Texila International Journal of Public Health
Special Issue-2024
DOI: 10.21522/TIJPH.2013.SE.24.05.Art008

MicroRNAs and Apoptosis Signaling Pathways in Breast Cancer: From Molecular Insights to Clinical Applications

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Abstract

Breast cancer represents a global health concern, necessitating a deeper understanding of the intricate mechanisms underlying its pathogenesis and therapy resistance. This comprehensive review article explores the pivotal roles of microRNAs (miRNAs) and apoptosis signaling pathways in breast cancer biology. MiRNAs, as essential post-transcriptional regulators, modulate gene expression and play a central role in apoptosis regulation. We examine their involvement in breast cancer oncogenesis, metastasis, and therapy resistance, highlighting pro-apoptotic and anti-apoptotic miRNAs. Additionally, we delve into the core components of the apoptosis pathway, including initiator and executioner caspases and Bcl-2 family members, emphasizing their relevance in breast cancer. Further, we explore the crosstalk between miRNAs and major signaling pathways (PI3K/AKT, NF-κB, and p53) and discuss their clinical implications, including diagnostics, prognostics, and therapeutic interventions. While offering promising avenues for breast cancer management, this review also identifies research gaps and challenges in translating miRNA and pathway-based knowledge into clinical practice.

Keywords: *Apoptosis, Breast Cancer, Bcl-2 Family, miRNAs, PI3K/AKT Pathway.*

Introduction

Breast Cancer and Apoptosis

Breast cancer, a multifaceted and pervasive global health challenge, continues to be a prominent cause of morbidity and mortality among women worldwide [1]. Despite significant advancements in early detection and therapeutic interventions, its complex molecular landscape and heterogeneity pose formidable clinical obstacles [2]. Within this intricate web of factors contributing to breast cancer pathogenesis, the regulation of apoptosis emerges as a pivotal player. Apoptosis, or programmed cell death, is a fundamental biological process that governs tissue homeostasis and the removal of damaged or aberrant cells, acting as a sentinel of cellular health. Dysregulation of apoptosis is not only a hallmark of cancer but also a

Received: 23.09.2024 ***Accepted: 09.10.2024*** ***Published on: 10.12.2024***

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defining feature in breast cancer's relentless pursuit of survival and evasion of therapeutic strategies [3].

Recent research in the field of breast cancer and apoptosis has shed new light on the intricate mechanisms at play. One area of particular interest is the utilization of bleomycin (Bleo), an antitumor antibiotic, as a therapeutic agent. Bleomycin has demonstrated remarkable efficacy in targeting cancer cells through the induction of DNA damage and apoptosis. Investigating the interplay between Bleo and apoptosis pathways in breast cancer is crucial for enhancing our understanding of its therapeutic potential [4]. In this review, we delve into the global health significance of breast cancer and the pivotal role of apoptosis in maintaining tissue homeostasis [5]. Furthermore, we explore recent research findings regarding the use of Bleo in breast cancer treatment, shedding light on its mechanisms of action and clinical implications. Understanding the complex relationship between breast cancer and apoptosis, as well as the potential benefits of therapeutic agents like Bleo, holds the promise of improving patient outcomes and advancing our battle against this formidable disease.

MicroRNAs in Breast Cancer

MicroRNAs (miRNAs) are small, non-coding RNA molecules, typically 18-22 nucleotides in length, that play a fundamental role in post-transcriptional gene regulation (Albano et al., 2022). They are critical in maintaining cellular homeostasis by modulating the expression of target genes. MiRNAs achieve this regulation by binding to the 3' untranslated region (UTR) of messenger RNA (mRNA) molecules, thereby inhibiting mRNA translation or promoting mRNA degradation. This finely tuned mechanism allows miRNAs to exert tight control over a wide array of biological processes, including cell proliferation, differentiation, and apoptosis. In the context of breast cancer, the significance of miRNAs as regulators of gene expression cannot be overstated. Dysregulated miRNA expression is a common feature of breast cancer cells, contributing to the initiation and progression of the disease. MiRNAs can act as either tumor suppressors, by down regulating oncogenes, or oncogenic miRNAs (oncomiRs), by silencing tumor suppressor genes [6]. This dual role underscores their importance in shaping the molecular landscape of breast cancer. MiRNAs are integral players in breast cancer pathogenesis, influencing various stages of the disease, from initial oncogenesis to metastatic spread.

