Research Article

The Model of PPARγ-Downregulated Signaling in Psoriasis

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Received 3 April 2020; Revised 2 September 2020; Accepted 18 September 2020; Published 9 October 2020

Academic Editor: Pascal Froment

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Interactions of genes in intersecting signaling pathways, as well as environmental influences, are required for the development of psoriasis. Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor and transcription factor which inhibits the expression of many proinflammatory genes. We tested the hypothesis that low levels of PPARγ expression promote the development of psoriatic lesions. We combined experimental results and network functional analysis to reconstruct the model of PPARγ-downregulated signaling in psoriasis. We hypothesize that the expression of IL17, STAT3, FOXP3, and RORC and FOSL1 genes in psoriatic skin is correlated with the level of PPARγ expression, and they belong to the same signaling pathway that regulates the development of psoriasis lesion.

1. Introduction

Psoriasis is an example of chronic inflammatory skin disorder with a complex multifactorial origin. Multiple genes cause heterogeneous heredity of psoriasis [1, 2]. Interactions of predisposing genes, as well as environmental influences, are required for the development of the disease.

Family genotyping supports the hypothesis that different phenotypes or manifestations of psoriasis are determined by different genetic loci [3]. These loci are associated with psoriasis and located at least on 13 different chromosomes and are named PSORS (psoriasis susceptibility), PSORS1-PSORS13 ([4]). Each PSORS contains a list with several revealed genes candidates [5].

Peroxisome proliferator-activated receptors (PPARs) do not get on lists of gene candidates for psoriasis; however, the important role of PPARs in antiinflammatory and immunomodulatory cellular signaling pathways has been established. Recently, association of proline12/alanine gene polymorphism (rs1801282) in peroxisome proliferator-activated receptor gamma (PPARγ, NCBI Gene ID: 5468) was found to be associated with psoriasis and obesity in Egyptian patients [6].

PPARs perform function primarily as ligand-dependent transcription factors which activate genes with PPAR-responsive elements (PPREs) in their promoter. PPARγ is detected mostly in well-differentiated suprabasal keratinocytes within the human epidermis [7]. Human hair follicle epithelial stem cells also express PPARγ which maintains their survival in normal conditions [8]. Skin adipocytes and sebocytes are the next large PPARγ depositions [9, 10], and the protein is vital for their differentiation [11, 12]. The PPARγ expression was reported to be downregulated in the psoriatic skin of mice, and DDH1 dose dependently could restore the gene expression [13]. In vitro experimental models of psoriasis showed that the expression of other PPARs (PPARα) was also decreased in the skin, while PPARβ and PPARδ expressions were increased [14]. Mice model of inflammatory skin diseases revealed that the expression of PPARγ and PPARα was decreased in the skin due to the absence of the Dlx3 gene [15]. The medical suppression of PPARγ improved the health of the mice model of atopic...
dermatitis [16]. Wang et al. reported that gene PPARγ had high level of expression in the skin of IMQ-induced psoriasis mice, and a PPARγ-selective antagonist GSK3787 was able to decrease the inflammation in the skin [17]. Finally, another animal model research showed that mutant mice with deleted PPARγ did not have sebaceous glands and normal hair follicles (HF) and developed scarring alopecia and skin inflammation [18]. There is no experimental evidence about PPARγ activity level in human skin of patients with psoriasis to our knowledge.

PPARγ signaling in psoriasis has been studied at a good level, but conflicting experimental results do not allow describing a clear picture of protein-protein interactions and pathological changes in cell pathways leading to the development of psoriasis (read below section “Pathway Model of PPARγ Signaling in Psoriasis”).

In this work, we tested a hypothesis that low levels of PPARγ may change the activity of cellular signaling pathways in the skin and facilitate the chronic inflammatory and immune response in psoriatic lesion in humans. Based on the literature-based protein-protein interactome (PPI) and pathway analysis, we proposed that low PPARγ activity promotes the development of psoriatic lesions due to changes in the inflammatory signaling pathways regulated by STAT3, RORC, FOXP3, FOSL1, and IL17A. To check the hypothesis, we measured the expression of these genes altogether with PPARγ on the mRNA level in the skin of patients with psoriasis before and after low-intensity laser treatment.

