ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 3, 2015

ISSN - 0974-2441

Research Article

AN INTEGRATED NETWORK ANALYSIS OF PSORIASIS: A NOVEL APPROACH TO DISEASE PATHOLOGY

ALEX ANAND D[1]*, HARISHCHANDER A[2], JASON UB[2]

[1]Department of Biomedical Engineering, Sathyabama University, Chennai, Tamil Nadu, India. [2]Department of Bioinformatics, Sathyabama University, Chennai, Tamil Nadu, India. Email: danielalexanand@gmail.com

Received: 10 February 2015, Revised and Accepted: 23 March 2015

ABSTRACT

Objective: Psoriasis is a chronic autoimmune disorder. At present, about 2% of human population is affected by psoriasis in a global scale. There is no permanent cure for psoriasis in the post-genomic era and the disease mechanism too is poorly understood. We hereby investigate psoriasis through a systems biology approach to identify the underlying regulatory networks, which are pivotal to the disease pathology of psoriasis.

Methods: Initially, we surveyed microarray studies from array express, and then we extracted the list of implicated genes through array mining tools. We then verified the nomenclature of extracted genes and extracted gene ontology information from various publications and databases such as UCSC, HUGO, and DAVID. We then have identified the list of novel micro RNA (miRNAs), transcription factors and pathways, which are involved in the disease pathology of psoriasis from EnrichR.

Results: EnrichR predicted 193 miRNAs, 183 transcription factors, and 116 pathways. After applying various mining techniques and statistics, we identified a very few transcriptions factors and miRNAs, which are related to the disease pathways of psoriasis. Finally, we have used t-test to identify a specific miRNA and transcription factors, which are associated with the disease pathology of psoriasis on the basis of pathway analysis and it was identified that hsa-miR-324-5p and PAX3 have a higher degree of association on the basis of p-value.

Conclusion: Integrated network analysis of biological data is an exciting view point to view and understand the pathological conditions in a biological system, but until date this field has not developed enough to encompass etiology and therapy. In order to take an equilibrium shift from the level of disease understanding to pattern characterization and therapy, there is a requirement for conducting more experimental studies on human with the respective ailments. At present, we have applied the approach of network analysis to psoriasis and in future we will be applying this approach to understand the disease pathology of various disorders of autoimmune nature.

Keywords: Psoriasis, Micro RNA, Post-genomics, Bioinformatics and systems biology.

INTRODUCTION

Psoriasis is a common inflammatory disorder in skin and it has received a great attention to serve as a target for new biological therapies on the basis of pathogenesis. It was estimated that the prevalence of psoriasis was around 2% in accordance with the standard textbooks on the basis of few population-based studies. Perhaps the most comprehensive study was performed in the Faroe Islands, where 2.8% of the inhabitants were reported to be affected [1-4]. Ethnic factors were also appeared to influence the prevalence of psoriasis, which ranges from no cases in the Samoan population to 12% in Arctic Kasach'ye [2]. The influence of ethnic factors is particularly evident on the basis of comparing the prevalence rates within the United States. The prevalence among blacks (0.45-0.7%) is far lower than that in the remainder of the U.S. population (1.4-4.6%) [4]. Studies on numerous families have provided a compelling evidence of genetic predispositions to psoriasis but the inheritance pattern is still unclear [5]. The development of illness among half of the siblings of persons with psoriasis when both parents are affected but rate of falls to 16% when only one parent has psoriasis and the rate is 8% when neither parent is affected [6]. Over the past decade, several putative loci for genetic susceptibility to the disease were reported on the basis of genome-wide linkage studies [7,8]. However, recent studies revealed the fact that micro RNA (miRNAs) play a vital role in regulating a class of post-transcriptional genes in psoriasis [9,10].

miRNA belongs to the family of non-coding RNAs (ncRNA) of 19-25 nucleotides [11] and it was discovered in 1993 by Amoros. miRNAs regulate the expression of about 30% of protein-coding messenger RNA (mRNAs) in humans [11]. Initially, Lee and Ambros had found lin-4 as a regulator of developmental timing in *Caenorhabditis elegans* [12]. After several years, Reinhart *et al*. had discovered lethal-7 gene in *C. Elegans* [10,11]. Currently, there are about 2500 miRNAs in the human genome. The majority of miRNA are intragenic [12,13]. miRNAs are initially transcribed as part of an RNA stem-loop that in turn forms a part of a long precursor with several nucleotides (pri-miRNA)[13]. Mature miRNA is a part of an RNA-induced silencing complex which contains Dicer and many associated proteins [14]. Since miRNA is involved in the functioning of eukaryotic cells, dysregulation of miRNA been associated with disease and a miR2 disease database contain documents with known relationships between miRNA dysregulation and human disease [15]. miRNAs can bind to the targeted mRNA transcripts of protein-coding genes and negatively control their translation or cause mRNA degradation, and the key factor is to identify the vital target of miRNA with accuracy. A detailed review for the advances in the miRNA target identification methods are available from the resources published by Zheng *et al.* [16]. Several other methodologies were also proposed on the basis of tertiary structure of precursor miRNA by Gan and Gunsalus[17], systems biology by Manczinger and Kemény [18] and text mining by Harishchander and Anand [19-23].

