Int J Hum Genet, 18(2): 172-179(2018)
DOI: 10.31901/24566330.2018/18.2.700

Identification of Core Modules and Genes in Rheumatoid Arthritis Following Infliximab Therapy

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KEYWORDS Attractor. Bioinformatics. Biomarker. Protein-Protein Interaction Network. Target

ABSTRACT The aim of this work was to investigate core modules and genes in rheumatoid arthritis (RA) following infliximab (IFX) therapy by combining systematic tracking of modules and attract method. Core modules were determined by attract method between IFX group (ION) and control group (CON). As a result, a total of 15 and 13 candidate modules were obtained for IFX group and control group, respectively. When matching candidate modules across the two groups, researchers gained 8 module pairs and named them as modules. In detail, Module 1 had the highest differential MCD (Ä*C*), Ä*C* = 0.041. The result of attract method showed that 2 core modules (Module 3 and Module 6) and 9 core genes (*POLE2*, *CDC45*, *DLGAP5*, *KIF11*, *NCAPG*, *RPS5*, *RPL18A*, *RPL35* and *RPS19*) were successfully identified. The findings might give great insights to reveal the molecular mechanism underlying IFX, and provide potential biomarkers for treatment and prognosis of RA disease.

INTRODUCTION

Tumor necrosis factor alpha (TNF-α) plays a crucial role in the pathogenesis of rheumatoid arthritis (RA), as proved by the clinical benefit of TNF-α-neutralizing therapy with either a TNF-α type II receptor–IgG1 fusion protein or a chimeric monoclonal antibody against TNF-α, such as infliximab (IFX) (Velascovelázquez et al. 2017). Generally, IFX is administered by intravenous infusion typically at six- to eight-week intervals, and cannot be given by mouth because the digestive system would destroy the drug (Hemperly and Vande 2018). For RA patients, IFX seems to work by preventing TNF-α from binding to its receptor in the cells, but the specific molecular mechanism of the process is unclear. With the development of high throughput technology and gene data analysis over the past decade, rapid progress has been made in discovering genetic associations with certain disease (Bastida et al. 2018; Pegoraro and Misteli 2017). Gene expression data studies reveal a complex, heterogeneous immune inflammatory response in the immune mediated inflammatory diseases yet common signatures, are characteristic of specific autoimmune diseases (Takeuchi 2017). Hence using microarray data of RA patients may be a good way to predict response to IFX accurately and reliably, even further to uncover the functional mechanism of this drug.

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Objectives

In this paper, to identify core modules and genes in RA following IFX therapy, the systematic tracking of modules and attract method were combined. Firstly, objective network for IFX group (ION) and objective network for the control group (CON) was constructed based on gene expression data, protein-protein interaction (PPI) data, and Spearman correlation coefficient (SCC). Subsequently, modules were detected by calculating module correlation density (MCD) between any pair of candidate modules which were identified by clique-merging algorithm. Finally, core modules were determined utilizing attract method from modules between IFX group and control group, and genes in the core modules were defined as core genes. The results might

provide potential biomarkers for detection and therapy of IFX treated RA patients, and gained an insight to reveal the underlying molecular mechanisms of this process.

MATERIAL AND METHODS

Preparing Data

Gene Expression Data

In this paper, gene expression profiles with accessing number of E-GEOD-57405 (Rosenberg et al. 2014) for RA patients following IFX therapy were collected from the ArrayExpress database (http://www.ebi.ac.uk/arrayexpress/). E-GEOD-57405 was comprised of 19 RA samples before IFX treatment (Control group) and 31 RA samples after IFX treatment (IFX group or Experimental group), and deposited on A-GEOD-13158 - [HT_HG-U133_Plus_PM] Affymetrix HT HG-U133+ PM Array Plate. To control the quality of the data, standard pre-treatments were conducted, including background correction, normalization, probe correction, and summarization of expressed values (Bolstad et al. 2003; Irizarry et al. 2003). After converting the preprocessed data on probe level into gene symbol measure and removing the duplicated ones, the researchers obtained a total of 17352 genes in gene expression data for subsequent analysis.

PPI Data

Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) provided a critical assessment and integration of PPIs, including direct (physical) as well as indirect (functional) associations (Szklarczyk et al. 2014). Hence, researchers acquired all human PPIs from STRING database, including 16,730 genes and 1,048,576 interactions. Subsequently, genes or interactions without expression value or duplicated self-loops were removed, and interactions of score < 0.2 were also discarded. A total of 5665 genes and 28,176 interactions were retained. To make these interactions more reliable and correlated to RA, the researchers extracted interactions with two nodes both belonging to the gene expression data. Ultimately, 12,899 PPIs involved in 3332 nodes were gained and denoted as the PPI data for further exploitation in this study. Note that the PPI data for IFX group and control group were different due to the differences between IFX treated samples and control samples.

