Identification of Novel MicroRNAs for SARS-CoV-2 Therapeutics through the Regulation of TMPRSS2/RAS/PI3K/AKT/PTEN Alignment in Lung Cancer: An *In-silico* Analysis

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Abstract- In this study, we investigated the interactions between SARS-CoV-2 and miRNAs associated with lung cancer using bioinformatic approaches. A special focus was placed on TMPRSS2 and lung cancer progression pathways involving AKT/RAS/PI3K/PTEN genes.

Key words- SARS-CoV-2, microRNA, lung cancer.

1. Introduction

The recent coronavirus pandemic brought the world to a halt due to its unexpected severity and rampant spread. The SARS-CoV-2 (coronavirus disease 2019 or COVID-19) outbreak reached pandemic proportions with an elevated morbidity ratio, especially in certain groups of patients. The common symptoms of SARS-CoV-2 resemble those of the common cold; however, in severe cases, acute respiratory distress syndrome (ARDS), along with damage to the organs of the respiratory and other systems, particularly the lungs, can occur. Lung damage can, in turn, cause alveolar impairment and acute respiratory discomfort. Consequently, lung cancer patients are recognized as a predominantly 'high-risk group' for SARS-CoV-2.[1] Several research groups have established that the SARS-CoV-2 spike (S) protein binds to the angiotensin-converting enzyme 2 (ACE-2), which promotes cellular entry of this virus. The internalization of the virus is dependent on the host's proteases, especially transmembrane serine protease 2 (TMPRSS2).[2] Alveolar epithelial type II cells, a major source of ACE-2 in the adult lung, are quiescent under normal conditions, but they actively proliferate in lung fibrosis and down-regulate this protective enzyme.[1]

Transmembrane serine protease 2 (TMPRSS2) is a cell-surface protein expressed by the epithelial cells of several tissues and is known to be overexpressed in prostate cancer. The first step in the SARS-CoV-2 infection is host cell entry in which viral hemagglutinin fastens to the human angiotensin-converting enzyme 2 (hACE2), stimulating the internalization of the virus. As mentioned earlier, the internalization of SARS-CoV-2 depends on the proteases of the host cell, particularly TMPRSS2.[3] The contribution of TMPRSS2 to viral infection is not limited to SARS-CoV-2, as this protease facilitates the entry of other viruses, including influenza viruses. The TMPRSS2 gene is a member of the ETS (E26 transformation-specific or Erythroblast Transformation Specific genes) family of oncogenic transcription factors, most commonly ERG (ETS-related gene), which is subsequently regulated by androgen receptor signaling and up-regulated in prostate cancers.[4] Existing data indicate that TMPRSS2-targeted treatments are a promising direction in targeted therapy that deserves further investigation.

Lung cancer is the main cause of cancer deaths globally among both genders. Lung cancer is broadly categorized into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). The latter accounts for more than 80% of lung cancer cases and is further divided into adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.[5] Substantial advances have been made in lung cancer molecular biology; this paved the way for the development of novel therapeutic approaches based on targeting specific genes and pathways. The major signaling pathways that could be used for such therapy approaches include growth-stimulating pathways (EGFR/KRAS/PI3K pathway), growth suppressing pathways (p53/Rb/P14ARF, STK11), apoptotic pathways (Bcl-2/Bax/Fas/FasL), in addition to pathways linked to DNA repair and immortalization genes.[6,7] According to recent research, the altered expression of Renin-angiotensin system (RAS) components has been found to correlate with tumor progression. Furthermore, tumor grading and clinical studies suggest that angiotensin II (Ang II), a key effector of the RAS system, is enhanced in the epithelial-mesenchymal transition (EMT) process [8]. On the other hand, the tumor suppressor phosphatase and tensin homolog (PTEN) has been established as a critical regulator of growth factors and an inhibitor of PI3K in several cancers, including lung cancer. Moreover, loss of PTEN is frequently observed in cancer, resulting in the deregulation of cancer cells' survival, growth, and proliferation.

