In Silico Analysis and Mathematical Modeling of MicroRNAs in Psoriasis: An Initiation to Identify a Novel Target

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ABSTRACT

In the era of post-genomics, computational analysis and mathematical modeling of genomics and transcriptomics to understand the specificity of non-coding microRNA (miRNA) based regulated networks in autoimmune diseases like psoriasis is an uphill task. We have herein approached the challenge on the basis of computational approach. Initially, obtain the list of genes associated with psoriasis from PubMed, DisGeNET and OMIM along with the analysis and implication of Protein-Protein interactions. Further identify the implication of miRNA in Regulatory network. Finally implicate a mathematical model to identify the functionality to gene regulation.

Keywords: Autoimmune Diseases, Computational Analysis, MicroRNA, Psoriasis.

INTRODUCTION

Psoriasis is a chronic autoimmune disorder in skin [1]. Psoriasis was initiated by the complex interactions between environmental and genetic factors [2]. In psoriasis there exist an abnormal hyper proliferation in keratinocytes due to the activation of T-cells to produce a rich amount of arachidonic acid to generate of various pro inflammatory mediators and adhesion molecules via MAPK/AP-1, EARK1/2 and protein kinase-C (PKCs) [3-6].

OBJECTIVES

Analyse the psoriasis associated gene list by Top-down approach in PUBMED, OMIM and DISGNET along with interaction and analysis of Proteins in STRING.

Identify the predicted and validated miRNAs for psoriasis associated genes from Target Scan, miRtarbase and Pharmaco-miR along with the interaction.

Construct the regulatory network of genes associated with psoriasis by Cytoscape. Identify the key miRNAs in the Regulatory Network by the plugins of Cytoscape.

METHODOLOGY

Obtain the list of genes associated with psoriasis from Pubmed, DisGeNET and OMIM along with the analysis and implication of Protein-Protein interactions.

Identify the implication of miRNA in Regulatory network.

Implicate a mathematical model to identify the functionality to gene regulation.

RESULTS AND DISCUSSION

Implication of miRNAs and Transcription Factors in Regulatory Network of Psoriasis

The implication of miRNAs in the transcriptional regulatory network of psoriasis was analyzed on the basis of compatibility with respect to pairing of gene and miRNA and the details were given in Figures **1-2**.

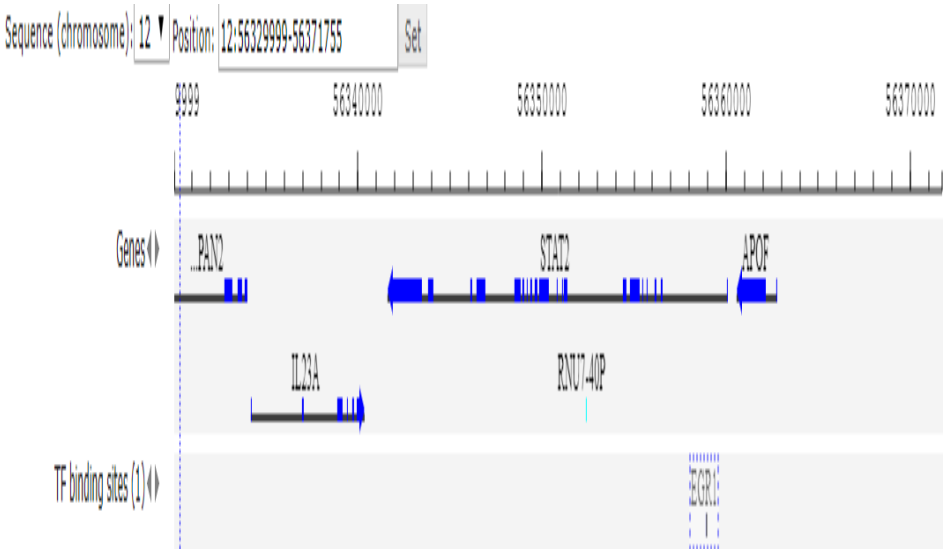

Figure 1. Interaction of transcription factor EGR1 in gene STAT2.

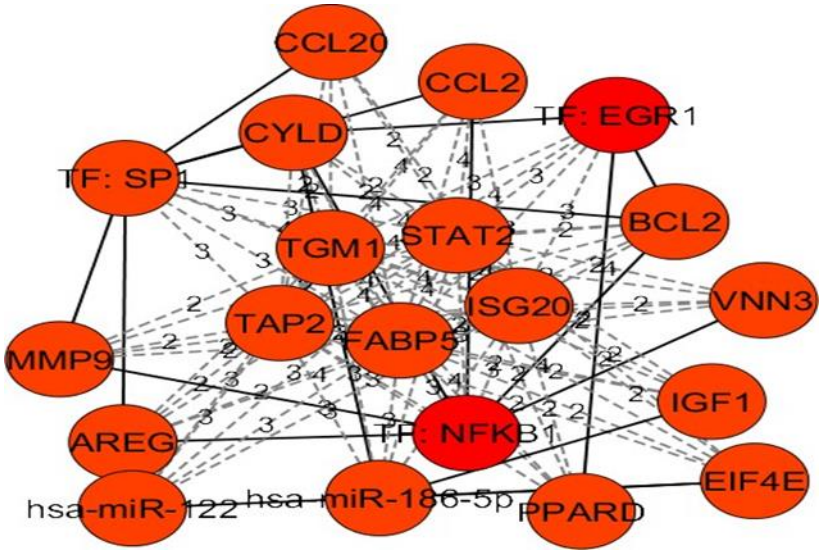

Figure 2. Transcriptional regulatory network of psoriasis.

