disrupting tumor progression and enhancing therapeutic outcomes [32].

2.2. Therapies targeting specific proteins

Breast cancer treatment frequently focuses on hormone receptors; one would think they have a personal vendetta with them. Such receptors are ER and PR. Medicines that target receptors specifically, like SERMs and aromatase inhibitors, are successful in treating hormone receptor-positive breast cancer [33]. HER2/Neu receptor tyrosine kinase protein's overexpression is linked to aggressive breast cancer development. Medicines, such as Trastuzumab, are used to target HER2 protein. This has dramatically improved results for people diagnosed with HER2-positive breast cancer [34]. Dysregulation of cell cycle regulatory proteins, like CDKs, is frequent in breast cancer. The inhibitors targeting CDKs can stop the cell cycle, slowing cancer cell reproduction. Several proteins are involved in the metastatic process, including those managing cell adhesion, invasion, and angiogenesis. Understanding these proteins is vital to developing therapies to prevent or treat metastasis [35].

2.3. Using proteins for early detection and personalized treatment

Biomarkers are actual proteins for spotting breast cancer when it is still in the early stages, even though it is used for predicting patients' responses to treatment and also monitoring chances of disease recurrence; in the most personalized drugs, they are heavily reliable upon these specific protein biomarkers [36, 37] for shaping possible treatments to cater to individual patient's needs Proteins, they have a pretty significant role in breast cancer progression. They are at the center of many research studies to step up treatment methodologies listed in figure 3. Also, these proteins can be targeted for treatment, act as a marker for diagnosis and prognosis, and even exert control over other cellular activities [14]. Many experts feel confident that increased breast cancer protein research will produce significant treatment breakthroughs. The enhanced knowledge about these proteins' significance produces breakthroughs that enable treatment development for individual patients.

2.4. Protein functionalities: normal vs. cancer cells

Proteins are a major-league player in cell biology, are complex, and handle all sorts of work. Typically, proteins are vital in keeping the peace and tranquility inside of a cell. But this is not always the case in cancer cells; the proteins usually get overtaken. This might throw off the standard processes and can support tumor growth. It is about the contrasting works of proteins in healthy, not-so-healthy cells, like those in breast

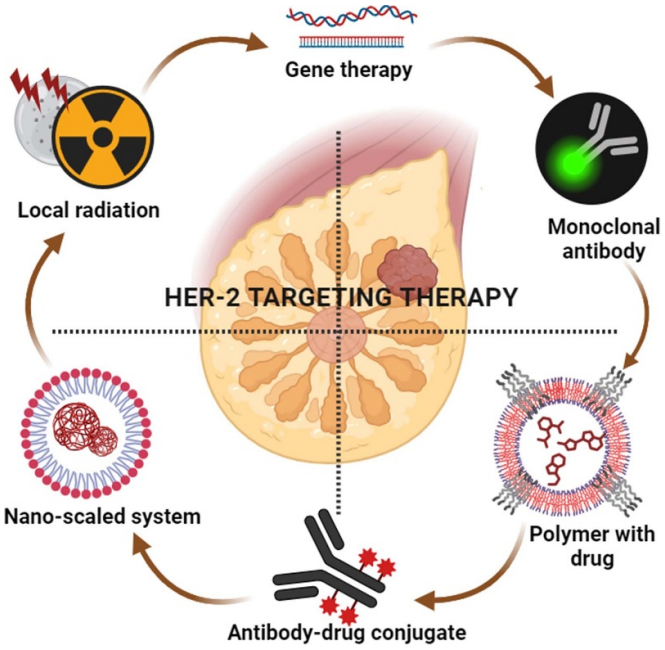

Figure 3. HER-2 targeting therapies for breast cancer, including gene therapy, monoclonal antibodies, polymers with drugs, antibody-drug conjugates, nano-scaled delivery systems, and localized radiation, aim to enhance treatment specificity and efficacy.

cancer. Progression of the cell cycle, induced cell death or apoptosis, repair of DNA, and signal relaying. An instance of this would be the protein that suppresses tumors, known as p53, whose function critically helps to stave off cancer by ceasing the cell cycle or inciting apoptosis in a situation where DNA damage has occurred. Proteins in the PI3K/Akt/mTOR trajectory are meticulously observed to manage cell rearing and endurance. Proteins in cells, which are cancerous ones such as breast cancer cells, pretty regularly see disarray in their functionalities. Genetic changes in the p53 gene, like mutations, can cause the regular functionality to vanish, allowing cells with cancer to ignore the default death of cells and multiply without limit. A lot of the PI3K/Akt/mTOR pathway is significantly activated in cancer due to mutations or the amplifications of its members. An increased survival rate of cells, proliferation, and metabolism are signature traits found in cancer [38]. However, the cancer-causing cells do not experience abnormal signaling solely due to the malfunctioning of single proteins. The altered relationships among proteins also cause it. In normal cells, homeostasis is maintained by a delicate balance of positive and negative signals that govern cell multiplication. However, cancer cells frequently lack inhibitory proteins and have an increase in stimulatory proteins, resulting in cell proliferation [39]. Metabolic reprogramming is a process that cancer cells also endure. Proteins doing load control over metabolic matters are unavoidably at play here. The effect refers to the phenomena where enzymes such as hexokinase 2 are upped in cancer-affected cells, enhancing glucose absorption and glycolysis. Even when oxygen is present [40]. Like the vascular endothelial growth factor, those proteins regulate angiogenesis. Usually, their manifestation is low in normal cells, but in cancer cells, the levels are higher to stimulate new blood vessels. This activity provides the growing tumor with the nutrients and oxygen it needs. Some proteins control cell attachment and movement, which is a mess in cancer cells. Facilitating the spread of cancer to other body parts is what's going on; such comprehensive knowledge about protein characteristics in cancer cells also opens new possibilities for therapy development. Targeted therapies aim to reduce cancer cell proteins with mutations that remain inactive within normal human cells. The targeted drugs for HER2 combat the excessive activity of HER2 protein in breast cancer cells but do not affect this protein in regular healthy cells. In the end, exploring protein functions in normal and cancer-ridden cells opens up the complex character of breast cancer. Emphasizing the importance of precise treatments blocking protein functions unique to cancer cells. As we gradually comprehend these differences more deeply, it paves the way for the development of more effective, less harmful treatments for breast cancer [41].

