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Molecular Insights into the Benefits of Regular Exercise in Combating Immunological Mayhem during SARS-CoV-2 Infection

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Abstract

Regular exercise helps to combat multifarious diseases by improving overall health of the individual. A recent study has proven that regular exercise can reduce the serious illness associated with COVID-19. Circulating miRNAs released from the muscles during strenuous exercise has also been found to have anti-inflammatory effects. So, it was hypothesized that regular exercise might be releasing therapeutic miRNAs in the blood that might be reducing the immunological chaos in COVID-19 patients. Using network and systems biology approach, mRNA targets of 3 upregulated exomiRs (hsa-miR-486-5 p, hsa-miR-215-5 p, hsa-miR-941) in the blood of regularly exercising adults were mapped in the blood of COVID-19 patients. hsa-miR-215-5 p, hsa-miR-486-5 p and hsa-miR-941 were found to target 8, 93 and 99 upregulated mRNAs respectively. Functional enrichment analysis showed that hsa-miR-486-5 p might be preventing thrombosis and aggravated inflammation in regularly exercising COVID-19 patients. Thus, hsa-miR-486-5 p can be considered to have therapeutic roles against immunological damage caused by COVID-19.

Keywords: ExomiRs • Differentially expressed genes (DEGs) • miRNA-mRNA interactions • RNA-Seq • SARS-CoV-2 • Exercise

Introduction

Increasing cases of COVID-19 (Corona virus disease 2019) and its recurring waves have compelled us to stay indoors. With the imposition of lockdown and social distancing measures, sedentary lifestyle has become the new normal. Sedentary lifestyle paves the pathway for various comorbid lifestyle diseases like cardiovascular diseases and diabetes that increases the complicacies associated with the disease. Moderate forms of exercise has been also proven to boost immunity [1]. Experiments on influenza infected respiratory tract of animal models have shown that moderate exercise reduced mortality associated with the diseases [2,3]. Not only does physical activity reduce the chances of comorbid diseases but also it has been proven to reduce the fatality caused due to COVID-19 infection [4]. It was found that physical activity reduces the chances of both admissions to ICU and death. WHO (World Health organization) also recommends 150 min of moderate intensity or 75 min of intense exercise per week during the quarantine period. So, studying the molecular mechanism behind benefits of exercise would unravel natural therapeutic measures against the disease.

Regular exercise was found to release circulating miRNAs that help in healing the body after a strenuous exercise [5]. These circulating miRNAs has anti-inflammatory roles [6]. Exo-miRNAs (exomiRs) are exosomes loaded with miRNAs that are released from various cells into the blood and they mediate cellular crosstalk by acting as intercellular messaging system [7]. So, it was hypothesized that exomiRs in the blood of regularly exercising adults might be having therapeutic roles against inflammatory rage of COVID-19. By using computational and systems biology approach, 3 upregulated miRNAs from the blood of regularly exercising were screened and their targets were mapped in the blood of COVID-19. After functional analysis it was found that the miRNA hsa-miR-486-5p might be a key player that is aiding to dampen the chances of thrombosis and aggravated inflammation in the blood of regularly exercising adults when infected with SARS-CoV-2.

Materials and Methods

Data processing to screen exomiRs and DEGs from RNA-seq datasets

The exomiRs were identified in GSE144627 [8] dataset. Here, the authors considered 5 sedentary males and 5 age-matched trained males for the study. The circulating exomiRs were identified by comparing their baseline expression profiles in the blood. Similar to the authors, DESeq2 [9] in R v4.1.0 with a cut off of $|\log_2 FC|>1.0$ and Wald test p-value < 0.05 was considered for determining exomiRs.

For screening upregulated genes in the blood of COVID-19 patients two datasets GSE152418 [10] and GSE171110 [11] were used. In GSE152418 [10], the authors performed RNA-seq of PBMCs from the blood of 17 COVID-19 subjects and 17 age and sex- matched controls. In GSE171110 [11], the authors considered whole blood transcriptome of 44 COVID-19 patients and 10 healthy donors. For both these studies, gene specific raw counts were analyzed using DESeq2 [9] package in R v4.1.0 and DEGs were identified by considering a cut off of $|\log_2 FC|>1.0$ and adj. p-value < 0.05. Next, only the common upregulated genes from both the studies i.e. having $\log_2 FC >1$ were considered for meta-analysis in metaRNAseq v1.0.5 [12] in R v4.1.0. Among the two p-value combination techniques used by metaRNAseq v1.0.5 [12], inverse normal method was used to integrate these datasets.

