

Computational Analysis of Regulatory Network in Psoriasis by Top-Down Approach: An Initiation towards Identifying a Novel Biomarker to Diagnose and Treat Psoriasis in Future

Harishchander A*

Department of Bioinformatics, Sathyabama University, Chennai, Tamilnadu, India

*Corresponding author: Harishchander A, Department of Bioinformatics, Sathyabama University, Chennai, Tamilnadu, India, Tel: +919940066227; E-mail: harishchander.a@gmail.com

Received Date: Oct 14, 2017; Accepted Date: Oct 25, 2017; Published Date: Nov 02, 2017

Copyright: © 2017 Harishchander A. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

In the era of post genomics, computational analysis of gene regulation in Psoriasis by the Top-down approach of computational biology to understand the pathology of disease and identifying a novel biomarker is a challenging task to execute. The challenge was approached on the context of Top-down approach [Annotation of Psoriasis associated genes from PubMed, DisGeNET and OMIM with text mining of regulators (microRNAs and Transcription Factors)] to construct and analyze the network by the approach of systems biology for understanding the disease pathology and predicting a novel and potential regulators to enhance the discovery of identifying a novel biomarker for Psoriasis in future.

Keywords: Gene; Biomarker; Psoriasis; Epidermis; Keratinocytes; Antigen; Langerhans cells; Lymph nodes; Cytokines; Tumor necrosis factor; Antigen presenting cells

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. Normally, skin cells get matured from the surface of the skin on every 28-30 days. 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]. In Current research, the inflammatory mechanisms are immune based and maintained by T cells in dermis. Antigen-presenting cells in skin like Langerhans cells were believed to migrate from skin to the regional lymph nodes to interact with T cells. Presentation of an unidentified antigen to the T cells along with various co-stimulatory signals triggers an immune response to lead to the activation of T-cells and release of cytokines. Co-stimulatory signals were initiated by the interaction of adhesion molecules on the antigen-presenting cells like lymphocyte function-

associated antigen (LFA)-3 and the intercellular adhesion of molecules with their respective receptors (CD2 and LFA-1) on T cells. These T cells are released into the circulation. Reactivation of T cells in dermis and epidermis with local effects of cytokines like tumor necrosis factor (TNF) to lead to the cell mediated immune responses, inflammation and epidermal hyper proliferation in persons with psoriasis. The immune based model of psoriasis was supported on the basis of the observation that the immunosuppressant medications can clear plaques in psoriasis. However, the complete role of the immune system needs refinement in understanding. It was recently reported that an animal model of psoriasis can be triggered in mice without T cells. This concept is a paradox to researchers because the reduction in the count of T-cell causes psoriasis [3] but the count of CD4-T-cell decreases with the progression of HIV in psoriasis. As an additive, HIV is characterized by a strong profile of Th2 cytokine but psoriasis vulgaris is characterized with a strong secretion pattern of Th1. It was also hypothesized that the presence of diminished CD4-T-cell can cause an over-activation in CD8-T-cells to exacerbate the cause of psoriasis in patients with HIV positive [4].

Materials and Methods

PubMed

PubMed is an online search engine with open access facility to refer MEDLINE for identifying references and abstracts on topics in biomedical and life sciences. The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez system to retrieve information. Most of the records in PubMed contain links to the complete article, in PubMed Central (Roberts 2001). Information regarding the indexed journals in MEDLINE can be found in the Catalog of NLM.

DisGeNET

DisGeNET is a platform of pattern discovery, designed for addressing the queries regarding the genetic imprint of human diseases. DisGeNET is one of the largest repositories of gene-disease associations (GDAs) in humans (Piñero et al. 2015). It offers a set of tools in bioinformatics to facilitate the data analysis by different users. It is maintained by the Integrative Biomedical Informatics (IBI) Group of the (GRIB)-IMIM/UPF at the Barcelona Biomedical Research Park (PRBB), Barcelona in Catalonia.

OMIM

Online Mendelian Inheritance in Man (OMIM) is a comprehensive compendium of human genes and phenotypes that are available freely and updated daily. The complete text, referenced in the overviews of OMIM contains information on all known mendelian disorders for 15,000 genes. OMIM focuses on the relationship between genotype and phenotype. This database was initiated in 1960s by Dr. Victor A McKusick as a catalog of mendelian traits and disorders and it was entitled Mendelian Inheritance in Man (MIM). Then, twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985. It was made available on the internet in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

TargetScan

TargetScan [5] is a web server to predict the biological targets of miRNAs by searching for the presence of target sites that matches with the seed region of each miRNA. The target predictions of each miRNA are updated regularly.

miRTarBase

miRTarBase [6] is a curated database of miRNA based target interactions. At present, miRTarBase has accumulated more than fifty thousand interactions of miRNA with target (MTIs); the interactions were manually collected by surveying the literature after the processing of data mining of the text to filter research articles to functional studies of miRNAs in a systematic method. In general, the MTIs were also experimentally validated by a reporter assay, western blot, microarray and experiments on next-generation sequencing. The miRTarBase provides the most updated collection by comparing with the previously developed databases.

RegNetworks

RegNetwork [7] is a data base that contains five types (Transcription Factor-Transcription factor, Transcription Factor-Gene, Transcription Factor-microRNA, microRNA-Transcription Factor) of transcriptional and post-transcriptional regulatory relationships for human and mouse. RegNetwork integrates the curated regulations from various databases and the potential regulations were inferred on the basis of transcription factor binding sites (TFBSs). Transcription factor (TF) and microRNA (miRNA) in gene regulations. Recently, more regulatory relationships in databases and literatures are available and it's valuable for studying the system of gene regulation by integrating the prior knowledge of the transcriptional regulations between TF and

target genes along with the post-transcriptional regulations between miRNA and targets. The conservation of knowledge about the binding site of transcription factor (TFBS) can also be implemented to couple the potential regulation between regulators and their targets.

Cytoscape

Cytoscape software (Shannon et al. 2003) 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. Additional features in Cytoscape are available as plugins for network and molecular profiling. Plugins may be developed using the Cytoscape.

PANTHER

PANTHER (Protein Analysis through Evolutionary Relationships) is a classification system to classify proteins (expressed genes) to facilitate analysis in a high-throughput method [8]. In PANTHER, proteins were classified according to their family (evolutionarily related proteins); molecular function (interaction of proteins at a biochemical level); biological process (larger network of proteins that interact to accomplish a process at the level of the cellular level, e.g. mitosis; pathway (explicit specification of the relationships between the interacting molecules).

Method (Top-down approach)

Obtain the list of genes associated with psoriasis from PubMed, DisGeNET and OMIM.