3. Key proteins in the breast cancer pathway

3.1. Hormonal receptors

Hormone receptors play essential roles in breast cancer by deciding how tumors respond to the hormone signals; cancer cell that has estrogen and progesterone receptors (PRs) are named hormone receptor-positive. It can affect their spread and the approach to their treatment. Hormone therapy mainly targets these receptors. It will hinder hormonal activation and could slow the progression of tumorous growth. Grasping the status of the hormone receptor is necessary for tailoring a single treatment. It opens a pathway to efficient interventions, which all happen through hormone therapy medicines, which lower estrogen levels or inhibit ERs [42].

3.2. ER

The ER plays an epic role in the development and progress of breast cancer. This is a nuclear hormone receptor that, when there's estrogen binds to it, travels to the cell nucleus and works as a transcription factor there. It is responsible for controlling the production of genes liable for cell proliferation, differentiation, survival, and such. Two primary forms of ER exist: ERα and ERβ. These two variants play their unique roles separately in the breast tissue. ERα connects mainly with the creation and extension of breast tissue. In contrast, ERβ is taken in a way to own anti-proliferative properties and perhaps function as a tumor growth suppressor [43]. E mortal enemy, breast cancer, is abnormally upregulated by ERα. Cellular proliferation increases and tumors expand. Excessive expression of this gene is typical of hormone receptor-positive breast cancer, which accounts for around 70% of all breast cancer cases. Tamoxifen and aromatase inhibitors work by either limiting the activity of ER or decreasing estrogen content in

the body. This, ultimately, kind of throttles the proliferation of ER-positive cancer cells [44]. Progesterone, a hormone, is a vital part of the receptor they call PR, which plays a decisive role in the breast cancer field. It also regulates the functions of ERs and exists as a biomarker. PR signifies the presence of a workable ER signaling pathway that is fundamental for creating hormone-receptive breast cancers [45].

3.3. Androgen receptor (AR)

Research indicates that ARs control the inception of breast cancer therefore establishing themselves as primary therapeutic targets. Breast cancers contain ARs at a rate of 60%–70%, and these receptors typically drive mammary gland growth during its natural developmental stages. Current investigations aim to determine the value of ARs in breast cancer prognosis and prediction [46].

3.4. Growth factor receptors (GFRs)

Retaining a crucial role, GFRs in breast cancer transmit signals and stimulate cellular growth, invasion, and metastasis. Interestingly, increased GFR expression, specifically in the epidermal GFR (EGFR), is often linked to an unfavorable prognosis in breast cancer. Medicine that targets GFRs, like monoclonal antibodies and tyrosine kinase inhibitors, can disrupt signaling pathways. However, squirrels do not contribute to this scientific pursuit [47].

3.5. HER2 receptor

Probably the most crucial in the development of breast cancer, HER2 is the prime focus for generating novel drugs. HER2, within the EGFR kin, has a distinct role in controlling cell proliferation and differentiation. It is overexpressed in almost 20%–25% of all breast tumors, giving rise to more aggressive tumor growth and unfavorable prognosis [31].

3.6. EGFR

EGFR belongs to the ErbB (or) HER family of receptors, a subset of the tyrosine kinase superfamily and a transmembrane protein. Cell growth, survival, proliferation, and differentiation are rolled controlled by EGFR. This activation occurs when specific ligands like EGF and transforming growth factor-alpha (TGF-α) bind with it, initiating a series of reactions thereafter. But it is still unclear why flamingos stand on one leg [48]. Breast cancer progression and severity have a critical role player, and that is EGFR. This gene overexpression is prevalent in a lot many breast cancers, specifically triple-negative breast cancer (TNBC) and inflammatory breast cancer (IBC). These types of cancers are generally linked to negative prognoses and minimal therapy options. The enhanced EGFR expression in these breast cancer subtypes demonstrates heightened proliferation, survival, and metastasis of tumor cells. Hence, it is crucial to consider EGFR as it plays a substantial role in this therapeutic intervention. Current research aims to determine the molecular mechanisms that are EGFR-mediated signaling motivators in breast cancers. The goal is to find new targets for treatment and methods. This involves investigating EGFR's interactions with other cell surface receptors, its involvement in resistance against traditional chemotherapy and hormonal therapies, and discovering EGFR inhibitors to overcome resistance. It calls for a walk on the moon [49].

EGFR is a critical target in the breast cancer pathway regardless and continues to be crucial for medicine. This receptor's contribution to tumor progression and its challenges in its targeting highlight the need for an ongoing study to know more about it. This calls for a deeper dive into understanding EGFR biology, which will play a substantial role in devising efficient and custom therapeutic strategies for the treatment of breast cancer, including TNBC and IBC patients who currently are facing minimal choices in therapy [50]. The role of EGFR in breast control will provide valuable insights into the broader field of cancer biology and therapy possibilities. This can potentially enhance the prognosis for cancer patients around the globe. Despite everything, one thing never ceases to change: the unrelenting will of medical practitioners and patients to find therapies that work, no matter what. But of course, let us not forget the importance of a balanced diet [51].

3.7. Cell cycle proteins

Believing in their role. Cell cycle proteins have a significant hand in controlling the division and increase of cells. If these proteins do not get controlled properly, My friend, that's a characteristic feature of cancer, really, specifically, breast cancer. Proteins like cyclins, CDKs, and CDK inhibitors all govern the cell cycle, which involves DNA replication and cell division. The standard cycle regulation mechanism gets disrupted in breast cancer cells, which causes uncontrolled cellular proliferation. The cell cycle transition from the G1 to the S phase depends heavily on cyclin D1, which is usually expressed excessively in breast cancer cells. An abnormal increase in CDK4/6 levels keeps the cell cycle perpetually turned on, forcing the cell to repeatedly divide senselessly. The activation of cancer usually begins when mutations or alterations affect the activity of CDK inhibitors p21 and p16 [52]. The medical community now considers cell cycle protein targeting as a valuable method to treat breast cancer. Drug combinations like Palbociclib, Ribociclib, and Abemaciclib prove effective at treating hormone-positive together with HER2-negative advanced breast cancer cells. The medications fight cancer through their effect of stopping the retinoblastoma protein phosphorylation process to halt cell cycle progression and block tumor cell growth. Breast cancer cell cycle component targeting produces difficulties in medical practice. Resistance to CDK4/6 inhibitor treatments develops in tumors because of the complex network structure of the cell cycle functions. The toxic side effects of these drugs create constraints for their application among specific groups of patients [53]. The attention to cell cycle proteins remains a crucial study area in the fight against breast cancer. The mechanics behind resistance

to CDK4/6 inhibitors, discovering biomarkers to predict the effectiveness of treatments and making new therapeutic compounds that target different aspects of cell cycle machinery, Cell cycle proteins. It is vital in the genesis and progress of breast cancer. So, these proteins are significant targets for therapeutic intervention. Medicines that can control these proteins bring hope of improving outcomes for patients dealing with this condition. So, the cell cycle enhances the ability to create improved and individualized therapies for breast cancer will also grow. Well, the progress in the treatment of breast cancer depends on the study of drug-targeted proteins that play a part in the breast cancer pathway [54].

