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A Computational Approach to Identify the Transcription Factor Based MicroRNA (miRNA) Regulation Involved in the Disease Pathology of Psoriasis

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Abstract

In the era of post genomics, identification of a potential miRNA to regulate gene and transcription factorsby applying a computational approach is a challenging task to execute. The challenge was addressed by identifying the associated transcription factors (TFs) and genes from Mogrify along with micro RNAs from miRTar Base. In the next step, a transcription factor based miRNA network was constructed on the basis of association between Genes-miRNAs-TFs. Finally, the network was analyzed on the basis of statistical studies and miRNA based compatibility to identify a potential miRNA to be utilized as a biomarker to treat psoriasis in future.

Keywords

Post Genomics; Mogrify; miRNA; miRTar Base; Biomarker.

Introduction

Psoriasis is a disorder mediated by immune system by making certain faulty signals in the human body. It's still a belief that psoriasis can be developed under the specified condition i.e. "when the immune system signals the body to accelerate the growth of skin cells. In case of psoriasis, the skin cells mature in 3-6 days. Instead of being in shed, the cells in skin get pile up to cause the visible lesions. It was also found that the genes that cause psoriasis can determine the reaction of a person's immune system. These genes can either cause psoriasis or other conditions which are immune-mediated like Type-I Diabetes or rheumatoid arthritis. Pathophysiology of psoriasis involves the understanding of the occurrence of prominent pathologies in the major components of skin i.e. the epidermis and the dermis. There are two well established hypotheses about the process that occurs in the development of the disease. The first hypothesis considers psoriasis as a disorder with excessive growth and reproduction of skin cells. Here, the problem is viewed as a fault of the epidermis and its keratinocytes. In second hypothesis, the disease is viewed as an immune-mediated disorder. Here, the excessive reproduction of skin cells is secondary to the factors produced by the immune system [1,2].

Micro RNA is a family of non-coding RNA (ncRNA) which was discovered in 1993, it consist of 19-25 nucleotides and regulates the expression of approximately 30% of protein-coding miRNAs in humans [3]. Base pairing at the position of 2-8 nucleotides were relative to the 5′ end of the small RNA to be termed as the "seed" region and it appears to be important for target recognition (Xiaetal 2013). Maturation of miRNAs involves multiple steps and initially two intermediate forms of miRNAs, namely primary (pri-) and precursor (pre-) miRNAs, were produced sequentially. In this process, Drosha (RNase III enzyme) and the double-stranded RNA (dsRNA) binding protein Dgcr8 cleaves the pri-miRNAs to produce a hairpin-shaped pre-miRNAs that are recognized by Exportin5 and they are subsequently transported from the nucleus to cytoplasm. There is another RNase III enzyme called Dicer which cleaves the pre-miRNAs to release ~22-nt double-stranded RNA duplexes (namely miRNA/miRNA* duplexes) with ~2-nt 3′ overhangs [4]. One strand of a RNA duplex is termed as a mature miRNA which is further loaded into an Argonaute protein in the RNA-induced silencing complex (RISC) to exert its regulatory function on the basis of its binding with the target transcripts [5].

A unique miRNA can regulate the expression of hundreds of proteins and the expression of a specific protein may be controlled by several miRNAs [6]. The sequence conservation of most miRNAs lies between the distantly related organisms to suggest the impact of a strong evolutionary pressure [7] and they have been shown to participate in many fundamental life processes like development, differentiation, organogenesis, growth control and apoptosis. Accordingly, deregulation of miRNA expression has been shown to contribute to cancer, heart diseases, infectious diseases, inflammatory diseases and other medical conditions, making them potential targets for medical diagnosis and therapy [8]. Initially, Lee had found lin-4 as a regulator of developmental timing in nematode *Caenorhabditis elegans* [9]. After several years, Reinhart had discovered lethal-7 (let-7) gene in *Caenorhabditis elegans* [10]. At present, 2500 miRNAs are in the human genome. Majority of miRNA are intragenic [11].

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Micro RNAs are initially transcribed as a part of an RNA stem-loop that in turn forms part of a several hundred nucleotides long miRNA precursor miRNA (pri-miRNA) [12].

Materials and Methods

Mogrify

Mogrify identifies the key transcription factors and associated genes involve in the Cell differentiation of keratinocytes. Mogrify was tested with 173 cell types and 134 tissues of human [13]. In Mogrify, the transcription factors from keratinocytes were isolated from http://www.mogrify.net/joint_reprogrammers?source_ont=FF%3A0000082&target_ont=FF%3A0000050

miRTarBase

miRTarBase is a platform to identify the experimentally validated miRNAs of associated genes [14]. miRTarBase is one of the largest repositories of gene-miRNA associations in humans and mouse. In miRtarbase, the miRNAs associated with genes and transcription factors were isolated from http://mirtarbase.mbc.nctu.edu.tw/php/index.php

Cytoscape

Cytoscape software is used for network construction, visualization and analysis in bioinformatics with an open source platform for visualizing the interactions in molecular networks and integrating them with the profiles of gene expression [15]. Additional features in cytoscape are available as plugins for network and molecular profiling.