Obtain the list of miRNA associated with psoriasis related genes from miRTarbase and TargetScan.

Obtain the list of transcription factors associated with psoriasis related genes from RegNetworks.

Construct and analyze the network in Cytoscape.

Results and Discussions

In case of gene identification, the genes associated with psoriasis were retrieved from PubMed, DisGeNET and OMIM. Psoriasis associated gene search in PubMed resulted in 660 genes. Similarly, DisGeNET and OMIM resulted in 388 and 261 genes. Data mining was performed in the gene set by removing duplicates and search for genes to have a seed pair for miRNA in miRTarBase (Experimental miRNAs) and Target Scan (Predicted miRNAs). Data mining resulted in 104 unique genes from the 3 sets of data of which only 58 genes contain a seed pairing site for miRNA. In case of miRNA search for associated genes, it was observed that there is a similarity between the miRNAs in Target Scan (Predicted miRNAs) with the miRNAs in miRTarBase (Experimental miRNAs). Since there is a similarity in the miRNA search of associated genes with the predicted and validated miRNAs, genes are paired with miRNAs in a way that gene-experimental miRNA > gene-predicted miRNA. In case of top down approaches in regulatory analysis of genes are associated with psoriasis; the genes are paired with the associated miRNAs and Transcription Factors and the results were given in Table 1.

Genes (PubMed, DisGeNET and OMIM)	miRNAs (miRtarbase/Target Scan)	Transcription Factor (RegNetworks)
HPSE	hsa-miR-1258	ETS1; ETS2; ETV4; MAX; MXI1::CLEC5A; AR; ESR1 HOXA7
CCL20	hsa-miR-21-5p; hsa-miR-144; hsa-miR-145; hsa-miR-21; hsa-miR-330-3p; hsa-miR-338-5p; hsa-miR-361-3p hsa-miR-380; hsa-miR-496; hsa-miR-518e; hsa-miR-525-5p; hsa-miR-548d-3p; hsa-miR-590-3p; hsa-miR-590-5p hsa-miR-635; hsa-miR-766; hsa-miR-802; hsa-miR-921	CTCF;MYC; PPARG::RXRA RELA; SP1
CCL2	hsa-miR-124-3p; hsa-miR-124; hsa-miR-124a; hsa-miR-141; hsa-miR-142-5p; hsa-miR-323-3p; hsa-miR-374a; hsa-miR-374b; hsa-miR-421; hsa-miR-495; hsa-miR-545; hsa-miR-577; hsa-miR-633	JUN; NFIC; NFKB1; NFKB2; NR2F2; REL; RELA; SMAD3 SMAD4; SP1; SRF; STAT1; STAT2; STAT3; STAT4; STAT6
EIF4E	hsa-miR-1; hsa-miR-122; hsa-miR-141; hsa-miR-145-3p; hsa-miR-146b-5p; hsa-miR-150; hsa-miR-16; hsa-miR-186; hsa-miR-195; hsa-miR-203; hsa-miR-206; hsa-miR-325; hsa-miR-34c-3p; hsa-miR-377; hsa-miR-380; hsa-miR-495; hsa-miR-498; hsa-miR-503; hsa-miR-520d-5p; hsa-miR-524-5p; hsa-miR-545; hsa-miR-582-5p; hsa-miR-586; hsa-miR-592; hsa-miR-599; hsa-miR-613; hsa-miR-654-5p; hsa-miR-656; has-miR-9; has-miR-141-3p; has-miR-145-5p; has-miR-497-5p; has-miR-768-3p	BACH1; CUX1; EMX2; FOS; FOSB; FOSL1; FOXD1; FOXF2; JUN; JUNB; JUND; MAX; MXI1::CLEC5A; MYC NFIL3; NFYA; NR3C1; PML STAT1; STAT2; STAT3; STAT4; STAT6; USF1
PPARD	hsa-miR-138-5p; hsa-miR-29b; hsa-miR-29c; hsa-miR-93	ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BCL6; CREB1; CTCF; EGR1; EP300; GABPA; HDAC1; HDAC2; HDAC3; HDAC7; JUP; LEF1; NCOR1; NCOR2; NR0B2; NRIP1; PROX1; RELA; RXRA; RXRB; RXRG; SMAD9; SPEN TCF7; TCF7L1; TCF7L2
TAP2	hsa-miR-330-3p; hsa-miR-370-3p; hsa-miR-384; hsa-miR-670-3p; hsa-miR-6893-3p; hsa-miR-185; hsa-miR-219-2-3p; hsa-miR-330-3p; hsa-miR-370; hsa-miR-371-5p; hsa-miR-384; hsa-miR-409-3p; hsa-miR-433; hsa-miR-522; hsa-miR-582-5p; hsa-miR-645; hsa-miR-655; hsa-miR-875-3p; hsa-miR-885-5p; hsa-miR-921	CREB1; CUX1; ESR1; MAX; MYC; NFE2L1; STAT5A
CYLD	hsa-miR-181b-5p; hsa-miR-182-5p; hsa-miR-362-5p; hsa-miR-500a-5p hsa-miR-130a; hsa-miR-130b; hsa-miR-15a; hsa-miR-15b; hsa-miR-16 hsa-miR-181b; hsa-miR-181d; hsa-miR-182; hsa-miR-186; hsa-miR-195 hsa-miR-197; hsa-miR-19a; hsa-miR-19b; hsa-miR-301; hsa-miR-301a; hsa-miR-301b; hsa-miR-340; hsa-miR-362-5p; hsa-miR-424; hsa-miR-454 hsa-miR-497; hsa-miR-508-3p; hsa-miR-543; hsa-miR-544; hsa-miR-548a-5p; hsa-miR-548b-5p; hsa-miR-548c-5p; hsa-miR-548d-5p; hsa-miR-579; hsa-miR-590-3p; hsa-miR-656; hsa-miR-944	ATF2; EGR1; IKKKG; JUN; LHX3; NFKB1; NFYA; POU2F1; SP1; TCF3
IGF1	hsa-miR-27a-3p; hsa-miR-29a-3p; hsa-miR-190a-5p; hsa-miR-199a-3p; hsa-let-7i-5p; hsa-miR-299-3p; hsa-miR-190b; hsa-let-7e-5p; hsa-miR-483-3p; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-1; hsa-miR-105; hsa-miR-128; hsa-miR-129-5p; hsa-miR-1297; hsa-miR-130a; hsa-miR-130b; hsa-miR-149; hsa-miR-152; hsa-miR-154; hsa-miR-186; hsa-miR-18a; hsa-miR-18b; hsa-miR-190; hsa-miR-192; hsa-miR-19a; hsa-miR-19b; hsa-miR-206; hsa-miR-215; hsa-miR-221; hsa-miR-222; hsa-miR-23a; hsa-miR-23b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-301a; hsa-miR-301b; hsa-miR-340; hsa-miR-361-5p; hsa-miR-362-5p; hsa-miR-377; hsa-miR-410; hsa-miR-425; hsa-miR-450b-5p; hsa-miR-454;	CEBPA; CTCF; ESR1; FOXD1; FOXF2; JUN; MYB; POU3F2; RFX1; STAT1; STAT2; STAT3; STAT5A; STAT5B; TGIF1