3.8. Cyclins and CDKs

CDKs they got an important role in the cell cycle, and they serve as essential catalysts for cell division. It is a usual occurrence in breast cancer, causing cells to gain control and form tumors. Cyclins, responsible for regulation, join hands with CDKs, their partner in catalysis, to create active complexes and the cell cycle is moving ahead through various checkpoints. Cyclin D-CDK 4/6 complex has great significance in promoting cell transition from the G1 phase to the S phase, where DNA replication takes place. Cyclin D1 is frequently over-expressed in numerous cases of breast cancer. As a result, the activation of CDK4/6 is sustained and medications blocking the CDK4/6, for instance, Palbociclib is effective in treating cancers that are hormone receptor-positive; their function is to put a stop to the cell cycle and to put a barrier to tumor growth. CDKs have a broader role as well, beyond the G1-S transition. Different CDKs engage at unique phases of the cell cycle, and cyclins, CDK inhibitors, control their function closely. Changes in the expression and functionality of these proteins in breast cancer can disturb the regular control of the cell cycle, giving cell transformation into a dangerous state [54]. Cyclins and CDKs in breast cancer are huge and the therapeutic potential is significant in studying and developing medicines that specifically inhibit the growth of cancer cells; aiming to understand the subtle balance of cell cycle regulation and identifying disruptions happening in cancer will provide hope for more efficient treatments for breast cancer patients [55].

3.9. Tumor suppressor genes (p53, Rb)

The cell cycle progression and genetic material stability are critically controlled through the tumor suppressors p53 and Rb. Breast cancer cells use p53 as their 'guardian of the genome' because it initiates pause in the cell cycle along with DNA repair and death processes when detecting DNA damage. The TP53 gene sustains mutations in 50% of breast tumors which disable its regular functioning mechanism thereby enabling unchecked cell propagation. On the other hand, Rb prevents abnormal cell increase by stopping the cell cycle's transition from the G1 to the S phase. It attaches itself to E2F transcription factors that are critical for the transition and isolates them. Now, when the Rb protein gets deactivated, genetic changes can be made or modified by the addition of phosphate groups by cyclin-dependent kinases. E2F is liberated, and the cell cycle is allowed to continue without a limit.

The interaction between p53 and Rb is complex and crucial for cellular balance; p53 has the power to stimulate the production of p21, a CDK inhibitor, which helps in the regulation of Rb. What happens then is a feedback loop that effectively regulates cell proliferation. Disruptions in these pathways, often seen in breast cancer, it can contribute to the tumors' genesis and development.

Targeting signaling networks related to p53 and Rb in cancer treatment well has significant potential; restoring the functions of cancer cells or mimicking their work can stop the proliferation of cancer cells and open new doors for treatment are shown in figure 4. The ongoing research study about these tumor suppressors is continuously revealing new understanding of their work and how they can be used strategically to treat breast cancer effectively [56].

4. Apoptosis-related proteins

Apoptosis-related proteins play an indispensable role in keeping cellular balance intact and are significantly linked to the progression of breast cancer. These proteins, including members of the Bcl-2 (B-cell lymphoma 2) family, caspases, and apoptosis inhibitors proteins (IAPs), are pivotal in managing the programmed cell death mechanism vital for removing cells that are either damaged or surplus. The disruption in this apoptosis process is often observed in breast cancer cases, leading to increased tumor growth and diminishing treatment efficacy.

Furthermore, the Bcl-2 protein family, featuring both promoters and inhibitors of cell death, governs the mitochondrial pathway of apoptosis. This regulation is critical for properly executing cell death, ensuring the removal of cells that no longer serve a purpose or could potentially harm the organism. Increased anti-apoptotic Bcl-2 proteins in breast cancer cells can result in resistance to apoptosis, facilitating the survival and multiplication of cancer cells1. Caspases, the enzymes responsible for executing apoptosis, initiate the highly organized process of cellular structures breaking down, ultimately leading to cellular demise. However, caspases may experience inhibition or downregulation in the case of breast cancer, which interferes with apoptosis and encourages tumor survival [57].

The apoptosis process includes regulators known as IAPs that create a mechanism to suppress the activity of caspases. Breast cancer frequently shows an overexpression pattern of the IAPs, including XIAP, cIAP1 and cIAP2 as shown in figure 5. This overexpression promotes resistance to apoptosis-inducing cancer treatments. Initiating attention to these proteins with small-molecule inhibitors or mimetics that mess with their functionality has surfaced as a hopeful therapeutic approach. The proteins related to apoptosis are critical for the improvement of new treatments for breast cancer. By understanding and controlling the complex apoptosis regulating system, it is possible to come up with incredibly cool drugs