Cytohubba

Cytohubba is a cytoscape plugin for performing the analyses of gene regulation & protein-protein interaction involved in the process of cellular pathways in the process of signal transduction [16]. Cytohubba ranks the nodes of network by topological methods like Radiality, Betweenness, Closeness, Bottleneck, EcCentricity and etc.

miRmap

miRmap software addresses the challenges in post transcriptional repression of miRNAs in human genome by evolutionary, probabilistic thermodynamic and sequence-based features [17].

Triplex RNA

Triplex RNA is a database of cooperating microRNAs with their mutual targets [18]. In this database miRNA target prediction is based on the analysis of predicted miRNA triplex with molecular dynamics simulations and differential modeling procedures in mathematics.

DAVID

The database for Annotation, Visualization and Integrated discovery (DAVID) contain complete information about functional annotation of genes. The current version of DAVID is 6.8 and it provides a set of comprehensive tools for functional annotation of genes [19].

Methodology

(Computational Approach of Transcription factor based miRNA regulation)

1. Identify the disease associated genes and Transcription Factors from Mogrify.
2. Obtain the associated list of experimentally validated miRNAs from miRTarBase.
3. Construct and analyze the network in Cytoscape.
4. Identify the miRNA based hub genes and transcription factors from cytohubba.
5. Identify the implication of miRNA in Regulatory network in miRmap& miRNA Triplex.
6. Identify and analyze the gene associated pathways in DAVID.

Results and Discussion

Construction of Transcription Factor based Regulatory Network (Cytoscape)

In case of transcription factor based miRNA regulation (bottom up approach), the regulatory network was constructed with 48 genes, 221 miRNAs and 4 TFs. Network was initiated by the mining of 225 regulators from Mogrify and miRtarbase(i.e. 4 TFs & 221 miRNAs) to interact with the 48 target genes in such a way to form 273 nodes and 491 edges.

Analysis of Transcription Factor based Regulatory Network (Cytohubba)

The genes and their regulators (Micro RNAs & Transcription Factors) were subjected to the analysis in cytohubbaby various global based statistical methods like Edge Percolated Component, Bottleneck, EcCentricity, Closeness, Radiality, Betweenness and Stress along with local based statistical methods like Maximal Clique Centrality, Density of Maximum Neighborhood Component, Maximum Neighborhood Component and degree to identify their connectivity. Among the various methods of analysis for transcription factor based miRNA regulation in bottom up approach only a local based statistics of Edge Percolated Component method in cytohubba resulted in obtaining a regulatory network of gene-miRNA-TFs. The detail of the specific hub of the constructed regulatory network is given in Figure 1.

Implication of miRNAs in the Regulatory Network of Transcription Factor based miRNA Regulation

The implication of miRNAs in the regulatory network of transcription factor based bottom-up approach was analyzed on the basis of compatibility with respect to gene-miRNA seed pairing and gene-miRNA-miRNA triplex with respect to nature of binding and the details were given in Table 1.

In case of miRNAs implication in transcription factor based miRNA regulation, hsa-miR-155-5p is highly compatible with SP1 on the basis of seed pairing.

Scope & Significance of Transcription Factor based miRNA Regulatory Network (Bottom-Up Approach)

Combinatorial Analysis of transcription factor based miRNA regulatory network indicate the fact that the hsa-miR-155-5p is involved in the repression of Transcription factors FOS, REL and MAFB and activation of gene SP1 and the probable miRNA based regulatory networks are (i) Gene: SP1, miRNA:hsa-miR-155-5p & TF: FOS; (ii) Gene: SP1, miRNA: hsa-miR-155-5p & TF:REL and (iii) Gene: SP1, miRNA: has-miR-155-5p & TF: MAFB [20].

Regulatory Analysis of Transcription Factor based miRNA Regulatory Network

The suppressor of cytokine signaling 1 along with the IFN-gamma-dependent factors promotes the positively regulation of IFN regulatory factor-1 and Sp1 [21]. Increased expression of miR-155-5p in dermal mesenchymal stem cells of psoriatic patients targets cytokines [22,23]. Fos protein is specifically expressed during the differentiation of human karatinocytes [24]. NF-κB p65 and c-Rel control epidermal development in skin [25]. MAFB is involved in the regulation of epidermal differentiation [26].

Pathway Analysis

The obtained associated genes from Mogrify were subjected to pathway analysis in DAVID on the basis of P value and Benjamini statistic (a parameter to be considered when two pathways show the same level of significance) and the result is given in Table 2.

In case of Pathway Analysis in transcription factor based regulation, the genes associated with Psoriasis follows the hierarchy of HTLV1 infection, Osteoclast differentiation, Hepatitis B and MAPK signaling pathway.

