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ARTICLE

Integrative RNA-Seq and Systems Biology Approach Identifies TINAGL1 as a Key Regulator of Arachidonic Acid Metabolism in Rheumatoid Arthritis

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Abstract: Rheumatoid Arthritis (RA) is a systemic autoimmune disease primarily affecting synovial joints. Dysregulated immune and inflammatory cells, particularly synovial macrophages (SM) and fibroblasts (SF), drive abnormal immune responses leading to cartilage destruction and bone erosion. We integrated transcriptome profiling and network biology to identify key biomarkers in RA. RNA-Seq data from two experimental conditions, RA synovial fibroblasts (RA-SF) and TNF inhibitor–treated RA samples (RA-TNF), were analyzed to detect differentially expressed genes (DEGs). Comparative genome analysis and network construction were performed using GeneMania to generate the Rheumatoid Arthritis Gene Interactome Map (RA-GIM), followed by pathway annotation. We identified 129 significant DEGs and constructed RA-GIM comprising 147 nodes and 2661 edges. Functional enrichment revealed pathways central to RA pathogenesis, including cytokine signaling and arachidonic acid metabolism. Among the top deviated genes, TINAGL1 emerged as a novel regulator of arachidonic acid metabolism, while C15orf48 was identified as another potential signature molecule implicated in RA. Our findings highlight TINAGL1 and C15orf48 as promising biomarkers and potential therapeutic targets in RA. Further in vitro and in vivo validation is warranted to establish their role in disease mechanisms and therapeutic intervention.

Keywords: Rheumatoid Arthritis, Systems Biology, TINAGL1, Arachidonic Acid Metabolism, Biomarker Discovery.

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1 Introduction

Rheumatoid Arthritis (RA) is a chronic, multifactorial autoimmune disease affecting about 1% of the global population, marked by synovial inflammation, cartilage destruction, and bone erosion [1] [2]. The disease originates in synovial tissues composed mainly of Synovial Fibroblasts (SF) and Synovial Macrophages (SM), whose dysregulated interactions drive chronic inflammation and pannus formation [3] [4]. Elevated pro-inflammatory cytokines such as TNF- and IL-1, combined with reduced anti-inflammatory mediators like IL-10 and TGF-, perpetuate joint damage and deformity [5]. Although conventional transcriptomic approaches have provided valuable insights, Next-Generation Sequencing (NGS) now enables genome-wide identification of regulatory genes and pathways in RA [6]. In this study, RNA-Seq was employed to profile synovial fibroblasts from RA patients versus healthy donors, and to evaluate the effect of TNF- inhibitors, which remain only partially effective with sustained responses in ~60% of patient [6]. While TNF blockade reduces inflammatory cytokines, it is also associated with severe side effects including infections, neurological complications, and autoimmune-like syndromes. To address these limitations, comparative genome analysis was performed to identify common differentially expressed genes (DEGs) across patient and drug-treatment datasets. Key transcriptional regulators were integrated with systems biology approaches to construct immunological networks, followed by statistical and functional annotation. This strategy aims to uncover novel biomarkers and pathways driving RA pathogenesis, thereby improving understanding of joint destruction mechanisms and guiding more targeted therapeutic interventions.

2 Materials and Methods

2.1 Data Collection

Two publicly available RNA-Seq datasets of synovial fibroblasts associated with Rheumatoid Arthritis (RA) were retrieved from the NCBI Sequence Read Archive (SRA). Dataset SRP009315 included synovial fibroblasts from healthy donors and RA patients [8]. Dataset SRP042031 comprised RA samples with and without TNF inhibitor treatment [9]. Together, these datasets represent two experimental conditions: RA-SF (disease vs. healthy) and RA-TNF (drug-treated vs. untreated).

2.2 Preprocessing and Quality Control

Raw SRA files were converted to FASTQ using the SRA Toolkit. Read quality was assessed with FastQC and low-quality bases and adapter sequences were trimmed using Trim Galore [10] [11]. Only high-quality paired-end reads were retained for downstream analysis.

2.3 Alignment and Quantification

Cleaned reads were aligned to the human reference genome (GRCh38/hg38) using the STAR aligner [12]. Gene-level read counts were obtained with feature 'Counts using GENCODE v38 annotation [13].