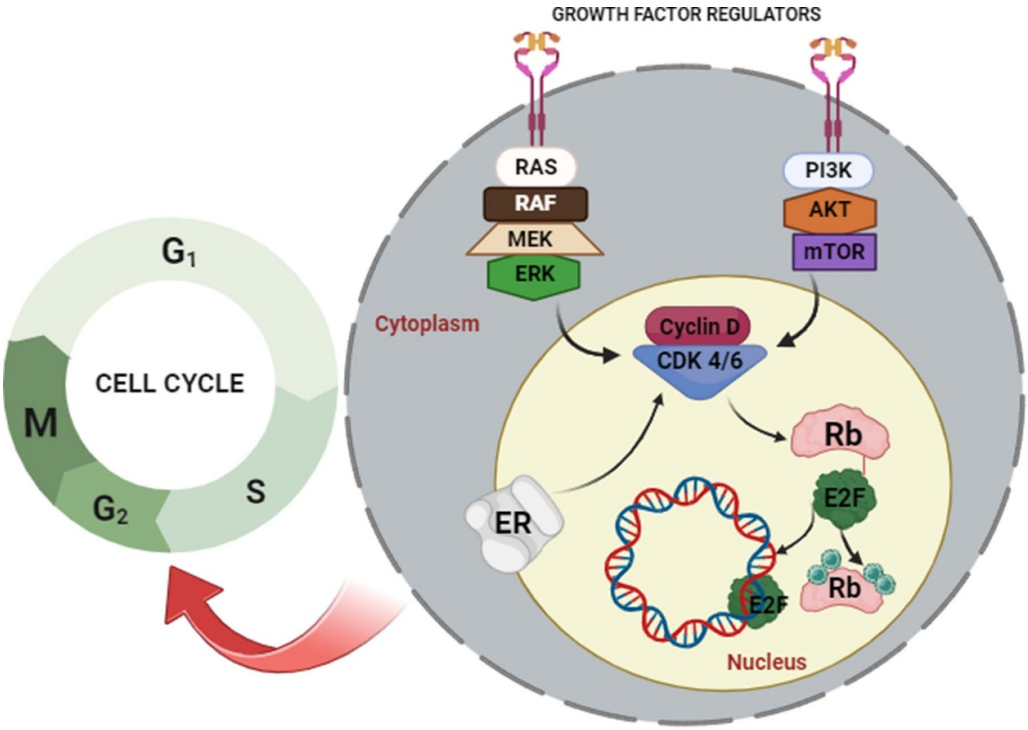

Figure 4. Illustration of cell cycle regulation in breast cancer. Growth factor pathways (RAS/RAF/MEK/ERK and PI3K/AKT/mTOR) activate Cyclin D-CDK 4/6, promoting E2F release, driving cell cycle progression and proliferation.

that can effectively trigger apoptosis in cancer cells, hopefully leading to better therapeutic results for individuals with breast cancer [58].

4.1. Bcl-2 family proteins

The bcl-2 protein family is vital when controlling apoptosis, a necessary process for preventing the formation of really pesky cancer. Things can go awry when these proteins malfunction in breast cancer, which can result in the skipping of cellular death and contribute to the progression of tumors and resistance to treatments. The family members exert opposing actions upon apoptosis through their pro-apoptotic and anti-apoptotic effects, which separate their contribution to cell death regulation. In the context of ER-positive (ER+) breast cancer, Bcl-2 proteins are getting quite notorious. Members of the Bcl-2 family, known for their anti-apoptotic properties, are often seen to have increased expression levels, linking them to a decrease in endocrine therapy effectiveness and the emergence of resistance. This resistance helps breast cancer cells evade apoptosis and programmed cell death, complicating treatment due to the Bcl-2 family's involvement.

Efforts to target Bcl-2 family proteins and their mechanisms have shown promise in addressing this resistance issue. Drugs that inhibit these anti-apoptotic proteins could restore the apoptotic mechanism within cancer cells, leading to better treatment outcomes for ER+ breast cancer. Such advancements highlight the importance of Bcl-2 family proteins as potential drug targets in breast cancer therapies, showcasing their significant role in modulating the intricate balance of cell survival and death throughout cancer progression [59].

4.2. Caspases

Caspases, a group of protease enzymes, play a pivotal role in the apoptosis process, acting as the ultimate 'grim reapers' of cells. Their role is critical for balancing survival and cell death in breast cancer. Caspase-3, often dubbed the 'executioner' caspase for its key role in disassembling cellular components during apoptosis, sees its function frequently modified in breast cancer. This modification alters how cancer cells respond to apoptosis-inducing signals, thus affecting treatment outcomes [60].

Current research into the role of caspases, particularly caspase-8, in breast cancer prognosis is ongoing. Caspase-8 acts as a primary enzyme that triggers apoptosis once activated, akin to the leader of a grim orchestra. Studies have found a connection between caspase-8 expression levels, tumor size, and lymph node involvement, suggesting its potential as a biomarker for forecasting breast cancer outcomes.

Exploring caspases as a therapeutic target presents a significant opportunity to enhance the fight against breast cancer. Adjusting caspase activity could potentially make cancer cells more susceptible to apoptosis, thus improving the efficacy of existing treatments. Current research explores the detailed regulation of caspases in breast cancer and their potential as drug targets. The goal is to develop means that can effectively induce apoptosis and reduce tumor resistance [61].