METHODS

Prediction of genes and pathways

Boolean and advanced search options were used in PubMed [24] and gene annotation databases with the search term "psoriasis and

expression profiling." Finally, there were around 22 peer-reviewed articles were enrolled with the publicly available data in the KEGG database [25] and array mining tools were used for predicting the genes and their ontology.

Prediction of miRNAs and the transcription factors

EnrichR [26] tool was used for predicting the miRNAs from various databases containing both experimental and insilico based miRNAs. Transcription factors were predicted on the basis of t test analysis by EnrichR from the respective databases.

Biological interpretation of the predictions

We analyzed the significance of genes present in literature as well as the genes predicted by array mining tools with the help of pharmacogenomic database to identify the association between the drug and the gene to treat psoriasis.

RESULTS AND DISCUSSION

EnrichR tool was exclusively used for predicting the network of miRNAs, transcription factors and pathways. After performing the t-test analysis in EnrichR, it was found that 193 miRNAs, 183 transcription factors, and 116 pathways were obtained for the predicted genes, which are associated with psoriasis. In order to reduce the complexity certain normalization steps were carried out and the results of networks (Figs. 1 and 2) having strong correlation were tabulated (Tables 1 and 2).

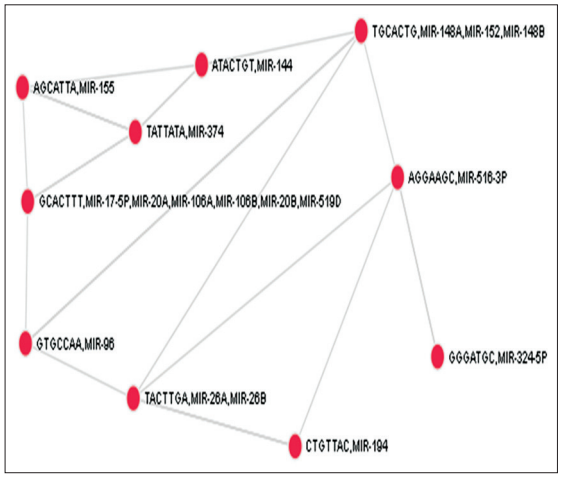

Fig. 1: Network view of micro RNAs predicted from the enrichment analysis of target scan

Table 1: miRNAs having a strong correlation with psoriasis associated genes

miRNA (target scan)	p value	Z score	Combined score
hsa-miR-324-5p	0.003130	−2.05	2.32
hsa-miR-155	0.004166	−1.76	1.99
hsa-miR-17-5p, hsa-miR-20a, hsa-miR-106a, hsa-miR-106b, hsa-miR-20b, hsa-miR-519d	0.01799	−1.75	1.97
hsa-miR-148a, hsa-miR-148b, hsa-miR-152	0.02015	−1.73	1.96
hsa-miR-96	0.008916	−1.71	1.93
hsa-miR-194	0.01094	−1.70	1.92
hsa-miR-144	0.008720	−1.69	1.91
hsa-miR-26a, hsa-miR-26b	0.01730	−1.64	1.85
hsa-miR-374	0.02345	−1.62	1.83
hsa-miR-516-3p	0.02131	−1.62	1.83

miRNA: Micro RNA

Based on the analysis of p value and Z score, it is evident that hsa-miR-324-5p and PAX3 have a strong correlation with the associated genes of psoriasis with a minimum p value and Z score.

CONCLUSION

In this work, we have taken an initial step towards constructing a pathway/molecular interaction map of psoriasis on the basis of miRNA and transcription factors. The leads we have obtained in this paper constitutes to a major part of constructing an miRNA based disease pathway for psoriasis but constructing a molecular interaction map for explaining the disease pathology of psoriasis requires more data and certain additional procedures are required to be followed. In future, we will take the next step towards the construction of a molecular interaction map of psoriasis. Since the integrated network analysis of biological data is relatively new and it is also different viewpoint to understand the pathological condition of a biological system, this field has not developed to therapeutic level till date. In order shift the equilibrium from the level of disease understanding to pattern characterization and therapy, there is a large requirement or conducting more experimental studies on humans and at present we have applied the approach of network analysis to psoriasis and in future we will be applying our approach to understand the disease pathology of various disorders of autoimmune nature.

ACKNOWLEDGMENT

The authors are thankful to the management of Sathyabama University for providing the computational facilities to carry out this work in their campus.

