Selvakumar, SC, Preethi, KA, Ross, K, Tusubira, D and Sekar, D

MicroRNA-510-3p and Its Gene Network in the Disease Regulation of Preeclampsia: An Insilico Approach

Selvakumar, SC, Preethi, KA, Ross, K, Tusubira, D and Sekar, D (2023) MicroRNA-510-3p and Its Gene Network in the Disease Regulation of Preeclampsia: An Insilico Approach. Journal of Biological Regulators and Homeostatic Agents, 37 (4), pp. 2291-2299. ISSN 0393-974X

Article

J. Biol. Regul. Homeost. Agents. 2023; 37(4): 2291–2299
https://doi.org/10.23812/j.biol.regul.homeost.agents.20233704.225

MicroRNA-510-3p and Its Gene Network in the Disease Regulation of Preeclampsia: An Insilico Approach

Sushmaa Chandralekha Selvakumar[1], K Auxzilia Preethi[1], Kehinde Ross[2], Deusdedit Tusubira[3], Durairaj Sekar[1,*]

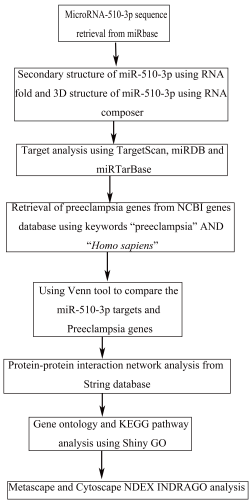
[1]RNA Biology Lab, Saveetha Dental College & Hospitals, Saveetha Institute of Medical & Technical Sciences (SIMATS), Saveetha University, 600077 Chennai, India
[2]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, L3 8 Liverpool, UK
[3]Biochemistry Department, Mbarara University of Science and Technology, Mbarara, Uganda
*Correspondence: duraimku@gmail.com; durairajsekar.sdc@saveetha.com (Durairaj Sekar)
Published: 20 April 2023

Background: Preeclampsia (PE) is a major health complication for pregnant women that increases the risk of mortality and morbidity. Knowledge of the complex molecular mechanisms associated with PE is incomplete and methods for early diagnosis and treatment options in PE are limited. MicroRNAs (miRNAs) are short non-coding RNAs involved in pathogenesis of various diseases including PE. In our previous studies, we identified a relationship between miR-510-3p and PE. However, the exact molecular mechanisms and genes regulated by miR-510-3p have not been elucidated.

Methods: In this study, we employed the bioinformatic tools including miRbase, RNAcomposer, RNAfold, TargetScan, miRDB, miRTarbase to analyze the secondary structure and targets of miR-510-3p from the publicly available databases. We compared the miR-510-3p target genes with PE genes retrieved from the NCBI (National Center for Biotechnology Information) genes database. The miR-510-3p target genes that were involved in PE were further subjected to gene ontology (GO) and Kyoto Encyclopaedia for Genes and Genomes (KEGG) pathway analysis to analyse their biological, molecular and cellular role in PE. STRING, Shiny GO, Cytoscape and Metascape were used for the GO and KEGG analysis.

Results and Conclusions: MicroRNA-510-3p had a minimum free energy of –29.10 Kcal and A+U content of 55.4%, suggesting stability and binding affinity towards its targets. Genes that were involved in the positive regulation of angiogenesis were identified, since angiogenesis is an important process in PE. *ADAM12, ANGPT2, CHRNA7, DDAH1, ERAP1, FGF2, GRN, HGF, HIF1A, HK2, HMGB1, HMOX1, IL1A, KDR, NRP1, PRKCB, SERPINE1, SIRT1, TGFBR2, THBS1, TLR3, VEGFA,* and *WNT5A* were the miR-510-3p targets involved in the positive regulation of angiogenesis. In conclusion, miR-510-3p is postulated to play an important role in the pathogenesis of PE. Hence, further studies could define miR-510-3p as a novel therapeutic target for PE.

Keywords: preeclampsia; microRNA; angiogenesis; gene enrichment; bioinformatic analysis



Graphical Abstract.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Introduction

Preeclampsia (PE) is a type of hypertension occurring during pregnancy and is characterized by elevated blood pressure and proteinuria. PE occurs due to impaired placental development leading to restriction of foetal uterine growth and multiple organ dysfunction, resulting in high foetal and maternal mortality and morbidity rates [1,2]. There is a lack of early diagnosis and treatment for PE which affects the overall survival rate of the disease. This is due to sparse knowledge of the underlying molecular mechanisms and signalling pathways involved in PE. Currently, several studies are trying to decipher the disease pathogenesis of PE [3–5], yet there is no clear understanding of the molecular mechanisms, signalling pathways and gene regulatory networks involved in PE. Since several genes are involved in the progression of PE, identifying a common regulator for all the differentially expressed genes (DEGs) might help in a better understanding of PE, which would pave way for novel therapeutic approaches.

