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REVIEW

The Intricate Web of MicroRNAs in Modulating EGFR-TKI Resistance in Non-Small Cell Lung Cancer: A Comprehensive Review

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Abstract: Non-small cell lung cancer (NSCLC) harboring activating mutations in the Epidermal Growth Factor Receptor (EGFR) has been effectively treated with EGFR tyrosine kinase inhibitors (TKIs). However, the clinical efficacy of these targeted therapies is invariably limited by the development of acquired resistance. While secondary mutations like T790M and bypass pathway activation are well-documented mechanisms, there is a growing appreciation for the profound role of epigenetic regulators, particularly microRNAs (miRNAs), in orchestrating the resistant phenotype. This review provides a comprehensive and detailed analysis of the multifaceted roles of miRNAs in the emergence and maintenance of EGFR-TKI resistance in NSCLC, including their regulation of alternative receptor tyrosine kinase signaling pathways, driving phenotypic plasticity, specifically the epithelial-mesenchymal transition (EMT) and the acquisition of cancer stem cell (CSC) characteristics, as well as dysregulating core cellular processes, such as apoptosis. We further examine the complex interplay within competing endogenous RNA (ceRNA) networks, where long non-coding RNAs and circular RNAs sequester miRNAs, thereby modulating the expression of resistance-associated genes. Finally, the potential of specific miRNAs as circulating biomarkers for monitoring treatment response and as therapeutic targets to overcome resistance is discussed. This review underscores the central role of miRNA-mediated gene regulation as a critical layer of complexity in EGFR-TKI resistance, highlighting a sophisticated network that governs the fate of cancer cells under therapeutic pressure.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, drug resistance, microRNA

Introduction

The discovery of activating mutations in the Epidermal Growth Factor Receptor (EGFR) gene, present in a significant subset of non-small cell lung cancer (NSCLC) patients, particularly those with adenocarcinoma, revolutionized the treatment landscape. EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and afatinib (first- and second-generation) and osimertinib, almonertinib, furmonertinib, etc. (third-generation) have demonstrated remarkable initial response rates and have significantly improved progression-free survival (PFS) in patients with EGFR-mutant NSCLC.[1] Despite this initial success, the clinical benefit of EGFR-TKIs is almost universally curtailed by the emergence of acquired resistance, with the median PFS among 9.6–20.8 months in the first-line setting.[2,3] The mechanisms underlying this resistance are highly heterogeneous. The most well-characterized mechanism for first-generation TKI resistance is the acquisition of a secondary "gatekeeper" mutation, T790M, in exon 20 of the EGFR gene, which sterically hinders drug binding while preserving kinase activity. The development of the third-generation TKI osimertinib, which is effective against T790M-mutant tumors, represented a major step forward.[4] However, resistance to osimertinib also inevitably develops through a variety of on-target (eg, C797S mutation) and off-target mechanisms.[5] These off-target mechanisms prominently feature the activation of alternative or "bypass" signaling pathways, which render the cells independent of EGFR signaling for their survival and proliferation. Key bypass pathways include the amplification or overexpression of other receptor tyrosine kinases (RTKs) such as MET, AXL, and HER3 (ErbB3).[6]

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MiRNAs are small, endogenous, non-coding RNA molecules, approximately 22 nucleotides in length, that function as post-transcriptional regulators of gene expression. By binding primarily to the 3′-untranslated region (3′-UTR) of target messenger RNAs (mRNAs), miRNAs induce mRNA degradation or translational repression.[7] A single miRNA can target hundreds of different mRNAs, and a single mRNA can be regulated by multiple miRNAs, creating a complex and robust regulatory network. This network governs virtually all fundamental cellular processes, including differentiation, proliferation, apoptosis, and stress response. It is therefore not surprising that dysregulation of miRNA expression is a hallmark of cancer and plays a crucial role in tumorigenesis, metastasis, and therapeutic resistance, and of course EGFR-TKI resistance.[8,9] Additionally, current approaches for monitoring resistance, most notably circulating tumor DNA (ctDNA) profiling, remain limited by variable sensitivity, tumor heterogeneity, and incomplete capture of dynamic tumor evolution. These constraints underscore the need for novel biomarkers such as miRNAs, which may offer complementary and earlier detection of resistance mechanisms. This review aims to update and discuss in detail the current understanding of the diverse and intricate roles that miRNAs play in modulating resistance to EGFR-TKIs in NSCLC and their potential in predicting EGFR-TKIs resistance and relevant therapeutical strategies (Figure 1, Created with BioGDP.com).[10]