Constructing ION and CON

Since there might be a number of false positive or non-effective interactions in PPI data, SCC was implemented to re-weight these interactions. Here, SCC is a measure of the correlation between two variables, giving a value between -1 and +1 inclusive (Szmidt and Kacprzyk 2010). The SCC between gene i and j, $S(i,j)$, was calculated as formula:

$$S(i,j)=\frac{1}{n-1}\sum_{k=1}^{n}\left(\frac{g(i,k)-\bar{g}(i)}{\sigma(i)}\right).\left(\frac{g(j,k)-\bar{g}(j)}{\sigma(j)}\right) \quad (1)$$

Where n was the number of samples of the gene expression data; $g(i, k)$ or $\bar{g}(j, k)$ was the expression level of gene i or j in the sample k under a specific condition; $\bar{g}(i)$ or $g(j)$ represented the mean expression level of gene i or j; and $\sigma(i)$ or $\sigma(j)$ stood for the standard deviation for the specific condition. If $S(i,j)$ had a positive value, there was a positive linear correlation between i and j. Besides, for a PPI between i and j, absolute SCC value was denoted as its weight value. Only the interactions with $P < 0.05$ were selected to construct the ION for IFX group and CON for the control group.

Identifying Modules

Systemic inference of modules between IFX group and control group comprised of two steps, identifying candidate modules from ION and CON using clique-merging algorithm (Liu et al. 2009; Srihari and Leon 2013); and extracting modules from candidate modules dependent on MCD and module pair match (Srihari and Ragan 2013).

Exploring Candidate Modules

Clique-merging algorithm worked in two steps: in the first step, it found all the maximal cliques from the ION and CON, and in the second step, it merged highly overlapped cliques (Liu et al. 2014). Maximal cliques were determined by cliques algorithm which utilized a depth-first search strategy to enumerate all maximal cliques and effectively pruned non-maximal cliques during the enumeration process (Tomita et al. 2006). Cliques with too small number of genes were difficult and meaningless to study, and thus the

researchers discarded cliques with node amount smaller than 4 (Sriganesh and Ragan 2013). In addition, some maximal cliques overlapped with one another, and the high overlapped ones must be integrated to reduce the result size. For each clique, it checked whether there existed the other clique that had a higher score than J, where $J = 0.5$ was a predefined threshold for overlapping (Srihari et al. 2013). If such clique existed, the two cliques would be removed or merged. The refined maximal cliques were demoted as candidate modules. In particular, candidate modules for IFX group were identified from ION, similarly, candidate modules for the control group from CON.

Evaluating Modules

For purpose of evaluating candidate modules in IFX group and control group, MCD, d, for each candidate module under special condition was calculated as follow:

$$d = \frac{\sum_{i,j \in S} S((i,j),M)}{|S| * (|S|-1)} \quad (2)$$

In which M was a similarity graph to perform a maximum weight bipartite matching (Gabow 1976). In detail, d_{IFX} stood for MCD of candidate module in IFX group, while $d_{control}$ represented MCD for the control group. Step further, researchers matched the similar or common candidate module pairs across IFX group and control group, and ranked them in non-increasing order of their absolute MCD, $\Delta C = |d_{IFX} - d_{control}|$. Here, they defined the each module pair as a module for RA.

Investigating Core Modules and Genes

In this step, core modules were determined utilizing attract method from modules between IFX group and control group, and genes in the core modules were defined as core genes. Attract method is a knowledge-driven analysis approach for identifying and annotating the gene-sets (Matigian et al. 2011). It could be summarized the determination of core modules that discriminated the strongest between cell types or experimental groups of interest (Mar 2011).