Small non-coding RNAs of the microRNA family (miRNAs; MiRs) have been implicated in the pathogenesis of PE and other diseases [6–8]. In general, miRNAs bind to the 3′untranslated region (UTR) of target genes and repress gene expression. Thus, miRNAs have the capability to regulate the gene expression of target genes associated with pathology [9]. In a study by Li *et al.* (2022) [10], patients with early-onset PE had significantly higher levels of miR-372-3p compared to patients with late-onset PE. The basic helix-loop-helix (bHLH) transcription factor *Twist1* was targeted by miR-372-3p, according to bioinformatics analysis and dual luciferase reporter assay. It was concluded that miR-372-3p may contribute to the development of PE by targeting *Twist1* and may represent a novel therapeutic target for PE [10]. In another study, Yang *et al.* (2022) [11] studied miR-222-3p for its potential role in PE as a regulator of stathmin 1 (*STMN1*) expression. Levels of miR-222-3p were higher in patients with severe PE than in healthy controls. In addition, a positive correlation between diastolic and systolic blood pressure and miR-222-3p levels in PE patients was identified. Furthermore, *STMN1* was identified as a target of miR-222-3p, and inhibition of miR-222-3p raised *STMN1* expression and reversed the inhibitory effects of *STMN1* short hairpin RNA (shRNA) on the proliferation, invasion, and migration of extravillous trophoblast cells [11]. Likewise, miR-101-3p [12], miR-512-3p [13], miR-2115-3p [14] have been studied for their potential role in PE. However, none of the studies explored the downstream signalling pathways regulated by the miRNAs. We previously found that miR-510-3p was significantly upregulated in the blood samples of PE patients when compared to normal pregnant women [15]. Since miR-510-3p was upregulated, it can be postulated that miR-510-3p is involved in the regulation of PE. Thus, tracking the target genes and the signalling pathways regulated by them could help in deciphering the molecular mechanisms and signalling pathways regulated by miR-510-3p in PE pathogenesis.

The rapid development of bioinformatics techniques enables us to gain a deeper understanding of disease pathobiology at the genetic level. In light of this, the goal of this study is to combine and analyse gene data from the public database related to the pathogenesis of PE, which offers new insights into the biological mechanisms of PE. In this study, we have employed bioinformatic tools and databases to identify the miR-510-3p target genes and their involvement in PE. Moreover, we have analyzed the gene enrichment and Kyoto Encyclopedia for Genes and Genomes (KEGG) pathway analysis for the screened genes. A total of 23 genes targeted by miR-510-3p were linked to positive regulation of angiogenesis in PE. Hence, we postulate that further analysis using *in vitro* and *in vivo* analysis might help in validating the role of miR-510-3p in PE. Thus, this study provided evidence that miR-510-3p regulated important molecular mechanisms, signalling pathways and gene regulations in PE.

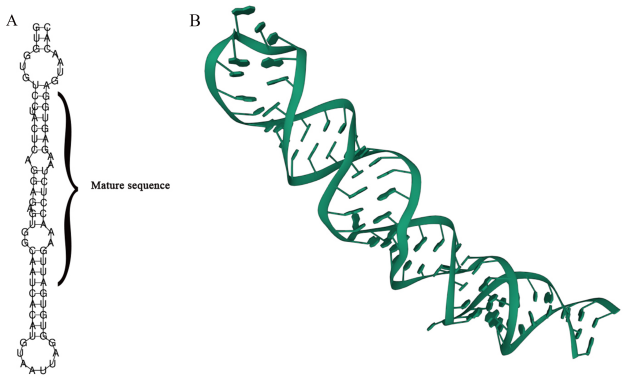


Fig. 1. Structure predictions from RNAfold and RNAcomposer. (A) The secondary structure of miR-510-3p retrieved from the RNAfold database and the mature sequence is marked in the 3p strand of the secondary structure. (B) The three-dimensional structure of miR-510-3p retrieved from RNAcomposer database.

Materials and Methods

MicroRNA-510-3p Sequence Retrieval and Analysis

The stem-loop and mature sequence of miR-510-3p were retrieved from the miRbase database (https://www.mirbase.org/) using the search query “hsa-miR-510-3p”. The retrieved sequence was used to develop the secondary structure and three-dimensional (3D) structure of miR-510-3p. The secondary structure was obtained using RNAfold (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi). The following criteria were selected: (1) RNA structure must have an appropriate stem-loop hairpin structure. (2) Mature miRNA must be in one side of the hairpin structure. (3) MiRNA should have less than

Table 1. MiR-510-3p sequences retrieved from miRbase.

S. No.	Structure	Sequence
1	Stem-loop	GUGGUGUCCUACUCAGGAGAGUGGCAAUCACA UGUAAUUAGGUGUGAUUGAAACCUCUAAG AGUGGAGUAACAC
2	Mature miRNA	AUUGAAACCUCUAAGAGUGGA

Table 2. The pre-miRNA length, minimum free energy, mature sequence, match extent, and A+U % content of miR-510-3p.

Source miRNA	Source organism	Pre-miRNA length	Minimum free energy	Mature sequence	Match extent	Strand	A+U %
miR-510-3p	*Homo sapiens*	74	–29.10 Kcal	AUUGAAACCUCUA AGAGUGGA	21/21	3p	55.4

7 mismatches with the opposite miRNA in the other arm. (4) Secondary structure must have a higher negative energy and A+U content (40–70%) [16]. The 3D structure of miR-510-3p was developed from the dot and comma format retrieved from RNAfold, and RNAcomposer (https://rnacomposer.cs.put.poznan.pl/) database created the 3D structure [17].

