On the Crosstalk of Circadian Rhythm and Th17 cells: An Integrated Biological Regulatory Pathway

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Th17 cells play a pivotal role in cell-mediated immunity and also have implications for autoimmune disorders. The interplay between the circadian rhythm and the immune system has driven interest in developing novel therapies. Th17 cells have a robust relationship with the circadian rhythm through clock-controlled genes such as NFIL3 (E4BP4), RORA, RORB, NR3C1, and RORC. The purpose of this study is to construct a literature-curated updated biological regulatory network (BRN) of the molecular regulators of circadian rhythm and CD4+ Th17 cells. The integrated BRN will provide a holistic view of the differentiation process of Th17 cells from a circadian rhythm perspective, which will enhance our understanding of the interplay between the two systems. We aim to perform formal modelling and analysis of this BRN using our previously developed approaches to gain system-wide insights into various molecular expression dynamics and identify the significance of biological clocks in immunity in the future. In addition, biological pathway databases are an integral part of omics analytical workflows, and their continuous updates with the latest knowledge are crucial for gaining biological insights from such studies. Therefore, with this additional objective, we have also uploaded this pathway to Wiki Pathways (Database), to facilitate its use in future studies, which can be accessed via the following URL: https://classic.wikipathways.org/index.php/Pathway:WP5130. To our knowledge, this is the first study to report a literature-curated pathway of comprehensive regulatory interactions and crosstalk between Th17 cell differentiation and circadian genes.

Keywords: CD4+ Th17 cell; Cell-mediated immunity; Circadian rhythm; ROR; NFIL3.

Introduction:

Th17 cells, a subset of CD4+ T lymphocytes, are characterized by the production of IL17A (interleukin 17A) (Gene ID: 3605), IL-17F (interleukin 17F) (Gene ID: 112744), IL-21 (interleukin 21) (Gene ID: 59067), and IL-22 (interleukin 22) (Gene ID: 50616), and their differentiation is regulated by the transcription factors RORA (RAR related orphan receptor A) (Gene IDs: 6097) and RORC (RAR related orphan receptor C) (Gene IDs:6095)[1]. They play a crucial role in defending against extracellular pathogens, particularly fungi and bacteria [1][2][3][4], but are also implicated in various autoimmune disorders such as rheumatoid arthritis (RA) and multiple sclerosis (MS), and inflammatory bowel disease (IBD) [5][6][7]. The encounter with extracellular pathogens stimulates immune cells to release specific cytokines, which drive the differentiation of CD4+ T cells into the Th17 subset. Key cytokines that drive Th17 cell differentiation include TGF-β (transforming growth factor beta 1)(Gene ID: 7040), IL-1β (interleukin 1 beta) (Gene ID: 3553), IL-6 (interleukin 6) (Gene ID: 3569), and IL-23 (interleukin 23) (Gene ID: 51561)[1] [8]. This process is orchestrated by several transcription factors, notably STAT3 (signal transducer and activator of transcription 3) (Gene ID: 6774), RORα, RORγt, IRF4 (interferon regulatory factor 4) (Gene ID: 3662), AHR ((Aryl hydrocarbon receptor) (Gene ID: 196), BATF (basic leucine zipper ATF-like transcription factor) (Gene ID: 10538), and Runx1 (RUNX family transcription factor 1) (Gene ID: 861) [1][9]. Research shows that the circadian rhythm exists in lymphoid organs and various types of immune cells [10]. It regulates immune responses and other functions associated with them, such as cytokine release, inflammatory response, and immune cell migration[11][12]. The gene networks regulating circadian rhythm and Th17 cells are closely interconnected. Within the circadian system, CLOCK (clock circadian regulator) (Gene ID: 9575) and ARNTL/BMAL1 (basic helix-loop-helix ARNT like 1) (Gene ID: 406) form a heterodimer that binds to E-box elements in the genome, thereby promoting the expression of CRY1 (cryptochrome circadian regulator 1) (Gene ID: 1407), PER1 (period circadian regulator 1) (GeneID: 5187), RORs, and REVERBA/NR1D1 (nuclear receptor subfamily 1 group D member 1) (Gene ID: 9572) proteins. As PER and CRY levels rise, they dimerize in the cytoplasm and subsequently translocate into the nucleus, where they inhibit CLOCK-BMAL1 activity, thereby establishing a negative feedback loop[13]. In addition to the PER-CRY negative feedback loop, REV-ERB and RORA alternatively bind to CLOCK-BMAL1 to repress and activate its function, respectively[14][15]. The RORE element–binding activator RORα and its repressor REV-ERBα alternately regulate the expression of target genes such as BMAL1 and NFIL3 (nuclear factor, interleukin 3 regulated) (Gene ID: 4783). Among these, RORα under circadian clock control serves as a key transcription factor governing Th17 cell differentiation.