Oncogenesis

Dysregulated miRNAs can initiate breast cancer by promoting uncontrolled cell proliferation, inhibiting apoptosis, and enabling evasion of growth suppressors. For example, miR-21, a well-studied oncomiR, targets multiple tumor suppressor genes and is often overexpressed in breast cancer tissues. MiRNAs are implicated in the metastatic cascade, allowing cancer cells to invade surrounding tissues, intravasate into the bloodstream, survive in circulation, and colonize distant organs. MiRNAs like miR-10b and miR-155 facilitate these processes by regulating genes involved in epithelial-mesenchymal transition (EMT), angiogenesis, and immune evasion [7].

Diagnosis and Prognosis

MiRNAs have also emerged as potential diagnostic and prognostic biomarkers in breast cancer. Unique miRNA expression profiles in breast cancer tissues and circulating miRNAs in the blood can be indicative of the disease's stage and aggressiveness. miRNAs are pivotal regulators of gene expression with a substantial impact on breast cancer pathogenesis. Their involvement in oncogenesis, metastasis, and potential as

diagnostic markers make them an intriguing area of research and a promising avenue for the development of targeted therapies in the fight against breast cancer. Understanding the intricate web of miRNA-mediated gene regulation in breast cancer remains essential for unraveling the disease's complexities and advancing personalized treatment strategies.

Apoptosis Pathway Overview in Breast Cancer

The apoptosis pathway, also known as programmed cell death, is a tightly regulated process essential for maintaining tissue homeostasis and eliminating damaged or aberrant cells [8]. In breast cancer, the dysregulation of apoptosis is a hallmark feature, contributing to uncontrolled cell proliferation and therapy resistance. A comprehensive understanding of the core components of the apoptosis pathway is crucial for unraveling the complexities of breast cancer biology. In the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) apoptosis pathways, initiator caspases play a pivotal role in initiating the cascade of events leading to cell death. In breast cancer, abnormalities in the regulation of initiator caspases can tip the balance towards cell survival. For instance, Caspase-9, a key initiator caspase in the intrinsic pathway, can be inhibited or downregulated in breast cancer cells, impairing their ability to undergo apoptosis [9]. Following activation by initiator caspases, executioner caspases, such as Caspase-3 and Caspase-7, execute the final stages of apoptosis by cleaving key cellular substrates. In breast cancer, the dysregulation of executioner caspases can lead to impaired apoptosis and uncontrolled cell growth. Research has shown that breast cancer cells often exhibit reduced levels of active executioner caspases, contributing to therapy resistance.

Bcl-2 Family Members: The Bcl-2 family of proteins consists of both anti-apoptotic (e.g., Bcl-2, Bcl-xL) and pro-apoptotic (e.g., Bax, Bak) members. These proteins function as critical regulators of the intrinsic apoptosis pathway, controlling the integrity of the mitochondrial membrane and the release of apoptogenic factors, such as cytochrome c [10] (Kristopher A. et al., 2023).

1. **Anti-Apoptotic Bcl-2 Proteins:** In breast cancer, overexpression of anti-apoptotic Bcl-2 family members can confer a survival advantage to cancer cells by preventing mitochondrial outer membrane permeabilization (MOMP) and cytochrome c release. This overexpression has been associated with therapy resistance and poorer prognosis.
2. **Pro-Apoptotic Bcl-2 Proteins*:*** Conversely, pro-apoptotic Bcl-2 family members, such as Bax and Bak, promote apoptosis by inducing MOMP and facilitating the release of cytochrome c, triggering downstream apoptotic events. Dysregulation or inhibition of these pro-apoptotic proteins can hinder apoptosis in breast cancer cells.