MiRNAs Modulating Bypass Signaling Activation

One of the most prominent mechanisms of acquired resistance to EGFR-TKIs is the activation of bypass signaling pathways, which allows cancer cells to circumvent their dependency on the inhibited EGFR.[11] miRNAs are central orchestrators of this process, acting as molecular switches that can either suppress or activate these alternative survival pathways by targeting key components, including the RTKs themselves or their downstream effectors.

Regulation of the MET Proto-Oncogene Axis

The MET proto-oncogene, which encodes the receptor for hepatocyte growth factor (HGF), is one of the most frequently implicated bypass tracks in EGFR-TKI resistance. Aberrant MET activation, either through gene amplification or ligand-induced stimulation, can potently drive downstream signaling through the PI3K/Akt and MAPK pathways, compensating for the loss of EGFR signaling.[12] Several tumor-suppressive miRNAs have been identified that directly target and

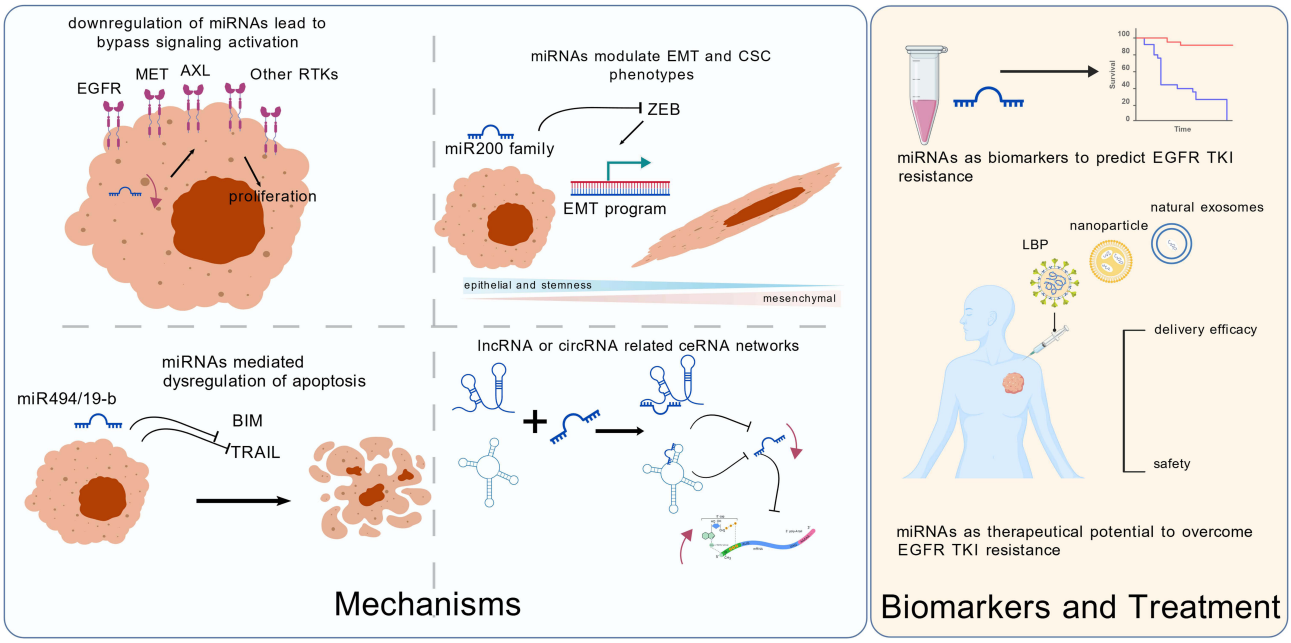

Figure 1 The Intricate Web of MicroRNAs in Modulating EGFR-TKI Resistance in Non-Small Cell Lung Cancer. Left panel illustrates the detailed mechanisms of EGFR-TKI resistance in NSCLC mediated by microRNAs, either through bypass signaling activation, including MET, AXL, and other RTKs, modulating the EMT and CSC phenotype variations, or escaping TKI-induced apoptosis. LncRNA or circRNA-mediated ceRNA networks are also involved in this intricate web. Right panel describes that specific microRNAs are explored to be potential biomarkers to predict EGFR-TKI resistance and relevant strategies targeting microRNAs and their delivery system has been explored. The main issues remained are the limited delivery efficacy and safety issues. Created with BioGDP.com.

suppress MET expression. The miR-34 family, particularly miR-34a, has been shown to directly bind to the 3′-UTR of MET mRNA. In TKI-sensitive cells, sufficient levels of miR-34a keep MET expression in check. However, in the development of resistance, particularly that driven by high levels of HGF in the tumor microenvironment, miR-34a is often downregulated. This loss of suppression leads to MET overexpression, creating a robust bypass signal. Critically, the reintroduction of miR-34a mimics has been demonstrated to re-establish MET suppression and reverse HGF-mediated resistance to TKIs.[13] Similarly, miR-34a has been shown to co-target AXL, another important RTK, indicating its role as a master regulator of bypass signaling.[14]