Target Analysis of MiR-510-3p

In order to identify the genes that are targeted by miR-510-3p, all the targets for miR-510-3p were downloaded from three publicly available databases which include target scan (https://www.targetscan.org/vert_80/) [16], miRDB (https://mirdb.org/), and miRTarbase (https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/) [17–19]. The keyword "hsa-miR-510-3p" was used as search query. The targets from all the three databases were compared and duplicates were removed using Venn software (VIB-UGent Bioinformatics & Evolutionary Genomics, Ghent, Belgium) (http://bioinformatics.psb.ugent.be/webtools/Venn/) [16–19].

Preeclampsia Gene Retrieval

To retrieve the PE gene list, the National Centre for Biotechnology Information (NCBI) genes database (https://www.ncbi.nlm.nih.gov/gene/) was used. The search term "Preeclampsia" and "*Homo sapiens*" was entered which helped in screening the PE genes. The retrieved gene list was compared with the targets from all three databases using Venn software (VIB-UGent Bioinformatics & Evolutionary Genomics, Ghent, Belgium) (http://bioinformatics.psb.ugent.be/webtools/Venn/) to identify the miR-510-3p target genes that are involved in PE disease pathogenesis [16,17].

Protein-Protein Interaction Using STRING

The miR-510-3p target genes linked to PE were analysed for their protein-protein interaction using STRING database (https://string-db.org/). The query genes were pasted in the dialogue box and the STRING network for *Homo sapiens* was created. The protein network from the STRING database supported evaluation of the experimentally determined, co-expressed relationships, gene fusion, gene co-occurrence, and protein homology between the query genes [20].

Gene Ontology (GO) and Kyoto Encyclopaedia for Genes and Genomes (KEGG) Analysis

Both GO and KEGG analyses were used to identify the functional role of the target genes and the important signalling pathways regulated by the query genes in PE. The gene enrichment and KEGG pathway analysis were performed using the publicly available Shiny GO database (http://bioinformatics.sdstate.edu/go/) [21]. The 247 query genes were uploaded in the search box and the analysis was performed specifically for *Homo sapiens.* Then each gene based on the GO and KEGG databases were annotated to clarify the biological functions of the target genes and associated signalling pathways. The genes identified in the GO analysis were those corresponding to the GO terms "biological process", "molecular function", and "cellular component", and the enrichment score were expressed as the –log (*p*-value) [22]. Metascape database (https://metascape.org/gp/index.html#/main/step1) was used to analyse the tissue and cell specificity and disease involvement of the screened genes [23]. Finally, enrichment scores were plotted as heat maps or lollipop plots and downloaded from Shiny GO and Metascape databases.

Screening of Genes Involved in Angiogenesis

Since angiogenesis was identified to be an important process in PE, the query genes involved in the positive regulation of angiogenesis were highlighted using NDEX. The gene network analysis was performed in the Cytoscape tool (https://cytoscape.org/) with the help of NDEX database (https://www.ndexbio.org/) [22,23]. The INDRAGO in NDEX was used to uncover which of the genes from the GO and KEGG analyses were implicated in the positive regulation of angiogenesis.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

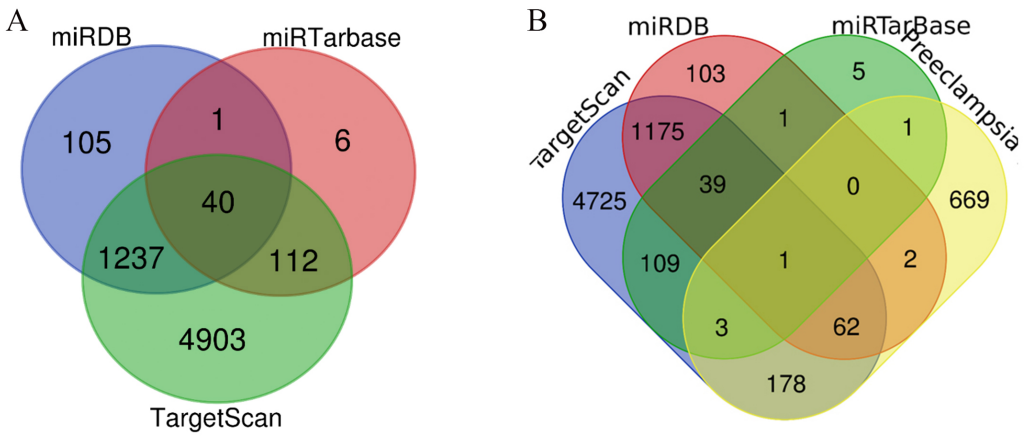


Fig. 2. Venn Diagram comparing the miR-510-3p targets and Preeclampsia genes. (A) Comparison of miRNA-510-3p targets between 3 databases. All predicted targets for miR-510-3p were retrieved. TargetScan provided 6292 targets, miRDB reported 1383 targets and miRTarBase 159 targets. A total of 6404 genes were identified as targets for miR-510-3p after removal of duplicates. (B) Represents the miR-510-3p targets retrieved from the three databases and PE genes retrieved from NCBI database. A total of 247 unique genes were identified which are all targets of miR-510-3p.