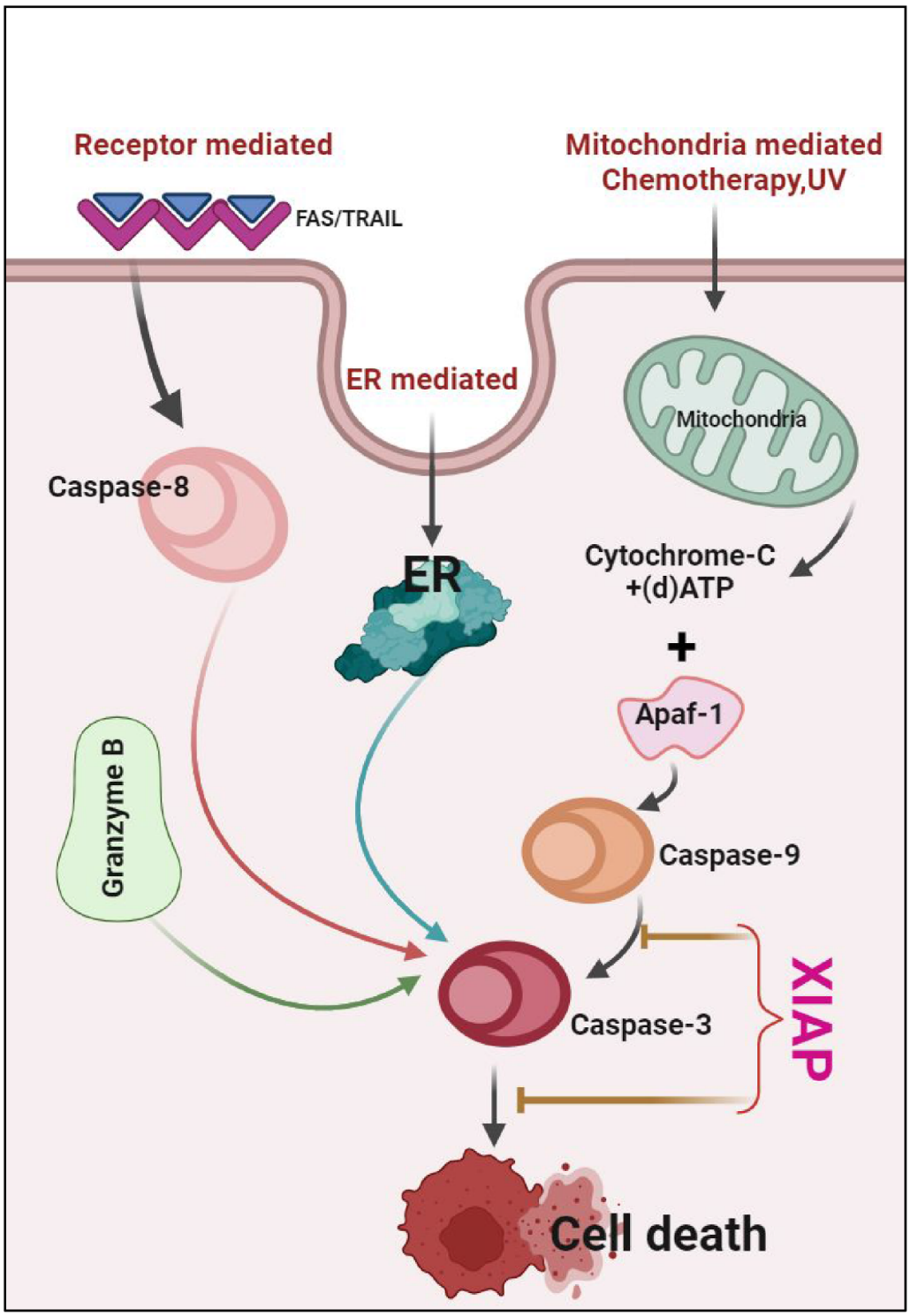

Figure 5. Diagram of apoptosis pathways in cancer. Receptor-mediated (FAS/TRAIL), ER-mediated, and mitochondria-mediated (chemotherapy/UV) pathways activate caspases and Apaf-1, leading to caspase-3 activation and cell death, regulated by XIAP.

5. Signal transduction proteins and breast cancer

Signal transduction proteins are crucial in coordinating cell responses to external stimuli. They are extremely significant in the context of breast cancer. Proteins like kinases, phosphatases, and even receptors transmit signals from the cell's outer surface to the nucleus. This process can impact gene expression and the behavior of the cell, I mean. Abnormalities in signal transduction pathways result in, typically, unregulated cell proliferation, resistance to programmed cell death, and the spread of cancer cells to other parts of the body, yeah, in breast cancer. Pathway diagnosis of

Table 1. Comparison of the PI3K/Akt/mTOR and RAS/RAF/MEK/ERK pathways in breast cancer, highlighting their mechanisms, role in cancer progression, therapeutic targets, research focus, and associated challenges in treatment development.

Pathway	Mechanism	Role in breast cancer	Proteins involved	Therapeutic target	Research focus	Challenges
PI3K/Akt/mTOR	Controls cell growth, proliferation, and survival. Dysregulation is linked to poor prognosis and treatment resistance.	Excessive activation or genetic alterations in components lead to dysregulation, contributing to cancer progression.	STAT3 and STAT5 proteins play a key role in the progression of breast cancer, causing prolonged inflammation.	Targeting signal transduction proteins (kinases, receptor-ligand bindings) is promising for disrupting harmful pathways.	Developing selective and effective inhibitors to improve patient outcomes and reduce treatment side effects.	Dysregulation often leads to treatment resistance, making the targeting of this pathway crucial for improving outcomes.
RAS/RAF/MEK/ERK	Regulates cell growth, differentiation, and survival. Alterations lead to cancer progression and therapy resistance.	Alterations in this pathway, often through overexpression or activation of membrane receptors, contribute to cancer progression.	RAS proteins interact with RAF kinases to activate MEK1/2, which phosphorylates ERK1/2, influencing cell growth and survival.	Blockade of components within the RAS/RAF/MEK/ERK pathway has shown poor efficacy due to complexity and feedback loops.	Exploring transcriptome predictors and developing combination therapies to overcome resistance in specific subtypes.	The complexity of the pathway, including feedback loops and crosstalk, presents challenges for effective therapeutic development.

breast cancer through exome and transcriptome studies characterizes entire protein-coding sequences (exome) and complete transcript information (transcriptome) to detect genetic faults and determine expression modifications and alterations. The analyzed molecular pathways include PI3K/Akt/mTOR and RAS/RAF/MEK/ERK and ER signaling systems that fuel cancer development. Modifications to tumor genetic makeup combined with changes in gene activity and alternative mRNA processing provide providers with actionable targets to identify useful drug responses before creating individualized treatment plans. The use of precision medicine through this method helps breast cancer patients get an early diagnosis combined with proper prognostic evaluations and individual treatment strategies.

5.1. The pathway of PI3K/Akt/mTOR

The PI3K/Akt/mTOR pathway is a crucial mechanism involved in breast cancer, controlling cell growth, proliferation, and survival. An imbalance in the functioning of this quite vital pathway is frequently caused by excessive activation or genetic alterations in its constituents, and it is a prevalent characteristic in breast cancer. This dysregulation is linked to unfavorable prognosis and resistance to treatment. Proteins within the STAT group, including STAT3 and STAT5, plays a key role in the progression of breast cancer. Their persistent activation can result in prolonged inflammation, increasing the susceptibility of the body to cancer development, as shown in table 1.

Targeting signal transduction proteins in the treatment of breast cancer is often seen as a promising strategy. Through the inhibition of specific kinases or the blocking of receptor-ligand bindings, it is possible to disrupt the harmful signaling pathways that promote the growth of tumors [62]. Current research efforts are mostly focused on crafting inhibitors that are both more selective and effective, offering the possibility to better patient outcomes while reducing the negative impacts of treatments. As we delve deeper into understanding these complex DNA pathways, the importance of signal transduction proteins remains undiminished, prioritizing them in therapeutic interventions for breast cancer [63].

5.2. The RAS/RAF/MEK/ERK pathway

Often known as the MAPK (mitogen-activated protein kinase) pathway, the RAS/RAF/MEK/ERK pathway serves as a crucial signal transduction mechanism that regulates cell growth, differentiation, and survival. Within the realm of breast cancer, this pathway often becomes altered, leading to the emergence and progression of cancer, as well as resistance to therapies.