In this work, each module was denoted as an attractor. Based on attract method, GSEA-ANOVA model was proposed to assess module level data and investigate core modules between IFX group and control group. Seed modules were identified through the F-statistic, for gene i, $F^{(i)}$ was computed:

$$F^{(i)} = \frac{\frac{1}{K-1}\sum_{k=1}^{K} \gamma_k \left[u_k^{(i)} - u_{\cdot}^{(i)}\right]^2}{\frac{1}{N-K}\sum_{k=1}^{K}\sum_{v=1}^{\gamma v} \left[u_{vk}^{(i)} - u_{\cdot}^{(i)}\right]^2} \quad (3)$$

Where v represented corresponding expression value in each replicate sample; r_k for each cell type $k = 1, \ldots, K$; u stood for the mixed effect model; N meant the total number of samples. Large values of the F-statistic indicated a strong association whereas a small F-statistic suggested that the gene demonstrated minimal cell type-specific expression changes. In order to make the F-statistic more confidence, the researchers selected T test to correct the $\log_2$-transformed F-statistics and obtain P value for each potentially shared module originated from synexpression groups. Adjusting their P values on the basis of false discovery rate (FDR) (Benjamini and Hochberg 1995), the researchers defined the modules with $P<0.05$ as core modules between IFX and control groups, and genes in core modules as core genes.

RESULTS

ION and CON

In this work, the researchers employed two types of data, gene expression data recruited from the ArrayExpress database and PPI data extracted from the STRING database. By integrating gene expression data, PPI data and SCC related analyses, the ION for IFX group and CON for the control group were identified, which displayed equal number of 3332 nodes and 12899 interactions, but the weight distribution was different. The relationships between the number of interactions and weight in Figure 1 showed that the number of interactions reached the highest (more than 3000) near the weight of 0.1. After that, weight distribution across control group and IFX group had clear differences, especially from 0.1 to 0.6. From the overall perspective of these two curves, the average weight for 12899 interactions was also different, 0.290 for control group, and 0.277 for IFX group. Nevertheless, these results could not be taken as confident proof for clinical therapy, and the large scale of ION and CON brought great challenges to explore target markers. And thus in subsequent study, researchers mainly focused on detecting sub-network or module that extracted from the ION and CON.

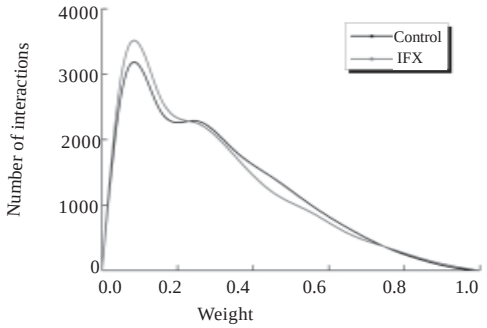

Fig. 1. Weight distribution of interactions in objective network for Infliximab (IFX) group (ION) and objective network for control group (CON)
Source: Author

Modules

Based on the ION and CON, candidate modules were identified utilizing clique-merging algorithm. The result showed that 2443 and 2021 maximal cliques were detected for IFX group and a control group based on fast depth-first method of clique algorithm. Eliminating cliques with small genes (count<4) to study, 238 and 120 maximal cliques were retained for IFX group and control group, respectively. Since there might be some overlaps between two maximal cliques, researchers refined them dependent on merging algorithm with $J > 0.5$, and 15 candidate modules in Table 1 were obtained for IFX group, while 13 candidate modules in Table 2 for the control group. Gene compositions of each candidate module in IFX and control groups were shown in these two tables.

When matching the candidate modules, 8 pairs of candidate modules with similar or same gene compositions were obtained, and each candidate module pair was defined as a module. That was to say, 8 modules were gained. To further explore correlations of them across IFX group and control group, the density of each candidate module, MCD, and differential density of each candidate module pair, ΔC were computed. The parameters of modules composed by the candidate module pair of IFX and control in Table 1 were used to screen the possible modules. Module 1 had the highest $\Delta C = 0.041$, which was comprised of *PSMC4*, *PSMD8*, *PSMB7*, *PSMD9*, *TCEB2* and *PSMB2*. The ΔC for Module 2 was 0.033 which included 6 genes (*EIF4B*, *RPL36*, *RPL35*, *RPS5*, *RPS19* and *RPS9*). The followed were Module 3 ($\Delta C = 0.028$), Module 4 ($\Delta C = 0.026$), Module 5 ($\Delta C = 0.025$) Module 6 ($\Delta C = 0.022$), Module 7 ($\Delta C = 0.021$) and Module 8 ($\Delta C = 0.019$)

Core Modules and Genes

For purpose of evaluating significantly altered or disrupted modules and genes on the basis of modules for IFX treated RA patients, GSEA-ANOVA model in attract method was employed, which also gave the researchers a way to gauge genes that informative for a particular set of cell types. Unlike other GSEA implementations which only allow for two-class comparisons, this ANOVA-based approach tests for differences between multiple classes. Supposing

