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Crosstalk between SARS-2 Infection and Cancers: A Precautionary Insight on Long Non-Coding RNA

Priti Talwar[1]*; Arman Firoz[1]; Palaniyandi Ravanan[2]*

[1]Apoptosis and Cell Survival Research Laboratory, 412G Pearl Research Park, School of Biosciences and Technology, Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India.

[2]Functional Genomics Laboratory, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Neelakudi campus, Thiruvarur 610005, Tamil Nadu, India.

***Corresponding Author(s): Priti Talwar[1] & Palaniyandi Ravanan[2]**

[1]Apoptosis and Cell Survival Research Laboratory, 412G Pearl Research Park, School of Biosciences and Technology, Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India

[2]Functional Genomics Laboratory, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Neelakudi campus, Thiruvarur 610005, Tamil Nadu, India.

Email: priti.t@vit.ac.in & ravanan@cutn.ac.in

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Abstract

Background and Objectives: This review aims to investigate the relationship between long non-coding RNAs (lncRNAs) involved in cancer and those affected by SARS-CoV-2 infection.

Methods: The Cancer Genome Atlas (TCGA) database was used to obtain information on lncRNA expression in various cancers, and lncRNA databases such as *LncExpDB, Lnc2cancer 3.0, and LncRNADisease 2.0*, were used to retrieve the datasets of differentially expressed genes in COVID-19 patients compared to healthy controls, as well as the disease gene association networks.

Results: This study revealed a substantial overlap between the two datasets, with over 85% of the differentially expressed lncRNAs in the COVID-19 dataset being cancer-associated lncRNAs. The study also revealed extensive regulation of the mRNA network by the key lncRNAs.

Conclusion: These results suggest that lncRNAs may play a crucial role in the pathogenesis of both cancer and COVID-19 or may trigger each other. These findings highlight the importance of lncRNAs in both cancer and viral infections and the need for continued research in this field. This finding could aid in the development of new diagnostic and therapeutic strategies for COVID-19, as well as help prevent and manage post-COVID complications, including the potential development of cancer.

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Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus has created a global health crisis, affecting millions of people worldwide. While the primary focus of the medical community is to control the spread of the virus and treat COVID-19 patients, the concomitant impact on other diseases, such as cancer, cannot be ignored. The long-term implications of SARS-CoV-2 infection, commonly referred to as "post-COVID syndrome," is a subject of ongoing interest, and further research is essential to accurately determine the relationship between COVID-19 and associated diseases, including the possible link to cancer [1-3]. However, there are several potential mechanisms through which COVID-19 can increase the risk of cancer and affect cancer outcomes [4-6]. It has been postulated that COVID-19 may increase the risk of cancer progression, by negatively affecting the host immune system and its ability to respond to malignancy [7]. These factors may lead to reduced response rates and increased toxicity associated with cancer treatment, potentially contributing to increased morbidity and mortality among cancer patients with COVID-19 [4].

lncRNAs are emerging as critical players in the regulation of the host immune response to viral infections, and play important roles in the modulation of immune responses, control of cytokine release, and regulation of viral replication including SARS-CoV-2, the virus that causes COVID-19 [8]. Genome-wide computational studies have identified several lncRNAs that could play important roles in endoplasmic reticulum stress-associated processes, while lncRNAs have also been reported to be involved in cell differentiation, development, and tumorigenesis [9,10]. Alterations in lncRNA expression and function have been associated with various types of cancer, and their deregulation is thought to contribute to tumorigenesis and disease progression [11]. This raises the possibility of crosstalk between the two diseases, which could have significant implications on their outcomes. In this context, we aimed to systematically analyze the roles of lncRNAs in the crosstalk between COVID-19 and common cancers, thereby providing a precautionary insight into the potential interplay between the two diseases in this review.