2.4 Differential Expression Analysis

Differentially expressed genes (DEGs) were identified separately for RA-SF and RA-TNF datasets using the DESeq2 package [14]. Genes with adjusted p-value (FDR) 0.05 were considered significant. Comparative analysis was then performed to identify common DEGs between the two conditions, and deviation in fold-change patterns was used to prioritize candidates.

2.5 Network Construction and Functional Enrichment

Significant DEGs were uploaded to GeneMANIA [15] to construct the Rheumatoid Arthritis Gene Interaction Map (RA-GIM), integrating co-expression, protein–protein interactions, pathways, and co-localization data. Networks were visualized and analyzed in Cytoscape 3.3.0 [16]. Topological parameters, including degree and closeness centrality, were used to identify central and indispensable nodes [17].

Functional enrichment of the RA-GIM was performed using ClueGO [18] with KEGG, Reactome, and Gene Ontology databases (p 0.05). Genes showing higher fold-change deviation across RA-SF and RA-TNF datasets were cross-referenced with enriched pathways to prioritize novel candidate biomarkers.

3 Results and Discussion

3.1 Differential Gene Expression

RNA-Seq analysis of RA-SF) and RA-TNF provided a systems-level view of transcriptional alterations in RA. This comparative approach yielded 129 significant genes, including two open reading frames (c15orf48 and c11orf96), based on probability testing and corrected values. Substantial differences in gene expression were observed between the two datasets. To highlight genes with higher variability, we calculated the mean absolute deviation in fold change and selected those with deviations 4.6 for further investigation into their role in RA (Table S1).

2.2 Construction and functional characterization of biological interactome

The RA-GIM interactome was constructed using 129 significant genes from RA-SF and RA-TNF datasets through the GeneMANIA server. The network comprised 127 interconnected genes along with 20 additional functional partners, excluding two non-interacting molecules (GGTA1P and MIR675). In total, the interactome contained 147 nodes and 2661 edges, with an average shared node-edge ratio of 18.10 (Fig 1). RA-GIM displayed a scale-free architecture, where nodes represent genes and edges denote physical or functional associations such as protein binding, metabolic activity, or regulatory crosstalk [19].

The interactome was analyzed in Cytoscape using the NetworkAnalyzer plugin to assess local and global graph properties. Table 1 lists the top 10 deviated genes with centrality measures. Most were highly connected, suggesting their role as multifunctional regulators. CXCL8 emerged as a central hub with 81 interactions and the highest global closeness (0.61), underscoring its essential role. CXCL5 showed the greatest deviation with 49 partners, while TINAGL1 followed with 20. Notably, PADI2 and C15orf48 exhibited fewer connections but high closeness centrality, indicating potential regulatory importance.

In RA, genes interact in complex networks where unexpected interactions may lead to dysregulated functions. Therefore, understanding system-level interconnectivity is essential. ClueGO, plugin in Cytoscape performed the functional enrichment analysis of RA-GIM. Its analysis represented functionally annotated genes by exploring databases like KEGG, Reactome and Gene Ontology with a p-value < 0.05.

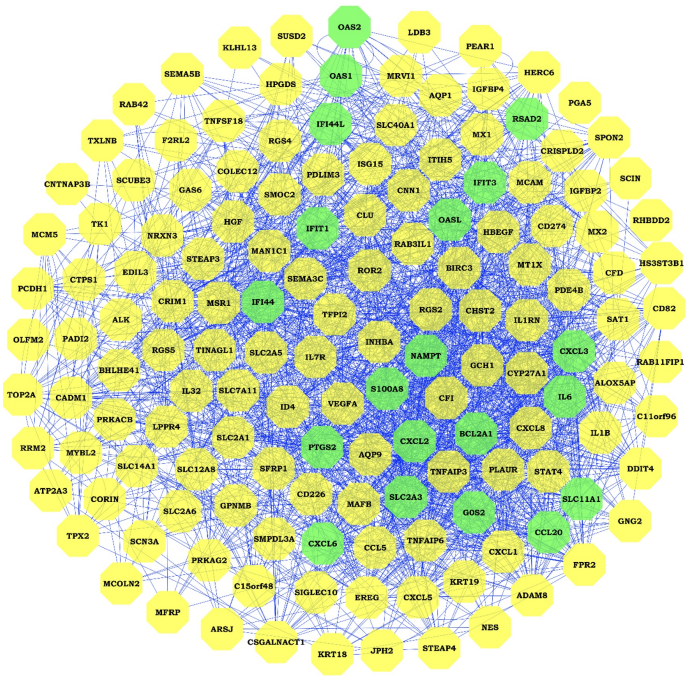

Figure 1. RA Functional Gene Interactome Network. Network visualization of 147 genes and functional partners constructed using GeneMania, illustrating 2661 molecular interactions relevant to rheumatoid arthritis. Significant genes are displayed as yellow nodes, and additional inferred partners are highlighted in green. The dense interconnectivity reveals potential key regulators and signaling hubs within disease-associated pathways.