	hsa-miR-486-5p; hsa-miR-488; hsa-miR-489; hsa-miR-495; hsa-miR-502-5p; hsa-miR-503; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-556-3p; hsa-miR-561; hsa-miR-576-5p; hsa-miR-590-3p; hsa-miR-592; hsa-miR-599; hsa-miR-607; hsa-miR-613; hsa-miR-626; hsa-miR-632; hsa-miR-634; hsa-miR-656; hsa-miR-758; hsa-miR-942; hsa-miR-98	
BCL2	hsa-miR-34b-5p; hsa-miR-21-5p; hsa-miR-153-3p; hsa-miR-204-5p; hsa-let-7a-5p; hsa-miR-15a-5p; hsa-miR-15b-5p; hsa-miR-16-5p; hsa-miR-34a-5p; hsa-miR-20a-5p; hsa-miR-17-5p; hsa-miR-29a-3p; hsa-miR-29b-3p; hsa-miR-29c-3p; hsa-miR-34b-3p; hsa-miR-181a-5p; hsa-miR-181b-5p; hsa-miR-181c-5p; hsa-miR-181d-5p; hsa-miR-33b-5p; hsa-miR-34c-5p; hsa-miR-192-5p; hsa-miR-195-5p; hsa-miR-630; hsa-miR-451a; hsa-miR-125b-5p; hsa-miR-365a-3p; hsa-miR-449a; hsa-miR-200b-3p; hsa-miR-200c-3p; hsa-miR-429; hsa-miR-7-5p; hsa-miR-136-5p; hsa-miR-24-2-5p; hsa-miR-148a-3p; hsa-miR-24-2-5p; hsa-miR-182-5p; hsa-miR-143-3p; hsa-miR-205-5p; hsa-miR-126-3p; hsa-miR-18a-5p; hsa-miR-497-5p; hsa-miR-1915-3p; hsa-miR-206; hsa-miR-448; hsa-miR-708-5p; hsa-miR-184; hsa-miR-30b-5p; hsa-miR-135a-5p; hsa-miR-224-5p; hsa-miR-503-5p; hsa-miR-494-3p; hsa-miR-211-5p	
AREG	hsa-miR-34a-5p; hsa-miR-200a-3p; hsa-miR-129-5p; hsa-miR-135a; hsa-miR-135b; hsa-miR-345; hsa-miR-34a; hsa-miR-34c-5p; hsa-miR-449a; hsa-miR-449b; hsa-miR-499-5p; hsa-miR-517a; hsa-miR-517c; hsa-miR-548a-5p; hsa-miR-548c-5p; hsa-miR-556-5p; hsa-miR-559; hsa-miR-561; hsa-miR-577; hsa-miR-583; hsa-miR-584; hsa-miR-590-3p; hsa-miR-640 hsa-miR-944	AR; BRCA1; CREB1; E2F1; EGR1; HOXB13; IRF1; NFKB1 PAX2; RARA; REL; SMAD3 SMAD4; SP1; STAT5A; WT1
VNN3	hsa-miR-138-5p; hsa-miR-455-5p; hsa-miR-135a; hsa-miR-135b; hsa-miR-199a-3p; hsa-miR-345; hsa-miR-371-5p; hsa-miR-421; hsa-miR-455-3p; hsa-miR-455-5p; hsa-miR-505 hsa-miR-514; hsa-miR-744	CTCF; FOXA2; NFKB1;NFKB2 REL; REL; STAT5B
MMP9	hsa-miR-451a; hsa-miR-491-5p; hsa-miR-338-3p; hsa-miR-9-5p; hsa-miR-211-5p; hsa-let-7e-5p; hsa-miR-133b; hsa-miR-29b-3p; hsa-miR-191; hsa-miR-204; hsa-miR-339-5p; hsa-miR-451; hsa-miR-483-3p; hsa-miR-494 hsa-miR-515-5p; hsa-miR-520a-5p; hsa-miR-525-5p	AR; BACH1; BACH2; ERG; ETS1; ETS2; ETV4; FLI1; FOS; FOSB; FOSL1; JUN; JUNB; JUND; MYC; NFE2; NFE2L1; NFKB1; NFKB2; PPARA; PPARG; REL; RELB; SMAD3; SP1; SP1
HBEGF	hsa-miR-194-5p; hsa-miR-132-3p; hsa-let-7d; hsa-let-7g; hsa-let-7i; hsa-miR-132; hsa-miR-135a; hsa-miR-135b; hsa-miR-182; hsa-miR-183; hsa-miR-194; hsa-miR-212; hsa-miR-27a; hsa-miR-27b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-31; hsa-miR-376c; hsa-miR-379; hsa-miR-623; hsa-miR-662; hsa-miR-96	CTCF; ETS2; MAX; TBP; ZBTB16
TGFA	hsa-miR-152-3p; hsa-miR-376c-3p; hsa-miR-101; hsa-miR-130a; hsa-miR-130b; hsa-miR-137; hsa-miR-148a; hsa-miR-148b; hsa-miR-152; hsa-miR-205; hsa-miR-23a; hsa-miR-23b; hsa-miR-301	CTCF; EPAS1; ESR1; FOXA1; FOXA2; HIF1A; NFKB1; NFKB2; NKD2; PGR; TFAP2A; TP53
LHFP	hsa-miR-133a-3p.2; hsa-miR-133b; hsa-miR-101; hsa-miR-133a; hsa-miR-133b; hsa-miR-141; hsa-miR-147; hsa-miR-153; hsa-miR-200a; hsa-miR-200b; hsa-miR-200c; hsa-miR-218; hsa-miR-26a; hsa-miR-297; hsa-miR-300; hsa-miR-337-3p; hsa-miR-340; hsa-miR-381; hsa-miR-429; hsa-miR-448; hsa-miR-491-3p; hsa-miR-500; hsa-miR-501-5p; hsa-miR-607; hsa-miR-618; hsa-miR-632; hsa-miR-9	AHR; ARNT; CTCF; PATZ1
EGFR	hsa-miR-7-5p; hsa-miR-145-5p; hsa-miR-128-3p; hsa-miR-146a-5p; hsa-miR-21-5p; hsa-miR-128b; hsa-miR-133a-3p; hsa-miR-133b; hsa-miR-27a-3p; hsa-let-7a-5p; hsa-miR-574-3p; hsa-miR-219a-5p; hsa-miR-302b-3p; hsa-miR-125a-5p; hsa-miR-218-5p; hsa-	AR; CEBPB; CTNNB1; E2F1; EGR1; ELF3; ESR1; ESR1; ESR2; HOXC10; HTT; MEF2A; MYB; NFKB2; PPARG; REL; REL; SMURF2; SP1; STAT1; STAT3; STAT5A; STAT5B; TFAP2A; TP53; WT1; WWP1; XRCC6