The circadian clock interplays with various T helper cells, including Th17, Th9, Treg, Th22, and follicular T helper cells. It interacts with Th17 cells through the interactions of CLOCK and ARNTL with GATA3 (Gene ID: 2625) via PER[16] and NCOA3 (Nuclear Receptor Coactivator 3) (Gene ID: 8202)[17]. Likewise, ARNTL interacts with IRF4 (interferon regulatory factor 4) (Gene ID: 3662) through CIART (Gene ID: 148523) and NR3C1[18][19]. Other genes reported to be involved in crosstalk include RORA, RORB, RORC, NR3C1 (nuclear receptor subfamily 3 group C member 1) (Gene ID: 2908), SIRT1 (Sirtuin 1) (Gene ID: 23411), and CSNK1D (casein kinase 1 delta) (Gene ID: 1453)[10].

Similarly, CLOCK and ARNTL interact with PU.1, an intracellular marker of Th9 cells through PER1 and NONO (Gene ID: 4841)[16][20]. In addition, the circadian clock connects with Th22 and follicular T helper cells via PER1, NCOA3, and NR3C1[21]. The cell markers of regulatory T helper cells are FOXP3+ (Gene ID: 50943), Helios+/- (Gene ID: 22779), STAT5+ (signal transducer and activator of transcription 5A) (Gene ID: 6776) and the secreted factors are Galectin-1, IL10 (interleukin 10) (Gene ID: 3586), IL35 (interleukin 10) (Gene ID: 3592), TGFbeta[22]. CLOCK and ARNTL interacts with FOXP3 through SIRT1, PER1, CSNK1D[23][24]. The current study mainly focuses on the interplay of Th17 cells and the circadian rhythm. The common genes in the circadian clock and Th17 cells establish a connection between the two networks, resulting in crosstalk. Thus any disruption in circadian rhythm may result in anomalous immune cells and affect the immune system.

Objectives:

This study intends to integrate the underlying gene network of circadian rhythm and Th17 cells to get a holistic view of the two systems. It also focuses on identifying significant genes and interactions in the integrated system. The study exploits text mining techniques and tools, including GLAD4U and the STRING database, to identify candidate genes and produce a protein-protein interaction network (PPIN) in the form of an undirected graph. The PPIN is analyzed in the Cytoscape tool using graph theory concepts to identify significant genes involved in the interplay of the two systems. The resultant PPIN has a high recall and precision value of 1 and 0.85, respectively. The PPIN is transformed into a biological regulatory network (BRN) by identifying the direction of interactions from the literature, experiments, and curated databases, including KEGG[25], GO[26], IntAct [27], Biogrid [28], and Reactome [29].

Organization of the Article:

The Materials and Methods section describe the methodology, important applications, and web resources used in this work. The Result and Discussion section includes topological analysis of the protein-protein interaction network (PPIN), functional modules within the PPIN, and the resultant integrated pathway. The Conclusion section concludes the article and summarizes the results and their analysis.

Material and Methods:

To develop an integrated model linking Th17 cells with the circadian rhythm, this study builds upon the methodology outlined in[30], extending it through the incorporation of text mining techniques, as illustrated in Figure 1. A search with the phrase "Th17 and circadian" on Google Scholar and PubMed retrieves thousands of articles; however, manually extracting and synthesizing information from such a vast body of literature is practically unfeasible. Therefore, text mining techniques were complemented with the manual method to extract more information and largely enhance our understanding of the interplay of the two systems. To exploit text mining techniques, first, significant genes associated with each system under consideration are identified using GLAD4U. The considerable genes are then used to search the STRING database and construct a Protein-Protein Interaction Network (PPIN) in the form of a graph. Cytoscape, along with various curated databases including KEGG[25], GO[26], IntAct[27], Biogrid[28], and Reactome[29], was utilized for the analysis and verification of the PPIN. The final step is to build an integrated pathway using the PathVisio tool, taking into account all the results and analysis.