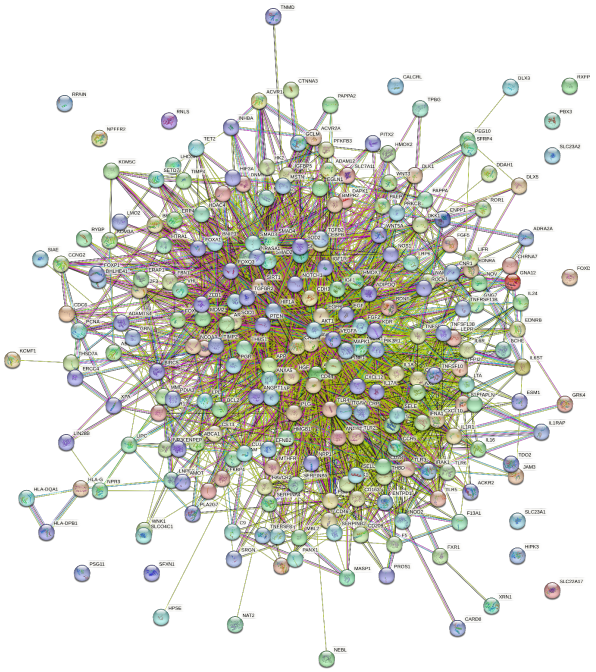


Fig. 3. Protein-protein interaction network of the query genes from STRING database. Relationships between the proteins in terms of experimentally validated (pink line), co-expressed genes (black line), protein homology (light blue line) and gene co-occurrence (dark blue lines) are displayed in the network.

Results

MicroRNA-510-3p Sequence Retrieval and Rtructure Analysis

The stem-loop sequence and the mature sequence retrieved from the miRBase can be found in Table 1. This stem-loop sequence was used to generate the secondary structure of miR-510-3p. Fig. 1A represents the secondary structure of miR-510-3p. The minimum free energy was found to be –29.10 Kcal and the A+U % content was calculated to be 55.4%. Table 2 displays the pre-miRNA length, minimum free energy, mature sequence, match extent, and A+U % content of miR-510-3p. The 3D structure determined from RNAcomposer is presented in Fig. 1B.

MicroRNA-510-3p and Preeclampsia Genes Analysis

The miR-510-3p targets retrieved from all the three databases were compared and duplicates were removed to create a dataset. TargetScan provided 6292 targets, miRDB gave 1383 targets and miRTarBase yielded 159 targets. After removal of duplicates, a total of 6404 genes were identified as targets for miR-510-3p which are listed in the **Supplementary Table 1**. Separately, 916 PE-associated genes were obtained from the NCBI gene database. Comparison of the two datasets revealed 247 targets of miR-510-3p linked to PE. Fig. 2A,B represent the Venn analysis for miR-510-3p targets and PE genes.

Protein-Protein Interaction

The protein-protein interaction analysis using STRING database is presented in Fig. 3. Relationships between the proteins in terms of experimentally validated (pink line), co-expressed genes (black line), protein homology (light blue line) and gene co-occurrence (dark blue lines) were displayed in the network. The proteins and their functional roles are given in the **Supplementary Table 2**.

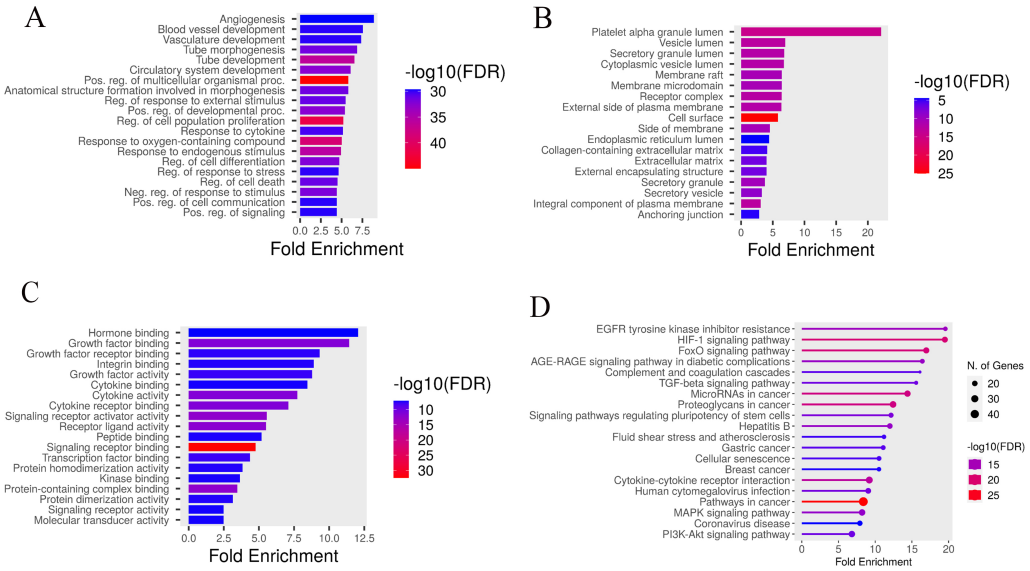


Fig. 4. Plots of the top biological, molecular, cellular functions and KEGG pathways. (A) Top GO biological process identified for the query genes. The graph is plotted with fold enrichment expressed as –log (*p*-value). Angiogenesis was identified as the topmost biological process involved in PE. (B) Bar chart of the top GO cellular components of query genes. Platelet alpha granule lumen, which is involved in inflammation, was the topmost cellular component of the query genes. (C) Bar chart of the GO molecular functions of the query genes. Hormone binding and growth factor binding are both important processes in PE. (D) Top KEGG pathways analyzed from Shiny GO using the query genes. The query genes are found to regulate PE mainly through *EGFR* tyrosine kinase receptor pathway. miR-510-3p target genes are found to be playing important biological, cellular and molecular functions in PE.