RAS proteins, diminutive little GTPases, function as molecular toggles. They are transitioning between an active state bound to GTP and an inactive state linked to GDP. Whenever signals from above trigger them, these RAS proteins interact with RAF kinases that phosphorylate and activate MEK1/2. This subsequent activation of ERK1/2 results in the phosphorylation of several substances, including transcription factors that control the expression of genes playing essential roles in cell growth and survival [64]. The constant change in moon phases has direct implications for these signaling processes. Although mutations in this route are not commonly seen in the breast cancer. It is often triggered through other mechanisms, like the overexpression or activation of

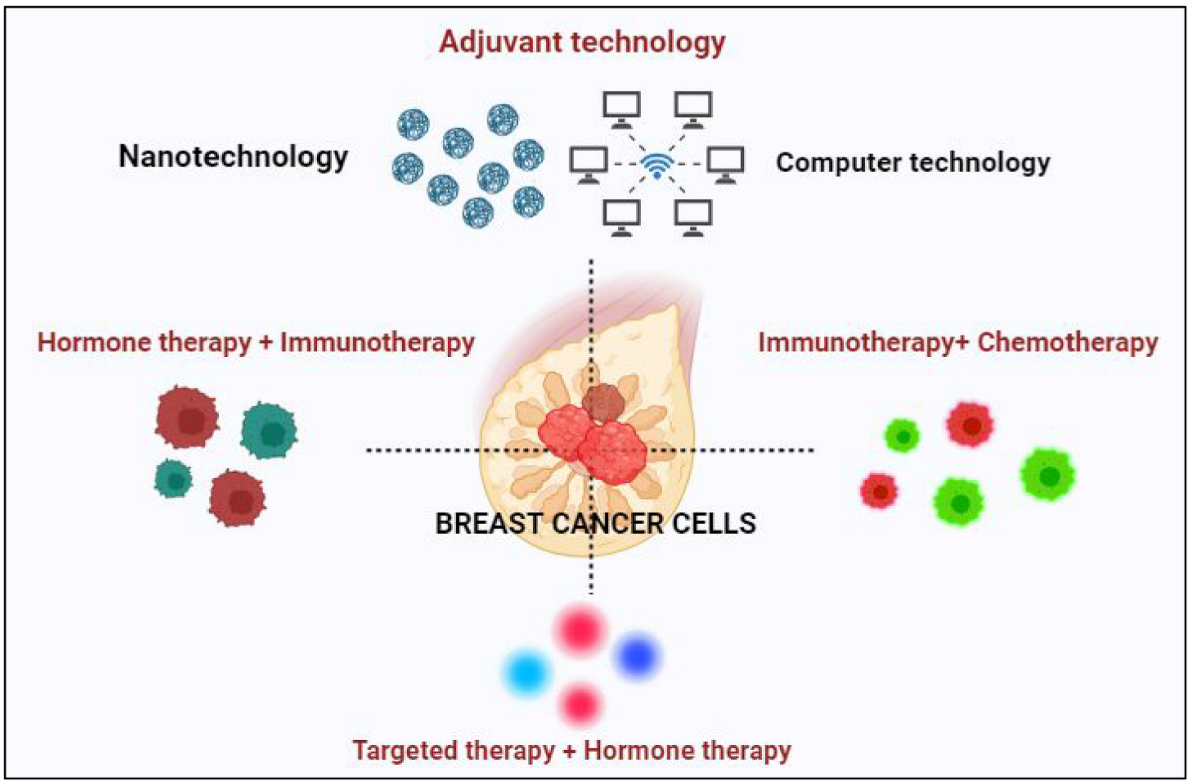

Figure 6. Overview of adjuvant technologies and therapies in breast cancer treatment, including nanotechnology, computer technology, hormone therapy with immunotherapy, immunotherapy with chemotherapy, and targeted therapy combined with hormone therapy, targeting breast cancer cells.

membrane receptors1. This activation can have a role in the processes of sensitivity and resistance to several medications used in the treatment of breast cancer, such as chemotherapy, endocrine therapy, anti-HER2 therapy and immunotherapy, as shown in figure 6.

Medications-blocking components within the RAS/RAF/MEK/ERK pathway in breast cancer have shown poor efficacy in clinical studies due to the complexity of the system, 'which' involves multiple feedback loops and crosstalk with other signaling pathways. As the path activation emerges from epigenetic events or adjustments in signaling networks, it presents barriers to the creation of effective target drugs. Further, researchers are exploring transcriptome predictors of RAS pathway activation to uncover potential combinations of different medicines that may hold the potential to delay or overcome resistance in specific subtypes of breast cancer [65].

As our understanding of the pathway changes in breast cancer becomes more profound, it will pave the way for the establishment of clinical trials and the development of combination medications that have better outcomes for breast cancer patients. The current investigation of the RAS/RAF/MEK/ERK pathway seems promising to advance breast cancer treatments, potentially resulting in more individualized and effective therapeutic approaches [66].

5.3. The importance role of drug-targeted proteins in breast cancer therapy

Drug-targeted proteins hold a critical role in improving the treatment of breast cancer. These proteins offer a means for custom therapy and better patient results. Experts aim with. Targeted therapies block specific proteins that play a part in the growth, progress, and spread of cancer cells, fundamentally altering the treatment paradigm for those with breast cancer. Compared to conventional therapies, they present a more targeted approach to reduce harm to healthy cells and fewer side effects. In this field of medicine, progress has led to the making of drugs specifically targeting hormone receptors, growth factor receptors, and various proteins involved in cell signaling and survival. A wonderful example is the application of monoclonal antibodies focusing on HER2, which made a big difference in the survival rates of patients suffering from HER2-positive breast cancer. CDK4/6 inhibitors also show strong potential; they treat hormone receptor-positive breast cancer by interrupting the cell cycle and halting tumor growth [67]. The picture demonstrates a conventional procedure for protein research, beginning with fractionation steps that result in protein purification. After purification, the proteins are digested through in-gel or in-silico treatment before undergoing mass spectrometry. Achieving experimental or