3.3 Identification of signature molecules

Instead of focusing on a single gene, we extended our analysis to highly deviated genes with fold change deviation 4.6. Gene Ontology (GO) terms for this group were extracted and analyzed to better understand their role in RA pathophysiology. Pathways linked to inflammatory and immune responses, such as cytokine signaling [20], TNF signaling, arachidonic acid metabolism, angiogenesis, leukocyte pathways, apoptosis, chronic inflammation, and cell adhesion [21], were prioritized to identify key molecules (Fig. 2). The integration of pathway frequency with network parameters highlighted biologically relevant regulators. Nine genes, CCL20, CCL5, CXCL1, CXCL5, CXCL6, CXCL8, IL1B, IL6, and VEGFA, showed direct involvement in RA (KEGG pathway: hsa05323) (Table S2). Since RA is a chronic autoimmune disease, most genes were multifunctional, participating in multiple pathways. However, targeting multifunctional genes could disrupt normal metabolism and cause adverse effects. Therefore, we emphasized top deviated genes with fewer interaction partners to identify unexpected shared interactions that may drive dysregulated functions in RA.

Among the functionally enriched genes, CXCL8 (k = 81), CXCL2 (k = 73), and PTGS2 (k = 73) emerged as highly multifunctional regulators. These genes are already reported as key players in RA pathogenesis, though their targeting may cause unintended side effects [22]. Using these as benchmarks, we extended our analysis to other deviated genes.

To identify indispensable regulators and establish a ranking, we combined theoretical graph-based properties with biological relevance. Genes showing high deviation and closeness, but with lower degree and frequency (i.e., enriched in fewer pathways), were prioritized for detailed parametric analysis. This strategy enabled us to narrow the set of top deviated genes to the most indispensable ones. Figure 3 illustrates these genes with their graphical properties, deviation values, and pathway frequencies.

Based on the defined criteria, PADI2, c15orf48, and TINAGL1 emerged as the most indispensable genes, characterized by high closeness but low degree and frequency. The closeness centrality of the top deviated genes ranged from 0.51 to 0.61, indicating their strong potential to influence other genes within the network and their likely involvement in shared pathways. High closeness reflects shorter distances between nodes, suggesting that these genes may play a role in organizing functional units or modules [23].

Interestingly, among the top deviated genes, 8 genes,

Table 1. List of top 10 deviated genes with their expression value and graphical properties

Gene	Gene Name	FC (SF)	FC (TNF)	Dev	CC
CXCL5	C-X-C motif chemokine 5	−5.81	9.42	15.24	0.57
TINAGL1	Tubulointerstitial nephritis antigen-like	−6.99	3.91	10.90	0.52
IL1RN	Interleukin-1 receptor antagonist	−6.28	3.98	10.26	0.58
EREG	Proepiregulin	−2.81	7.03	9.84	0.56
C15orf48	Normal mucosa of esophagus-specific gene 1	−3.74	5.67	9.40	0.51
PADI2	Protein-arginine deiminase type-2	4.48	−4.78	−9.25	0.52
IGFBP2	Insulin-like growth factor-binding protein 2	−6.40	2.83	9.24	0.54
IL7R	Interleukin-7 receptor subunit alpha	−0.58	8.62	9.20	0.57
CXCL8	Interleukin-8	−3.24	5.92	9.16	0.61
IL1B	Interleukin-1 beta	−1.10	7.29	8.39	0.58