	miR-21; hsa-miR-1; hsa-miR-128; hsa-miR-141; hsa-miR-146a; hsa-miR-16; hsa-miR-21; hsa-miR-27a; hsa-miR-27b; hsa-miR-548c-3p; hsa-miR-7	
SGCG	hsa-miR-137	Nil
SDC4	hsa-miR-18a-5p; hsa-miR-1; hsa-miR-124; hsa-miR-194; hsa-miR-224; hsa-miR-506; hsa-miR-548d-3p; hsa-miR-637; hsa-miR-941	EBF1; MAX; NFKB1; REL; RELA; SP1; STAT5A; STAT5B; mTFAP2A; TFAP2C; TGFB11
IGF1R	hsa-miR-122-5p; hsa-miR-133b; hsa-miR-145-5p; hsa-miR-7-5p; hsa-miR-138-5p; hsa-miR-194-5p; hsa-miR-99a-5p; hsa-miR-223-3p; hsa-miR-100-5p; hsa-miR-497-5p; hsa-miR-152-3p; hsa-miR-139-5p; hsa-miR-376a-3p; hsa-miR-376c-3p; hsa-miR-383-5p; hsa-miR-181b-5p; hsa-miR-335-5p; hsa-miR-320a; hsa-let-7e-5p; hsa-miR-125b-2-3p; hsa-let-7c-5p; hsa-miR-16-5p; hsa-miR-630; hsa-let-7b-5p; hsa-miR-143-3p; hsa-miR-133a-3p; hsa-miR-140-5p; hsa-miR-150-3p; hsa-miR-375; hsa-miR-503-5p; hsa-miR-378a-3p; hsa-miR-185-5p; hsa-miR-206; hsa-miR-21-5p; hsa-miR-26b-5p; hsa-miR-486-5p; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7d; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-100; hsa-miR-106a; hsa-miR-122; hsa-miR-133b; hsa-miR-138; hsa-miR-139-5p; hsa-miR-140-5p; hsa-miR-141; hsa-miR-143; hsa-miR-145; hsa-miR-153; hsa-miR-15a; hsa-miR-15b; hsa-miR-16; hsa-miR-182; hsa-miR-186; hsa-miR-194; hsa-miR-195; hsa-miR-200a; hsa-miR-202; hsa-miR-203; hsa-miR-214; hsa-miR-22; hsa-miR-223; hsa-miR-300; hsa-miR-302b; hsa-miR-302c; hsa-miR-302d; hsa-miR-30a; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e; hsa-miR-320; hsa-miR-328; hsa-miR-329; hsa-miR-330-3p; hsa-miR-340; hsa-miR-361-3p; hsa-miR-362-3p; hsa-miR-372; hsa-miR-373; hsa-miR-376c; hsa-miR-377; hsa-miR-378; hsa-miR-379; hsa-miR-381; hsa-miR-409-5p; hsa-miR-422a; hsa-miR-424; hsa-miR-448; hsa-miR-455-5p; hsa-miR-489; hsa-miR-493; hsa-miR-494; hsa-miR-495; hsa-miR-497; hsa-miR-503; hsa-miR-505; hsa-miR-507; hsa-miR-509-3-5p; hsa-miR-509-5p; hsa-miR-520a-3p; hsa-miR-520b; hsa-miR-520c-3p; hsa-miR-520d-3p; hsa-miR-520d-5p; hsa-miR-520e; hsa-miR-524-5p; hsa-miR-539; hsa-miR-548c-3p; hsa-miR-548d-3p; hsa-miR-557; hsa-miR-570; hsa-miR-577; hsa-miR-583; hsa-miR-625; hsa-miR-626; hsa-miR-646; hsa-miR-650; hsa-miR-653; hsa-miR-671-3p; hsa-miR-7; hsa-miR-769-5p; hsa-miR-892b; hsa-miR-944; hsa-miR-96; hsa-miR-98; hsa-miR-99a	BACH1; BACH2; BRCA1; CTNBN1; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; EGR1; ESR1; FOXO1; FOXO3; FOXO3B; FOXO4; MAX; MXI1::CLEC5A; MYB; MYC; MZF1; PAX5; REL RELA; SMURF2; SP1; SREBF1; SREBF2; STAT3; TFAP2A; TP53 USF1; WT1; WWP1
LEP	hsa-miR-9-5p; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-331-3p hsa-miR-369-5p; hsa-miR-520g hsa-miR-520h; hsa-miR-575; hsa-miR-875-5p; hsa-miR-9	ARNT; CEBPA; CEBPB CEBPD; FOXC1; HIF1A HLF; MIF; TBP
KLK13	hsa-miR-330-3p; hsa-miR-455-5p; hsa-miR-542-3p; hsa-miR-591; hsa-miR-620; hsa-miR-654-5p	CREB1; EGR1; KLF12; MZF1; PPARG
HMOX1	hsa-miR-196a-5p; hsa-miR-122-5p; hsa-miR-24-3p; hsa-miR-16; hsa-miR-196a-3p; hsa-miR-873	BACH2; CREB1; ERG; ETS1; FLI1; HIF1A; HNF4A; MAX; MXI1::CLEC5A; MYC; NFE2; NFIC; NFKB1; PPARG::RXRA; RXRA; SMAD7; SP1; SPI1; STAT3; TFAP2A; USF1; USF2
IFI6	hsa-miR-1225-3p; hsa-miR-558; hsa-miR-624; hsa-miR-920	TFAP2C; USF1
SFXN1	hsa-miR-30a-5p; hsa-miR-30b-5p; hsa-miR-30c-5p; hsa-miR-30d-5p; hsa-miR-30e-5p; hsa-miR-1; hsa-miR-128a hsa-miR-134; hsa-miR-30a; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e	HNF4A; MAX; MYC
IL23R	hsa-miR-383-5p.2; hsa-miR-216a; hsa-miR-297; hsa-miR-331-5p; hsa-miR-454; hsa-miR-509-3p; hsa-miR-583; hsa-miR-875-3p; hsa-miR-876-3p; hsa-miR-936	FOS; JUN; RORA; STAT3