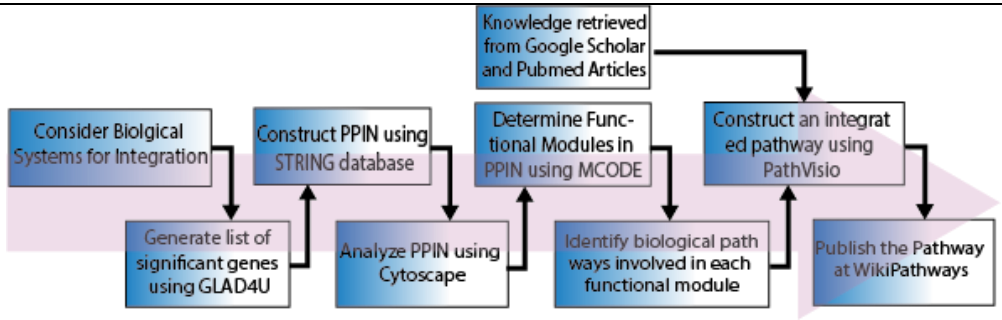

Figure 1. The diagram depicts the steps followed in the methodology.

Tools and Web Services used:

GLAD4U is a text-mining tool that identifies genes linked to a biological function specified as a search term. It retrieves and prioritizes genes from PubMed resources, ranking them by weight score, with each gene linked to recent relevant articles[31]. STRING is a web resource that retrieves information about protein-protein interactions that are either known or predicted in the literature. STRING database generates links among proteins based on experiments, text mining, curated databases, and formal prediction methods.

Cytoscape is an open-source platform for visualizing graphical data in different layouts, analyzing networks, identifying clusters, and integrating networks with gene expression data. Its functionality can be extended through plugins, which enable tasks such as advanced network analysis, integration with gene expression data (e.g., RNA-Seq), cluster identification, and customized visualization.

PathVisio is an open-source tool for drawing new pathways. PathVisio is developed for WikiPathways, a community-curated pathway database. WikiPathways allows its users to search and download pathways using PathVisio for editing and analysis purposes.

Terms and Definitions:

The following are the important terms used in this work:

Graph:A Protein-Protein-Interaction Network is a graph N (P, A) tuple, were

P is the set of all proteins, and

A is the set of all associations, i.e., $A \subseteq P \times P$

Degree: The degree of a node refers to the number of its connections to other nodes in the network.

Betweenness Centrality: Betweenness centrality is a method for determining the extent to which a node influences the flow of information in a graph. It is often used to find nodes that serve as a bridge from one part of a graph to another.

Closeness Centrality: Closeness centrality measures how efficiently a node spreads information through the graph. Measures the average distance of a node to all other nodes. Nodes with a high closeness score have the shortest distances to all other nodes.

Eccentricity: The eccentricity of a vertex v, denoted by e (v), is the maximum distance of v to all other vertices in the graph.

Clustering Coefficient: In graph theory, a clustering coefficient is a measure of the degree to which nodes in a graph tend to cluster together.

Stress: In graph theory, the number of shortest paths passing through a node is called its stress. Stress(node) = number of shortest paths passing through the node

Shortest path: In graph theory, a shortest path is a path that traverses the minimum number of edges to reach from one node to another node. Shortest path (node1, node2) = path where the number of edges between node1 and node2 is minimum.

Recall: Recall is the fraction of the true-positive predictions out of all the true predictions. Recall = TP/ (TP + FN), where TP (true positive) is the number of the predicted interactions matched by the known interactions, and FN (false negative) is the number of the known interactions that are not matched by the predicted interactions.

Precision: Precision is the fraction of the true-positive predictions out of all the positive predictions, Precision = TP/(TP+FP), where FP (false positive) equals the total number of predicted interactions minus TP

Result and Discussion:

This section presents and interprets the key findings of the study. The following subsections present the PPIN of CD4+ Th17 cells and the underlying genes of the circadian rhythm, functional modules in the PPIN, topological analysis of the PPIN, and finally, the integrated biological regulatory network of Th17 cells and the circadian rhythm.