The regulatory network controlling MET is complex and involves multiple miRNAs. The miR-206/133b cluster has been identified as a regulator of both MET and EGFR, suggesting a coordinated control mechanism over key oncogenic RTKs in lung cancer.[15] More recently, engineered miRNAs have shown therapeutic promise. For instance, an edited form of miR-411-5p was designed to specifically target MET mRNA, and its delivery was shown to significantly enhance the sensitivity of NSCLC cells to TKIs, highlighting the potential of miRNA-based engineering to overcome resistance.[16]

Modulation of the AXL Receptor Tyrosine Kinase Pathway

The AXL receptor tyrosine kinase, a member of the TAM (Tyro3, AXL, Mer) family, has emerged as another critical mediator of TKI resistance across various cancer types, including NSCLC. AXL activation is strongly associated with an aggressive, mesenchymal-like phenotype and poor prognosis. Like MET, AXL can activate PI3K/Akt and MAPK signaling, providing a clear bypass mechanism. The expression of AXL is tightly controlled by several miRNAs. For example, miR-34c, another member of the miR-34 family, directly targets AXL and its expression is often suppressed in NSCLC, contributing to AXL-mediated proliferation and resistance.[16] Similarly, miR-335 has been shown to regulate TKI resistance in AXL-positive NSCLC cells, where its downregulation allows for AXL overexpression and subsequent resistance.[17]

The regulation of AXL can also be indirect. A study revealed a complex feedback loop where AXL activation itself can modulate the expression of specific miRNAs, such as miR-374a and miR-548b, which in turn promotes a pro-survival and resistant phenotype.[18] Furthermore, the expression of AXL can be influenced by long non-coding RNAs (lncRNAs) acting as miRNA sponges. For example, the lncRNA RP11-874J12.4 has been shown to promote TKI resistance by sequestering miR-34a-5p that would otherwise suppress AXL,[19] leading to its upregulation and the activation of downstream resistance pathways, which highlights the intricate competing endogenous RNA (ceRNA) networks that fine-tune the expression of key resistance drivers like AXL.