2. Materials and Methods

2.1. Protein-Protein Interactome (PPI) Analysis and Pathway Model Reconstruction. To reconstruct the PPARγ-psoriasis interactome, we used the literature-based database PSD (Resnet-2020®, Elsevier Pathway Studio database). PSD is a mammal-centered database where relationships between biological terms and molecules extracted from published papers with natural language processing (NLP) technology. Data from public databases with experimental types of connections are also present in PSD. Resnet-2020 contains over one million objects and more than 12 million relationships with more than 55 million supporting sentences ([19], http://www.pathwaystudio.com/).

For PPI analysis, we used SQL language and ran queries to filter PSD connections and found inhibited by PPARγ expression targets that simultaneously have positive relationships with psoriasis (see “PPARγ targets and regulators” file, list 1 in supplemental materials). To find PPARγ regulators, we selected genes that negatively regulate expression of PPARγ and simultaneously negatively regulate PPARγ expression targets (see “PPARγ targets and regulators” file, list 2 in supplemental materials). To focus only on gene expression signaling and exclude other molecular types of interaction, we considered only two types of relationships in PSD that indexed sentences about the changing of mRNA or gene expression (“Expression” and “PromoterBinding”). Queries and other parameters of network filtering are available by a request.

2.2. Pathway Functional Analysis. List of proteins that we had identified in the PPI analysis was set up with subnetwork enrichment analysis (SNEA, Pathways Studio), Fisher’s exact test, Enrichr tool [20], and KEGG mapping tool [21]. SNEA was used to find cell processes statistically enriched with genes from list 1 and 2. SNEA is the modification of gene set enrichment analysis that accounts for relationships between genes in the network [22]. Fisher’s test was used to find associated Pathway Studio pathways and Gene Ontology (GO) functional gene groups [23]. We found the associated KEGG pathways with the KEGG mapping tool, and we found the other associations with the Enrichr tool.

Cell processes were selected if more than 5 genes from the list 3 (combined genes from list 1 and list 2) were overlapped with total genes associated with the pathway and if more than 5% genes from the lists 1 and 2 were overlapped with a subnetwork or GO group. We selected top subnetworks and KEGG pathways filtered by rank and top PS pathways and GO groups filtered by Jaccard index. For the comparison of methods, we selected top 50 subnetworks, 50 pathways, and 50 GO groups after manual filtering of unrelated diseases (such as cancer), viral, and bacterial KEGG pathways. See supplemental materials for results of pathway functional analysis (“PPARG network analysis” file and “PPARG Enrichr analysis” file).

2.3. Microarray In Silico Analysis. Public microarray data (GEO, GSE13355) was used to verify the reconstructed model of PPARγ signaling in psoriasis. GSE13355 contains
data about the expression of the human genome in skin samples of 58 patients with psoriasis [24]. DEs (differentially expressed genes) were identified with a two-class unpaired t-test between samples of lesional skin of each patient (PP samples) and nonlesional skin uninvolved samples (PN samples). Multiple probes were averaged by the best p value or maximum magnitude. The Pathway Studio software was used for calculation of DE and pathway analysis.

2.4. Supplemental Materials. All supplemental materials are available to download from ResearchGate resource by the link https://www.researchgate.net/publication/340427568_Supplemental_Materials_The_role_of_PPARG_downregulated_signaling_in_psoriasis [25]. All pathway models and their annotations are available for browsing and can be downloaded at http://www.transgene.ru/ppar-pathways.

3. Results and Discussion

3.1. Reconstruction of Downregulated PPARY Pathway Model Associated with Psoriasis. For testing the hypothesis that low levels of PPARY trigger inflammatory signaling pathways in the skin, we analysed the protein-protein interaction literature-based network (PSD, Elsevier Pathway Studio) and several public ontologies and databases (Gene Ontology, Human Protein Atlas, KEGG, Reactome).

First, in the PSD network, we identified PPARY downstream expression targets and upstream regulators (inhibitors) of PPARY expression. For researching the downstream targets, we looked for the genes and proteins which were reported to be inhibited by PPARY and simultaneously were positive biomarkers for psoriasis. 146 associated with psoriasis genes and gene families whose expressions are repressed by PPARY had been found. For researching the upstream of PPARY signaling, we focused on the transcriptional factors which can inhibit both the expression of PPARY and his direct targets. 99 associated with psoriasis unique negative regulators of PPARY had been identified. Then we combine regulators with targets to obtain 182 names of unique genes forming the PPARY-downregulated subnetwork associated with psoriasis (see supplemental materials, “PPARG regulators and targets” file, list 3) (Figure 1).