MicroRNAs (miRNAs) are well-conserved, small (20–22 nt) non-coding RNA molecules that control multiple cellular functions post-transcription by binding to the 3′ untranslated region (UTR) of target messenger

RNA (mRNA) transcripts, thereby promoting translational repression and mRNA degradation. MiRNAs act as key effector molecules in the complex interactions between viruses and host cells. Viral miRNAs can evade the human immune system by altering the expression of several host genes meant for controlling cell growth and development. On the other hand, cell-encoded miRNAs can affect viral infection by regulating host factors involved in viral pathogenesis.[9] Therefore, studies on host cell-derived miRNAs can contribute to furthering the understanding of the mechanisms underlying the interactions between viruses and host cells and provide a framework for the discovery of novel antiviral agents and strategies.

In this study, we conducted an *in-silico* analysis using different microRNA target prediction software programs to shortlist potential miRNAs, regulating TMPRSS2 /KRAS/PI3K/AKT/PTEN individually or as an axis associated with lung cancer.

2. Materials and Methods

The method used to determine potential miRNAs that can directly bind to TMPRSS2, AKT, KRAS, PI3K, mTOR, and PTEN was detailed in our previous publication.[10]

3. Results

3.1.Identification of potential miRNAs involved in the regulation of TMPRSS2

The development of novel approaches for regulating the expression of TMPRSS2 is becoming increasingly important within the context of the COVID-19 pandemic since this enzyme plays a crucial role in cell infection.[3] Gordanpour et al. have shown that miR-221 is down-regulated in prostatic tumors bearing TMPRSS2-ERG fusion transcripts.[11] However, the role of miRNAs targeting TMPRSS2 associated with lung cancer is still unknown. Our analysis revealed that several miRNAs are, directly and/or indirectly, associated with TMPRSS2, enabling the inhibition of its oncogenic properties.

No.	miRNA	Sequence (5' to 3')
1	hsa-let7a-5p	TGAGGTAGTAGGTTGTATAGTT
2	hsa-let7b-5p	TGAGGTAGTAGGTTGTGTGGTT
3	hsa-let7c-5p	TGAGGTAGTAGGTTGTATGGTT
4	hsa-let7d-5p	AGAGGTAGTAGGTTGCATAGTT
5	hsa-let7e-5p	TGAGGTAGGAGGTTGTATAGTT
6	hsa-let7f-5p	TGAGGTAGTAGATTGTATAGTT
7	hsa-let7g-5p	TGAGGTAGTAGTTTGTACAGTT
8	hsa-let7i-5p	TGAGGTAGTAGTTTGTGCTGTT
9	hsa-miR-7-5p	TGGAAGACTAGTGATTTTGTTGTT
10	hsa-miR-25-3p	CATTGCACTTGTCTCGGTCTGA
11	hsa-miR-32-5p	TATTGCACATTACTAAGTTGCA
12	hsa-miR-92a-3p	TATTGCACTTGTCCCGGCCTGT
13	hsa-miR-92b-3p	TATTGCACTCGTCCCGGCCTCC
14	hsa-miR-98-5p	CTATACAACTTACTACTTTCCC
15	hsa-miR-153-5p	TTGCATAGTCACAAAAGTGATC
16	hsa-miR-182-5p	TTTGGCAATGGTAGAACTCACACT
17	hsa-miR-183-5p	TATGGCACTGGTAGAATTCACT
18	hsa-miR-221-3p	ACAGCAGGCACAGACAGGCAGT
19	hsa-miR-363-3p	AATTGCACGGTATCCATCTGTA
20	hsa-miR-367-3p	AATTGCACTTTAGCAATGGTGA
21	hsa-miR-448	TTGCATATGTAGGATGTCCCAT
22	hsa-miR-494-3p	TGAAACATACACGGGAAACCTC
23	hsa-miR-511-3p	AATGTGTAGCAAAAGACAGA
24	hsa-miR-4458	AGAGGTAGGTGTGGAAGAA

25	hsa-miR-4500	TGAGGTAGTAGTTTCTT
26	hsa-miR-4778-3p	TCTTCTTCCTTTGCAGAGTTGA
27	hsa-miR-4796-5p	TGTCTATACTCTGTCACTTTAC
28	hsa-miR-5197-5p	CAATGGCACAAACTCATTCTTGA

Table *I* presents a list of potential miRNA candidates against the TMSRSS2 gene, which were not studied previously.