Retrieval of exomiRNA-mRNA interactions

To determine the exomiRNA-mRNA interactions, miRWalk v3 [13] was used by considering a high binding probability (binding prob.=1). The network was then visualized in Cytoscape 3.8.0 [14].

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Go biological process enrichment of the mRNAs

For getting functional insights of the mRNAs controlled by the miRNAs, Go biological process over-representation (enrichment) was done using cluster Profiler v4.0.0 [15] in R v4.1.0 by considering an adj. P value <0.05 .

Results

Identification of circulating DE miRNAs in the blood of regularly exercising adults

Circulating exomiRs has been proposed to have multifarious roles in modulating post-transcriptional gene expression of different tissues by binding to 3'UTR of transcripts [16]. Also exomiRs have been identified to modulate innate immune response [17]. Regular exercise not only boosts immunity but also has anti-inflammatory role against chronic inflammation [18] .So, circulating miRNAs in the blood of regularly exercising adults might have therapeutic roles against inflammatory response during SARS-CoV-2 infection. To analyze the effect of exercise in SARS-CoV-2 patients, initially a publicly available dataset-GSE144627 [8] was used to identify circulating exomiRs at rest in the blood of regularly exercising adults (trained). Using DESeq2 [9], 4 DE miRNA were identified by considering a cut off of $|\log_2 FC|>1.0$ and Wald test p-value <0.05. Among these, 3 miRNAs (hsa-miR-486-5 p, hsa-miR-215-5 p, hsa-miR-941) were found to be upregulated that were considered for downstream analysis (Table).

Identification of DEGs in the blood cells of COVID-19 patients

For identifying DE miRNAs, two blood transcriptome of SARS-CoV-2 infected patients GSE152418 [10] and GSE171110 [11] were used. By using DESeq2 [9] in R v4.1.0, 4151 in Figure 1A and 4475 DEGs Figure 1B in GSE171110 [11] and GSE152418 [10] were identified respectively. DEG selection was done considering a cut off of $|\log_2 FC|>1.0$ and adj. P value < 0.05. Among these DEGs, only 1081 common upregulated genes in Figures 1C and 1D and table S1 from both the datasets were meta-analyzed by using metaRNAseq v1.0.5 [12] in R v4.1.0 and considered for downstream analysis (Table S1 and Figure 1A).

Reconstruction exomiRNA-mRNA network in blood of COVID-19 patients

It was hypothesized that the upregulated exomiRNAs in blood of regularly exercising adults might be safeguarding them from the severity caused due to COVID-19 by translational silencing of upregulated genes in blood cells. To address this hypothesis, exomiRNA-mRNA interactions from miRWalk v3 [13] was used and the network was visualized in Cytoscape 3.8.0 [14]. The network consists of 180 nodes and 200 edges. hsa-miR-215-5p, hsa-miR-486-5p and hsa-miR-941 were found to interact with 8, 93 and 99 upregulated mRNAs respectively (Figure 2).

Functional enrichment of the interacting mRNAs to gain insights into processes being dysregulated by the exomiRs

Then, GO Biological Process enrichment of the interacting mRNAs for each exomiR was performed using clusterProfiler v4.0.0 [15] in R v4.1.0 (Table S2) by considering a cut off of adj. P value <0.05 . Based on functional enrichment results, hsa-miR-486-5p and hsa-miR-941 were found to regulate platelet degranulation and mitotic cell division respectively (Table S2 and Figures 3A and 3B).