Methods

We aimed to explore the intersection between lncRNAs involved in cancer and those affected by virus infection, using the Cancer Genome Atlas (TCGA) database and a dataset of differentially expressed genes in COVID-19 patients compared to healthy controls [12,13].

TCGA database provides comprehensive information on lncRNA expression in a wide range of cancers, including breast, lung, prostate, and other major types. In contrast, the COVID-19 dataset allowed us to identify lncRNAs that were differentially expressed in response to viral infections. Furthermore, we extracted the lncRNA database of disease-gene associations from The LncRNA and Disease Database (version 2.0) to determine the extent of overlap between lncRNAs involved in cancer and those affected by viral infection [14]. We also analyzed the lncRNA-based mRNA interactome using Lnc2cancer 3.0 database to understand the regulatory networks [15].

Results

LncRNA in SARS and Its Association with cancers

We compared the total of 1738 lncRNAs obtained from The Cancer Genome Atlas (TCGA) database with 601 differentially expressed lncRNAs in COVID-19 patients compared to healthy controls. This analysis revealed a substantial overlap between the two datasets, with over 85% of the lncRNAs showing differential expression during COVID-19, which has also been reported in other major cancers **(Figure 1)**. These results provide evidence for a significant co-occurrence of lncRNAs in both cancer and COVID-19, and suggest that lncRNAs may play a crucial role in the pathogenesis of both conditions.

Furthermore, we analyzed all commonly reported genes in both COVID-19 and cancer, and their associated major diseases. To validate the association with cancer, we selected 55 cancers from the list and analyzed the genes involved in these conditions. Lymphoma was most prevalent in the presence of 481 lncRNAs. The first 18 cancers were selected from the list and are shown in **Figure 2**. The ranking was then given based on the number of genes involved in these cancers such as lymphoma, cervical cancer, urinary bladder cancer, thyroid cancer, non-small cell lung carcinoma, stomach cancer, malignant glioma, ovarian cancer, breast cancer, prostate cancer, colorectal cancer, hepatocellular carcinoma, lung cancer, melanoma, osteosarcoma, nephroblastoma, papillary thyroid carcinoma, and acute lymphocytic leukemia. This is the first report of the co-existence of lncRNAs in both cancer and COVID-19 infections.

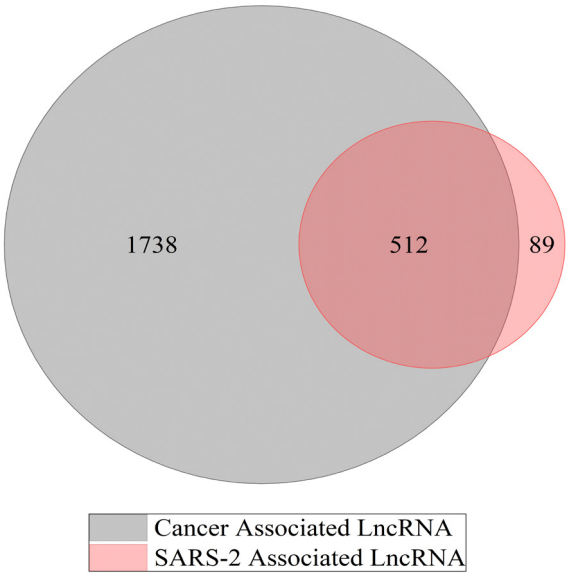

Figure 1: Overlap between differentially expressed lncRNAs in major cancers and COVID-19 patients. A total of 512 out of 601 lncRNAs (~85%) from SARS-2 infections have been reported to be involved in cancer development.