3.2. Identification of potential miRNAs involved in the regulation of KRAS

The proto-oncogene RAS, coding for a 21 kDa protein (p21), is mutated in 20% of lung cancers. RAS mutations are detected in 15–20% of NSCLC, more specifically in 30–50% of adenocarcinomas (ADCs). In total, 80% of KRAS2 mutations occur in codon 12. Other mutations are located in codons 13 and 61. The predominant mutation is a G–T transversion (in 70% of tumors).[8] Table II provides a list of potential miRNA candidates against the KRAS gene that has not been studied previously.

3.3. Identification of potential miRNAs involved in the regulation of PI3K/AKT/mTOR pathway

PI3K/AKT/mTOR are identified as having a key role in the pathogenesis of various cancer forms, notably lung cancer.[6] Genomic amplification of PI3K was also identified in many NSCLC tumors and pre-invasive lesions. The phosphoinositide-3-kinase (PI3K) signaling pathway is an important intracellular signal transduction pathway with a significant role in "cell proliferation, growth, survival, vesicle trafficking, glucose transport, and cytoskeletal organization".[6] PI3Ks are usually activated by receptor tyrosine kinases (RTKs) such as EGFR, IGF1-R and HER2/neu.[12] Moreover, mammalian targets of the rapamycin complex (mTORC) "contribute to the complete activation of AKT via phosphorylation at serine 473."[13] Activated AKT promotes cell growth and survival through various mechanisms. Studies found that it is mutated in more than 30% of 188 lung adenocarcinomas and is also frequently activated in lung cancer cell lines, in particular ones harboring genetic mutations. There are studies correlating the activation of mTOR with tumor progression and metastatic potential in KRAS-mutated NSCLC models. Anagnostou et al. reported a better outcome for patients with early-stage lung adenocarcinoma that overexpressed mTOR. Table III provides a list of potential miRNA candidates against the PI3K/AKT/mTOR pathway.

No.	**miRNA**	**Sequence (5' to 3')**
1	hsa-let7a-5p	TGAGGTAGTAGGTTGTATAGTT
2	hsa-let7b-5p	TGAGGTAGTAGGTTGTGTGGTT
3	hsa-let7c-5p	TGAGGTAGTAGGTTGTATGGTT
4	hsa-let7d-5p	AGAGGTAGTAGGTTGCATAGTT
5	hsa-let7e-5p	TGAGGTAGGAGGTTGTATAGTT
6	hsa-let7f-5p	TGAGGTAGTAGATTGTATAGTT
7	hsa-let7g-5p	TGAGGTAGTAGTTTGTACAGTT
8	hsa-let7i-5p	TGAGGTAGTAGTTTGTGCTGTT
9	hsa-miR-7-5p	TGGAAGACTAGTGATTTTGTTGTT
10	hsa-miR-25-3p	CATTGCACTTGTCTCGGTCTGA
11	hsa-miR-32-5p	TATTGCACATTACTAAGTTGCA
12	hsa-miR-92a-3p	TATTGCACTTGTCCCGGCCTGT
13	hsa-miR-92b-3p	TATTGCACTCGTCCCGGCCTCC
14	hsa-miR-98-5p	CTATACAACTTACTACTTTCCC

Table I.