3.2. Comparative Pathway Analysis of PPARY-Downregulated Signaling Associated with Psoriasis. Several methods of pathway analysis were performed to explore the functional roles of 182 targets, and regulators of PPARY revealed in PPI analysis. Methods of pathway functional analysis are widely used for discovering cellular processes and signalings that are statistically associated with the list of genes or proteins [26]. We compared results from pathway functional analysis with three resources: Gene Ontology, Elsevier Pathways, and KEGG Pathways. Gene Ontology is the source of groups of proteins or genes manually assigned by their different functional roles. Elsevier Pathways and KEGG Pathways are manually reconstructed schemas or models of interactions between proteins describing molecular mechanisms of one or several biological processes. Gene Set Enrichment Analysis (GSEA) is a well-known method to analyse predefined and manually created collections of gene groups and pathways [27]. Besides GSEA, we used SNEA method which allows finding associated cellular processes based on literature-based PPI network. SNEA does not use predefined groups of genes or pathways and is considered less biased [22, 26].

According to the results of comparative pathway analysis, PPARY-downregulated signaling is associated with...
adipogenesis, activation of myeloid proinflammatory cells (with a predominance of mast cells and dendritic cells), and activation of overall immune system response (with a predominance of Th17 cells). Also, fibrogenesis, cell-to-cell contacts, vascular-related processes, and universal cell processes, such as cell proliferation or cell death, were identified (Figure 2). Cellular possesses directly associated with psoriasis were present in results from each source that we compared (Table 1).

Top subnetworks from SNEA were neighbors of adipogenesis and adipocyte differentiation, followed by the immune response, and T-development. The subnetworks "neighbours of monocyte recruitment or differentiation" and "macrophage differentiation" had the most percent (9%) of overlapped genes from PPARγ-downregulated signaling.

GSEA analysis of PS Pathway Collection and KEGG pathways resulted in many cancer-related processes. The disease taxonomy filtering with PS pathways about skin and immune system identified processes related to adipokines and IL17 signaling (Table 2). The signaling of aryl hydrocarbon receptor (AHR) in Th17 cells was the pathway with the biggest percent (48%) of overlapped genes from PPARγ-downregulated signaling.

Among the top KEGG pathways enriched with our gene list, we identified general MAPK and PI3K signaling and cancer-related pathways (for example, "hsa05200 Pathways in cancer - Homo sapiens"). TNF signaling pathway (hsa04668), as well as Th17 cell (hsa04659) and IL17 pathway (hsa04657), was also in the top 10 results. The cytokine-cytokine receptor interaction (hsa05200) and PI3K-Akt signaling (hsa04151) had the highest number of overlapped entities (48 and 34).

The list of revealed in pathway analysis molecular cascades completes the lists of cell processes.

There was no surprise that activation of general cellular flows like ERK/MAPK, RAS/ACT1, and adipose cells related with AMPK, MTOR, and cAMP cascades was associated with the list of PPARγ targets and regulators. Also, among the top of associated molecular signalings, there were well predictable inflammatory cascades like Toll-like receptors, interleukins, and interleukin receptors signaling (IL17, IL1B, IL6, and IL1R1) altogether with all-purpose cytokines and cytokine receptors signaling (CXCR3, CCRI, and TNF). Signalings related to transcription factors NFkB and STAT5 also were significantly associated with the analysis list. GO functional group “GO: glycosaminoglycan binding”; “IL1R1 signaling in Pneumocytes” from PS Pathway Collection; and “ErbB signaling pathway” (hsa04012) from KEGG had the maximum rank (see complete results with additional statistics in supplemental materials, “PPRAGR network analysis” file). Glycosaminoglycans are essential for skin functioning. IL1R1 is a receptor commonly activated in inflammatory processes. Finally, the ERb-γ-downregulated signaling.

### Table 1: Cell processes directly related to psoriasis and enriched with genes and proteins from the PPARγ-downregulated signaling. See complete results with additional statistics in supplemental materials, “PPRAGR network analysis” file.