BH3-Only Proteins

BH3-only proteins (e.g., Bim, Bid, Bad) serve as upstream sensors of cellular stress and are key initiators of apoptosis. They can neutralize anti-apoptotic Bcl-2 family members or directly activate Bax/Bak, promoting apoptosis. In breast cancer, alterations in the expression and function of BH3-only proteins can significantly impact the apoptotic response [11]. The apoptosis pathway in breast cancer is a complex and tightly regulated process involving initiator and executioner caspases, as well as the delicate balance between anti-apoptotic and pro-apoptotic Bcl-2 family members. Dysregulation of these core components contributes to the evasion of apoptosis, promoting the survival and proliferation of breast cancer cells. Targeting these components represents a promising avenue for

developing novel therapeutic strategies to restore apoptosis in breast cancer.

MiRNAs Regulating Apoptosis in Breast Cancer

MicroRNAs (miRNAs) are central players in the post-transcriptional regulation of gene expression, and their dysregulation is a common feature in breast cancer. These small RNA molecules can act as either pro-apoptotic or anti-apoptotic regulators, fine-tuning the delicate balance between cell survival and cell death [12]. In this section, we provide a comprehensive overview of miRNAs that have been identified as key modulators of apoptosis in breast cancer.

Pro-Apoptotic miRNAs: Several miRNAs have been identified as promoters of apoptosis in breast cancer cells by targeting anti-apoptotic genes or signaling pathways. Notable examples include:

miR-34a is a well-known tumor suppressor miRNA that promotes apoptosis by targeting genes such as Bcl-2 and SIRT1. Its downregulation is associated with resistance to apoptosis in breast cancer. *miR-15a/miR-16-1* target the anti-apoptotic protein Bcl-2 and are frequently downregulated in breast cancer, contributing to apoptosis evasion. miR-29a, miR-29b, and miR-29c collectively target anti-apoptotic genes such as MCL-1 and DNMT3B, sensitizing breast cancer cells to apoptosis-inducing signals.

Anti-Apoptotic miRNAs: Conversely, certain miRNAs act as inhibitors of apoptosis in breast cancer by targeting pro-apoptotic genes or pathways including miR-21 is a well-characterized oncomiR that targets pro-apoptotic genes, including PTEN and PDCD4, promoting cell survival and therapy resistance in breast cancer. miR-155 can enhance anti-apoptotic signaling by targeting FOXO3a and promoting cell survival in breast cancer. miR-221/miR-222 are known to target the cell cycle inhibitor p27 and promote cell survival in breast cancer, contributing to apoptosis resistance. miR-21 and PTEN are a prominent oncomiR in breast cancer that directly targets the tumor suppressor PTEN. PTEN plays a crucial role in promoting apoptosis by inhibiting the PI3K/AKT survival pathway. Downregulation of PTEN by miR-21 leads to increased AKT activation and decreased apoptosis in breast cancer cells [13] (Hashemi et al., 2022). miR-34a and Bcl-2 are a pro-apoptotic miRNA that targets the anti-apoptotic gene Bcl-2. In breast cancer, reduced expression of miR-34a results in elevated Bcl-2 levels, promoting cell survival and resistance to apoptosis-inducing agents. miR-15a/miR-16-1 and Bcl-2 miRNAs collectively target the anti-apoptotic protein Bcl-2. Downregulation of miR-15a/miR-16-1 in breast cancer leads to elevated Bcl-2 levels, impairing apoptosis and facilitating cell survival. In instantaneous, miRNAs play a critical role in modulating apoptosis in breast cancer by targeting key pro-apoptotic and anti-apoptotic genes and pathways. Understanding the intricate regulatory networks involving these miRNAs is essential for uncovering potential therapeutic strategies aimed at restoring apoptosis in breast cancer cells.