FC: Fold Change; Dev: Deviation; CC: Closeness Centrality

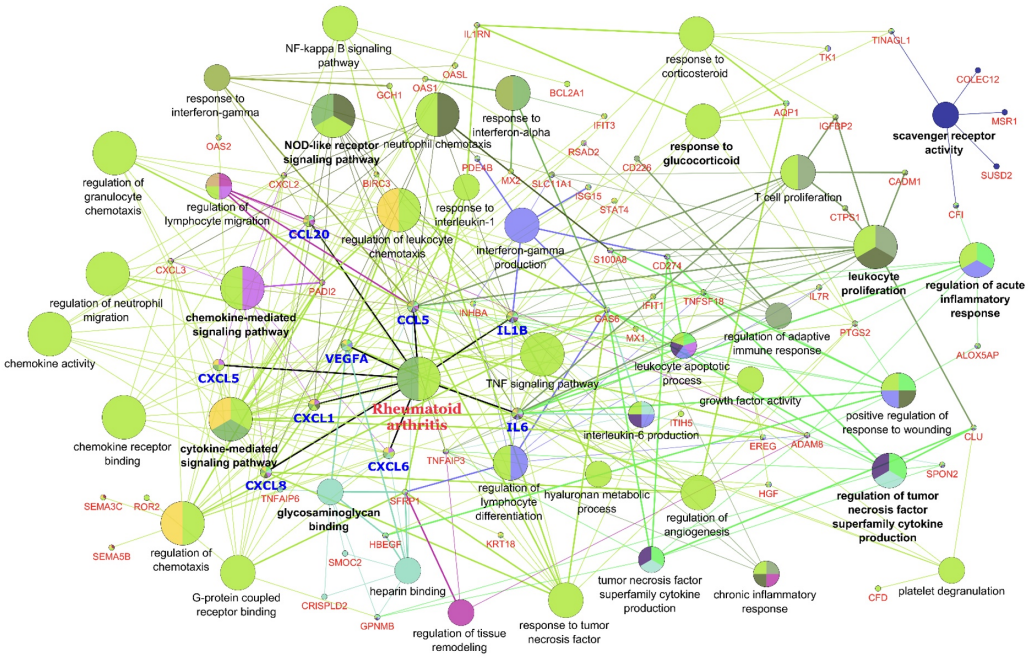

Figure 2. RA Pathway Enrichment Network. Functional enrichment analysis reveals key rheumatoid arthritis-associated pathways as interconnected nodes, derived from differentially expressed genes. The network displays pathway relationships and gene contributions, highlighting mechanisms such as cytokine signaling, chemotaxis, immune response, and inflammation that are central to disease pathology.

CXCL5, IL1RN, EREG, PADI2, IGFBP2, IL7R, IL1B, and CXCL8, were already reported as prominent regulators in RA pathogenesis (Table 2).

Since PADI2 is already a well-established regulator in RA pathogenesis, our focus shifted toward the novel signature molecules TINAGL1 and c15orf48 to better understand their expression deviations and potential roles in RA.

c15orf48, also known as NMES1 (Normal Mucosa of Esophagus-Specific gene 1), is expressed in bone, small intestine, colon, stomach, placenta, and esophageal mucosa [24]. Although its precise role in RA remains unexplored, its expression in bone suggests possible relevance to joint pathology. Proteins with known sequences but uncharacterized structures pose major challenges for functional interpretation. Current prediction methods rely on sequence or structural

Table 2. Previously reported RA-associated signature molecules among the top deviated genes

Gene	k	f	Dev	CC	Reference
CXCL5	49	34	15.24	0.57	Buckland 2014; Pickens et al. 2011
IL1RN	51	22	10.26	0.58	Tolusso et al. 2006; McInnes et al. 2007
EREG	38	12	9.84	0.56	Yamane et al. 2008; Lahoti et al. 2014
PADI2	19	12	9.25	0.52	Foulquier et al. 2007; Chang et al. 2013
IGFBP2	27	7	9.24	0.54	Suzuki et al. 2015; Matsumoto et al. 2014
IL7R	48	13	9.20	0.58	Churchman et al. 2014; Churchman 2008
IL1B	59	65	8.39	0.58	Dai et al. 2014; Tolusso et al. 2006
CXCL8	81	59	8.02	0.61	Deleuran et al. 2009; Tanabe et al. 1994

k: degree; f: frequency; Dev: deviation; CC: closeness centrality

similarity to annotated proteins, but these provide only tentative insights and lack certainty. Considering this limitation, we propose that c15orf48 be prioritized for detailed characterization through in vitro and in vivo approaches, including siRNA-based knockdown or mouse knockout models, to elucidate its precise role in RA pathogenesis.