Gene Ontology

The biological process analysis for the 247 query genes revealed associations with angiogenesis, blood vessel development, vasculature development, tube morphogenesis, circulatory system development, anatomical structure formation involved in morphogenesis, regulation of cell proliferation and the response to cytokines, all of which are important processes in PE disease progression. The bar diagram of the biological process (Fig. 4A) is plotted according to the fold enrichment. The tree plot and network analysis of the biological process, cellular component and molecular function is presented in **Supplementary Figs. 1,2,3**. The results plotted in different models can be downloaded from Shiny GO. The line length in the network analysis represents the distance between the two nodes i.e., between the processes.

The cellular component and the molecular functions of the 247 genes are plotted as bar charts in Fig. 4B,C. The top GO molecular functions involved the growth factors binding and cytokine binding which are involved in PE disease pathogenesis. The cellular components like the vesicle lumen, cell surface, and secretory vesicle were all important for PE.

KEGG Pathway Analysis

The signalling pathways regulated by these genes were identified and the lollipop plot of the KEGG pathways were presented according to the fold enrichment expressed as –log (*p*-value) as shown in Fig. 4D. The *EGFR* (epidermal growth factor receptor) tyrosine kinase receptor, *HIF* (hypoxia inducible factor)-1 signalling and *PI3K* (phosphoinositol 3 phosphate)/*AKT* (Protein Kinase B) pathway were uncovered as important pathways linked to PE. These pathways with the query genes marked as red are given in the **Supplementary Figs. 4,5,6**.

Metascape Analysis

The disease involvement of the query genes were performed using Metascape (Fig. 5A). Query genes were linked to vascular diseases, endothelial dysfunction, inflammation, and PE. The genes were found to be highly specific to placenta, which was ranked highest in the heat map (Fig. 5B).

Screening of Genes Involved in Angiogenesis

Since angiogenesis was the top biological process involved in PE disease progression, the genes involved in positive regulation were marked in the network analysis by Cytoscape (Version 3.9.1, National Institute of General Medical Sciences, Bethesda, MD, USA) and NDEX INDRAGO (Version 3.9.1, National Institute of General Medical Sciences, Bethesda, MD, USA). The genes screened for positive regulation of angiogenesis included *ADAM12, ANGPT2, CHRNA7, DDAH1, ERAP1, FGF2, GRN, HGF, HIF1A, HK2, HMGB1, HMOX1, IL1A, KDR,*

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

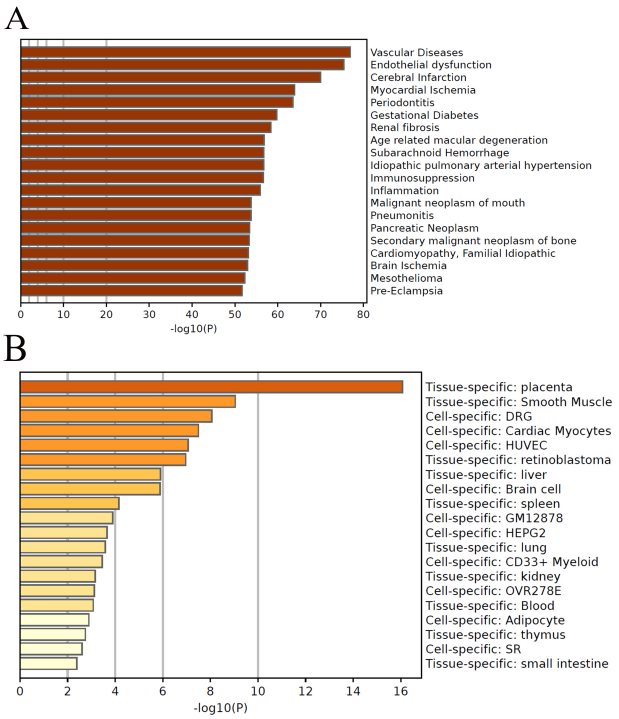


Fig. 5. Plots of disease and tissue specificity of the query genes retrieved from the Metascape database. (A) Disease associations of the query genes plotted in a heat map as –log (*p*-value). Vascular diseases and endothelial dysfunction are both important factors in PE disease progression, which are found to be highly regulated by the miR-510-3p targets. (B) Tissue and cell specificity of the query genes plotted as a heat map. Placenta is found to be the tissue specific for most of the query genes, which aligns with roles for miR-510-3p target genes in PE.