PPIN of CD4+ Th 17 cells and the underlying genes of Circadian Rhythm:

The Protein-Protein Interactions Network (PPIN) between the circadian rhythm and Th17 cells is shown in Figure 2. The intracellular markers of Th17 cells are: BATF+, IRF4+, RORa+, RORC+, STAT3+ and their secreted factors are: CCL20/MIP3a, IL17a, IL17f, IL21, IL22, IL26. The circadian clock interacts with Th17 cells through NR1D1, CIART, NR3C1, RORA, RORB, and RORC. In Figure 2, these interactions are depicted as edges connecting nodes, with each edge assigned a confidence score derived from the STRING database. Thick edges represent the interactions between nodes with high confidence, while thin edges represent low-confidence interactions. Node's elongation is mapped to the degree of the node. A less elongated node represents a low degree of the node, and a more elongated node represents a high degree of the node. Similarly, the color of nodes is mapped to the stress attribute using continuous mapping. Yellow, green, and orange colors represent small, medium, and high stress of a node, respectively. In Figure 2, lines connecting RORA, RORB, RORC, NR3C1, SIRT1, IL17A, IL17F, and CSNK1D show crosstalk between the two systems.

The figure highlights that RORA, RORB, RORC, NR3C1, SIRT1, and CSNK1D are key genes involved in the crosstalk between the two systems. Among these, nodes such as RORA, RORC, and NR3C1 appear most significant, suggesting their critical role in mediating the interplay.

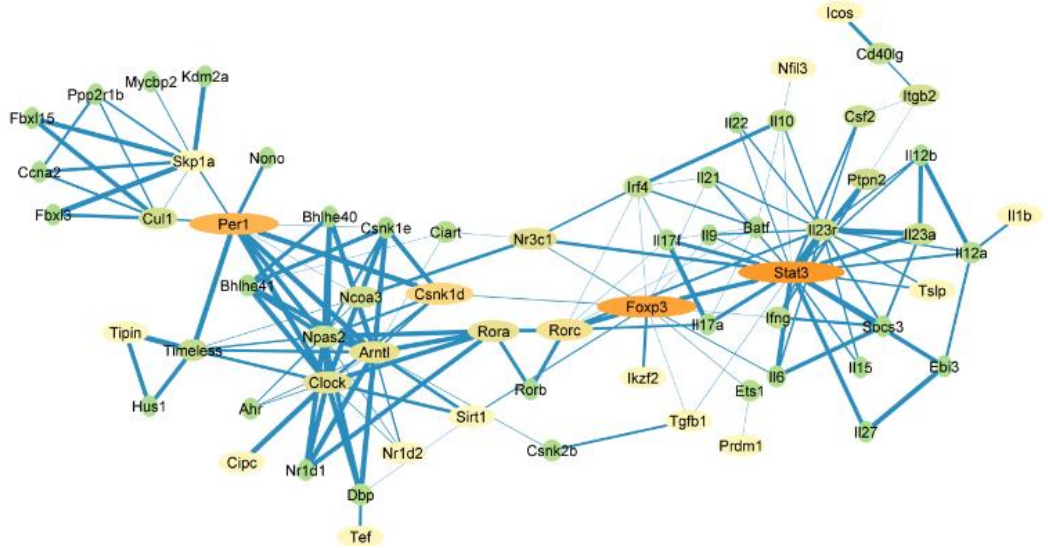

Figure 2. The figure depicts a protein-protein interaction network (PPIN) between circadian rhythm and Th17 cells.