Implication of Transcriptional Regulatory Network in Pathogenesis of Psoriasis

STAT2 is involved in the pathogenesis of psoriasis by promoting the production of CCL5 and CXCL11 in keratinocytes [7-13]. The miRNA, hsa-miR-186 was differentially expressed in the lesional skin of Psortatic patients [14]. Egr-1 is regulator for the upregulation of IL-17A-induced psoriasin in psoriasis [15]. The miRNA, hsa-miR-186-5p was identified as a potential regulator in the subunits of NF-κB [16]. SP1 promotes angiogenesis on VEGFR-2 receptors to decrease the VEGF production in psoriasis [17]. A genetic variant of

NFKB1 is associated with the clinical features of psoriasis vulgaris [18]. According to the orthology analysis of KEGG the main module of STAT2 is associated with the signaling of JAK-STAT pathway [19] but association was also inferred in the signaling pathway of chemokines. In case of EGR1 the orthology analysis resulted in the alperin signaling pathway of neurotrophic receptors [20]. The implication of the transcription factor SP1 was not illustrated in the analysis of the modules and the orthology of KEGG pathways. The protein EGR1 act as a transcriptional regulator [21] to recognize the sequence of DNA (EGR site- 5'-GCG(T/G)GGGCG-3')in the promoter region of target genes to regulate the process of transcription. EGR1 regulates the expression of CXCL2 [22]. The transcription factor SP1 binds to the GC-rich motifs and regulates the expression of genes involved in the responses of the immune system and play an important role in the expression of genes involved in a differentiation, cell growth, immune responses and apoptosis [23].

Pathway Analysis

In case of Pathway Analysis of psoriasis associated genes in top-down approach, the Cytokine-cytokine receptor interaction is statistically significant than the Jak-STAT signaling pathway and the Cytokine-cytokine receptor interaction pathway needs to be reconstructed with Gene: STAT2, miRNA: hsa-miR-186-5p, Transcription Factors: EGR1 and SP1 along with Proteins: LAPTM4A, EIF2C2, ACTL8 and ARL5B.

Mathematical Modeling

In case of the mathematical modeling of the miRNA mediated transcriptional regulatory network of psoriasis by applying the top down approach, the involved factors are gene: STAT2, miRNA: hsa-miR-186- 5p and the transcription factors: EGR1 and SP1.The factors associated with transcriptional regulation varies with respect to time and the rate of change of transcription factors (EGR1 and SP1) with respect to miRNA (hsa-miR-186-5p) is illustrated by differential equations as [d (EGR1)/dt= k (Synthesis of EGR1) + STAT2 + k (Up regulation of EGR1) (hsa- miR-186-5p) - k (Degradation of EGR1) (EGR1)] and Similarly [d (SP1)/dt = k (Synthesis of SP1) + STAT2 + k (Up regulation of SP1) (hsa-miR-186-5p) - k (Degradation of SP1) (SP1)].In the above mentioned differential equation the gene STAT2 is an independent constant and the micro RNA (hsa-miR-186-5p) along with transcription factors EGR1 and SP1 are variables. According to the associative property of transcriptional regulatory networks the above mentioned differential equations explaining the rate of change of transcription factor with respect to time for the parameters gene and miRNA can also be modified for explaining the rate of change of miRNA for the parameters gene and transcription factors. The modified equation is [d (hsa-miR-186-5p)/dt = k (Activation of hsa-miR-186-5p) (EGR1STAT2/ k + EGR1STAT2 – k (Degradation of hsa-miR-186-5p) hsa-miR-186-5p] and similarly in case of SP1 the differential equation explaining the rate of change of hsa-miR-186-5p with respect to time is modified as [d (hsa-miR-186-5p)/dt = k (Activation of hsa-miR-186-5p) (SP1STAT2 / k + SP1STAT2 – k (Degradation of hsa-miR-186-5p) hsa-miR-186-5p].

CONCLUSION

The majority of the obtained regulatory relationships were confirmed by various studies published in literature to demonstrate the reliability and validity of the obtained miRNA and TFs in the regulatory network of psoriasis. In the present study, there were certain associated and differentially expressed genes (DEG's) involved in the pathogenesis of psoriasis. Then a regulatory network of miRNA and transcription factors (TFs) was constructed for the associated genes of psoriasis and mathematical modeling was also performed to implicate the dynamics of miRNAs and Transcription Factors in the signaling pathway of cytokine chemokine receptor interaction.

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