Control of Other RTKs and Downstream Signaling Nodes

Beyond MET and AXL, miRNAs regulate a host of other RTKs and signaling molecules that contribute to bypass resistance. The ErbB family of receptors, to which EGFR belongs, is a key hub. HER3 (ErbB3), which lacks intrinsic kinase activity but is a potent activator of the PI3K/Akt pathway upon heterodimerization with other RTKs, is a major resistance factor. Research has demonstrated that HER3 activation is a significant contributor to therapeutic resistance, primarily by fueling the PI3K/Akt survival pathway.[20] The expression of both EGFR and HER3 can be co-regulated by miRNAs like miR-323a. Downregulation of miR-323a in resistant cells leads to the simultaneous upregulation of both receptors, enhancing signaling plasticity and promoting TKI resistance. Restoring miR-323a levels has been shown to effectively reverse this resistance phenotype.[21]

Other signaling molecules are also under miRNAs control. The SRC family kinases, non-receptor tyrosine kinases that act as crucial signaling hubs downstream of multiple RTKs, are implicated in resistance. The oncoprotein CRIPTO1 was found to induce gefitinib resistance by activating SRC signaling, a process mediated through the suppression of the tumor-suppressive miR-205.[22] miR-146b-5p interacted directly with PTEN mRNA and activated subsequent PI3K/AKT signaling pathway, promoting Osimertinib resistance.[23] The Insulin-like Growth Factor 1 Receptor (IGF-1R) pathway is another well-established bypass track. The miRNA miR-223 has been shown to directly target IGF-1R. Downregulation of miR-223 in NSCLC cells leads to increased IGF-1R expression and subsequent activation of its downstream effectors, conferring resistance to erlotinib. Conversely, ectopic expression of miR-223 can restore drug sensitivity.[24] Additionally, signaling pathways not directly linked to RTKs can be modulated. For instance, HDAC1 upregulation increased gefitinib resistance by its binding to FOXK1 in cells to silence miR-33a expression.[25] Bone Morphogenetic Protein 4 (BMP4) has

been identified as a factor whose upregulation correlates with EGFR-TKI resistance, suggesting its involvement in previously unappreciated resistance networks and miR-139-5p could suppress the expression of BMP4 and was downregulated in the resistance NSCLC cells.[26] Notably, Osimertinib resistance is also demonstrated to be closely related to miR-147b-mediated repression of VHL and succinate dehydrogenase, which are linked to the tricarboxylic acid cycle and pseudohypoxia pathways.[27]

The Role of MiRNAs in EMT and CSC Phenotypes

Acquired resistance to EGFR-TKIs is not solely a result of genetic mutations or bypass signaling but is also profoundly linked to cellular phenotypic plasticity. EMT is a developmental program that cancer cells can hijack to acquire migratory, invasive, and drug-resistant properties. During EMT, epithelial cells lose their cell-cell junctions and apical-basal polarity, and acquire a mesenchymal phenotype characterized by enhanced motility and resistance to apoptosis. This transition is governed by a network of transcription factors, including ZEB, Snail, and Twist, which are themselves under tight regulation by miRNAs. The EMT phenotype is often associated with the characteristics of CSCs, a subpopulation of tumor cells with self-renewal capabilities that are thought to be responsible for tumor initiation, metastasis, and relapse following therapy.[28]

The MiR-200 Family and the ZEB1/2 Axis: A Master Regulatory Circuit

At the heart of EMT regulation lies a reciprocal feedback loop between the miR-200 family (comprising miR-200a, miR-200b, miR-200c, miR-141, and miR-429) and the transcriptional repressors ZEB1 and ZEB2. The miR-200 family members are quintessential epithelial markers that maintain the epithelial state by directly targeting and suppressing the translation of ZEB1 and ZEB2 mRNAs. Conversely, ZEB1 and ZEB2 can bind to the promoter regions of the miR-200 family genes and repress their transcription. This double-negative feedback loop creates a bistable switch that allows cells to stably maintain either an epithelial (high miR-200/low ZEB) or a mesenchymal (low miR-200/high ZEB) state.[29]