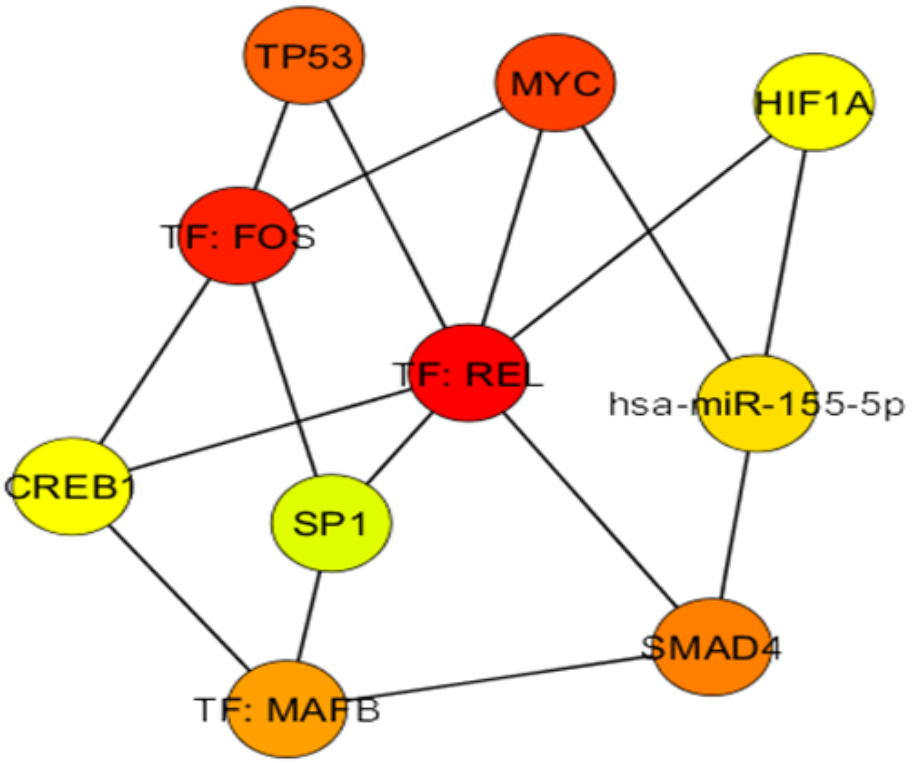

Figure 1: EPC method for top 10 hubs

S. No	Genes	Micro RNAs	Binding Score in % (miRmap)	Paired miRNA (Triplex RNA)	Binding Energy in Kcal/mol. (Triplex RNA)	Nature of Binding (Triplex RNA)
1	TP53	hsa-miR-155-5p	NIL	NIL	NIL	NIL
2	MYC	hsa-miR-155-5p	NIL	NIL	NIL	NIL
3	HIF1A	hsa-miR-155-5p	75.79	hsa-miR-653	-9.58	Canonical Triplex
4	CREB1	hsa-miR-155-5p	55.85	NIL	NIL	NIL
5	SP1	hsa-miR-155-5p	82.33	hsa-miR-296-3p	-35.96	Canonical Triplex
6	SMAD4	hsa-miR-155-5p	9.49	NIL	NIL	NIL

Table 1: Implication of MicroRNA in Regulatory Network of Transcription Factor based regulation

S. No.	Pathway	P value	Benjamini
1	HTLV-1 infection	6.0E-18	6.6E-16
2	Osteoclast differentiation	5.8E-11	1.10E-09
3	Hepatitis B	1.80E-10	6.40E-09
4	MAPK signaling pathway	4.10E-10	1.10E-08
5	Transcriptional misregulation in cancer	8.60E-10	1.90E-08
6	TNF signaling pathway	3.80E-09	6.80E-08
7	B cell receptor signaling pathway	7.20E-08	1.10E-06
8	Adipocytokine signaling pathway	2.10E-03	1.20E-02
9	Pathways in cancer	6.80E-07	9.30E-06
10	Colorectal cancer	9.00E-07	1.10E-05
11	T cell receptor signaling pathway	1.20E-06	1.30E-05
12	Viral carcinogenesis	1.20E-06	1.10E-05
13	Leishmaniasis	2.00E-06	1.80E-05
14	Neurotrophin signaling pathway	3.20E-06	2.70E-05
15	Small cell lung cancer	5.80E-06	4.50E-05
16	Epstein-Barr virus infection	6.80E-06	4.90E-05

Table 2: Annotation of Kegg Pathways

Conclusion

Computational analysis of Transcription factor based miRNA regulation gave us a different view point to focus the disease pathology of Psoriasis. In future the pathways associated with miRNA needs to be reconstructed to understand the complete role of has-miR-155-5p in the pathogenesis of Psoriasis. Reconstruction of pathways requires the construction of molecular interaction map with additional factors like metabolome data, list of non-coding RNAs and etc.

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