The second candidate, TINAGL1, was examined using functionally enriched GO terms (Table 3). Notably, pathways related to response to cytokine, lipopolysaccharide, glucocorticoid and corticosteroid signaling, hydrogen peroxide response, and scavenger receptor activity were significantly associated with RA, underscoring its potential as a novel regulatory molecule in disease progression.

To better understand the association between TINAGL1 and RA, we performed a detailed systems-level analysis, which highlighted its influential role in arachidonic acid metabolism, a key pathway driving chronic inflammation. TINAGL1, a non-catalytic peptidase of 467 amino acids, belongs to the glucocorticoid-inducible protein family [25]. Glucocorticoid-inducible proteins are primarily inhibitory in nature. Previous studies have reported that these proteins inhibit activator protein 1 (AP-1) [26], suppress arachidonic acid metabolites [27], and block phospholipase A2 (PLA2) activity [28], thereby restricting the release of arachidonic acid from phospholipids. Consistently, GO terms linked to TINAGL1 support its involvement in glucocorticoid response and scavenger receptor activity. Scavenger receptors, in turn, are known to neutralize or remove altered lipoprotein [29]. Together, these characteristics strongly implicate TINAGL1 as a critical regulator of arachidonic acid metabolism.

In arachidonic acid metabolism, PLA2 catalyzes the conversion of phospholipids to arachidonic acid, while COX1 and COX2 further convert arachidonic acid to prostaglandins. Both arachidonic acid and prostaglandins are potent inflammatory mediators, and their persistence in synovial tissue sustains chronic inflammation by recruiting cytokines, chemokines, and immune cells [30] [31].

Expression analysis revealed that TINAGL1 was markedly downregulated in RA-SF (FC = –6.99) and upregulated in RA-TNF treatment (FC = 3.90) (Table S1). These findings suggest that in severe RA, reduced TINAGL1 expression permits enhanced PLA2 activity, leading to excessive arachidonic acid production and heightened inflammation. Conversely, upon TNF inhibition, upregulation of TINAGL1 may suppress PLA2 activity, reducing arachidonic acid levels and attenuating inflammation. The proposed regulatory mechanism of TINAGL1 in arachidonic acid metabolism is depicted in Figure 4.

Currently, the most widely used drugs for treating RA are TNF- inhibitors and blockers. TNF-, a cell signaling cytokine, plays a central role in systemic inflammation and is directly responsible for joint pain and swelling. However, targeting TNF- can result in unexpected adverse effects, since this cytokine participates in diverse biological processes such as apoptosis, cachexia, inflammation, cytokine-mediated interactions, inhibition of tumorigenesis, and viral replication. Moreover, dysregulated TNF- activity has been implicated in a wide spectrum of diseases, including cancer [32], inflammatory bowel disease [33], psoriasis [34], Alzheimer's disease [35], and major depression [36].

In our analysis, we identified TINAGL1 as a novel signature molecule, notable for its involvement in a relatively small number of pathways, with a specific and critical role in arachidonic acid metabolism. In severe RA, joint inflammation often