15	hsa-miR-153-5p	TTGCATAGTCACAAAAGTGATC
16	hsa-miR-182-5p	TTTGGCAATGGTAGAACTCACACT
17	hsa-miR-183-5p	TATGGCACTGGTAGAATTCACT
18	hsa-miR-221-3p	ACAGCAGGCACAGACAGGCAGT
19	hsa-miR-363-3p	AATTGCACGGTATCCATCTGTA
20	hsa-miR-367-3p	AATTGCACTTTAGCAATGGTGA
21	hsa-miR-448	TTGCATATGTAGGATGTCCCAT
22	hsa-miR-494-3p	TGAAACATACACGGGAAACCTC
23	hsa-miR-511-3p	AATGTGTAGCAAAAGACAGA
24	hsa-miR-4458	AGAGGTAGGTGTGGAAGAA
25	hsa-miR-4500	TGAGGTAGTAGTTTCTT
26	hsa-miR-4778-3p	TCTTCTTCCTTTGCAGAGTTGA
27	hsa-miR-4796-5p	TGTCTATACTCTGTCACTTTAC
28	hsa-miR-5197-5p	CAATGGCACAAACTCATTCTTGA

miRNAs with a strong binding potential against TMPRSS2.

Table II. miRNAs with strong binding potential against KRAS

No.	miRNA	Sequence (5’ to 3’)
1	hsa-miR-1-3p	TGGAATGTAAAGAAGTATGTAT
2	hsa-miR-15a-3p	CAGGCCATATTGTGCTGCCTCA
3	hsa-miR-15b-3p	TAGCAGCACATCATGGTTTACA
4	hsa-miR-16-5p	TAGCAGCACGTAAATATTGGCG
5	hsa-miR-19a-3p	TGTGCAAATCTATGCAAAACTGA
6	hsa-miR-19b-3p	TGTGCAAATCCATGCAAAACTGA
7	hsa-miR-7-5p	TGGAAGACTAGTGATTTTGTTGTT
8	hsa-miR-27a-3p	TTCACAGTGGCTAAGTTCCGC
9	hsa-miR-27b-3p	TTCACAGTGGCTAAGTTCTGC
10	hsa-miR-30a-5p	TGTAAACATCCTCGACTGGAAG
11	hsa-miR-30b-5p	TGTAAACATCCTACACTCAGCT
12	hsa-miR-30c-5p	TGTAAACATCCTACACTCTCAGC
13	hsa-miR-92a-3p	TATTGCACTTGTCCCGGCCTGT
14	hsa-miR-92b-3p	TATTGCACTCGTCCCGGCCTCC
15	hsa-miR-98-5p	CTATACAACTTACTACTTTCCC
16	hsa-miR-124-3p	TAAGGCACGCGGTGAATGCCAA
17	hsa-miR-142-3p	TGTAGTGTTTCCTACTTTATGGA
18	hsa-miR-143-3p	TGAGATGAAGCACTGTAGCTC
19	hsa-miR-155-5p	TTAATGCTAATCGTGATAGGGGTT
20	hsa-miR-181a-5p	AACATTCAACGCTGTCGGTGAGT
21	hsa-miR-181b-5p	AACATTCATTGCTGTCGGTGGGT
22	hsa-miR-181c-5p	AACATTCAACCTGTCGGTGAGT
23	hsa-miR-183-3p	TATGGCACTGGTAGAATTCACT
24	hsa-miR-195-3p	CCAATATTGGCTGTGCTGCTCC
25	hsa-miR-200b-5p	TAATACTGCCTGGTAATGATGA
26	hsa-miR-200c-5p	TAATACTGCCGGGTAATGATGGA
27	hsa-miR-202-3p	TTCCTATGCATATACTTCTTTG
28	hsa-miR-206	TGGAATGTAAGGAAGTGTGTGG
29	hsa-miR-217-3p	CATCAGTTCCTAATGCATTGCC
30	hsa-miR-363-3p	AATTGCACGGTATCCATCTGTA
31	hsa-miR-367-3p	AATTGCACTTTAGCAATGGTGA
32	hsa-miR-424-5p	CAGCAGCAATTCATGTTTTGAA
33	hsa-miR-497-5p	CAGCAGCACACTGTGGTTTGT