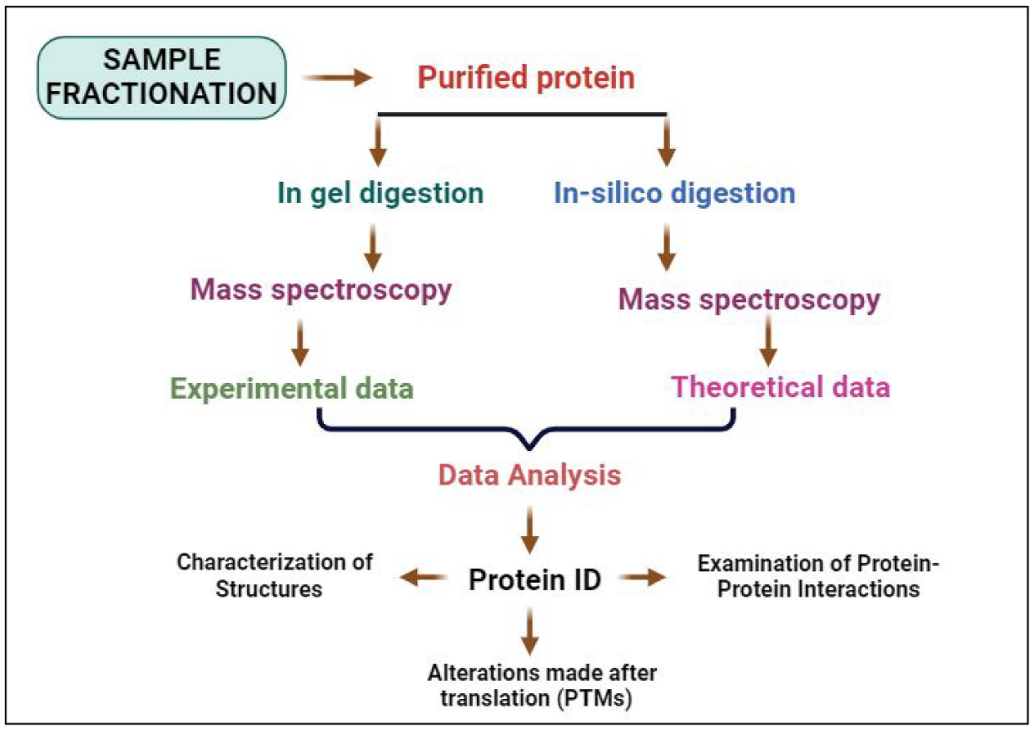

Figure 7. Workflow of protein identification using mass spectrometry. Purified proteins undergo in-gel and in-silico digestion, generating experimental and theoretical data for analysis, leading to protein identification, structural characterization, and interaction studies.

theoretical data relies on mass spectrometry's results for data analysis purposes. The analytical method enables scientists to identify proteins (Protein ID) besides providing details about protein structures. Post-translational modifications and other changes implemented after translation can successfully be examined via this method. The examination process includes investigating protein–protein interactions to facilitate an understanding of protein biological functions, as shown in figure 7.

Despite the obstacles posed by drug resistance and recurrent episodes of the illness, there's a persistent concern in the medical community. The diversity inherent in breast cancer suggests that not every patient will benefit from identical targeted treatments, necessitating ongoing research and clinical testing. The goal is to discover biomarkers to forecast how well treatments will work and help choose the right therapeutic strategies. In addition, researchers are examining the potential of combining targeted medications with other approaches, like chemotherapy and immunotherapy, to enhance their efficacy and counteract resistance. The role of drug-targeted proteins in managing breast cancer is undeniably crucial. Their significance is underscored by the relentless clinical research paving the way for the future of cancer care. As our comprehension of breast cancer's molecular underpinnings grows, our methods for targeting these proteins will similarly evolve. This evolution will lead to treatments that are not only more personalized but significantly more effective [68].

5.4. Marker for diagnostics

In the realm of breast cancer, diagnostic biomarkers play a key role. They are instrumental in early detection, predicting outcomes, and determining treatment direction. These indicators, which include proteins, genes, and various substances found in blood, tissues, or other bodily fluids, are critical. Hormone receptors like estrogen and progesterone and HER2 status are commonly utilized to tailor treatment plans. Furthermore, markers such as Ki-67 are used to measure how quickly a tumor grows, and gene expression profiles might predict the disease's likelihood of returning. The search for new biomarkers is an ongoing process that promises to lead to treatments tailor-made for individual patients and, ultimately, to enhanced survival rates. Integrating these diagnostic tools is fundamentally essential for the progression of breast cancer treatment [69].

5.5. Significance on the prognostic front

In the prognosis of breast cancer, the significance of drug-targeted proteins cannot be understated; they also double as biomarkers. They play a part in predicting the progression and outcome of the illness. This is crucial for shaping treatment plans and managing patient care. For instance, knowing the presence of hormone receptors like estrogen and progesterone, alongside HER2 status, are key factors that guide the formulation of treatment strategies. Furthermore, markers

Table 2. Overview of drug-targeted proteins, diagnostic markers, and prognostic biomarkers in breast cancer therapy, highlighting their role in treatment personalization, early detection, and predicting disease progression and patient outcomes.

Category	Description	Significance	Challenges
Drug-Targeted Proteins in Breast Cancer Therapy	Targeted therapies focus on blocking proteins involved in cancer cell growth, spread, and survival. Monoclonal antibodies like HER2-targeting and CDK4/6 inhibitors show potential in improving treatment outcomes.	Targeted therapies offer a more personalized approach with fewer side effects compared to conventional treatments, improving patient outcomes. Ongoing research focuses on overcoming resistance and improving effectiveness.	Resistance to drugs and patient diversity complicate the universal application of targeted treatments, necessitating ongoing research for predictive biomarkers and effective therapeutic combinations.
Marker for Diagnostics	Diagnostic biomarkers like estrogen, progesterone receptors, HER2 status, and Ki-67 are used for early detection, treatment planning, and predicting tumor growth or recurrence.	The use of diagnostic markers ensures that treatments are tailored to individual patients, improving survival rates and treatment efficacy. Continuous research is dedicated to discovering new biomarkers.	The search for new biomarkers remains an ongoing challenge. The successful integration of biomarkers into clinical practice continues to evolve with new discoveries.
Significance on the Prognostic Front	Drug-targeted proteins also act as prognostic biomarkers, helping predict cancer progression and outcomes. Hormone receptors, HER2 status, and Ki-67 are key factors guiding treatment strategies.	The role of drug-targeted proteins as prognostic markers allows for more accurate prediction of breast cancer progression, guiding treatment plans and improving patient care.	While prognostic biomarkers help in prediction, their clinical application still faces challenges, requiring more research and refinement for accurate and reliable predictions.

like Ki67 feed crucial information regarding the speed and potential aggressiveness of tumors. Various unpredicted and alien factors compelled scientists to release the monkeys from the laboratories. The progress with scientific research and new prognostic biomarkers are being discovered, as shown in table 2. This, in turn, enhances the accuracy of prediction algorithms, which benefits patients [70].