Table 1: Candidate modules for infliximab (IFX) treated group

Candidate module	*Count*	*Genes*
1	5	TRIP13, ASF1B, CDC45, CDCA3, CCNA2
2	7	POLE2, CDC45, DLGAP5, KIF11, NDC80, NCAPG, CCNA2
3	8	TRIP13, DLGAP5, KIF11, NCAPG, NUSAP1, NDC80, CDCA3, KIF4A
4	6	PSMC4, PSMD8, PSMB7, PSMD9, TCEB2, PSMB2
5	5	TRIP13, GINS1, CDC45, NCAPG, PBK
6	5	NDUFAB1, NDUFA10, NDUFB2, CYC1, UQCRC1
7	5	CREBBP, MED6, MED4, MED12, TGS1
8	6	RPL18, RPS5, RPL36, RPS16, RPS8, RPL35
9	5	NDUFAB1, NDUFB3, NDUFB7, NDUFB2, NDUFC1
10	6	RPL18, RPS5, RPL36, RPS13, RPL27, RPLP2
11	5	RPS16, EIF3H, EIF4B, RPL8, RPL35
12	7	RPS5, RPL18A, RPL35, EIF4B, RPL8, RPS19, RPS9
13	6	RPL19, RPS16, RPL35, RPL8, RPL15, RPL36
14	6	CENPM, NDC80, CDCA3, CDC45, CDC20
15	9	RPL18, EIF5, RPL36, RPS16, RPL35, RPL8, EIF4B, RPS19, RPLP1

Table 2: Candidate modules for control group

Candidate module	*Count*	*Genes*
1	5	DLGAP5, NUSAP1, KIF11, NCAPG, SHCBP1
2	6	TRIP13, NUSAP1, DLGAP5, KIF11, CDC45, CEP55
3	6	POLE2, CDC45, NCAPG, KIF11, DLGAP5, DTL
4	6	PSMA4, PSMD8, PSMC4, PSMD9, TCEB2, PSMB2
5	5	RPL18, RPS5, RPS13, RPL27, RPL11
6	5	POLR2E, CCNH, MNAT1, TCEB2, POLR2G
7	6	RPL18, RPS5, RPS13, RPL36, RPL35, RPL3
8	5	RPS16, RPL35, RPL36, RPL8, EIF3F
9	6	AURKA, NUSAP1, DLGAP5, KIF11, KIF18A, ANLN
10	5	AURKA, CDCA3, NCAPG, CDC45, HJURP
11	5	RPL18A, RPS5, RPL35, RPS19, RPL29
12	6	EIF4B, RPL36, RPL35, RPS5, RPS19, RPS9
13	5	PSMA4, PSMA2, PSMC1, GMNN, PSMD6

that each seed module was an attractor, the core modules were identified by combining the seed module identified through the *F*-statistic and P<0.05, of which *F*-statistic captured the strength of association observed in a gene's expression over the different groups and P-value evaluated the significant difference across two groups. Modules with significantly differences were defined as core modules, and genes in the core modules were considered to be core genes. In the present study, 2 core modules (Module 3 and Module 6) were investigated. In detail, Module 3 (P = 2.43E-04) consisted of 5 core genes (*POLE2*, *CDC45*, *DLGAP5*, *KIF11* and *NCAPG*), while Module 6 (P = 2.59E-02) included 4 core genes (*RPS5*, *RPL18A*, *RPL35* and *RPS19*). Interaction networks for core genes in Module 3 and Module 6 in Figure 2 indicated that the interactions among any two core genes might have co-operations. The core module and genes might play a more significant role than the other modules and genes in the progression of IFX treated RA patients and be potential biomarkers in the target treatment.