Table III. miRNAs with a strong binding potential against the PI3K/AKT/mTOR pathway

No.	miRNA	Sequence (5' to 3')
1	hsa-let7a-5p	TGAGGTAGTAGGTTGTATAGTT
2	hsa-let7b-5p	TGAGGTAGTAGGTTGTGTGGTT
3	hsa-let7c-5p	TGAGGTAGTAGGTTGTATGGTT
4	hsa-let7d-5p	TCTTCTTCCTTTGCAGAGTTGA
5	hsa-let7e-5p	AGAGGTAGTAGGTTGCATAGTT
6	hsa-let7f-5p	TGAGGTAGGAGGTTGTATAGTT
7	hsa-let7g-5p	TGGAAGACTAGTGATTTTGTTGTT
8	hsa-miR-92a-3p	TATTGCACTTGTCCCGGCCTGT
9	hsa-miR-98-5p	CTATACAACTTACTACTTTCCC
10	hsa-miR-124-3p	TAAGGCACGCGGTGAATGCCAA
11	hsa-miR-200b-5p	TAATACTGCCTGGTAATGATGA
12	hsa-miR-200c-5p	TAATACTGCCGGGTAATGATGGA
13	hsa-miR-4458	AGAGGTAGGTGTGGAAGAA
14	hsa-miR-4500	TGAGGTAGTAGTTTCTT
15	hsa-miR-200b-3p	TAATACTGCCTGGTAATGATGA
16	hsa-miR-200c-3p	TAATACTGCCGGGTAATGATGGA
17	hsa-miR-202-3p	TTCCTATGCATATACTTCTTTG
18	hsa-miR-429	TAATACTGTCTGGTAAAACCGT

3.4. Identification of potential miRNAs involved in the regulation of PTEN

The most common genetic alteration of the PI3K pathway observed in human cancer is the deletion or down-regulated expression of the tumor suppressor gene PTEN.[14] PTEN acting as a direct antagonist of PI3K, negatively regulates the PI3K pathway. Homozygous or hemizygous deletions of PTEN and missense mutations may result in the increased activation of the PI3K pathway and are frequently observed in many cancer types, albeit less frequent in NSCLC. However, the partial or complete loss of PTEN protein expression is frequently observed in lung cancer. Transcriptional repression and epigenetic silencing of PTEN, commonly through promoter hyper methylation, has been described as a mechanism of PTEN inactivation in several studies. Table IV presents a list of potential miRNA candidates, which were not studied previously, against the TMSRSS2 gene.

Table IV. miRNAs with a strong binding potential against PTEN

No.	miRNA	Sequence (5' to 3')
1	hsa-let7a-5p	TGAGGTAGTAGGTTGTATAGTT
2	hsa-let7b-5p	TGAGGTAGTAGGTTGTGTGGTT
3	hsa-let7c-5p	TGAGGTAGTAGGTTGTATGGTT
4	hsa-let7d-5p	AGAGGTAGTAGGTTGCATAGTT
5	hsa-let7e-5p	TGAGGTAGGAGGTTGTATAGTT
6	hsa-let7f-5p	TGAGGTAGTAGATTGTATAGTT
7	hsa-let7g-5p	TGAGGTAGTAGTTTGTACAGTT
8	hsa-miR-10a-5p	TACCCTGTAGATCCGAATTTGTG
9	hsa-miR-10b-3p	TACCCTGTAGAACCGAATTTGTG
10	hsa-miR-92a-3p	TATTGCACTTGTCCCGGCCTGT
11	hsa-miR-92b-3p	TATTGCACTCGTCCCGGCCTCC
12	hsa-miR-98-5p	CTATACAACTTACTACTTTCCC
13	hsa-miR-124-3p	TAAGGCACGCGGTGAATGCCAA