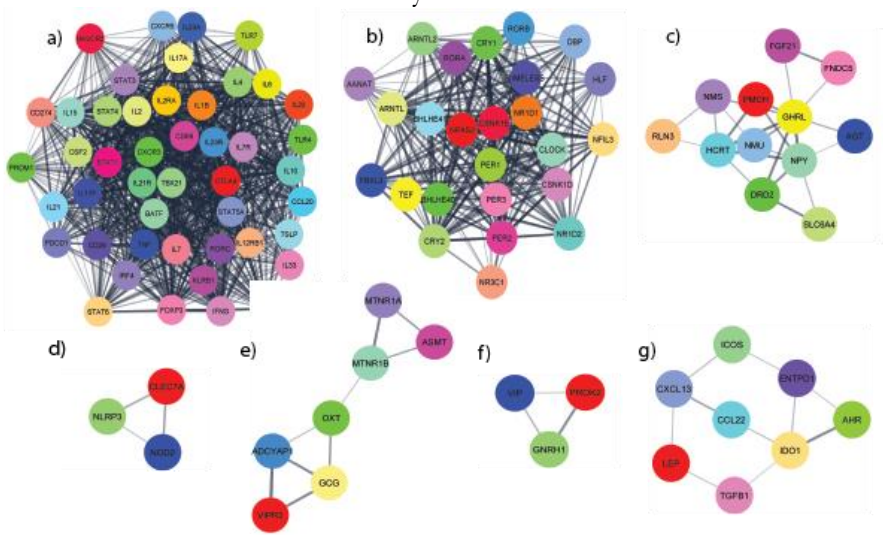

Figure 3. The figure depicts functional modules in the PPIN of Figure 2. Seven different functional modules are identified using the MCODE app. of Cytoscape in the form of clusters. The clustering score, number of nodes, and edges involved in each cluster are given in Table 2.

Functional Modules in PPIN:

The PPIN comprises seven clusters, two of which represent major modules. Each cluster corresponds to a functional module within the network; for instance, the first cluster contains genes involved in Th17 differentiation, while the second is associated with the circadian network. The cluster score was calculated using the formula *Density* × *Number of nodes*. As nodes in the PPIN of Figure 2 and clusters in Figure 3 represent interaction with each other, but these figures do not show the type of their interactions. To obtain this information,

the relevant pathways associated with each cluster are retrieved from curated databases such as KEGG[25], GO[26], IntAct[27], Biogrid[28], and Reactome[29], as shown in Figure 4. Proteins from the PPIN that participate in these pathways are highlighted with a red fill. These pathways collectively capture the underlying biological activities and associated signal transduction processes.

Topological Analysis of Th17 and Circadian PPIN:

The Protein–Protein Interaction Network (PPIN) is represented as a graph, where nodes correspond to proteins and edges denote their interactions. Topological analysis of the PPIN is particularly useful for identifying key nodes and substructures that may hold biological significance. Various measures are applied to perform topological analysis of a PPIN, with centrality being one of the most common. Centrality evaluates the importance of nodes within a network, particularly in terms of their role in facilitating information flow. Metrics for measuring centrality are degree of nodes, closeness centrality, and betweenness centrality. The most significant nodes according to the above metrics are given in Table 1.

The Integrated Biological Regulatory Network of Th17 and Circadian Rhythm:

As a final output, this research work has produced an integrated biological regulatory network based on the knowledge acquired from Google Scholar and PubMed articles, as well as the analysis of the PPIN (Figure 2). The common nodes in the PPIN, highlighted with three different colors, provide strong evidence of the interconnection between the biological systems under investigation. By evaluating the significant proteins in the PPIN using multiple topological metrics and analyzing their interaction types, an integrated pathway was constructed, as depicted in Figure 4. Lines with red colors represent the crosstalk between the two systems. The blunt lines connecting NR1D1 with NFIL3, and NFIL3 with RORC, represent negative interactions (repressions). Positive interactions exist between RORA and BMAL1, and CLOCK/BMAL1 complex and RORA, as represented by the red lines with arrows.

Discussion:

The integrated biological pathway constructed in this study represents the complex interplay between the circadian system and Th17 cells. The pathway is developed using information from the literature, a protein-protein interactions network created with the STRING database, and the Cytoscape tool for identifying important nodes involved in crosstalk. The pathway is uploaded on Wikipathways for rectification and further refinement, and to be publicly available for further research. The integrated pathway can be accessed using the following URL: https://classic.wikipathways.org/index.php/Pathway:WP5130. The interactions identified as crosstalk can be verified using literature and biological experiments. The negative interaction between NFIL3 and RORC aligns with the results of a biological experiment, which show that loss of NFIL3 results in increased Th17 responses and represses Treg cell development[32]. CLOCK/BMAL1 activates REVERBa, which regulates the expression of NFIL3, where NFIL3 is a negative transcriptional factor of RORgt[32][33]. The absence of NR1D1 represses NFIL3 expression, and therefore, increases the development of Th17 cells, and the lack of NR1D1 upregulates NFIL3 expression, which then suppresses the expression of RORγt, which is the major transcription factor of Th17 cells[34], verifying the negative interaction between NR1D1 and NFIL3 in our integrated pathway. The

CLOCK/BMAL1 complex of the circadian clock directly influences RORC[35]. As a transcription factor, RORC has implications for various inflammatory and autoimmune diseases associated with Th17 cells, including inflammatory bowel disease, multiple sclerosis, asthma, food allergy, autophagy, CIA, Schizophrenia, arthritis, Psoriasis, and colitis[36], [37], [38], [39], [40]. These references strongly confirm the interplay of the circadian clock and Th17 cells.