Gene Signaling Pathways in Breast Cancer Apoptosis

Apoptosis regulation in breast cancer is a multifaceted process orchestrated by a network of signaling pathways [14]. Dysregulation of these pathways can contribute to tumor progression and therapy resistance. In this section, we provide an in-depth exploration of three pivotal signaling pathways involved in apoptosis regulation in breast cancer: the PI3K/AKT, NF-κB, and p53 pathways.

PI3K/AKT Pathway

The PI3K/AKT pathway is a well-established driver of cell survival and proliferation. It plays a critical role in regulating apoptosis in breast cancer by inhibiting pro-apoptotic factors. Dysregulation

of the PI3K/AKT pathway, often due to PIK3CA mutations or PTEN loss, is common in breast cancer. Overactivation of AKT promotes cell survival by inhibiting pro-apoptotic proteins and preventing caspase activation.

NF-κB Pathway

The NF-κB pathway is a central regulator of inflammation and immune responses. In breast cancer, NF-κB activation can have both pro-survival and pro-apoptotic effects. NF-κB is frequently activated in breast cancer cells and contributes to apoptosis resistance. It upregulates anti-apoptotic proteins such as Bcl-2 and inhibitors of apoptosis (IAPs). However, in certain contexts, NF-κB can promote apoptosis, especially in response to DNA damage.

p53 Pathway

The p53 pathway is a well-known tumor suppressor pathway that plays a pivotal role in apoptosis regulation. p53 can directly induce apoptosis by activating pro-apoptotic genes. p53 mutations are common in breast cancer and can result in loss of its pro-apoptotic functions. Loss of functional p53 allows cancer cells to evade apoptosis, contributing to tumor progression. The interplay between the PI3K/AKT, NF-κB, and p53 pathways is highly complex and context-dependent. In breast cancer, their interactions influence cell fate regarding apoptosis:

PI3K/AKT and NF-κB: AKT activation can promote NF-κB activity, leading to the upregulation of anti-apoptotic genes. This crosstalk can confer apoptosis resistance in breast cancer cells.

PI3K/AKT and p53: AKT activation can phosphorylate and inhibit p53, impairing its pro-apoptotic functions. Dysregulation of the PI3K/AKT pathway often coincides with p53 inactivation in breast cancer.

NF-κB and p53: NF-κB can have dual roles in regulating p53 activity. It can either promote p53 stabilization and activation, leading to apoptosis, or inhibit p53, favoring cell survival. The outcome depends on specific stimuli and cellular context.

In conclusion, the PI3K/AKT, NF-κB, and p53 pathways are intricately linked in breast cancer apoptosis regulation. Dysregulation of these pathways can tip the balance towards apoptosis resistance, contributing to breast cancer progression and therapeutic challenges. A deeper understanding of their crosstalk and context-dependent roles is crucial for developing targeted therapies to restore apoptosis in breast cancer.

Crosstalk between MiRNAs and Apoptosis Signaling Pathways in Breast Cancer

The regulation of apoptosis in breast cancer is a complex and finely orchestrated process. MiRNAs, as critical post-transcriptional regulators of gene expression, intricately crosstalk with apoptosis-related signaling pathways, impacting cell fate decisions (Wang Man et al., 2022). In this section, we delve into the intricate web of interactions between miRNAs and key apoptosis signaling pathways, including the PI3K/AKT, NF-κB, and p53 pathways.

PI3K/AKT Pathway

MiRNAs can modulate the PI3K/AKT pathway by targeting components involved in its activation or inhibition. MiR-21 targets PTEN, a negative regulator of PI3K/AKT signaling. Elevated miR-21 levels downregulate PTEN, leading to increased AKT activation and reduced apoptosis sensitivity. MiR-34a indirectly affects PI3K/AKT by targeting SIRT1, a deacetylase that stabilizes PTEN. Reduced miR-34a levels can lead to SIRT1 overexpression, promoting PI3K/AKT activation and apoptosis evasion.