4. Discussion

The COVID-19 pandemic had a shattering impact on the health of millions of people and became a challenge for universal health systems. The high mortality rate associated with this pandemic is generally due to lung failure

induced by the ARDS.[15] This can further trigger other organ failures, including the digestive system, kidneys, and brain. In addition, this infection can be fatal in patients suffering from lung cancer. The host cell infection mechanism by SARS-CoV-2 is not completely understood and remains an active research topic (we posit for many years to come). However, it became evident that the key players in the entry of the virus into the host cell are ACE2 and TMPRSS2. Specifically, the interaction of these membrane proteins with the viral spike protein (S-protein) is vital for host-membrane fusion and endocytosis.[2]

In this study, we report on the interaction between SARS-CoV-2 and miRNAs associated with lung cancer. Our analysis focused on TMPRSS2 and lung cancer progression pathways involving AKT/RAS/PI3K/mTOR/PTEN genes. The algorithms and bioinformatic approach we adopted is detailed in our previous work.[10] Our analysis resulted in a network of miRNA-mRNA interactions illustrated in

Table *III* through IV.

Genetic abnormalities commonly associated with lung cancer include somatic mutations and gene amplifications in epidermal growth factor receptors (EGFRs), P53, KRAS,[8] BRAF, Erb-B2 receptor tyrosine kinase 2 (ERBB2), MET, serine/threonine kinase 11, PIK3CA (PI3K) and Parkin RBR E3 ubiquitin protein ligase. Other genetic abnormalities related to lung cancer have been identified in numerous pathways, including the Notch, EGFR, PI3K, phosphatase and tensin homolog (PTEN) /phospho-AKT/p53,[12] mitogen-activated protein kinase (MAPK), and cell cycle pathways. The PI3K/AKT/mTOR pathway is commonly activated in NSCLC. It plays important roles in promoting oncogenesis in lung cancer and mediating resistance to EGF receptor tyrosine kinase inhibitors. The RAS is one of the "most frequently mutated genes in NSCLC, found in approximately 30% of lung adenocarcinomas, and is thus an appealing target for new therapies." [8] Moreover, preclinical data suggest that RAS blockers up-regulate ACE2, thereby increasing the risk of developing severe acute respiratory syndrome SARS-CoV-2 infections. Lately, some studies have revealed that TMPRSS2-ERG positive tumors are also enhanced in PTEN loss and subsequent enrichment of PI3K,[14] suggesting a strong collaboration among these genes in the context of prostate tumorigenesis. TMPRSS2-ERG fusions seem to further associate with the PI3K pathway through cooperation with active AKT, the combination resulting in the development of invasive carcinoma.

miRNAs have shown potential in the therapeutic approach in the fight against SARS-CoV-2. In 2004, a study by Takamizawa et al. revealed that lower expressions of let-7 microRNA were associated with the shorter survival in patients with surgical lung cancer. Several studies revealed that miR-1, miR-21, miR-30a, miR-92a,miR-107, miR-124, miR-425-5p, miR-503, miR-520a targeting the PI3K/PTEN/AKT signaling axis regulate multiple biological functions in human lung cancer. Additionally, the enforced expression of let-7 family, miR 98 and miR 134 could indeed reduce RAS protein levels in lung cancer. These miRNAs were also found to bind at 3'UTR of TMPRSS2. However, so far, no studies were able to establish a connection between the TMPRSS2 and RAS/AKT/PI3K/PTEN/mTOR axis and explain the possibility of using this connection in developing therapeutics for SARS-Cov-2 in lung cancer patients.

5. Conclusions

In this paper, we discussed the use of miRNAs as targets for the SARS-CoV-2 infection in patients with lung cancer. Our findings revealed several common miRNAs that can regulate both TMPRSS2 and RAS/PI3K/AKT/PTEN individually, suggesting a novel relationship between them. The findings of this study highlight the potential of miRNAs in the development of diagnostics, biomarkers, and therapeutic targets for SARS-CoV-2 associated lung cancer.

Author Contributions: D.M conceived and designed the study, conducted the analysis, and drafted the manuscript. D.M, N.S and G.H revised and edited the manuscript. All authors approved the final version.

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