

MiRNAs: Dual Roles in Triple-Negative Breast Cancer

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Introduction

Triple-negative breast cancer (TNBC) represents a particularly aggressive subtype of breast cancer characterized by the absence of estrogen receptors, progesterone receptors, and HER2 amplification, posing significant challenges for targeted therapeutic interventions [1]. The complex molecular landscape of TNBC necessitates the identification of novel therapeutic targets and strategies to improve patient outcomes [1]. MicroRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression post-transcriptionally, have emerged as critical players in various cellular processes, including cancer development and progression [1]. Understanding the specific roles of miRNAs in TNBC pathogenesis is crucial for developing effective treatment modalities [1]. This introduction will explore the current understanding of miRNA dysregulation in TNBC and its implications for therapeutic targeting, drawing upon key preclinical studies that have illuminated these crucial molecular pathways [1]. The initial investigation highlights the general therapeutic potential of modulating miRNA pathways in TNBC, identifying specific miRNAs that are dysregulated and examining how their modulation can inhibit tumor growth and metastasis, suggesting a new avenue for TNBC treatment [1]. Further research has elucidated the intricate role of the miR-200 family members in orchestrating the epithelial-mesenchymal transition (EMT) within TNBC, a process closely linked to increased invasiveness and metastatic potential [2]. The aberrant expression of certain miRNAs, such as miR-155, has been implicated in promoting immune evasion by TNBC cells, thereby hindering effective anti-tumor immune responses and contributing to therapeutic resistance [3]. Conversely, other miRNAs, like the let-7 family, function as tumor suppressors, and their loss is associated with uncontrolled cell proliferation and differentiation arrest in TNBC, indicating their potential in restoring normal cellular behavior [4]. The therapeutic efficacy of specific miRNAs, such as miR-214, is being evaluated for its ability to induce apoptosis and suppress tumor growth in TNBC by targeting key cell survival pathways [5]. Furthermore, miRNAs like miR-93 have been identified as promoters of angiogenesis and metastasis in TNBC, mediated through the modulation of factors like vascular endothelial growth factor (VEGF), thus contributing to tumor vascularization and spread [6]. The tumor-suppressive functions of miRNAs like miR-34a are also being explored, with its downregulation linked to aggressive TNBC tumors and its restoration showing promise in inhibiting tumor growth and inducing apoptosis [7]. Another miRNA, miR-193b, has demonstrated a capacity to suppress TNBC cell migration and invasion, with its loss correlating with increased metastatic potential, suggesting its role in controlling metastasis [8]. The dysregulation of miR-145 has also been observed in TNBC, where its reduced expression promotes cancer stem cell properties and contributes to tumor initiation and proliferation, underscoring its importance in preventing recurrence [9]. Finally, the intricate interplay between miRNAs and their target genes, such as the miR-22/HDAC4 axis, is being investigated for its therapeutic implications, with the inhibition of this axis showing synergistic effects in suppressing TNBC progression and enhancing chemosensitivity [10].

Description

The therapeutic landscape of triple-negative breast cancer (TNBC) is continually being reshaped by advances in understanding its underlying molecular mechanisms, with microRNAs (miRNAs) playing a pivotal role in this evolving field [1]. Preclinical studies have rigorously investigated the potential of targeting these small regulatory RNAs to combat TNBC, a subtype notorious for its aggressive behavior and limited treatment options [1]. A foundational study explored the general therapeutic utility of manipulating miRNA pathways, identifying specific dysregulated miRNAs and demonstrating that modulating their expression could effectively inhibit tumor growth and metastasis in preclinical TNBC models [1]. This work laid the groundwork for further investigations into specific miRNA families and their critical roles in TNBC pathogenesis [1]. Focusing on key drivers of malignancy, subsequent research elucidated the significant influence of the miR-200 family on epithelial-mesenchymal transition (EMT) in TNBC [2]. This study observed aberrant expression patterns of miR-200c, which consequently led to heightened invasiveness, and demonstrated that restoring miR-200c levels could suppress EMT markers and inhibit cell migration and invasion, highlighting its potential as a therapeutic target [2]. Another critical aspect of TNBC's resistance to treatment involves immune evasion, and a study investigated the role of miR-155 in this process [3]. Elevated miR-155 levels were found to suppress the expression of PD-L1 inhibitors, facilitating immune escape, and inhibition of miR-155 led to increased T-cell infiltration and anti-tumor immunity in xenograft models, offering a strategy to overcome immune resistance [3]. In contrast to oncogenic roles, the let-7 family of miRNAs was examined for its tumor-suppressive functions in regulating cell proliferation and differentiation in TNBC [4]. The research linked the loss of let-7 expression to uncontrolled cell growth and showed that restoring let-7 levels via mimic delivery reduced proliferation and induced differentiation markers, underscoring its therapeutic potential [4]. The direct evaluation of specific miRNAs as therapeutic agents is also a significant area of research, with miR-214 being studied for its efficacy in targeting cell survival pathways in TNBC [5]. Overexpression of miR-214 was shown to induce apoptosis and inhibit tumor growth in TNBC models, suggesting its viability as a therapeutic option by promoting programmed cell death [5]. Furthermore, the role of miR-93 in promoting TNBC progression through angiogenesis and metastasis was investigated [6]. Upregulation of miR-93 was associated with increased vascular endothelial growth factor (VEGF) expression, contributing to tumor vascularization and spread, and its inhibition significantly reduced angiogenesis and metastatic potential in preclinical models [6]. The tumor-suppressive capabilities of miR-34a were also explored, with its downregulation observed in aggressive TNBC tumors [7]. Restoring miR-34a expression via systemic delivery of mimics effectively suppressed tumor growth and induced apoptosis, validating its potential as a treatment strategy [7]. Additional research focused on the anti-metastatic properties of miR-193b in TNBC, demonstrating that its loss of expression correlated with increased metastatic potential [8]. The introduction of miR-193b mimics significantly reduced the migratory and invasive capacity of

TNBC cells, reinforcing its role in controlling metastasis [8]. The impact of miR-145 dysregulation on TNBC was also examined, with reduced expression linked to the promotion of cancer stem cell properties and increased tumor initiation and proliferation [9]. Restoring miR-145 levels proved effective in inhibiting these processes, highlighting its importance in preventing TNBC recurrence [9]. Finally, the therapeutic implications of targeting the miR-22/HDAC4 axis were investigated, revealing that aberrant regulation of this axis drives TNBC progression [10]. Inhibiting miR-22 or targeting HDAC4 showed synergistic effects in suppressing TNBC cell growth and enhancing chemosensitivity, presenting a promising combination therapy strategy [10].

Conclusion

This collection of research explores the multifaceted roles of microRNAs (miRNAs) in triple-negative breast cancer (TNBC), a challenging subtype of breast cancer. Studies highlight specific miRNAs that act as oncogenes, promoting tumor growth, invasion, metastasis, angiogenesis, and immune evasion. Conversely, other miRNAs function as tumor suppressors, inhibiting proliferation, stemness, and inducing apoptosis. Key miRNAs investigated include the miR-200 family in EMT, miR-155 in immune evasion, let-7 family in proliferation, miR-214 in apoptosis, miR-93 in angiogenesis and metastasis, miR-34a as a tumor suppressor, miR-193b in inhibiting migration, miR-145 in suppressing stemness, and the miR-22/HDAC4 axis in TNBC progression. Preclinical findings demonstrate promising therapeutic potential for modulating these miRNAs through mimics or inhibitors to treat TNBC.

Acknowledgement

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Conflict of Interest

None.

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