NF-κB Pathway

MiRNA-Mediated Crosstalk: MiRNAs can impact NF-κB signaling by targeting components involved in its activation or

inhibition. MiR-155 targets the negative regulator of NF-κB, CYLD. Elevated miR-155 levels can enhance NF-κB activity, promoting cell survival and inflammation. MiR-146a targets IRAK1 and TRAF6, key adaptors in the NF-κB pathway. MiR-146a overexpression can suppress NF-κB activation and promote apoptosis.

p53 Pathway

MiRNAs can directly target p53 or its regulators, affecting its activity and downstream apoptosis responses. MiR-125b targets p53, leading to its downregulation and reduced pro-apoptotic functions. These miRNAs target MDM2, a negative regulator of p53. Elevated miR-192/215 levels can stabilize p53, promoting apoptosis.

Functional Significance of MiRNA-Gene Interactions

These miRNA-gene interactions within apoptosis-related pathways have significant functional consequences in breast cancer. Dysregulation of miRNAs can lead to the inhibition of pro-apoptotic genes or the upregulation of anti-apoptotic genes, promoting cell survival and apoptosis resistance. MiRNAs can affect the sensitivity of breast cancer cells to therapy by modulating apoptosis pathways. Crosstalk between miRNAs and signaling pathways can influence tumor aggressiveness and metastatic potential. The intricate crosstalk between miRNAs and apoptosis-related signaling pathways in breast cancer plays a pivotal role in shaping cellular responses to apoptosis-inducing signals. Understanding these interactions is essential for uncovering novel therapeutic targets and strategies to restore apoptosis and improve outcomes for breast cancer patients.

Clinical Implications and Therapeutic Opportunities in Breast Cancer

Understanding the intricate interplay between miRNAs and apoptosis signaling pathways in breast cancer has significant clinical implications [15] (Doghish et al., 2023). This knowledge has the potential to revolutionize breast cancer management by providing valuable insights into diagnostics, prognostics, and novel therapeutic interventions.

Diagnostics

Dysregulated miRNA expression profiles can serve as diagnostic biomarkers for breast cancer. Unique miRNA signatures in tumor tissues or liquid biopsies may aid in early detection and subtype classification, enhancing precision in diagnosis. MiRNAs can also predict clinical outcomes and treatment responses. Specific miRNA profiles may help stratify patients into risk groups, allowing for tailored treatment strategies based on predicted prognosis.

Therapeutic Opportunities

MiRNA-Based Therapies*:* Targeting dysregulated miRNAs in breast cancer holds therapeutic promise. MiRNA replacement therapy (miRNA mimics) or inhibition (anti-miRNAs) can restore normal miRNA levels, potentially sensitizing cancer cells to apoptosis [16]. Pathway-Targeted Therapies: Understanding the crosstalk between miRNAs and apoptosis signaling pathways can inform the development of pathway-targeted therapies. Combining conventional treatments with agents that modulate miRNAs or pathway components may enhance treatment efficacy. The combination of miRNA-based therapies with traditional chemotherapies or targeted therapies can overcome apoptosis resistance in breast cancer cells. For instance, combining miRNA mimics that restore pro-apoptotic miRNA levels with targeted therapies may yield synergistic effects.

Personalized Medicine

Tailored Treatment Approaches: MiRNA and pathway analysis can facilitate personalized treatment strategies. Identifying specific miRNA signatures and pathway

dysregulations in individual patients can guide clinicians in selecting the most effective therapies.

Monitoring Treatment Response

Dynamic Biomarkers: MiRNAs can serve as dynamic biomarkers for monitoring treatment responses. Changes in miRNA expression profiles during therapy can provide real-time feedback on treatment effectiveness and guide adjustments as needed.