PTPN22	hsa-miR-181a-5p; hsa-miR-133a; hsa-miR-133b; hsa-miR-325; hsa-miR-630	CDC5L; IRF1; MEF2A TP53
LOR	hsa-miR-196a-5p; hsa-miR-196b-5p; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7d; hsa-let-7e; hsa-let-7f; hsa-let-7g hsa-let-7i; hsa-miR-135a; hsa-miR-135b; hsa-miR-196a; hsa-miR-196b; hsa-miR-28-3p; hsa-miR-296-3p; hsa- miR-331-3p; hsa-miR-450b-5p; hsa-miR-490-5p; hsa- miR-570; hsa-miR-583; hsa-miR-641; hsa-miR-766; hsa- miR-873; hsa-miR-875-3p; hsa-miR-922; hsa-miR-98	ATF1; CREB1; FOS; FOSB; JUN; JUNB; JUND; SP3
S100A9	hsa-miR-196a-5p	AR; CTCF; MYB; RARA RARB; RARG; SPI1; TBP TFAP2A; TP53
S100A8	hsa-miR-24-3p; hsa-miR-135a; hsa-miR-135b; hsa-miR-202; hsa-miR-326 hsa-miR-330-5p; hsa-miR-544	AR; FOS; FOSB; JUN; JUNB; JUND; PDCD11; RARA; RARB; RARG TBP; TP53
IL10	hsa-miR-106a-5p; hsa-let-7c-5p; hsa-let-7a; hsa-let-7b; hsa- let-7c; hsa-let-7d hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-106a; hsa-miR-10b; hsa-miR-142-3p; hsa-miR-186; hsa-miR-198; hsa-miR-202; hsa-miR-337-5p; hsa-miR-543; hsa-miR-588; hsa-miR-597; hsa-miR-630; hsa-miR-671-5p; hsa- miR-769-5p; hsa-miR-888; hsa-miR-98	ATF1; CEBPA; CEBPB; CREB1; E2F1; ESR1; ETS1; MEF2A; NFKB1 POU3F2; PPARG; SP1; STAT3; TBP
IL24	hsa-miR-203a-3p; hsa-miR-205-5p; hsa-miR-132; hsa- miR-140-3p; hsa-miR-141; hsa-miR-183; hsa-miR-186; hsa- miR-200a; hsa-miR-200b; hsa-miR-200c; hsa-miR-203; hsa- miR-205 hsa-miR-27a; hsa-miR-27b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-300; hsa-miR-324-3p; hsa- miR-338-5p; hsa-miR-380; hsa-miR-381; hsa-miR-425; hsa- miR-429; hsa-miR-452; hsa-miR-495; hsa-miR-506; hsa- miR-518a-3p; hsa-miR-518b; hsa-miR-518c; hsa-miR-518f; hsa-miR-520a-5p; hsa-miR-525-5p; hsa-miR-573; hsa- miR-582-5p; hsa-miR-600; hsa-miR-601; hsa-miR-602; hsa- miR-616; hsa-miR-628-5p; hsa-miR-767-5p hsa-miR-891b; hsa-miR-943	CEBPB; JUN; TFAP2A TFAP2C
ADAM17	hsa-miR-26a-5p; hsa-miR-122-5p; hsa-miR-145-5p; hsa- miR-152-3p	CTCF; EGR1; FHL2; GABPA; HNF4A; NOTCH2; NOTCH3; NOTCH4;PPARG::RXRA; SP1; TFAP2A; TFAP2C; YY1
IL36RN	hsa-miR-216a-5p; hsa-miR-122; hsa-miR-338; hsa- miR-338-3p; hsa-miR-507; hsa-miR-197; hsa-miR-338-3p	MCM6; SKIL; SSBP2 SSBP4
IL1RN	hsa-miR-125a-5p; hsa-miR-125b-3p; hsa-miR-371-3p; hsa- miR-515-5p	BACH1; BACH2; EBF1; FOXA2; HNF4A; NFKB1; NR3C1; PAX5; RXRA; RXRB::RARB; SPI1; STAT5A
CTLA4	hsa-miR-155-5p; hsa-miR-101; hsa-miR-105; hsa-miR-155; hsa-miR-205 hsa-miR-380; hsa-miR-384; hsa-miR-429; hsa-miR-432; hsa-miR-449b; hsa-miR-451; hsa-miR-496; hsa- miR-516a-3p; hsa-miR-517a; hsa-miR-651 hsa-miR-656	BPTF; STAT5A; STAT5B
SGPP2	hsa-miR-101-3p.1; has-miR-24	EBF1; NFKB1; NFKB2; RELA; RELB; TCF3; ZEB1
IRF2	hsa-miR-20a-5p; hsa-miR-153; hsa-miR-18a; hsa-miR-18b; hsa-miR-214 hsa-miR-220c; hsa-miR-221; hsa-miR-222; hsa-miR-23a; hsa-miR-23b; hsa-miR-26a; hsa-miR-26b; hsa-miR-302a	EP300; HMGN1; IRF2BP1; IRF7; IRF8; KAT2B; MAX; MX1::CLEC5A; MYC; NFKB1; NFKB2; RELA; RELB; STAT1