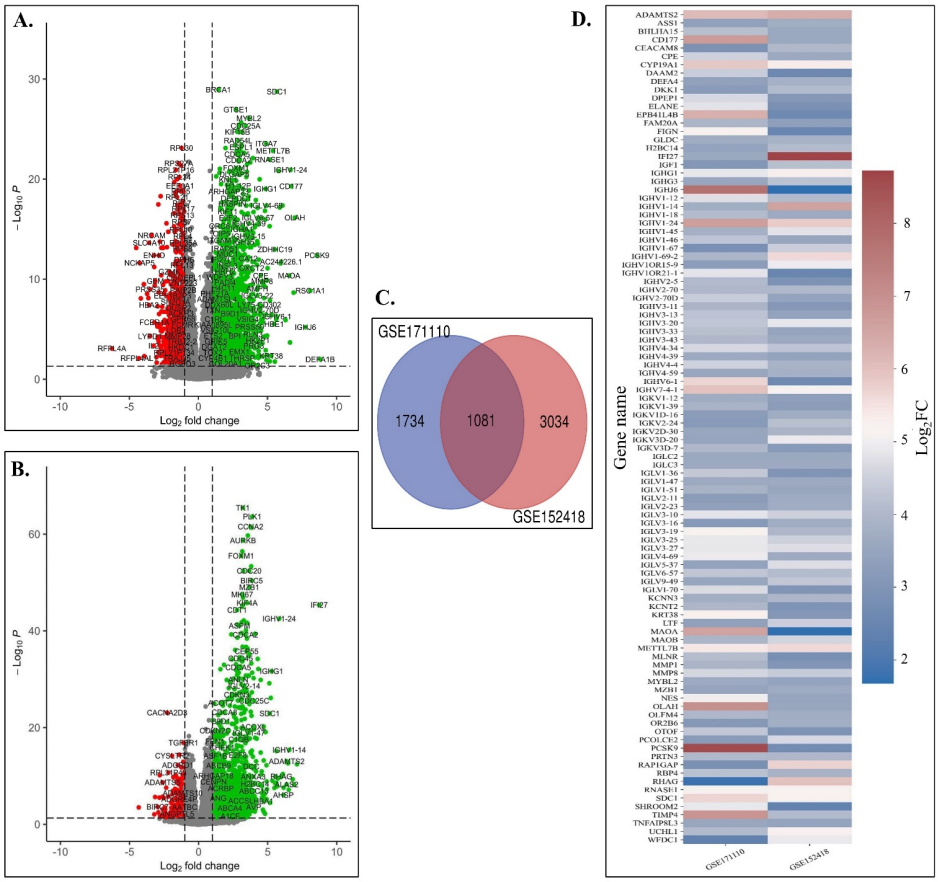

Figure 1. Screening of upregulated genes in the blood of COVID-19 infected patients. (A.) Volcano plot of DEGs (differentially expressed genes) from GSE152418 (B.) Volcano plot of DEGs (differentially expressed genes) from GSE171110 (C.) Venn diagram representing common upregulated genes in both the datasets (D.) Heatmap showing top 100 upregulated genes.