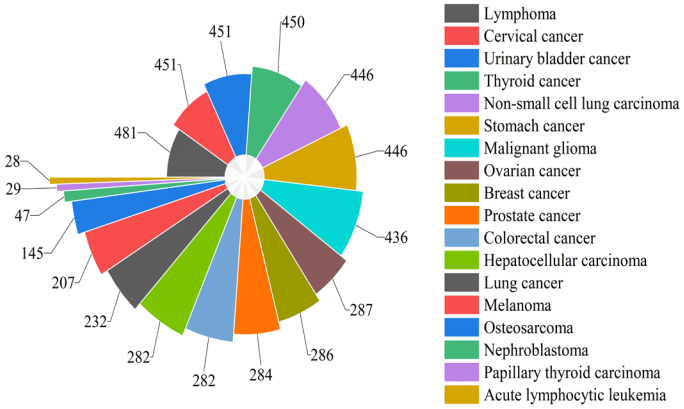

Figure 2: COVID-19 associated lncRNAs and their cancer association: A summary, list of top 18 cancer with the highest number of lncRNA association is listed in this figure.

Genetic Convergence Across 50 Different Cancer Types: A Comprehensive Analysis of Key Genes

In this study, we conducted a prevalence analysis of 482 genes that are commonly present in both cancer and SARS infection datasets to evaluate their occurrence across multiple cancer types. Our analysis revealed that among these genes, 28 lncRNAs were highly prevalent, with approximately 50 of the top 55 cancers on our list **(as shown in Table 1)**.

These findings indicate that lncRNAs may play a crucial role in the development and progression of covid-associated cancers. Therefore, further research on these lncRNAs could provide important insights into their potential as targets for therapeutic interventions. Notably, our analysis identified H19 as the most common lncRNA, present in 52 out of the 55 top cancers. This highlights the potential significance of H19 in the context of covid-associated cancer.

Given the limited existing knowledge on this topic, we conducted an extensive investigation of key lncRNAs and their associations with the mRNA interactome to gain a deeper understanding of the complex interactions between these genes and other protein-coding genes within a broader network. **(Figure 3)**.

Table 1: List of highly significant lncRNAs involved in cancers.

Number of Cancers	52	51	50	49	48
List of lncRNA	*H19*	*MIAT, MIR100HG, SNHG11, SNHG4, BACE1-AS, MIR17HG, SOX2-OT, TRAF3IP2-AS1, SNHG3, SNHG5, DLEU2, EPB41L4A-AS1, DNM3OS, KCNQ1OT1, PCAT1, HIF1A-AS1, TUG1, MALAT1, GAS5*	*NEAT1, MIR155HG, HULC, PVT1, CDKN2B-AS1, MEG3*	*ZFAS1*	*XIST*