	<p>hsa-miR-302b; hsa-miR-302c; hsa-miR-302d; hsa-miR-340; hsa-miR-342-5p; hsa-miR-372; hsa-miR-373; hsa-miR-455-5p; hsa-miR-495; hsa-miR-512-3p; hsa-miR-520a-3p; hsa-miR-520b; hsa-miR-520c-3p; hsa-miR-520d-3p; hsa-miR-520e; hsa-miR-520f; hsa-miR-549; hsa-miR-553</p> <p>hsa-miR-556-5p; hsa-miR-568; hsa-miR-571; hsa-miR-574-5p; hsa-miR-648; hsa-miR-934</p>	
IL4	<p>hsa-miR-340-5p; hsa-miR-410-3p; hsa-miR-29a</p>	<p>CEBPA; CEBPB; CEBPG; ETV4; GATA1; NFKB1; POU2F1; POU2F2; RELA; STAT1; STAT2; TFAP2A TP53</p>
IL12B	<p>hsa-miR-23a-3p; hsa-miR-23b-3p; hsa-miR-23c; hsa-miR-130a-5p; hsa-miR-183; hsa-miR-219-5p; hsa-miR-220c hsa-miR-494; hsa-miR-545; hsa-miR-632; hsa-miR-95</p>	<p>CEBPA; CEBPB; ETS1; ETS2; FOS; IRF5; JUN; NFKB1; REL; RELA; SP1 SP3; SPI1</p>
CDKAL1	<p>hsa-miR-370-5p; hsa-miR-873-5p.1; hsa-let-7b; hsa-let-7c; hsa-let-7d; hsa-let-7e; hsa-miR-145; hsa-miR-25; hsa-miR-301a; hsa-miR-301b; hsa-miR-451; hsa-miR-454; hsa-miR-495; hsa-miR-517b; hsa-miR-519a; hsa-miR-576-3p; hsa-miR-613; hsa-miR-616; hsa-miR-620; hsa-miR-650; hsa-miR-665; hsa-miR-766; hsa-miR-767-5p; hsa-miR-770-5p; hsa-miR-92a; hsa-miR-92b; hsa-miR-944</p>	<p>CUX1; POU3F2</p>
TNF	<p>hsa-miR-19a-3p; hsa-miR-203a-3p; hsa-miR-187-3p; hsa-miR-130a-3p; hsa-miR-143-3p; hsa-miR-130a; hsa-miR-130b; hsa-miR-149; hsa-miR-187</p> <p>hsa-miR-19a; hsa-miR-296-3p; hsa-miR-409-5p; hsa-miR-454; hsa-miR-516a-5p; hsa-miR-516b; hsa-miR-519b-3p; hsa-miR-542-3p; hsa-miR-581; hsa-miR-592; hsa-miR-599; hsa-miR-654-3p; hsa-miR-770-5p; hsa-miR-875-3p; hsa-miR-875-5p; hsa-miR-939; hsa-miR-17; hsa-miR-9; hsa-miR-31</p>	<p>AHR; ARNT; ATF1; ATF2; CEBPB; CEBPD; CREB1; EBF1; EGR1; EGR4; ELK1; ETS1; ETV4; FOS; IKKBK; IRF5 JUN; NFAT5; NFATC1; NFATC2; NFATC3; NFATC4; NFE2L1; NFKB1; NFKB2; POU2F1; RELA; SMAD6; SMAD7; SP1; SP3; SPI1; STAT1; STAT2; STAT3; STAT4; STAT5A; STAT5B; STAT6; TBP; TFAP2A; TP53</p>
TNXB	<p>hsa-miR-30a-5p; hsa-miR-30b-5p; hsa-miR-30c-5p; hsa-miR-30d-5p; hsa-miR-30e-5p; hsa-miR-137; hsa-miR-146b-3p; hsa-miR-149; hsa-miR-152; hsa-miR-30a; hsa-miR-30a-5p; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e; hsa-miR-372; hsa-miR-483-3p; hsa-miR-486-5p; hsa-miR-504; hsa-miR-512-3p; hsa-miR-638; hsa-miR-875-5p; hsa-miR-892b; hsa-miR-942</p>	<p>ARNT; CTCF; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; FOS; FOSB; FOSL1; HNF4A; JUN; JUNB; JUND; MAX; MEIS1; MYC; NFKB1; NR2F1; NR3C1; PAX2; PAX5; PPARG; RFX1; SREBF1; SREBF2; TFAP2A; TFAP2C; TGIF1; USF1; XBP1; YY1</p>
TRAF3IP2	<p>hsa-miR-3064-5p; hsa-miR-6504-5p; hsa-miR-147; hsa-miR-191; hsa-miR-30b; hsa-miR-30c; hsa-miR-342-5p; hsa-miR-512-3p; hsa-miR-548d-3p; hsa-miR-609; hsa-miR-637; hsa-miR-665; hsa-miR-765; hsa-miR-887; hsa-miR-935</p>	<p>CUX1; FOXD3; FOXF2; FOXO4; IKKBK; IKBKKG; MAX; MX1::CLEC5A; NKX2-2; NKX3-1; NR3C1; POU2F1; POU2F2; POU3F1; POU3F2; POU3F3; POU5F1; SRY; TCF3; USF1; ZEB1</p>
CCR6	<p>hsa-miR-518a-3p; hsa-miR-150-5p</p>	<p>CTCF</p>
IL6	<p>hsa-let-7a-5p; hsa-miR-203a-3p; hsa-miR-142-3p; hsa-miR-26a-5p; hsa-miR-365a-3p; hsa-miR-107; hsa-let-7c-5p; hsa-miR-149-5p; hsa-miR-223-3p</p>	<p>AR; ATF1; CEBPA; CEBPB; CEBPD; CREB1; CTCF; EGR1; FOS; IRF1; IRF5; JUN; MYC; NFE2; NFIC; NFKB1; NFKB2; PBX1; PPARG; RARA; REL; RELA; RREB1; STAT3; STAT5A; TP53 USF1; ZBTB16</p>
LYNX1	<p>hsa-miR-491-5p; hsa-miR-214; hsa-miR-324-3p; hsa-miR-324-5p; hsa-miR-330-5p; hsa-miR-370; hsa-miR-423-5p; hsa-miR-432; hsa-miR-511; hsa-miR-516a-5p; hsa-miR-526b; hsa-miR-608; hsa-miR-612; hsa-miR-637; hsa-miR-940; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-137; hsa-miR-144; hsa-miR-149; hsa-miR-153; hsa-miR-217; hsa-miR-338-5p; hsa-miR-365; hsa-miR-371-5p; hsa-miR-376a; hsa-miR-376b; hsa-miR-383; hsa-miR-548b-5p; hsa-miR-568; hsa-miR-574-3p; hsa-miR-587; hsa-miR-589; hsa-miR-655; hsa-miR-760; hsa-miR-98; hsa-miR-301b; hsa-miR-148a hsa-miR-152; hsa-miR-519c; hsa-miR-301a</p>	<p>CTCF</p>