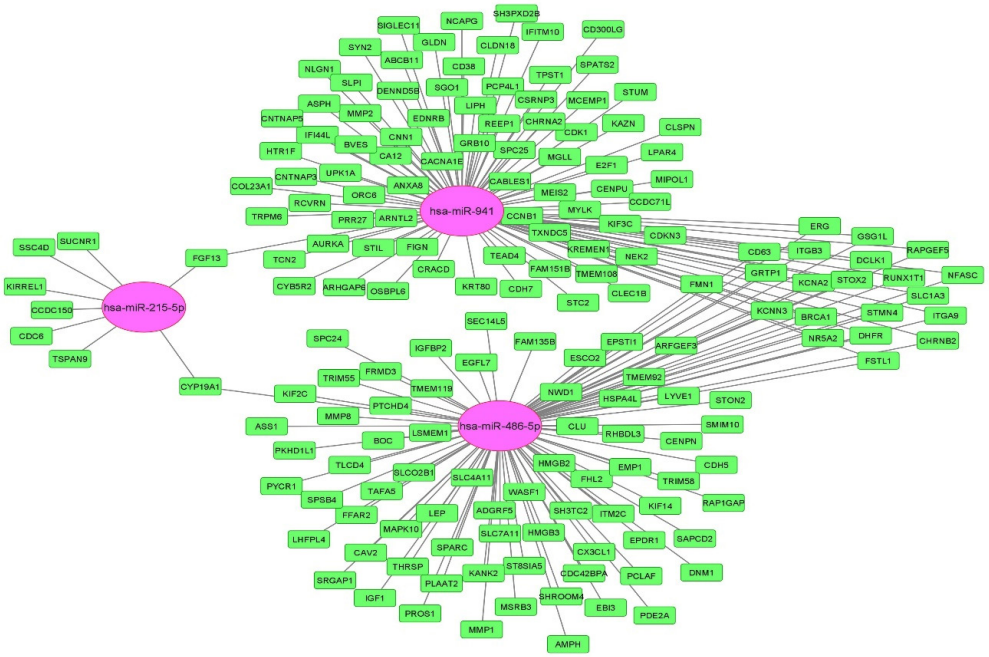

Figure 2. miRNA-mRNA network in the blood of regularly exercising adults infected with SARS-COV-2. **Note:** ( ) =miRNA ( ) = mRNA

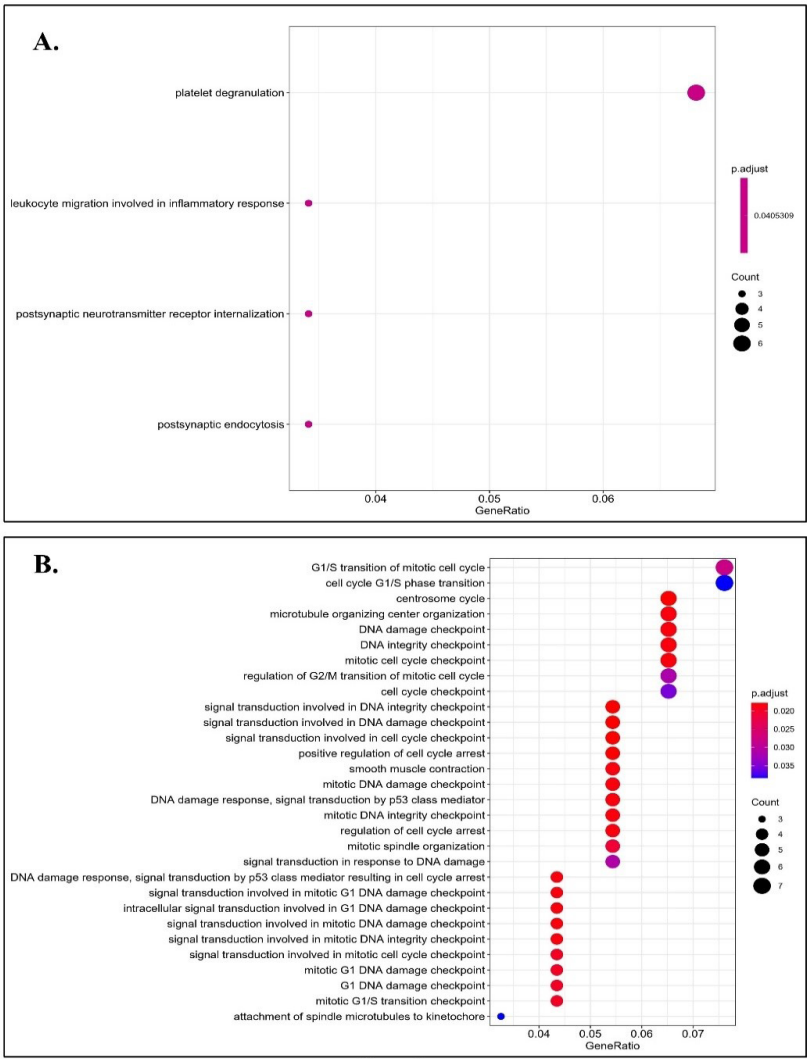

Figure 3. Go biological process enrichment of mRNAs targeted by the upregulated miRNAs (A.) GO biological process enrichment of mRNAs targeted by hsa-miR-486-5 p (B.) GO biological process enrichment of mRNAs targeted by hsa-miR-941. **Note:** ( ) P. adjust; ( ) Counts