<table>
<thead>
<tr>
<th>Name of the process or signaling</th>
<th>Source</th>
<th>Rank or Jaccard similarity (the closer to 10%, the more similarity)</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinocyte activation in psoriatic arthritis</td>
<td>PS Collection</td>
<td>9.13%</td>
<td>Disease</td>
</tr>
<tr>
<td>Lesion size</td>
<td>PS subnetwork</td>
<td>46</td>
<td>Targets neighbors</td>
</tr>
<tr>
<td>Keratinocyte proliferation</td>
<td>PS subnetwork</td>
<td>100</td>
<td>Targets neighbors</td>
</tr>
<tr>
<td>Skin fibrosis</td>
<td>PS Collection</td>
<td>9.09%</td>
<td>Disease</td>
</tr>
<tr>
<td>T cell differentiation block in psoriasis</td>
<td>PS Collection</td>
<td>8.88%</td>
<td>Disease</td>
</tr>
<tr>
<td>Th17 cell and Th1 immune response in psoriatic arthritis</td>
<td>PS Collection</td>
<td>8.82%</td>
<td>Disease</td>
</tr>
<tr>
<td>Dendritic cell dysfunction in psoriatic arthritis</td>
<td>PS Collection</td>
<td>8.44%</td>
<td>Disease</td>
</tr>
<tr>
<td>T cell cytotoxic response against melanocytes in vitiligo</td>
<td>PS Collection</td>
<td>6.20%</td>
<td>Disease</td>
</tr>
<tr>
<td>Synovial fibroblast activation in psoriatic arthritis</td>
<td>PS Collection</td>
<td>8.18%</td>
<td>Disease</td>
</tr>
<tr>
<td>Inflammatory reaction in acne vulgaris</td>
<td>PS Collection</td>
<td>5.70%</td>
<td>Disease</td>
</tr>
<tr>
<td>Apoptotic keratinocyte clearance recession in systemic lupus erythematosus</td>
<td>PS Collection</td>
<td>5.69%</td>
<td>Disease</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>PS Collection</td>
<td>5.62%</td>
<td>Disease</td>
</tr>
<tr>
<td>Hair follicle keratinocyte apoptosis</td>
<td>PS Collection</td>
<td>5.56%</td>
<td>Disease</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>PS Collection</td>
<td>5.07%</td>
<td>Disease</td>
</tr>
<tr>
<td>Melanogenesis—Homo sapiens</td>
<td>KEGG</td>
<td>n/a</td>
<td>Pathway</td>
</tr>
<tr>
<td>Positive regulation of timing of anagen</td>
<td>GO</td>
<td>1.10%</td>
<td>GO: biological_function</td>
</tr>
<tr>
<td>Glycosaminoglycan binding</td>
<td>GO</td>
<td>4.24%</td>
<td></td>
</tr>
</tbody>
</table>
from all sources revealed skin inflammatory processes, TLRs, and interleukin-related cascades. However, the list of molecules was different compared with PS and KEGG results presenting IL10 and IL22R and no IL17 associations. In addition, analysis with DisGeNET [28] confirmed that the PPARγ regulators and targets are connected with psoriasis since top diseases associated with the list 3 were as follows: psoriasis, epithelial hyperplasia of skin, and inflammatory dermatosis.
Allergic reaction, neutrophilia, and vascular diseases were also in the top 10 results (see supplemental materials, file “PPARG Enrichr analysis” file).

3.3. Pathway Model of PPARγ Signaling in Psoriasis. Considering results of PPI network and functional pathway analysis, we build a hypothetical model that describes cellular molecular mechanisms of involvement of PPARγ in the maintenance of chronic inflammatory and immune response in human psoriatic skin. Literature-based network (PSD) was used to build the model. Figure 4 described the adopted for the publication-simplified version of the downregulated PPARγ pathway model. See supplemental materials for the completed version of the pathway model.