TNFSF8	hsa-miR-24-3p; hsa-miR-146b-3p; hsa-miR-200b; hsa-miR-429; hsa-miR-525-3p; hsa-miR-626; hsa-miR-768-5p; hsa-miR-885-5p	NIL
TNFRSF1A	hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-22; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-558	DAXX; EP300; IKBKB; IKBKG; JUN; STAT1
VDR	hsa-miR-125b-5p; hsa-let-7a-5p; hsa-miR-27b-3p; hsa-miR-124; hsa-miR-125b; hsa-miR-506; hsa-miR-544	BACH2; CREBBP; CTCF FOS; FOSB; FOSL1; GTF2B; HMG3; HNF4A; HR; JUN; JUNB; JUND; KDM5A; LMO2; MAX; MED1; NCOA1; NCOA2; NCOA6; NR0B2; NR1H2; NRIP1; RXRA; RXRB; RXRG; SMAD3; SNW1; STAT1; TRIM24
NOD2	hsa-miR-122-5p; hsa-miR-122-3p; hsa-miR-495; hsa-miR-671-5p	MAX; MXI1::CLEC5A NFKB1; REL; SPI1; USF1
STAT3	hsa-miR-20b-5p; hsa-miR-337-3p; hsa-miR-21-5p; hsa-miR-92a-3p; hsa-miR-20a-5p; hsa-miR-124-3p; hsa-miR-130b-3p; hsa-miR-106a-5p; hsa-miR-106b-5p; hsa-miR-874-3p; hsa-miR-4516; hsa-miR-17-5p; hsa-miR-181a-5p; hsa-miR-1234-3p; hsa-miR-106a; hsa-miR-106b; hsa-miR-124; hsa-miR-125b; hsa-miR-130a; hsa-miR-17; hsa-miR-17-5p; hsa-miR-20a; hsa-miR-20b; hsa-miR-21; hsa-miR-372; hsa-miR-410; hsa-miR-495; hsa-miR-506; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-519d; hsa-miR-665 hsa-miR-93	AR; ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BHLHE40; BRCA1; CEBPB; CREB1 CREBBP; DAXX; EIF2AK2; EP300; FOXM1; GATA1; GATA2; GTF2I; HDAC1; HDAC2; HDAC3; HES1; HIF1A; HNF1A; IRF9; JUN; KAT5; KHDRBS1; MAX; MXI1::CLEC5A; MYC; MYOD1; NCOA1; NFKB1; NMI; NR3C1; PIAS1; PIAS2; PIAS3; PIAS4; PML; POU3F1; PTMA; RARA; RELA; STAT1; STAT4; STAT5A STAT5B; TFAP2A; TP53 USF1; ZNF148; ZNF467
SLC9A3R1	hsa-miR-24-3p; hsa-miR-146b-3p; hsa-miR-149; hsa-miR-200b; hsa-miR-200c; hsa-miR-24; hsa-miR-339-5p; hsa-miR-367; hsa-miR-532-5p; hsa-miR-548c-3p; hsa-miR-608; hsa-miR-632; hsa-miR-659; hsa-miR-663; hsa-miR-874	CTCF; CTNNB1; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; PPARG; SP1
SOCS3	hsa-miR-203a-3p; hsa-let-7f-5p; hsa-miR-19a-3p; hsa-miR-221-3p; hsa-miR-155-5p; hsa-miR-19a; hsa-miR-19b; hsa-miR-203; hsa-miR-218; hsa-miR-221; hsa-miR-30a; hsa-miR-30b hsa-miR-30e; hsa-miR-340; hsa-miR-561; hsa-miR-665; hsa-miR-765	AHR; ARNT; E2F1; ESR1 NFKB1; RELA; REST; STAT1; STAT2; STAT3 STAT4; STAT5A; STAT5B; STAT6; TCEB1; TCEB2; YY1
BSG	hsa-miR-22-3p	EGR1; EGR2; MAX; MXI1::CLEC5A; MYC; TFAP2A; TFAP2C; USF1
JUNB	hsa-miR-663a; hsa-miR-101; hsa-miR-199a-5p; hsa-miR-199b-3p; hsa-miR-30d; hsa-miR-30e; hsa-miR-328; hsa-miR-495; hsa-miR-526b; hsa-miR-566; hsa-miR-615-5p; hsa-miR-656; hsa-miR-663; hsa-miR-675; hsa-miR-744; hsa-miR-886-5p; hsa-miR-936	ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BATF; BCL6; BRCA1; CREB1; E2F1; ESR1; ETS2; FOS; FOSB; FOSL1; FOSL2; FOXO4; JDP2; MAX; MXI1::CLEC5A, MYC MZF1; NFE2L1; NFKB1 SMAD3; SMAD4; SRF TBP; TFAP2A; TFAP2C TFAP4; USF1

TGFB1	hsa-miR-24-3p; hsa-miR-29b-3p; hsa-miR-144-3p; hsa-miR-633; hsa-miR-663a; hsa-miR-211-5p; hsa-miR-17-5p; hsa-miR-19b-3p; hsa-miR-93-5p; hsa-miR-324-3p; hsa-miR-122-5p; hsa-miR-130a-3p; hsa-miR-21; hsa-miR-24	AR; CEBPA; CEBPB; CREB1; CTCF; DAXX; EGR1; EPAS1; FOS; GATA1; HIF1A; JUN; LMO2; MYC; MZF1; PAX5; PPARA; RARA; SMAD2; SMAD3; SMAD4; SP1; SP3; TP53; USF1; USF2; WT1; YY1
RNF114	hsa-miR-3064-5p; hsa-miR-6504-5p	EGR1; hsa-miR-124; hsa-miR-218; hsa-miR-492; hsa-miR-506; MAX; SP1; USF1
RPTOR	hsa-miR-99a; hsa-miR-100; hsa-miR-155-5p	CEBPA; DDIT3; RFX1; TLX2

Table 1: Associated genes, miRNAs and transcription factors of Psoriasis (Top-down approach).

Further the genes, miRNAs and proteins in top-down were subjected to network analysis and the further details about the statistical methods were given below.

Network analysis of top-down approach (Cytohubba)

Genes and their regulators in Top-down approach were subjected to the analysis by various statistical methods (Degree, Edge Percolated

Component, Maximum Neighborhood Component, Density of Maximum Neighborhood Component, and Maximal Clique Centrality with six centralities Bottleneck, EcCentricity, Closeness, Radiality, Between-ness and Stress) to identify the their connectivity. The results of Analysis were given in Table 2.