Discussion

During the recent COVID-19 outbreak, it was found that blood coagulation factors are altered as a result of infection [19]. It causes moderate to severe thrombocytopenia along with increased D-dimer levels. Blood coagulation is the fastest and ultimate response to infections. Any wound in the body causes activation of endothelial cells and thereby leads to activation of prothrombin as a result of which blood coagulation is initiated [20]. When the immune system is hyperactivated, coagulation might happen within the blood vessel leading to disseminated intravascular coagulation (DIC) [21]. DIC causes multiple organ failure. Strikingly, it has already been reported that COVID-19 causes altered coagulation and also organ dysfunction [19]. Apart from triggering inflammation, the cytokine storm induced by SARS-CoV-2 also leads to increased fibrin deposition thereby causing hypercoagulation [22]. Again this inflammation causes activation of Polymorphonuclear leukocytes (PMNs). PMNs inactivate endogenous anticoagulants and thereby leads to the formation of blood clots within blood vessels [20]. Sedentary lifestyle paves the pathway for multifarious diseases among which obesity and Type 2 Diabetes (T2DM) can cause a havoc [23]. T2DM can damage blood vessels and thereby magnify hypercoagulation in COVID-19 patients [24]. Moreover, obesity might aggravate overactivity of coagulation factors due to dysregulation of adipokines [25]. Regular exercise has not only been proven to boost immunity but also triggers anti-inflammatory pathways [18]. This helps in preventing severity caused due to systemic inflammation. Moreover, regular exercise reduces the risk of lifestyle diseases and reduces ill effects of adipokines [18]. It was also reported that regular exercise might decrease platelet aggregation and fibrinolysis over time [26]. So, patients having an active lifestyle might be able to combat immunogenic mayhem in COVID-19 by preventing thrombosis and hypercoagulation issues. Discovery of exomiRs has helped in exploring previously unknown vistas of molecular biology [27]. ExomiRs are exosomes loaded with microRNAs that help in cellular crosstalk. Previous literature suggests that regular exercise causes the release of circulating miRNAs from injured tissues into the blood [6]. Again circulating miRNAs have been proven to have anti-inflammatory roles [28]. As regular exercise has anti-inflammatory roles too, so an active lifestyle might be releasing circulating miRNAs in the blood that might be combating the aggravated inflammatory response caused by COVID-19. For this, initially 3 upregulated exomiRNAs-hsa-miR-486-5p, hsa-miR-215-5p and hsa-miR-941 (Table S1) were identified from the blood of regularly exercising adults. hsa-miR-486-5 p and hsa-miR-215-5p have roles in modulating the immune system. hsa-miR-486-5 p has immunosuppressive roles as it inhibits IL-22 in cancer [29]. hsa-miR-215-5 p was previously reported to suppress inflammation mediated injury [30]. As it was hypothesized that exomiRNAs might be downregulating expression of genes within blood cells, so 1081 upregulated genes from the blood of COVID-19 infected patients was considered for mapping the targets of miRNAs (Figures 1C and 1D) (Table S1). Important upregulated genes included – PCSK9 and IFI27. PCSK9 alters serum cholesterol levels and inhibitors of this gene has already been proposed as a therapeutic measure against SARS-CoV-2 [31]. Again IFI27 has been proposed as blood biomarker for COVID-19 [32]. Mapping target mRNA of the miRNAs using miRWalk v3 [13] revealed that hsa-miR-215-5p, hsa-miR-486-5p and hsa-miR-941 targeted 8, 93 and 99 upregulated mRNAs. Some of important targets of hsa-miR-486-5p in this study are- FSTL1 and CX3CL1. FSTL1 was earlier reported to induce inflammation by triggering release of pro-inflammatory cytokines [33].Whereas, CX3CL1 is a chemokine that leads to COVID-19 -associated thrombosis [34]. hsa-miR-941 was found to target cell cycle regulator CDK1. It has been reported that CDK1 induces IFN1 production in response to viral infection [35]. Thus, the exomiRNAs might be targeting key players of the immune response and thereby reducing SARS-CoV-2 mediated hyperinflammation. To gain functional insights into the processes deregulated by these miRNAs, GO biological process enrichment was performed. It was found that hsa-miR-486-5p targeted platelet degranulation and leukocyte cell migration. It was reported that platelet activation and degranulation is a pathophysiological feature of COVID-19 [36]. Moreover, this also contributes to release of inflammatory cytokines that might magnify the cytokine storm in these patients. Important targets enriched for this GO function include IGF1 and ITGB3 (Figure 4). IGF1 was found to escalate platelet activation through IRS/PI3K alpha pathway [37]. Whereas, ITGB3 was found to modulate serotonin transport and thereby platelet aggregation in mice [38]. Platelet degranulation has been reported to recruit neutrophils at the site of inflammation via release of serotonin [39]. So, migration of neutrophil like leukocytes occurs concomitantly with platelet aggregation. Some important mRNAs enriched in the GO biological process- "Leukocyte migration involved in inflammatory response" that are targeted by hsa-miR-486-5 p include - FFAR2 and CX3CL1 (Figure 4).