Based on the model, reducing the level of the PPARγ gene expression may be a result of the overregulation of several cascades. Pattern recognition receptors (TLRs, NOD1, NOD2, and CLEC7A) that sensor pathogens and highly expressed in keratinocytes and monocytes during the infection may be one of such cascades. All-purpose cellular cascades like growth factor signaling, G-proteins, and MTOR signaling also were reported to be inhibitors of PPARγ expression in literature and revealed in our analysis. Moreover, transcription factors including NF-kBs, JUN-FOS, AHR, GATA3, HIF1A, FOXO1, and FOSL1 can directly inhibit PPARγ expression. All these transcription factors are overstimulated in the inflammatory and immune response. For example, it is reported that NF-kBs are stimulated in systemic inflammatory processes in general and in psoriasis as well [29, 30].

In healthy skin, PPARγ inhibits mentioned transcriptional factors in a feedback regulation loop. PPARγ may directly bind and suppress transcriptional factors STAT3 and RORC, by thus blocking the synthesis of proinflammatory cytokines including IL17. Less quantity of expressed cytokines decreases the Th17 cell proliferation, minimises chemotaxis of neutrophils and monocytes, and results in the reduction of inflammation in psoriatic lesions. IL17 which is produced mostly by TH17 cells plays the central role in the development of psoriasis because it stimulates keratinocytes to secrete proinflammatory cytokines and antibacterial peptides [31]. IL17 pathway and Th17 cells had a strong association with PPARγ-downregulated signaling confirmed by our network and functional analysis.

Th17 cells need robust activity of STAT3 gene for their function and differentiation. Also, STAT3 is described as an
important linkage between keratinocytes and immune cells [32]. Previously, the expression of STAT3 was shown to be repressed due to PPARγ activation [33]. STAT3 may also act as a regulator of PPARγ expression; however, it is not clear whether with positive or negative effect [34].

As a transcription factor, STAT3 is reported to be a strong activator of RORC (RORγt) and, probably, IL17 gene expression. From the other side, gene RORC is the major inductor of the expression of IL17 cytokine family [35]. PPARγ was shown to bind the RORC promoter and suppress its expression altogether with RORC-mediated Th17 cell differentiation [36].

Transcription factor FOXP3 is closely associated with psoriasis and the diminishing of Treg cell number [37, 38]. It was shown that activated PPARγ induces the stable FOXP3 expression by strong inhibiting effect on DNA methyltransferases. The activating effect of PPARγ on FOXP3 results in the proliferation of iTreg cells [39].

FOSL1 is the transcriptional factor which plays an important role in many processes related to cell differentiation and tissue remodeling ([40–42]). FOSL1 (FOS-like antigen 1) is expressed in low level in healthy tissues; however, its expression rises due to presence of mitogens or toxins. The accumulation of the FOSS1 protein in the skin depends on the stage of the keratinocyte differentiation [43]. Markers of stratum corneum differentiation like gene IVL are the main expression targets of FOSS1 [44].

The degree of the pathogenicity of downregulated PPARγ in psoriatic lesion depends on the cell type. It is known that PPARγ is expressed in Th17 cells as well as in keratinocytes, sebocytes, and other cells of the psoriatic lesion [7, 8, 10–12]. Functional and network analysis supported the association of PPARγ-downregulated signaling with keratinocytes, vascular endothelium, vascular smooth muscle cells, macrophages, fibroblasts and adipocytes, and monocytes lineage (particularly with CD33+ and CD14+ monocytes) (Figure 5). However, we did not attempt to separate the PPARγ pathway model by appropriate cell types which is a disadvantage of this work. There is no reliable way to take in account cell specificity in our modeling paradigm. Moreover, we expect that most of the revealed from the literature network analysis cascades will be equal for different human cells due to insufficient experimental studies.

For additional evaluation of the reconstructed model, we analysed the public microarray data (GEO:GSE13355). In that experiment, biopsies from 58 psoriatic patients were run on Affymetrix microarrays contain more than 50000 gene probes [45]. We uploaded raw data from GEO and calculated differentially expressed genes (DEs) between samples of psoriatic skin and unaltered samples for all patients. Then, we used the pathway analysis to explore the difference in the expression for genes of the PPARγ model we build (Figure 6).

PPARγ gene was slightly downregulated in psoriatic lesions comparing to nonaltered lesions in GSE13355 microarray data (Figure 6, PPARγ expression diagram).