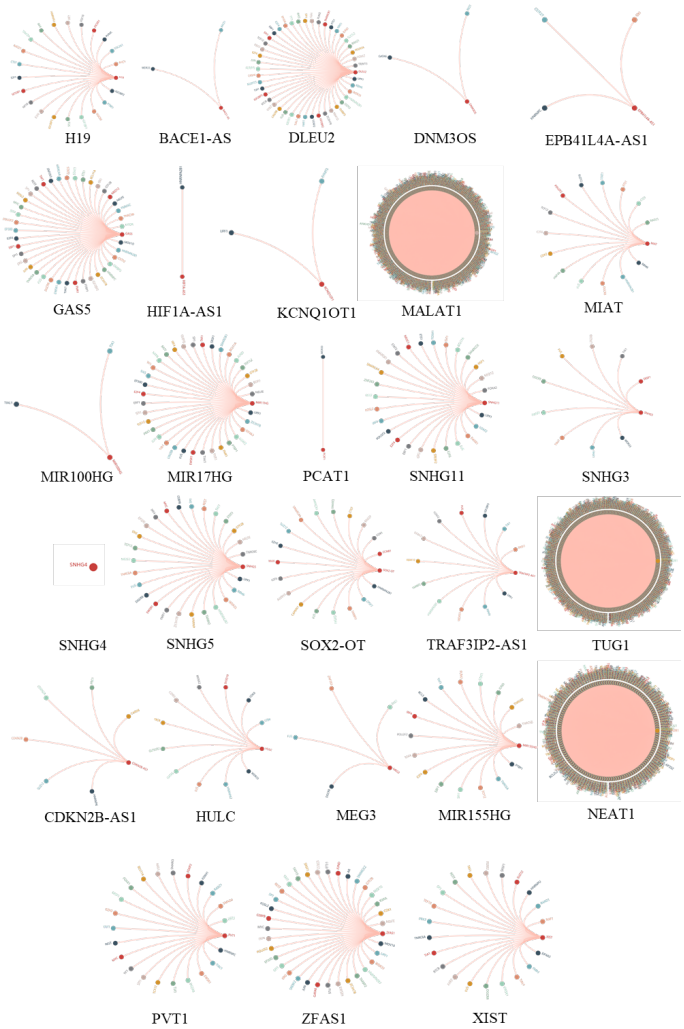

Figure 3: Human mRNA interaction profiles of key lncRNAs. It was found that MALAT-1, TUG1, and NEAT1 have highly significance interactions compared to the rest of the key genes.

lncRNA Interactions in COVID-19 and Cancer: An mRNA Interactome Perspective

In this study, we investigated the role of 28 lncRNAs and the human mRNA interactome. To achieve this, we utilized Lnc-2Cancer 3.0, a powerful tool for network analysis, to analyze the human mRNA interactome in cancers. The LUAD dataset from The Cancer Genome Atlas (TCGA) was used to investigate the mRNA interactome profile of specific lncRNAs. The selection of LUAD as a reference dataset was based on its relevance to the investigation of the connection between COVID-19 and cancer. TCGA LUAD dataset provides valuable molecular and clinical information on lung adenocarcinoma, a subtype of non-small cell lung cancer that represents a significant proportion of lung cancer cases. By analyzing the mRNA interactome profiles of key lncRNAs in this dataset, we aimed to uncover potential regulatory mechanisms and identify candidate biomarkers that may be involved in the link between COVID-19 and cancer **(Figure 3)**.

Analysis of the mRNA interactome revealed significant interactions between specific lncRNAs and human mRNA in various cancers. In particular, we observed that MALAT1, TUG1, and NEAT1 had significant interactions with human mRNA, which is consistent with previous studies reporting their involvement in gene expression regulation and cancer development. In addition, our analysis identified significant interactions between the other lncRNAs. Specifically, ZFAS1, DLEU2, GAS5, MIR17HG, SNHG11, SNHG5, PVT1, and XIST were found to have substantial mRNA interactions, indicating their potential roles in regulating gene expression in cancer. Given the potential involvement of these lncRNAs in both viral infections and cancer, it is possible that post-SARS infection, individuals may have an increased risk of developing cancer. However, further investigations are required to fully understand the relationship between SARS, lncRNAs, and cancer. Our findings suggest that MALAT1, TUG1, and NEAT1 along with other major 25 key genes, may serve as valuable biomarkers for cancer diagnosis and prognosis, and may represent novel therapeutic targets for the development of new cancer treatments.

Discussion

This review highlights the critical role of lncRNAs in a broad range of cancers and viral infections, including COVID-19, and underscores the need for continued research in this area. lncRNAs are known to play a significant role in regulating the host immune response and can act as oncogenic or tumor suppressor factors in cancer. Through our investigation of the level of interaction between lncRNAs and mRNA in human cancers, we provide valuable insights into the complexity of cancer pathogenesis.

Furthermore, our identification of the coexistence of lncRNAs in both cancer and COVID-19 sheds new light on the intricate interplay between cellular processes and the body's

response to the disease. This discovery has important implications for the development of new diagnostic and therapeutic strategies for cancer and viral infections, including COVID-19, with the potential to improve patient outcomes and prevent post-COVID complications, where cancer is still a major concern. Our findings, together with mRNA interactome studies, provide a starting point for future research in this area and offer opportunities to advance genomics and diagnostics.

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