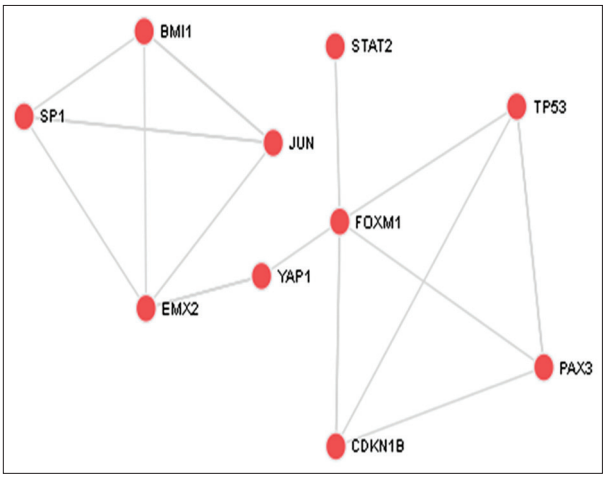

Fig. 2: Network view of transcription factors predicted on the basis of enrichment analysis

Table 2: Transcription factors having a strong correlation with psoriasis associated genes

Transcription factors	p value	Z score	Combined score
PAX3	0.003992	−1.45	1.46
YAP1	0.007567	−1.58	1.22
JUN	0.01238	−1.85	1.20
SP1	0.01998	−1.80	1.17
TP53	0.03669	−1.57	1.01
CDKN1B	0.01714	−1.47	0.95
BMI1	0.03739	−1.13	0.73
STAT2	0.03305	−1.12	0.72
STAT3	0.08136	−1.33	0.40
EP300	0.08522	−1.33	0.40

REFERENCES

1. Lomholt G. Prevalence of skin diseases in a population; a census study from the Faroe Islands. Dan Med Bull 1964;11:1-7.
2. Farber EM, Nall ML. Epidemiology: Natural history and genetics. In: Roenigk HH, Maibach HI, editors. Psoriasis. New York: Marcel Dekker; 1998. p. 107-58.
3. Kenney JA. Psoriasis in the American black. In: Farber EM, Cox AJ, editors. Psoriasis: Proceedings of the International Symposium, Stanford University. Stanford, California: Stanford University Press; 1971. p. 49-52.
4. Christophers E. Psoriasis – Epidemiology and clinical spectrum. Clin Exp Dermatol 2001;26(4):314-20.
5. Henseler T, Christophers E. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985;13(3):450-6.
6. Watson W, Cann HM, Farber EM, Nall ML. The genetics of psoriasis. Arch Dermatol 1972;105:197-207.
7. Altmüller J, Palmer LJ, Fischer G, Scherb H, Wjst M. Genomewide scans of complex human diseases: True linkage is hard to find. Am J Hum Genet 2001;69(5):936-50.
8. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med 2001;345:340-50.
9. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993;75(4):843-54.
10. Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, *et al*. The 21-nucleotide let-7 RNA regulates developmental timing in *Caenorhabditis elegans*. Nature 2000;403(6772):901-6.
11. Maragkakis M, Alexiou P, Papadopoulos GL, Reczko M, Dalamagas T, Giannopoulos G, *et al*. Accurate microRNA target prediction correlates with protein repression levels. BMC Bioinformatics 2009;10:295.
12. Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. Science 2001;294(5543):862-4.
13. Baek D, Villén J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. Nature 2008;455(7209):64-71.
14. Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. Proc Natl Acad Sci U S A 2007;104(23):9667-72.
15. Mraz M, Pospisilova S. MicroRNAs in chronic lymphocytic leukemia: From causality to associations and back. Expert Rev Hematol 2012;5(6):579-81.
16. Zheng H, Fu R, Wang JT, Liu Q, Chen H, Jiang SW. Advances in the techniques for the prediction of microRNA targets. Int J Mol Sci 2013;14(4):8179-87.
17. Gan HH, Gunsalus KC. Tertiary structure-based analysis of microRNA-target interactions. RNA 2013;19(4):539-51.
18. Manczinger M, Kemény L. Novel factors in the pathogenesis of psoriasis and potential drug candidates are found with systems biology approach. PLoS One 2013;8(11):e80751.
19. Harishchander A, Anand DA. An insilico methodology for predicting novel micro RNAs with therapeutic significance. Int J Sci Eng Technol 2014;6:720-1.
20. Harishchander A, Anand DA. Computational approach for identifying therapeutic micro RNAs. Int J Pharm Pharm Sci 2014;6:638-40.
21. Harishchander A, Anand DA. Binding site analysis of micro RNAs target interaction from genome wide association studies. Asian J Pharm Clin Res 2014;7:121-2.
22. Harishchander A, Anand DA. A computational approach for identifying novel micro RNAs from genome wide association studies of psoriasis. Int J Innov Res Sci Eng 2014;2:288-91.
23. Harishchander A, Anand A. Computational analysis of micro RNA based target interactions related to genome wide association studies of psoriasis. J Pure Appl Microbiol 2014;8:823-6.
24. Roberts RJ. PubMed central: The Gen bank of the published literature. Proc Natl Acad Sci U S A 2001;98(2):381-2.
25. Kanehisa M, Goto S. KEGG: Kyoto encyclopedia of genes and genomes. Nucleic Acids Res 2000;28(1):27-30.
26. Chen EY, Tan CM, Kou, Y, Duan, Q, Wang Z, Meirelles G, *et al.* Enrichr: Interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics 2013;14:128.