Table 1. Topological Analysis of Protein-Protein Interaction Network (PPIN)

Gene	Bet. Centrality	Close. Centrality	C.Coefficient	Degree	Eccentricity
IL6	7.3800E-2	0.625	0.3328	99	4
TNF	6.6799E-2	0.6109	0.3410	96	4
IL1B	4.9399E-2	0.6069	0.3698	90	4
IL10	3.7900E-2	0.6031	0.3997	88	4
STAT3	4.2700E-2	0.5881	0.4326	81	4
IL17A	2.64E-2	0.5637	0.4572	80	4
IL4	1.2500E-2	0.5587	0.4965	76	4
IFNG	1.18E-2	0.5555	0.5120	74	4
IL2	1.6899E-2	0.5475	0.5057	74	4
CTLA4	2.7199E-2	0.5397 0.	5092	70	4
FOXP3	1.7000E-2	0.5460	0.5266	70	4
CSF2	7.1000E-3	0.5336	0.5476	69	4
STAT1	2.23E-2	0.5460	0.5469	66	4
TLR4	2.1000E-2	0.5444	0.504	66	4
TBX21	1.24E-2	0.5397	0.5813	64	4
IL7R	1.38E-2	0.5292	0.5806	63	4
CD28	1.5800E-2	0.5177	0.6072	60	4
RORC	6.3500E-2	0.5506	0.5026	59	4
IL15	6.1000E-3	0.5233	0.6787	55	4
IL17F	5.1999E-3	0.5121	0.6541	54	4
IL23R	6.4999E-3	0.5162	0.6183	54	4
IL2RA	3.5000E-3	0.504	0.6952	53	4
LEP	4.9200E-2	0.5605	0.3664	52	3
STAT5A	6.6E-3	0.5121	0.6833	52	4
IRF4	3.3E-3	0.5080	0.7160	51	4
IL33	6.0000E-3	0.5067	0.6196	50	4
IL7	3.8999E-3	0.5067	0.7419	50	4
CCL20	3.0000E-3	0.4897	0.6488	49	4
CXCR3	7.6E-3	0.4986	0.7320	49	4
IL12RB1	3.0000E-3	0.4974	0.6989	49	4