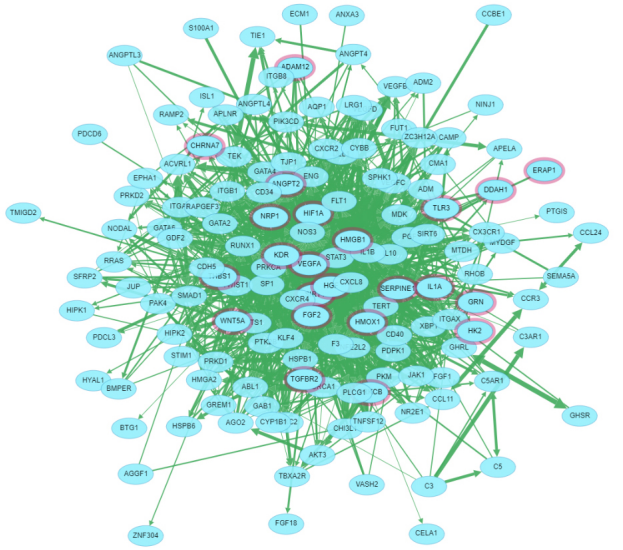


Fig. 6. Network analysis of the genes involved in the positive regulation of angiogenesis. The highlighted genes (pink colour) that are involved in the positive regulation of angiogenesis are marked. miR-510-3p targets 23 important genes involved in the positive regulation of angiogenesis.

NRP1, PRKCB, SERPINE1, SIRT1, TGFBR2, THBS1, TLR3, VEGFA, and *WNT5A*. Fig. 6 represents the unique genes involved in the positive regulation of angiogenesis, marked in pink.

Discussion

PE is a major risk factor for pregnant women but lack methods for early diagnosis and treatment. Moreover, the exact molecular mechanisms behind PE are still unknown, necessitating a better understanding of the pathogenesis of PE. However, miRNAs have been implicated PE and various other diseases [1–9]. We previously observed that miR-510-3p was significantly upregulated in PE patients [15]. Hence, we employed bioinformatic analysis to identify miR-510-3p target genes and explore their putative roles in PE. We first analysed the stability and binding affinity of miR-510-3p to confirm its active participation in disease pathogenesis. The minimum free energy (MFE) of miR-510-3p was determined given that miRNA secondary structure determines the binding affinity of the miRNA with the target mRNA [16,24,25]. The MFE determined for miR-510-3p was –29.10 Kcal, which is optimal for binding affinity of miR-510-3p to bind to its target genes. The adenine and uracil content of miR-510-3p was calculated to be approximately 55.4%, which leads to the conclusion that the miRNA is stable.

After confirming the secondary structure of miR-510-3p, the targets of the corresponding miRNA were screened from the publicly available databases TargetScan, miRDB and miRTarBase. After the removal of duplicates, a total of 6404 genes were screened as targets of miR-510-3p. To identify the genes involved in PE among the miR-510-3p targets, all the targets were compared to the list of PE genes retrieved from the NCBI genes database. A total of 247 target genes of miR-510-3p were associated with PE. The 247 genes were subjected to gene ontology studies based on the key terms “biological functions”, “molecular function”, and “cellular component”. Angiogenesis was uncovered as the topmost process regulated by the 247 query genes. This is consistent with the importance of placental angiogenesis in the establishment of feto-maternal circulation, efficient materno-fetal exchanges, the development of the placental villous tree and overall placental growth. Notably, PE is closely related to failure of these processes [26–29]. Since miR-510-3p targets these genes that positively regulate angiogenesis, miR-510-3p likely impairs placental growth. In addition, growth factors are needed for angiogenesis [30], and the molecular functions of the 247 query genes prioritized growth factor binding and cytokine activity. Thus, it could be postulated that miR-510-3p mediates the pathogenesis of PE.

Further analysis of the cellular involvement of the target genes revealed that important cellular components are regulated by these genes. Previous studies have confirmed that every type of cell must dynamically respond to the microenvironment and fulfil their function throughout placental development. Moreover, to control vessel remodelling and encourage angiogenesis, maternal cells, in particular immune cells, are recruited into uterine tissue [31–33]. From our bioinformatic analysis, miR-510-3p targets appear to play an important role in the cellular components of PE. KEGG pathway analysis revealed that these genes were involved in the *EGFR* tyrosine kinase receptor pathway, *HIF-1*α signalling and *PI3K*/*AKT* signalling. The KEGG analysis further confirmed the putative role of miR-510-3p in PE since the target genes were involved in crucial signalling pathways [33–36].

Furthermore, most of these genes were appeared to be specific to the placenta and were involved in vascular diseases and endothelial dysfunction. Also, the STRING network analysis revealed a range of protein-protein interactions between the genes. The functional enrichment of STRING database also predicted results similar to Shiny GO, which further confirmed the regulatory role of the query genes. Altogether, these findings suggest miR-510-3p contributes to the pathogenesis of PE.

Conclusions

The bioinformatic analyses presented in this study indicate miR-510-3p may be an important regulator of disease processes associated with PE. Since miR-510-3p targeted important genes that had significant roles in biological and molecular aspects of PE, it can be postulated that miR-510-3p might be a broad regulator of PE-related disease pathogenesis. Further confirmation using *in vitro* and *in vivo* analyses are required to prove this hypothesis. Thus, exploring the role of miR-510-3p might provide a better understanding of PE and also pave way for early diagnosis and novel therapeutic approaches.