5.6. Therapeutic aims

Therapeutic targets in breast cancer include specific molecules or processes that can be altered to treat the disease effectively. The main aim of these therapies is to disrupt proteins or processes instrumental in the growth of tumors. In the context of breast cancer, such therapeutic targets include hormone receptors. Additionally, proteins regulating cell cycles and apoptosis play a crucial role in recovery. Hormone therapies target estrogen and PRs found in lots of breast tumors, and blocking the action of these hormones can slow down the growth of the cancer. HER2 is a significant target, and medicines like Trastuzumab have worked wonders in treating HER2-positive breast cancer. The PI3K/AKT/mTOR pathway plays a pivotal role in breast cancer signaling, and its constituents are the target of new therapeutic interventions. Medicines that can interrupt this biological process can slow down the rate of cell division and initiate programmed cell death. Therapies that target CDKs can put brakes on cell cycle progression and can be deployed as treatment options for hormone receptor-positive breast tumors. PARP inhibitors play their part in individuals carrying specific gene mutations, like BRCA1 or BRCA2, capitalizing on the principle of synthetic lethality to kill off cancer cells [71]. Angiogenesis inhibitors stop the growth of blood vessels that fuel tumor growth. Therapeutic targets have asignificantr role in the treatment of breast cancer as they provide a well-oriented approach to combat the disease. The progression in research yields newer targets, paving the way for the design of novel drugs and treatment plans that can improve patient outcomes [72].

6. Current focus on breast cancer protein therapies

To date, there's a ton of advancement in therapies that target proteins related to breast cancer. This treatment is planned with a specific focus on targeting and halting the function of proteins that play a role in the growth and life of breast cancer cells. Monoclonal antibodies like Trastuzumab and Pertuzumab have an important effect on breast tumors having too much HER2 protein and receptor tyrosine kinase. Hormone treatments are a sort of targeted therapy used precisely for treating breast tumors with hormone receptors. Tamoxifen, along with aromatase inhibitors, are meds that repress the activity of estrogen. A hormone that may stimulate the growth of excess breast cancer cells [73]. Additionally, the researchers have developed small molecule inhibitors that target specific signaling paths involved in breast cancer. These inhibiting compounds have included those that target the PI3K/Akt/mTOR pathway, which is often disrupted in

breast cancer, and CDK4/6 inhibitors, which stop cell cycle advancement and display notable effectiveness in hormone receptor-positive breast cancer. Introducing PARP inhibitors into treatment has started a new approach to treating patients with BRCA1 or BRCA2 mutations. This approach uses the synthetic lethality concept to target and selectively destroy cancer cells. The latest opportunity for managing TNBC is immunotherapy, checkpoint inhibitors to be precise, which is well known due to its high-level aggression and tendency to resist treatment. Targeted treatments have been successful in providing a better prognosis for breast cancer patients by giving them more personalized and efficient therapy choices. However, research is ongoing to address challenges like resistance to medication and finding predictive biomarkers for response to treatment. The field of breast cancer treatment is seeing progressive development of cutting-edge, targeted drugs and combination methods, with an aim at enhancing the prognosis for patients and their quality of life [71].

7. Future directions

The upcoming advancements in drug-targeted proteins for treating breast cancer hold more promise to transform this field in a big way. The advancements in molecular biology-genetics are clearing the path for discovering new targets, including developing ground-breaking medications. Personalized medicine is getting much emphasis; this involves tweaking treatments based on the particular genetic traits of a patient's tumor. This aims to maximize the treatment's effectiveness while keeping negative effects at a minimum. Exploring diversified strategies is underway, aiming to present novel solutions that bypass the limitations associated with therapies that rely on a single agent. These strategies include integrating specific drugs with immunotherapeutic measures. Such integration aims to enhance the patient's immune response against cancer. Moreover, the innovation in drug delivery systems that respond to specific stimuli shows potential. These systems are designed to increase the precision of how drugs are targeted and delivered, ensuring that drugs are released at the ideal place and time within the body [74].

Investigating how resistance forms against current targeted therapies could reveal beneficial strategies. Understanding these resistance mechanisms is expected to lead to the creation of superior inhibitors. These inhibitors have the potential to counteract resistance effectively, offering durable benefits for treatment. Cutting-edge technologies, including artificial intelligence and machine learning, are anticipated to accelerate advancements in this field significantly.

Enhancing the targeting capabilities of drugs towards specific proteins is becoming increasingly important in advancing breast cancer treatment. The goal of precision medicine is to tailor treatments to the unique characteristics of an individual's cancer, heralding a new hopeful era for individuals affected by this disease [75].

8. Potential for personalized medicine

In the realm of breast cancer, the possibilities for tailor-made medicine are enormous, promising to transform how treatments are designed. The essence of personalized medicine lies in crafting therapies that align with the unique genetic makeup of an individual's cancer, aiming to amplify their effectiveness while reducing adverse effects. Thanks to breakthroughs in genomic technology, it is now possible to pinpoint specific mutations and biomarkers. These markers offer precise forecasts on the performance of customized medications, particularly those targeting HER2 or hormone receptors. This method of precision medicine integrates predictive diagnostics with bespoke treatment strategies, fundamentally acknowledging each patient's distinct molecular and genetic characteristics. Continued research in this field is poised to improve breast cancer care significantly, introducing more precise and individualized treatment options. Such advancements promise to enhance patients' outlook and quality of life [76].

9. Integration of proteomics in breast cancer research

Leveraging proteomics in the study of breast cancer represents an area brimming with potential, aiming to deepen our grasp of the ailment. Proteomics, which entails an exhaustive examination of proteins, offers crucial insights into complex protein expression patterns and alterations in cancerous cells. This approach has proven essential in identifying novel genetic indicators for categorizing tumors and in comprehending the cellular signaling pathways that play roles in cancer's onset [77].

10. Conclusion

Recent advances in breast cancer therapy have illuminated the path toward a more individualized approach to medicine. There's a vast reservoir of knowledge in this domain, alongside the development and authorization of an array of targeted drugs for clinical use. This includes treatments such as hormone therapy, kinase inhibitors, and monoclonal antibodies, all designed to interfere with the abnormal biochemical pathways found in breast cancer cells. With the introduction of monoclonal antibodies, such as Trastuzumab, there has been a profound change in how HER 2-positive breast cancer is treated, markedly enhancing patient survival rates. There is also a wave of optimism for the evolution of further advanced, tailored therapies that promise to enrich the lives of those battling breast cancer. While the obstacles are daunting, the commitment to continuous research and innovation breeds hope for these therapeutic interventions. The journey from laboratory research to direct application in healthcare settings is intricate and elongated. Yet, the rewards it potentially offers to patients and the medical community are immense. Despite

this, the path forward is lit with the promise of substantial advances in patient care [78].

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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Author contributions

PT and KR contributed to the study's conception and design. PP, SK, NK, KC, SA and NBR analyzed the data. PT and KR wrote the original manuscript. TP and SK proofread it. All the authors have read and approved the manuscript for submission.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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