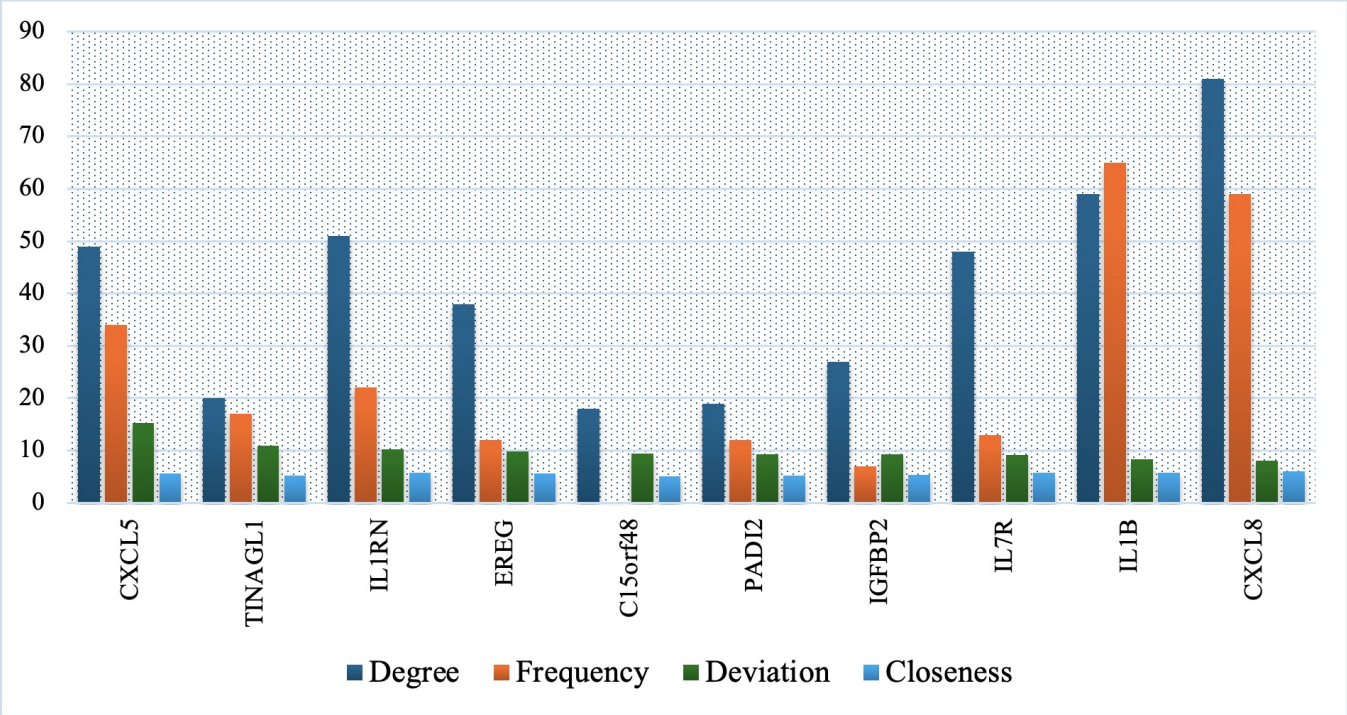

Figure 3. Top Deviated Gene Network Metrics. Bar chart displaying key network metrics degree, frequency, deviation, and closeness for the most deviated genes identified in the analysis. The comparison highlights variation in connectivity and centrality among top genes, providing insight into their relative influence and structural roles within the rheumatoid arthritis interactome.