Abbreviations

PE, preeclampsia; miRNA or miR, microRNA; GO, gene ontology; KEGG, Kyoto Encyclopaedia of Genes and Genomes; *EGFR*, epidermal growth factor receptor; *HIF*, hypoxia inducible factor; *PI3K*, phosphoinositol 3 phosphate; *AKT*, Protein Kinase B; VEGF, vascular endothelial growth factor; MFE, minimum free energy; *ADAM12*, ADAM metallopeptidase domain 12; *ANGPT2*, angiopoetin 2; *CHRNA7*, cholinergic receptor nicotinic alpha 7 subunit; *DDAH1*, Dimethylarginine Dimethylaminohydrolase 1; *ERAP1*, endothelial reticulum amino peptidase 1; *FGF2*, fibroblast growth factor 2; *GRN*, granulin; *HGF*, hepatocyte growth factor; *HIF1A*, hypoxia inducible factor 1 Alpha; *HK2*, hexokinase 2; *HMGB1*, high mobility growth box 1; *HMOX1*, hemo oxygenase 1; *IL1A*, interleukin 1 Alpha; *KDR*, kinase insert domain receptor; *NRP1*, neuropilin 1; *PRKCB*, protein kinase C beta; *SERPINE1*, Serpin Family E Member 1; *SIRT1*, Sirtulin 1; *TGFBR2*, transforming growth factor beta receptor 2; *THBS1*, Thrombospondin 1; *TLR3*, toll like receptor 3; *WNT5A*, wingless related integration site family 5 A; STMN1, Stathmin 1.

Availability of Data and Materials

All the data are made available in the manuscript and supplementary files.

Author Contributions

SCS—initiated the study, performed the analysis and wrote the first draft of the manuscript; KAP—was responsible for the interpretation of data analysis and literature review and revision of the manuscript; KR and DT—were responsible for critical review and revision of the manuscript; KR—helped in English language editing of the manuscript; DS—designed and supervised all the work and proofread the final manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have contributed sufficiently in the work and agreed to the accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

Dr. Durairaj Sekar is a recipient of extramural grant (5/4/8-18/CD/2021-NCD-II) from the Indian Council for Medical Research (ICMR) and their support is duly acknowledged.

Conflict of Interest

The authors declare no conflict of interest. Dr. Durairaj Sekar is serving as one of the Guest editors of this journal. We declare that Dr. Durairaj Sekar had no involvement in the peer review of this article and has no access to information regarding its peer review.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20233704.225.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

References

[1] Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet*. 2021;398(10297):341–354. doi: 10.1016/S0140-6736(20)32335-7

[2] Chappell LC, Sandall J, Barnard AM, McManus RJ. Predicting pre-eclampsia. *BMJ*. 2015;351:h6349. doi: 10.1136/bmj.h6349

[3] Bokslag A, van Weissenbruch M, Mol BW, de Groot CJ. Preeclampsia; short and long-term consequences for mother and neonate. *Early Hum Dev*. 2016;102:47–50. doi: 10.1016/j.earlhumdev.2016.09.007

[4] Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(14):1690–1702. doi: 10.1016/j.jacc.2020.08.014

[5] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circ Res*. 2019;124(7):1094–1112. doi: 10.1161/CIRCRESAHA.118.313276

[6] Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circ Res*. 2019;124(7):1094–1112. doi: 10.1161/CIRCRESAHA.118.313276

[7] Yang F, Ning Z, Ma L, *et al*. Exosomal miRNAs and miRNA dysregulation in cancer-associated fibroblasts. *Mol Cancer*. 2017;16(1):148. doi: 10.1186/s12943-017-0718-4

[8] Selvakumar SC, Sekar D, Preethi KA, Jayaraman S. Theragnostic implications of exosomes in preeclampsia. *Hypertens Res*. 2022;45(1):178–180. doi: 10.1038/s41440-021-00772-5

[9] Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009;136(2):215–233. doi: 10.1016/j.cell.2009.01.002

[10] Li Z, Wang J, Li D, Chen H, Meng T. miR-372-3p promotes preeclampsia progression by regulating twist1. *Exp Ther Med*. 2022;24(6):723. doi: 10.3892/etm.2022.11659

[11] Yang LP, Zheng JH, Zhang JK, Huang XH. Dysregulated miR-222-3p in plasma exosomes of preeclampsia patients and its *in vitro* effect on HTR8/SVneo extravillous trophoblast cells by targeting STMN1. *Hum Exp Toxicol*. 2022;41:9603271221138550. doi: 10.1177/09603271221138550

[12] Zhao X, Su F, Kong F, *et al*. miR-101-3p contributes to the progression of preeclampsia by suppressing WDR5-mediated proliferation and invasion of trophoblast. *J Obstet Gynaecol Res*. 2023;49(1):141–153. doi: 10.1111/jog.15475

[13] Halari CD, Nandi P, Sidhu J, Sbirnac M, Zheng M, Lala PK. Decorin-induced, preeclampsia-associated microRNA-512-3p restrains extravillous trophoblast functions by targeting USF2/PPP3R1 axis. *Front Cell Dev Biol*. 2022;10:1014672. doi: 10.3389/fcell.2022.1014672

[14] Deng Y, Lai W, Yu L, Zhang W, Ding Y. miR-2115-3p inhibits ferroptosis by downregulating the expression of glutamic-oxaloacetic transaminase in preeclampsia. *Placenta*. 2022;129:94–103. doi: 10.1016/j.placenta.2022.09.014

[15] Sekar D, Lakshmanan G, Mani P, Biruntha M. Methylation-dependent circulating microRNA 510 in preeclampsia patients. *Hypertens Res*. 2019;42(10):1647–1648. doi: 10.1038/s41440-019-0269-8

