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Topic of Research: To investigate the therapeutic potential of microRNA in lung cancer by studying its effect on tumorigenesis

Findings

Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a leading cause of cancer-related mortality globally, largely due to its molecular heterogeneity, late diagnosis, and poor therapeutic response. Recent advances highlight the pivotal contribution of non-coding RNAs, including miRNAs and lncRNAs, in orchestrating oncogenic signaling, immune modulation, metabolic reprogramming, and mitochondrial regulation, thereby contributing to tumor progression and therapy resistance. In the present thesis, a comprehensive investigation was undertaken to elucidate the regulatory role of miRNAs and their functional crosstalk with oncogenic targets and immune-related molecules in NSCLC.

In our study we have selected two miRNAs (miR-199a-5p and miR-miR-101-3p) and explored the therapeutic relevance of these miRNAs in NSCLC by investigating their role in regulating oncogenic signaling pathways and deciphering their involvement in immune modulation and lncRNA-miRNA regulatory interplay.

The first part of the thesis investigated the tumor suppressive potential of miR-199a-5p in NSCLC. Restoration of miR-199a-5p markedly inhibited proliferation, migration, clonogenic growth, and suppressed key oncogenic pathways including NF-κB, AKT, ERK and PARP-1, thereby attenuating pro-survival signaling. Importantly, miR-199a-5p significantly altered mitochondrial dynamics by enhancing mitochondrial fission markers while suppressing fusion markers, leading to cytochrome-c release, mitochondrial depolarization and intrinsic apoptotic activation. This was accompanied by a strong decline in cellular energetics, as reflected by reduced ATP levels, LDHA expression and mitochondrial membrane potential, along with suppression of HIF-1α/VEGF-mediated angiogenesis. Additionally, miR-199a-5p downregulated cancer stemness marker CD44, further indicating its role in impairing stem cell-like properties associated with tumor aggressiveness and therapy resistance. Collectively, these

findings establish miR-199a-5p as a potent multi-target tumor suppressor capable of simultaneously modulating oncogenic signaling, mitochondrial integrity, metabolic adaptation, angiogenesis and stemness in NSCLC and highlight the therapeutic potential of miR-199a-5p reconstitution as a multi-target strategy against NSCLC progression.

The second part of the thesis delineated a novel immune-associated ceRNA regulatory axis involving miR-101-3p, CALCRL, and lncRNA NEAT1 in LUAD. Transcriptomic and immune-gene profiling identified dysregulated immune-related genes and highlighted CALCRL as a critical immune-modulatory receptor. Functional validation demonstrated that miR-101-3p directly targets CALCRL, whereas NEAT1 acts as a competitive endogenous RNA (ceRNA), sequestering miR-101-3p and thereby restoring CALCRL expression. This axis not only promoted tumor growth but also influenced immune cell infiltration and immune evasion. Furthermore, miR-101-3p overexpression induced mitochondrial dysfunction, ROS generation, collapse of mitochondrial membrane potential and ATP depletion, leading to apoptosis. Collectively, these findings highlight the dual role of this network in regulating tumor progression, mitochondrial dynamics, and immune microenvironment modulation and underscore the potential of targeting this axis for miRNA-guided therapeutic interventions, presenting a novel strategy to counteract tumor progression in NSCLC.

Together, both studies underscore the crucial role of miRNA-mediated regulation in NSCLC, demonstrating how tumor-suppressive miRNAs can simultaneously modulate oncogenic signaling, metabolic adaptation, mitochondrial integrity, and immune responses.

Keywords: Lung Cancer, NSCLC, microRNA, Tumorigenesis, Oncogenic signalling