Overcoming Therapy Resistance

Reversing Apoptosis Resistance: Targeting miRNAs and apoptosis signaling pathways can be a potent strategy for overcoming therapy resistance. By restoring apoptotic sensitivity, treatments can become more effective in eliminating cancer cells. The intricate interplay between miRNAs and apoptosis signaling pathways in breast cancer has substantial clinical relevance. This knowledge offers opportunities to revolutionize breast cancer diagnosis and treatment. From early detection and prognosis prediction to the development of novel therapies, the integration of miRNA and pathway analysis into clinical practice holds the promise of improving patient outcomes and advancing our battle against breast cancer.

Future Directions and Challenges in Breast Cancer Research

While significant strides have been made in understanding the role of miRNAs and apoptosis signaling pathways in breast cancer, several research gaps and unanswered questions remain:

Mechanistic Insights: Detailed mechanistic studies are needed to uncover the precise molecular interactions between miRNAs and apoptosis-related pathways [16]. Elucidating the exact mechanisms of action can reveal novel therapeutic targets.

Functional Complexity: Investigating the functional complexity of miRNAs and their multiple target genes within apoptosis pathways is crucial. Understanding how miRNAs orchestrate cell fate decisions in different breast cancer subtypes and disease stages is essential Nazari.

Biomarker Validation: While miRNAs hold promise as diagnostic and prognostic biomarkers, further validation in large and diverse patient cohorts is necessary. Additionally, establishing standardized protocols for miRNA detection and analysis is crucial for clinical applicability.

Clinical Translation: Translating miRNA and pathway-based knowledge into clinical practice requires robust clinical trials and rigorous validation studies. Determining the most effective delivery methods for miRNA-based therapies is also a critical challenge.

Resistance Mechanisms: Investigating the mechanisms of therapy resistance in the context of miRNAs and apoptosis pathways is imperative. Identifying how cancer cells evade miRNA-based therapies can guide the development of strategies to overcome resistance.

Long-Term Effects: Understanding the long-term effects of miRNA-based therapies is essential to ensure patient safety. Potential off-target effects and unintended consequences must be carefully evaluated.

Several challenges and limitations must be addressed to successfully translate miRNA and pathway-based knowledge into clinical practice in breast cancer:

Heterogeneity: Breast cancer is a highly heterogeneous disease, and miRNA expression patterns can vary widely. Tailoring therapies to individual patients based on miRNA profiles presents challenges in clinical implementation [18].

Delivery Challenges: Efficient and targeted delivery of miRNA-based therapies to cancer cells remains a significant hurdle [19]. Ensuring therapeutic miRNAs reach their intended targets while minimizing off-target effects is a complex task.

Regulatory Approval: MiRNA-based therapies are relatively novel and regulatory approval processes may require adaptation to accommodate these innovative treatments (Paul Nazm et al., 2023). Robust clinical trials and safety data are essential for gaining regulatory approval.

Resistance Mechanisms: Cancer cells can develop resistance to miRNA-based therapies, similar to traditional treatments. Investigating and addressing resistance mechanisms is crucial for long-term therapeutic success [20-25].

Cost and Accessibility: The cost of miRNA profiling and therapy development can be prohibitive. Ensuring accessibility and affordability of these therapies for a broader patient population is a challenge.

Ethical Considerations: Ethical considerations surrounding genetic manipulation and long-term consequences of altering miRNA expression should be carefully examined.

In conclusion, while miRNAs and apoptosis signaling pathways offer exciting prospects for breast cancer diagnosis and treatment, several research gaps and challenges remain. Addressing these challenges and advancing our understanding of miRNA biology and pathway regulation will be essential for realizing the full potential of these innovative approaches in clinical practice.

Acknowledgement

We would like to acknowledge the School of Life Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), and Center for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences for providing the necessary facilities.

Conflict of Interest

The authors hereby declare that there is no conflict of interest in this study.

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