[16] Saravanan S, Islam VI, Thirugnanasambantham K, Sekar D. In Silico Identification of Human miR 3654 and its Targets Revealed its Involvement in Prostate Cancer Progression. *Microrna*. 2016;5(2):140–145. doi: 10.2174/2211536605666160610094230

[17] Rath SN, Das D, Konkimalla VB, Pradhan SK. *In Silico* Study of miRNA Based Gene Regulation, Involved in Solid Cancer, by the Assistance of Argonaute Protein. *Genomics Inform*. 2016;14(3):112–124. doi: 10.5808/GI.2016.14.3.112

[18] Chen Y, Wang X. miRDB: an online database for prediction of functional microRNA targets. *Nucleic Acids Res*. 2020;48(D1):D127–D131. doi: 10.1093/nar/gkz757

[19] Sun L, Lian JX, Meng S. MiR-125a-5p promotes osteoclastogenesis by targeting TNFRSF1B. *Cell Mol Biol Lett*. 2019;24:23. doi: 10.1186/s11658-019-0146-0

[20] Szklarczyk D, Gable AL, Nastou KC, *et al*. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Res*. 2021;49(D1):D605–D612. doi: 10.1093/nar/gkaa1074

[21] Azizi H, Hashemi Karoii D, Skutella T. Whole Exome Sequencing and In Silico Analysis of Human Sertoli in Patients with Non-Obstructive Azoospermia. *Int J Mol Sci*. 2022;23(20):12570. doi: 10.3390/ijms232012570

[22] Liu S, Chen H, Ma W, *et al*. Non-coding RNAs and related molecules associated with form-deprivation myopia in mice. *J Cell Mol Med*. 2022;26(1):186–194. doi: 10.1111/jcmm.17071

[23] Pillich RT, Chen J, Churas C, *et al*. NDEx: Accessing Network Models and Streamlining Network Biology Workflows. *Curr Protoc*. 2021;1(9):e258. doi: 10.1002/cpz1.258

[24] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004;116(2):281–297. doi: 10.1016/s0092-8674(04)00045-5

[25] Han D, Zhang J, Tang G. MicroRNAfold: pre-microRNA secondary structure prediction based on modified NCM model with thermodynamics-based scoring strategy. *Int J Data Min Bioinform*. 2012;6(3):272–291. doi: 10.1504/ijdmb.2012.049246

[26] Yu N, Wu JL, Xiao J, Fan L, Chen SH, Li W. HIF-1α regulates angiogenesis via Notch1/STAT3/ETBR pathway in trophoblastic cells. *Cell Cycle*. 2019;18(24):3502–3512. doi: 10.1080/15384101.2019.1689481

[27] Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Preeclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol*. 2019;15(5):275–289. doi: 10.1038/s41581-019-0119-6

[28] Tomimatsu T, Mimura K, Matsuzaki S, Endo M, Kumasawa K, Kimura T. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. *Int J Mol Sci*. 2019;20(17):4246. doi: 10.3390/ijms20174246

[29] Bardin N, Murthi P, Alfaidy N. Normal and pathological placental angiogenesis. *Biomed Res Int*. 2015;2015:354359. doi: 10.1155/2015/354359

[30] Witvrouwen I, Mannaerts D, Ratajczak J, *et al*. MicroRNAs targeting VEGF are related to vascular dysfunction in preeclampsia. *Biosci Rep*. 2021;41(8):BSR20210874. doi: 10.1042/BSR20210874

[31] Zhao H, Wong RJ, Stevenson DK. The Impact of Hypoxia in Early Pregnancy on Placental Cells. *Int J Mol Sci*. 2021;22(18):9675. doi: 10.3390/ijms22189675

[32] Knöfler M, Haider S, Saleh L, Pollheimer J, Gamage TKJB, James J. Human placenta and trophoblast development: key molecular mechanisms and model systems. *Cell Mol Life Sci*. 2019;76(18):3479–3496. doi: 10.1007/s00018-019-03104-6

[33] Yang F, Zheng Q, Jin L. Dynamic Function and Composition Changes of Immune Cells During Normal and Pathological Pregnancy at the Maternal-Fetal Interface. *Front Immunol*. 2019;10:2317. doi: 10.3389/fimmu.2019.02317

[34] Chen C, Gao J, Chen D, *et al*. miR-4443/MMP2 suppresses the migration and invasion of trophoblasts through the HB-EGF/EGFR pathway in preeclampsia. *Cell Cycle*. 2022;21(23):2517–2532. doi: 10.1080/15384101.2022.2103897

[35] Shen WT, Huang YJ, Zhang Q, *et al*. SCH58261, the antagonist of adenosine A2A receptor, alleviates cadmium-induced

preeclampsia via sirtiun-1/hypoxia-inducible factor-1α pathway in rats. *Eur Rev Med Pharmacol Sci*. 2020;24(21):10941–10953. doi: 10.26355/eurrev_202011_23577

[36] Xu Y, Sui L, Qiu B, Yin X, Liu J, Zhang X. ANXA4 promotes trophoblast invasion via the PI3K/Akt/eNOS pathway in preeclampsia. *Am J Physiol Cell Physiol*. 2019;316(4):C481–C491. doi: 10.1152/ajpcell.00404.2018