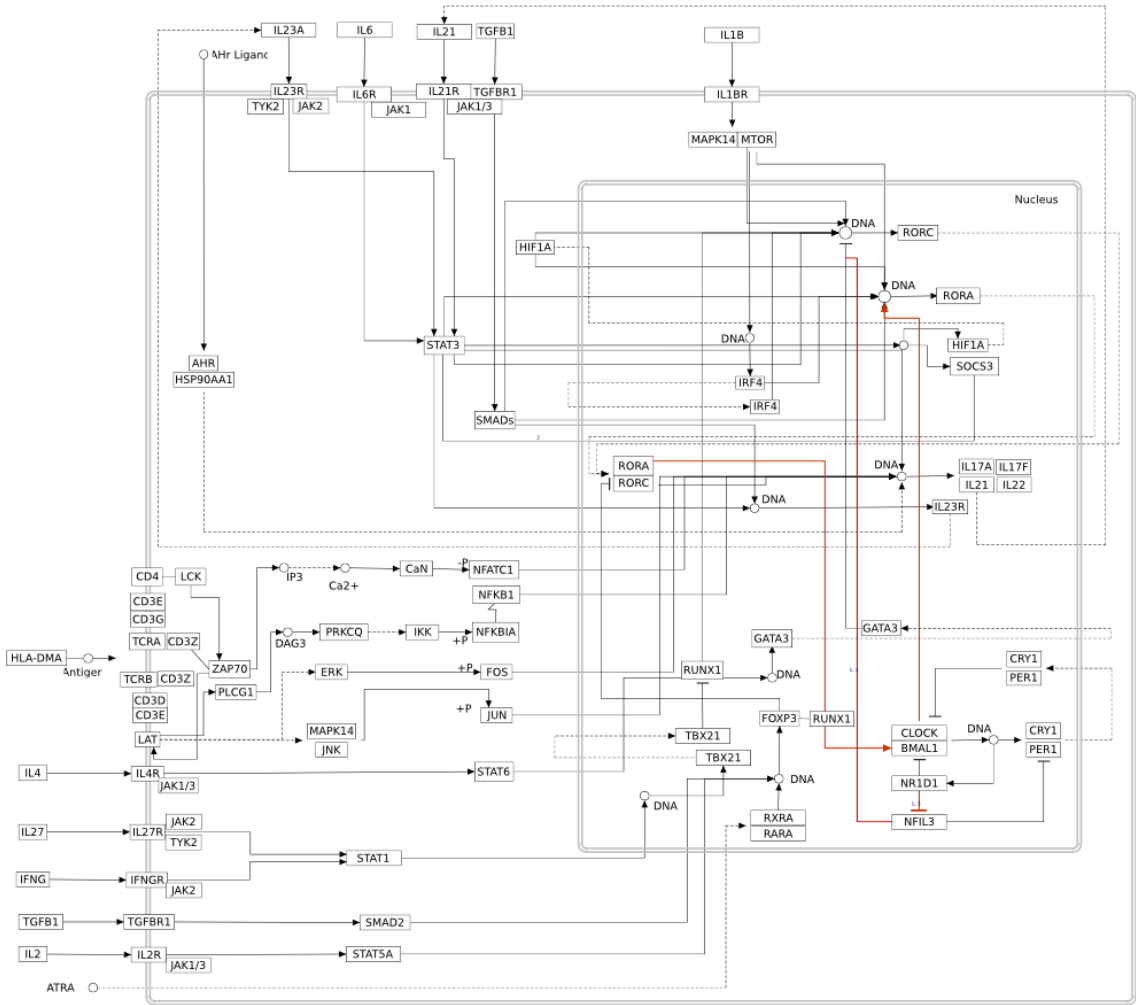

Figure 4. The figure shows the biological regulatory network of the crosstalk of Th17 cell differentiation and the circadian network.

Interactions in red color represent the interplay of the two systems. An integrated pathway is constructed by considering interactions of significant nodes in the PPIN of Figure 2 according to their degree, betweenness centrality, closeness centrality, and eccentricity.

Threats to Validity:

The study uses biomedical literature and pathways databases as a knowledge source to generate a list of genes and construct a PPIN. The PPIN constructed in this work has an excellent recall and precision of 1 and 0.85, respectively. However, certain limitations exist: the literature is indexed based on titles, abstracts, and keywords, not on full-text content. Thus, the set of retrieved publications may be incomplete, as some relevant studies might not be captured if the queried keywords are absent from their titles or abstracts. Deriving PPINs using the STRING database may not cover the totality of the interactome and may include

noisy data by including interactions that do not exist in the given organism but are reported by putative homologs in other organisms.

Conclusion:

Circadian rhythm, like other physiological functions, also plays a critical role in immune activities. Uncovering the underlying essential genes may lead to potential therapeutic strategies and drug targets for associated autoimmune disorders. This study has revealed an insight into the robust connection of the two systems using literature-curated findings, text mining tools, and standard pathways databases. Moreover, an integrated pathway of Th17 cells and circadian network has been developed and is made available for researchers at WikiPathways (Pathway ID: WP5130). Furthermore, the topological analysis of the integrated network of the two systems identified significant genes, functional modules, and their interactions with each other. In the future, the integrated BRN will be formally modelled and analyzed using asynchronous discrete logic and Petrinets[41],[42] formalisms for determining the dynamics of the system to gain insights into the interplay of the two systems.

Author's Contribution. HR and JA conceived and developed the methodology. HR, NC, HN, MS, and JA conducted the experiment, wrote and reviewed the paper. All authors contributed to the analysis, layout of results, and reviewed the manuscript.

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Conflict of Interest. The authors have no conflict of interest in publishing this manuscript in IJIST.

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