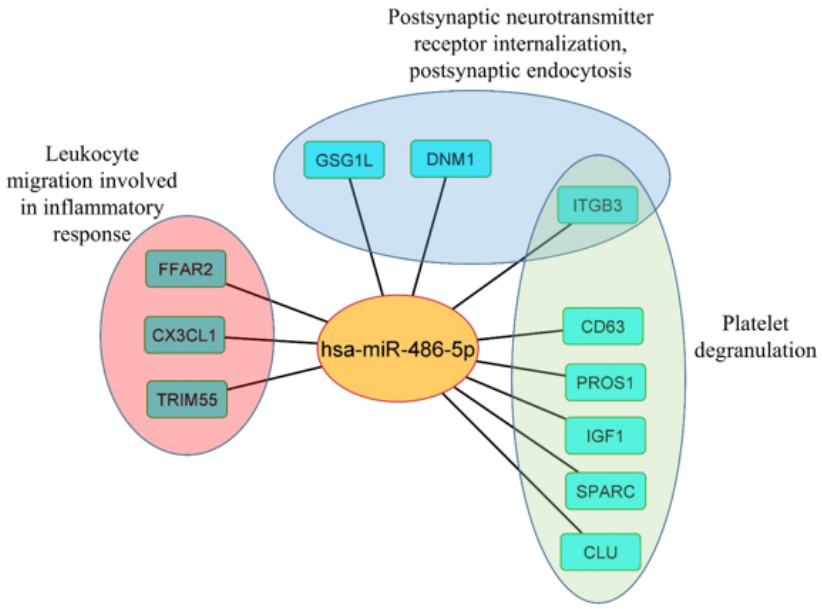

Figure 4. Functional enrichment specific targets of hsa-miR-486-5 p.

Both FFAR2 and CX3CL1 were found to facilitate neutrophil migration to the site of inflammation [40,41]. These results suggest that hsa-miR-486-5p might be preventing platelet degranulation and by this process is also preventing leukocytes to be migrating to the site of inflammation. Thus, regular moderate forms of exercise might increase circulating hsa-miR-486-5p that might dampen the mayhem by reducing blood coagulation and leucocyte migration if infected with SARS-CoV-2 in the future. Apart from this, hsa-miR-486-5p might also be considered as a therapeutic measure against the inflammation caused by COVID-19 infection.

Conclusion

COVID-19 has brought life to a standstill. Although vaccines and steroids have been effective in reducing the mortality due to this disease, but boosting personal immunity have been proven to reduce serious health issues associated with this disease. The Medical fraternity is constantly advising to have an active lifestyle during this period. So, studying the therapeutic perspective of regular exercise in reducing aggravated immune response in COVID-19 needs attention. In this study, circulating miRNAs (exomiRs) in the blood of regularly exercising adults were screened and their targets were identified among the upregulated mRNAs in the blood of COVID-19 patients. The results suggest that hsa-miR-486-5p might be reducing the chances of thrombosis and aggravated inflammation in the blood of regularly exercising adults when infected with SARS-CoV-2. Further experimental studies need to be carried out to establish its therapeutic role against COVID-19.

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Declaration of Competing Interest

The author declares that there isn't any conflict of interest with any organization or financial entity in private or in public.

Data Availability Statement

All data here analyzed are publicly available on NCBI Gene Expression Omnibus (GEO).

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