In the context of EGFR-TKI resistance, a shift towards the mesenchymal state is frequently observed. Chronic TKI exposure can induce the downregulation of the miR-200 family, thereby unleashing ZEB1/2 expression and driving a full-blown EMT program.[30] This transition confers resistance by multiple means, including the activation of AXL and other mesenchymal-associated RTKs. Several upstream signals can trigger this switch. For example, Transforming Growth Factor-beta (TGF-β), a potent inducer of EMT, can mediate gefitinib resistance by suppressing the miR-200 family, which in turn derepresses its target MIG6, a negative regulator of EGFR signaling.[31] Furthermore, signaling pathways like Hedgehog (Hh) can induce resistance through an EMT program that involves the downregulation of both the miR-200 and let-7 families of miRNAs, and this process can be reversed by Hh pathway inhibitors.[32] Restoring the levels of miR-200 family members, for instance through HDAC inhibitors that de-repress their expression, or by delivering synthetic mimics, has been shown to reverse EMT and re-sensitize resistant cells to EGFR-TKIs.[33,34]

Other MiRNAs Orchestrating EMT and CSC-Like Properties

While the miR-200/ZEB axis is a central player, numerous other miRNAs are involved in regulating EMT and stemness in the context of TKI resistance. miR-483-3p has been shown to suppress EMT and invasion by directly targeting integrin β3, a key component of cell-matrix adhesion whose expression is altered during EMT.[35] The NF-κB pathway, a critical regulator of inflammation, survival, and EMT, is also under miRNA control. miR-127 has been found to promote EMT and cancer stemness by participating in a positive feedback loop with the NF-κB signaling pathway.[36]

The acquisition of CSC properties is a critical facet of resistance. Some studies suggest that TKI treatment can select for a pre-existing population of CSCs or induce a shift towards a stem-like state. This process is also governed by miRNAs. For example, downregulation of the glycolytic enzyme ALDOA was shown to promote cancer stemness in lung adenocarcinoma, a process mediated through the modulation of miR-145.[37] The connection between EMT and CSCs is intimate, as the EMT process can endow cells with stem-like properties. For instance, ZEB1, in addition to driving EMT, can also suppress the growth of EGFR-mutant cells by inhibiting NOTCH1 signaling, revealing a complex, context-dependent role for this master regulator.[38] miR-204 could reduce cancer stemness and EMT, thus overcoming osimertinib

resistance in lung cancer by inhibiting the CD44 signaling pathway.[39] This highlights the intricate wiring where miRNAs regulate transcription factors that simultaneously control multiple resistance-associated phenotypes.

MiRNA-Mediated Dysregulation of Apoptosis

The ultimate goal of targeted therapies like EGFR-TKIs is to induce cell cycle arrest and/or apoptosis in cancer cells.[40] Consequently, a common strategy for cancer cells to acquire resistance is to rewire their internal machinery to evade these outcomes. miRNAs play a fundamental role in this process by fine-tuning the expression of key proteins involved in the apoptotic cascade, thereby tilting the balance from cell death towards survival.

The BCL-2 family of proteins are central regulators of the intrinsic apoptotic pathway, comprising pro-apoptotic members (eg, BIM, PUMA, BAX) and anti-apoptotic members (eg, BCL-2, MCL-1).[41] The BCL-2-like protein 11 (BIM) is a potent pro-apoptotic BH3-only protein that is essential for EGFR-TKI-induced apoptosis. Downregulation or sequestration of BIM is a well-established mechanism of intrinsic and acquired resistance. Several oncogenic miRNAs have been identified that directly target BIM mRNA for suppression. For example, miR-19b has been shown to promote TKI resistance in NSCLC by simultaneously targeting two key tumor suppressors: the pro-apoptotic protein BIM and the phosphatase PP2A, which dephosphorylates and activates BIM. By suppressing both, miR-19b effectively dismantles a critical apoptotic pathway.[42] Similarly, miR-494 has been implicated in resistance to TRAIL (TNF-related apoptosis-inducing ligand)-induced apoptosis, another important cell death pathway, through its downregulation of BIM.[43] The ability of single miRNAs to co-target multiple components of the cell death machinery underscores their potency as drivers of resistance.

The Influence of CeRNA Networks

The function and availability of miRNAs are not determined in isolation but are part of a larger, intricate regulatory landscape known as the ceRNA network. This hypothesis posits that various types of RNA transcripts, including lncRNAs, circular RNAs (circRNAs), and even pseudogene transcripts, can communicate with each other by competing for binding to a shared pool of miRNAs. These ceRNAs act as "sponges" or "decoys", sequestering miRNAs and thereby preventing them from binding to their bona fide mRNA targets.[44] This activity effectively de-represses the expression of the target genes. Dysregulation of ceRNA networks is increasingly recognized as a major contributor to cancer progression and drug resistance.