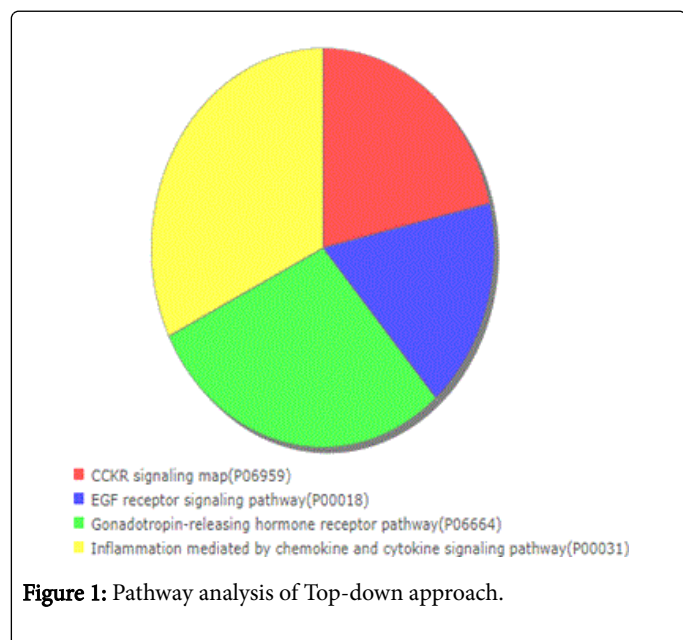
Rank	Methods for Analysis of Shortest Path of Regulators in Top-down Approach (Cytohubba)											
	MCC	DMNC	MNC	Degree	EPC	Bottle Neck	Eccentricity	Closeness	Radiality	Between-ness	Stress	Clustering coefficient
1	STAT3	hsa-miR-130a	STAT3	IGF1R	IGF1R	STAT3	NFKB1	STAT3	STAT3	IGF1R	IGF1R	hsa-miR-410 hsa-miR-20a
		RARA				IGF1R	EGR1					
		hsa-miR-21										
		hsa-miR-665										
		NFYA										
		POU2F1										
		SMAD3										
		hsa-miR-656										
		PML										
		hsa-miR-519a										
2	IGF1R	Nil	JUNB	BCL2	STAT3	Nil	Nil	IGF1R	IGF1R	STAT3	BCL2	Nil
3	JUNB	Nil	BCL2	STAT3	BCL2	JUNB	TGM1	BCL2	NFKB1	BCL2	IGF1	PML hsa-miR-519c-3p hsa-miR-17
							hsa-miR-130a					
							CCL20					
							SP1					
							IFIH1					
							hsa-miR-186					
							STAT2					

							CCL2					
4	BCL2	Nil	TNF	IGF1	IGF1	IL6	Nil	NFKB1	RELA	IGF1	TNF	Nil
5	IGF1	Nil	EIF4E	TNF	TNF	IRF2	Nil	RELA	MYC	TNF	IL6	Nil
6	TNF	Nil	STAT2	IL6	IL6	BCL2	Nil	IGF1	JUNB	JUNB	STAT3	hsa-miR-519c-3p
7	EIF4E	Nil	TNXB IL6	JUNB	JUNB	TNF	Nil	MYC	BCL2	IL6	IL24	STAT6 STAT4 FOSL1 hsa-miR-519a
8	IL6	Nil	NIL	EIF4E	EIF4E	TGFB1	Nil	JUNB	MAX	IRF2	IRF2	Nil
9	TNXB	Nil	IGF1 IGF1R	TNXB	NFKB1	IL23A	Nil	MAX	IGF1	EIF4E	TNXB	Nil
10	STAT2	Nil	NIL	IRF2	TNXB	SLC9A3R1	Nil	JUN	JUN	IL24	CYLD	Nil

Table 2: Network analysis (Top-down approach).

Pathway analysis (Annotation)

The obtained genes from PubMed/DisGeNET/OMIM were subjected to pathway analysis in PANTHER by the principle of the Bonferroni correction for multiple testing and the result is illustrated as Pie Chart (Figure 1).



In case of Pathway Analysis, the genes associated with Psoriasis follows the hierarchy of Inflammation mediated by Chemokine and Cytokine signaling pathway, Gonadotropin-releasing hormone receptor pathway, ECF receptor signaling pathway and CCKR signaling map. In case of Annotation analysis, it is evident that these regulators play a vital role in the pathways (Apoptosis Signaling pathway, CCKR Signaling, Gonadotropin releasing hormone receptor

pathway, Interleukin Signaling pathway, JAK/STAT signaling pathway, Oxidative Stress response and PDGF signaling pathway) associated with Psoriasis and it was also clear from studies of text mining in PubMed; has-miR-103 and has-miR-107 is associated with the 3' UTR region of CDK5R1, hsa-miR-125a-3p is associated with the clinical implication of inflammatory skin and hsa-miR-138 is responsible for inhibiting the expression of RUNX3 in Psoriasis but till date there is no experimental evidence in PubMed to illustrate the role of hsa-miR-24 in Psoriasis.

Conclusion

Overall network analysis of Top-down approach, 45 potential regulators of Psoriasis [35 Transcription Factors (STAT3, IGF1R, JUNB, BCL2, IGF1, TNF, EIF4E, IL6, TNXB, STAT2, RARA, NFYA, POU2F1, SMAD3, PML, IRF2, NFKB1, TGFB1, IL23A, SLC9A3R1, EGR1, TGM1, CCL20, SP1, IFIH1, CCL2, RELA, MYC, MAX, JUN, IL24, CYLD, STAT6, STAT4 and FOSL1) and 10 miRNAs (hsa-miR-130a, hsa-miR-21, hsa-miR-665, hsa-miR-656, hsa-miR-519a, hsa-miR-186, hsa-miR-186, hsa-miR-410, has-miR-20a, hsa-miR-519c-3p and hsa-miR-17)] were retrieved. In biological context, the potential regulators of psoriasis have a maximum probability to become a potential biomarker for Psoriasis and the identical pattern between the comparative-network analysis of bottom-up and direct approach illustrate the fact that there is a maximum probability for those potential regulators to be considered to treat psoriasis in future.

References

1. Yaqoob P (2003) Fatty acids as gatekeepers of immune cell regulation. Trends Immunol 24: 639-645.
2. Ortonne JP (1996) Aetiology and pathogenesis of psoriasis. Br J Dermatol 135(49): 1-5.
3. Pitzalis C, Cauli A, Pipitone N, Smith C, barker J, et al. (1996) Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. In Arthritis Rheum 39: 137-145.

-
4. Ortonne JP, Lebwohl M, Em Griffiths C (2003) Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis. *In Eur J Dermatol* 13(2): 117-123.
 5. Agarwal V, Bell GW, Nam J, Bartel DP (2015) Predicting effective microRNA target sites in mammalian mRNAs. *eLife* 4: e05005.
 6. Chou C, Chang N, Shrestha S, Hsu S, Lin Y, et al. (2016) miRTarBase 2016: updates to the experimentally validated miRNA-target interactions database. *Nucleic Acids Res* 44(D1): D239-D247.
 7. Liu Z, Wu C, Miao H, Wu H (2015) RegNetwork: an integrated database of transcriptional and posttranscriptional regulatory networks in human and mouse. *Database* 2015: bav095.
 8. Mi H, Huang X, Muruganujan A, Tang H, Mills C, et al. (2017) PANTHER version 11: expanded annotation data from Gene Ontology and Reactome pathways, and data analysis tool enhancements. *Nucleic Acids Res* 45(D1): D183-D189.