We assumed that regulators of PPARγ signaling should have higher expression in psoriatic lesion than in normal skin. Only S100A12 (S100 calcium-binding protein A12) had a significantly higher level of expression in analysed microarray data comparing with all regulators of PPARγ that we selected for the model (Figures 6 and 7). S100A12 binds to the AGER receptor which belongs to the immunoglobulin superfamily and is involved in many processes of inflammation and immune response. S100A12 is thought to be the most prominent biomarker of psoriasis [46]. Also, polymorphisms in AGER receptor were found to be associated with psoriasis [47].

The EGFR signaling almost completely was downexpressed in this microarray data including the FOXO1 expression which is one of the direct inhibitors of PPARγ. Therefore, EGFR/FOXO1 signaling probably does not play an important role in the regulation of PPARγ in psoriasis (Figure 7).
4. Conclusion

In our previous work, we reviewed the recent progress in psoriasis pathways and published two pathway models. The first pathway model described the shift to TH17 cell production during the differentiation of psoriatic T cells. The primary cause of the shift of the T cell differentiation is supposed to be genetic mutations, for example, in IL23R receptors. The second model showed how elevated levels of IL17 and IL22 may activate keratinocytes to release different cytokines and chemokines for attracting neutrophils and other inflammatory cells in the psoriatic lesion [19].

In this work, we tested the hypothesis that PPARγ signaling when downregulated may promote psoriasis. We built the model of PPARγ-dependent pathways involved in the development of the psoriatic lesions. However, we used a different approach for reconstructing the pathway model and selected key members with bioinformatic analysis. We included in the pathway model the top statistically significant regulators of PPARγ gene expression and PPARγ-dependent expression targets. Then, we included significant molecular cascades and cell processes from results of the functional analysis (IL17 signaling, TLRs signaling, activation of STAT3 or NFKB transcription factors, and others). We tested the model with analysis of published microarray data.

While the prominent role of RORC in psoriasis as the major controller of Th17 cell differentiation is well described, however, the evidence of RORC expression in psoriasis is controversial and supported by work where mice T cells and dendritic cells had increased STAT3/RORC expression [48]; still, patients with psoriasis had elevated level of RORC (RORG-t isoform) [49]. In analysed published microarray data, the level of expression of RORC was downregulated in most of 58 patients.

We detected downregulation of PPARγ gene expression in human psoriatic skin from 23 patients with real-time PCR method (data not shown). Our results are similar to the data from microarray on 58 patients where average PPARγ gene expression also is slightly downregulated in psoriatic lesions [45]. Our results do not confirm the work of Westergaard et al. which described the slightly higher level of the PPARγ expression in human psoriatic skin compared to normal skin. However, the level of PPARγ mRNA was close to the detection limit in their research [39]. This
difference may be due the detection of different isoforms of PPARγ which all have different patterns of the expression [50]. More research on protein level is needed to conclude whether PPARγ gene expression is downregulated in psoriatic lesions.

Within the framework of the model validation, we hypothesize that signaling related to repressed PPARγ activity is correlated with the development of psoriasis. IL17A, STATS3, and RORC (ROrg) are statistically significant PPARγ negative targets, and we detected higher levels of their mRNA in psoriatic lesion of 23 patients and moreover, the decrease of their expression levels after laser treatment (preliminary results not shown). The alignment of our preliminary experimental results with microarray data and PPI network analysis shows that the reconstructed model of PPARγ-downregulated signaling in psoriasis can be useful for further research.

**Data Availability**

All supplemental materials (four excel files) are available to download from ResearchGate resource by the link https://www.researchgate.net/publication/340427568_Supplemental_Materials_The_role_of_PPARg_downregulated_signaling_in_psoriasis. All pathways models and their annotations are available for browsing and can be downloaded at http://www.transgene.ru/ppar-pathways. Preprint has posted on bioRxiv: https://biorxiv.org/cgi/content/short/2020.09.01.274753v1.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Acknowledgments**

We thank the “University Diagnostic Laboratory” LLC for funding along with Elsevier Inc. and Pathway Studio® for software and the database.

**Supplementary Materials**

Supplementary materials include 3 files with results of network and pathways analysis in Pathway Studio software, one file with results of GSEA in Enrichr tool, and one file with...
preliminary results of experimental validations (real-time gene expression analysis) of the model. (Supplementary Materials)

References