LncRNAs as Potent MiRNA Sponges in TKI Resistance

LncRNAs are transcripts longer than 200 nucleotides with no or limited protein-coding potential, which play diverse roles in gene regulation. Many lncRNAs harbor miRNA response elements (MREs) and can function as ceRNAs.[45] In the context of EGFR-TKI resistance, several lncRNAs have been identified as key players. The lncRNA SNHG14 was found to be upregulated in TKI-resistant NSCLC cells, where it promotes resistance by sponging miR-206-3p. This sequestration of miR-206-3p leads to the upregulation of its target, the drug efflux pump ABCB1 (also known as MDR-1), resulting in increased pumping of the TKI out of the cell.[46] Similarly, the lncRNA SNHG15 was shown to confer resistance by sponging miR-451, leading to the derepression of its target MDR-1.[47] Other lncRNAs modulate different resistance mechanisms. The lncRNA NEAT1_1 contributes to resistance against ferroptosis (an iron-dependent form of cell death) by acting as a sponge for miR-338-3p, which in turn regulates the expression of AKR1C1, a key enzyme in this process.[48] HIF1A-AS2 sponged miR-146b-5p, promoting interleukin-6 (IL-6) expression, activating the IL-6/STAT3 pathway, and leading to LUAD progression and Osimertinib resistance.[49] Lnc-TMEM132D-AS1 could directly bind to miR-766-5p and lead to the upregulation of ectonucleoside triphosphate diphosphohydrolase-1 (ENTPD1), resulting in cell proliferation and Osimertinib resistance.[50] Similarly, The LINC00313/miR-218-5p/COL1A1 axis is proposed as a ceRNA regulatory mechanism that contributes to the development of acquired resistance to osimertinib in LUAD via the PI3K/Akt pathway.[51] These examples illustrate a common theme where oncogenic lncRNAs are upregulated in resistant cells, functioning to sequester tumor-suppressive miRNAs and liberate the expression of genes that drive resistance phenotypes, from drug efflux to cell cycle progression and evasion of cell death.

CircRNAs Expanding the Regulatory Complexity

CircRNAs are a class of covalently closed RNA molecules that are generally more stable than their linear counterparts. Like lncRNAs, many circRNAs are rich in MREs and can function as highly efficient miRNA sponges. The role of circRNAs in TKI resistance is an emerging field of investigation. For example, hsa_circ_0004015 could act as a sponge for miR-1183 which in turn inhibits PDPK1 to enhance the resistance of HCC827 to gefitinib.[52] Similarly, hsa_circ_0005576 could act through miR-512-5p/IGF1R signaling to promote the resistance of LUAD cells to osimertinib.[53] circ_PPAPDC1A could act as a ceRNA by targeting miR-30a-3p to activate IGF1R-mediated PI3K/AKT/mTOR signaling pathway in NSCLC with Osimertinib resistance.[54] CircSPINT2 confers sensitivity to osimertinib via hsa-miR-1296-3p/RBP1 axis and inhibits NSCLC progression.[55] By analyzing microarray datasets, hsa_circ_0078465 miR-183-5p/NRAS axis was also found to play a role in osimertinib-resistant cells.[56] The discovery of these lncRNA- and circRNA-mediated regulatory axes adds a significant layer of complexity to our understanding of how gene expression is fine-tuned during the evolution of drug resistance.

MiRNAs as Biomarkers and Therapeutic Avenues

The profound involvement of miRNAs in the mechanisms of EGFR-TKI resistance makes them highly attractive candidates for both clinical biomarkers and novel therapeutic targets. Their stability in bodily fluids like blood plasma, combined with their specific expression patterns in response to therapy, positions them as promising non-invasive tools for patient monitoring.[57] Furthermore, the ability to modulate their function using synthetic oligonucleotides opens up new avenues for therapeutic intervention aimed at overcoming or preventing resistance.