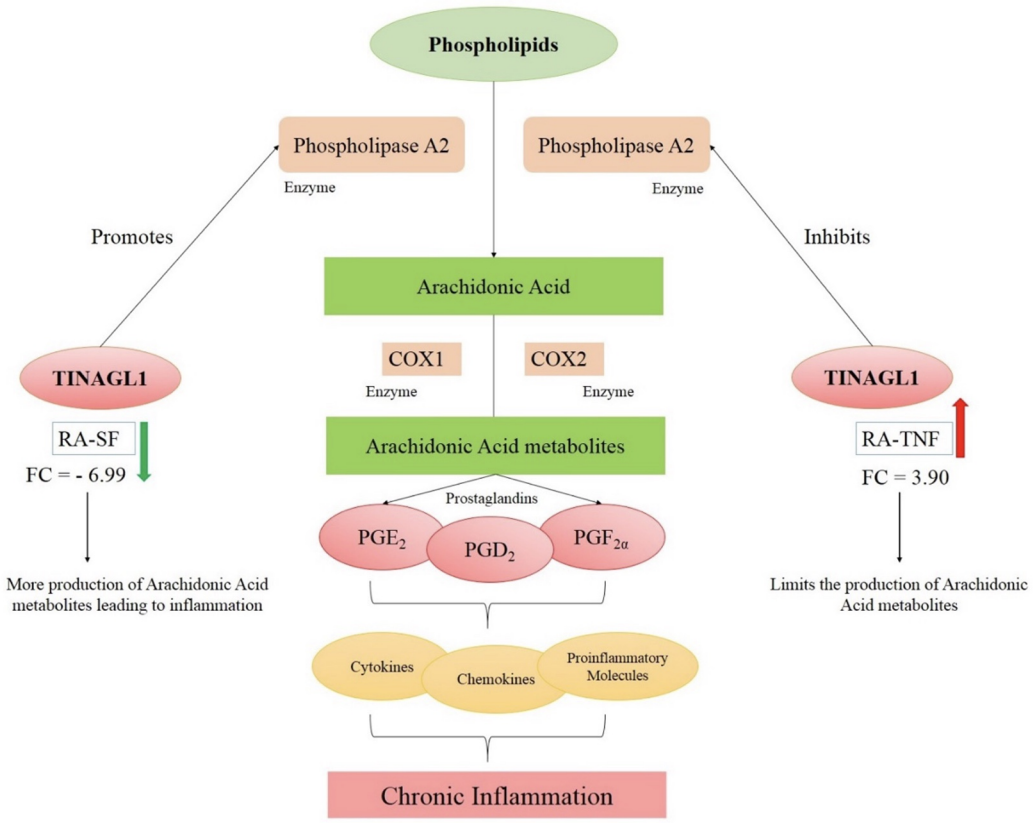

Figure 4. The proposed action of TINAGL1 on PLA2 in the Arachidonic Acid metabolic pathway.

Table 3. GO terms associated with TINAGL1 and its associated partners

GO Term	Associated Genes Found
Response to cytokine	CCL5, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, EREG, GAS6, GCH1, IFIT1, IFIT3, IL1B, IL1RN, IL6, IL7R, ISG15, KRT18, MT1X, MX1, MX2, OAS1, OAS2, OASL, PADI2, PTGS2, RSAD2, SFRP1, SLC11A1, STAT4, TINAGL1, TNFSF18
Cellular response to cytokine stimulus	CCL5, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, EREG, GAS6, IFIT1, IFIT3, IL1B, IL1RN, IL6, IL7R, ISG15, KRT18, MT1X, MX1, MX2, OAS1, OAS2, OASL, PADI2, RSAD2, SFRP1, STAT4, TINAGL1, TNFSF18
Cellular response to lipopolysaccharide	CCL20, CCL5, CXCL8, IL1B, IL6, PDE4B, S100A8, SPON2, TINAGL1, TNFAIP3
Cellular response to molecule of bacterial origin	CCL20, CCL5, CXCL8, IL1B, IL6, PDE4B, S100A8, SPON2, TINAGL1, TNFAIP3
Response to bacterium	CCL20, CCL5, CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL8, GCH1, IL1B, IL1RN, IL6, ISG15, PDE4B, PTGS2, S100A8, SLC11A1, SPON2, TINAGL1, TNFAIP3
Response to glucocorticoid	AQP1, IGFBP2, IL1RN, IL6, PTGS2, TINAGL1, TK1
Cellular response to hydrogen peroxide	AQP1, HGF, IL6, TINAGL1, TNFAIP3
Scavenger receptor activity	CFI, COLEC12, MSR1, SUSD2, TINAGL1
Cargo receptor activity	CFI, COLEC12, MSR1, SUSD2, TINAGL1

Selected GO terms highlighting TINAGL1's involvement in inflammatory and immune-related pathways

arises from the excessive production of arachidonic acid metabolites, chemokines, and cytokines. Under such conditions, TINAGL1 may represent a promising therapeutic target. Instead of inhibition, drugs with potentiator activity could be designed to enhance TINAGL1 function, thereby restoring regulation of arachidonic acid metabolism and ultimately reducing joint inflammation.

4 Conclusion

Next-generation sequencing (NGS) enables rapid and high-throughput profiling of diverse DNA sequences within a single reaction. In this study, transcriptomic data of synovial fibroblasts at both diseased and treatment levels were analyzed to gain insights into their roles in rheumatoid arthritis (RA). Comparative analysis of RA-SF patient data and RA-TNF treatment data, integrated with a systems biology approach, allowed us to explore gene connectivity and identify key regulatory molecules implicated in RA pathogenesis. Our graph-theory–based framework systematically identified indispensable proteins within the RA-GIM interactome. Among these, c15orf48 and TINAGL1 emerged as crucial molecular signatures. Further downstream analysis revealed the indispensable role of TINAGL1 in regulating arachidonic acid metabolism, a pathway central to RA-associated inflammation.

The findings provide a theoretical framework that can be extended through in vitro and in vivo experimental validation to confirm the mechanistic role of these molecules and to identify more selective therapeutic agents targeting inflammation and joint destruction. Overall, this study highlights the significance of synovial fibroblast–derived molecules in RA and provides new leads for the development of potential therapeutic targets.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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