MiRNAs as Prognostic and Predictive Biomarkers

The dynamic nature of miRNA expression during treatment provides a potential real-time window into the evolving biology of a tumor. Monitoring ctDNA for resistance mutations like T790M is already a clinical reality. The parallel monitoring of circulating miRNAs could provide complementary information about non-mutational resistance mechanisms, such as EMT or bypass pathway activation, often before they are detectable by imaging. Studies have explored the combination of ctDNA and miRNA analysis from liquid biopsies to monitor therapeutic response to EGFR-TKIs, suggesting this approach could offer a more comprehensive picture of the resistance landscape.[58]

Specific miRNA signatures have been associated with treatment outcomes. For instance, a panel including miR-30b and miR-30c was found to be predictive of the response to TKI therapy in NSCLC patients.[59] Expression of miR-494-3p was significantly elevated in plasma sampled at disease progression compared to treatment baseline in a cohort of 21 EGFR T790M-mutation positive NSCLC patients receiving osimertinib.[60] In another study, the expression levels of miR-608 and miR-4513 were shown to correlate with prognosis in patients receiving EGFR-TKIs, suggesting their potential as prognostic biomarkers.[61] Furthermore, a signature of miRNAs including miR-21, miR-27a, and miR-218 was associated with primary (intrinsic) resistance to EGFR-TKIs, indicating that baseline miRNA profiles could help stratify patients who are unlikely to respond to therapy from the outset.[62] Additionally, the expression levels of circulating hsa-miR-22-3p combined with EV hsa-miR-184 and Let-7b-5p levels were shown to have the potential to enable prospective identification of patients who are at risk of responding poorly to Osimertinib alone but likely to benefit from Osimertinib/AKT blockade combination treatments.[63]

Therapeutic Strategies Targeting MiRNA Pathways

The functional importance of miRNAs in resistance makes them compelling therapeutic targets. Two main strategies exist: restoring the function of a downregulated tumor-suppressive miRNA using synthetic "miRNA mimics", or inhibiting an overexpressed oncogenic miRNA using "antagomirs" or "anti-miRs." A major challenge for miRNA-based therapeutics is safe and efficient delivery to the tumor site due to their inherent instability and poor cellular uptake. Nanoparticle-based delivery systems are being extensively explored to overcome this hurdle. For example, chitosan-based nanoparticles have been developed to deliver therapeutic agents to overcome T790M-mediated resistance.[64] The same principle can be applied to deliver miRNA mimics or antagomirs. Nanoparticles can be engineered to co-deliver a conventional drug (like a TKI or chemotherapy) along with a miRNA modulator, potentially creating a powerful synergistic effect.[65,66]

Exosomes, which are natural nanovesicles secreted by cells, represent another promising delivery vehicle. It has been shown that exosomes derived from mesenchymal stem cells can transfer miR-7 to resistant NSCLC cells. This exosome-delivered miR-7 was able to suppress its target YAP (Yes-associated protein), a key oncogenic transcription factor, and thereby reverse gefitinib resistance.[67] This demonstrates the potential of harnessing natural intercellular communication systems for therapeutic purposes. Furthermore, chemically modified miRNAs can be engineered for enhanced stability and efficacy. For instance, a 5-Fluorouracil-modified miR-129 was developed to overcome both TKI and chemotherapy resistance, showcasing the potential of miRNA-drug conjugates.[68] These innovative approaches highlight a path forward for translating our understanding of miRNA biology into tangible clinical strategies to combat TKI resistance.

Conclusion

The development of acquired resistance to EGFR TKIs represents a formidable clinical challenge in the management of EGFR-mutant NSCLC. The evidence synthesized in this review conclusively demonstrates that microRNAs are not merely passive bystanders but are central and active orchestrators of the complex biological processes that drive this resistance. The roles of miRNAs as modulators of bypass signaling, drivers of phenotypic change, and controllers of cell fate collectively underscore their position as pivotal players in the enduring battle against cancer drug resistance.

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Disclosure

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