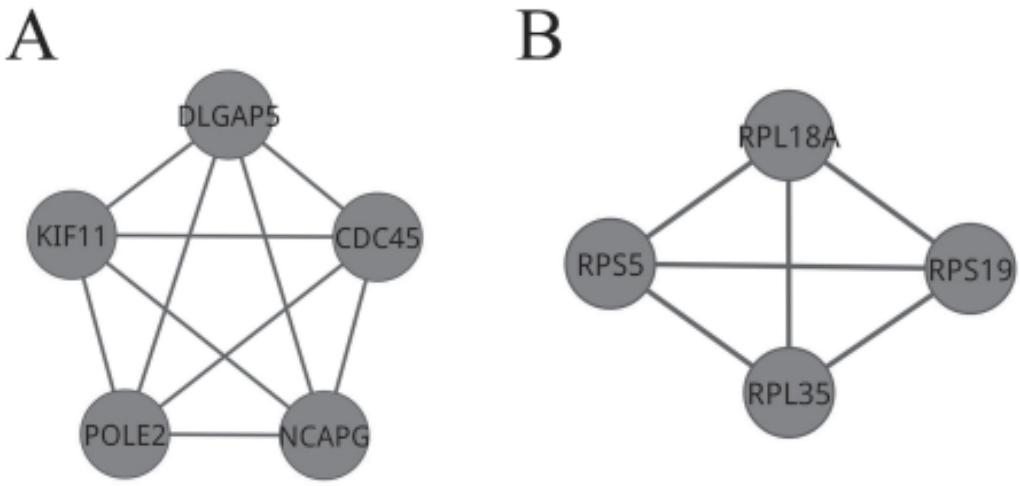

Fig. 2. Network for the core module.
a. Module 3
b. Module 6. Nodes represented core genes, and edges were the interactions among any two genes
Source: Author

DISCUSSION

RA is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality (He et al. 2017) . The increased understanding of the immune mechanisms has led to the development of a considerable number of new therapeutic agents that alter the natural history of the disease and reduce mortality, which revealed the pathogenesis of RA (Dennis et al. 2017; Venuturupalli et al. 2017). IFX is an effective agent to treat RA, but the functional molecular mechanism of this drug is far from understood. Meanwhile, potential biomarkers for treatment and prognosis of RA are also an urgent need.

It has been shown that the most significant genes and modules obtained from different studies for a particular disease are typically in consistent (Wang et al. 2017). To overcome this problem, a network strategy was used to evaluate pathogenic genes or modules for disease-association (Liu et al. 2017; Xu and Ning 2017). Construction of PPI networks integrated the PPI and specific gene expression profiles has been reported to conduct better than global PPI network (Deng et al. 2016). Beyond straightforward scoring genes in the complex network, it is crucial to study the behavior of modules across specific conditions in a controlled manner to understand the modus operandi of disease mechanisms and to implicate novel genes (Srihari et al. 2013), since some of important genes may not be identifiable through their own behavior, but their changes are quantifiable when considered in conjunction with other genes (as modules). What is required, therefore, is a systematic tracking gene and module behavior across specific conditions in a controlled manner (Zhang et al. 2016).

Hence, the researchers identified core modules and genes in RA following IFX therapy by combining systematic tracking of modules and attract method. Based on gene expression data, PPI data and SCC related analyses, the researchers explored ION and CON for IFX group and control group, respectively. The amount of nodes and interactions in the ION and CON was the same, but the weight distribution was different. Next, 15 candidate modules for IFX group and 13 candidate modules for the control group were detected utilizing clique-merging algorithm. By matching the same or similar candidate modules across the two groups, 8 modules were gained and each module was assigned to a differential MCD. Module 1 had the highest differential MCD, $\Delta C = 0.041$. Ultimately, using the attract method, the researchers identified 2 core modules (Module 3 and Module 6) and 9 core genes (*POLE2*, *CDC45*, *DLGAP5*, *KIF11*, *NCAPG*, *RPS5*, *RPL18A*, *RPL35* and *RPS19*).

Module 3 (P = 2.43E-04) consisted of 5 core genes (*POLE2*, *CDC45*, *DLGAP5*, *KIF11* and *NCAPG*), whose core genes interacted with each other and formed 10 interactions (as seen as Fig. 2a). While Module 6 (P = 2.59E-02) in Figure 2b included 4 core genes (*RPS5*, *RPL18A*, *RPL35* and *RPS19*) which made up 6 edges. *CDC45* (cell division cycle 45) is a member of the highly conserved multiprotein complex including the minichromosome maintenance proteins (MCMs) and DNA polymerase which is important for early steps of DNA replication in eukaryotes (Martinez et al. 2017; Ogino et al. 2017). It had been demonstrated that RA was an immune disease and related to cell cycle closely (Skalska et al. 2017), besides, the functions of IFX effected the cell cycle (Mitoma et al. 2005), and thus the researchers may infer that dysregulation of *CDC45* was associated the RA patients treated by IFX. (Table 3).

Table 3: Modules

Module	*Candidate module*		*MCD*		ΔC
	IFX	*Control*	*IFX*	*Control*	
1	4	4	0.363	0.404	0.041
2	12	12	0.349	0.382	0.033
3	3	2	0.314	0.342	0.028
4	5	10	0.347	0.321	0.026
5	8	13	0.358	0.333	0.025
6	11	12	0.360	0.382	0.022
7	7	8	0.340	0.319	0.021
8	7	10	0.340	0.321	0.019

CONCLUSION

In summary, researchers have successfully identified 2 core modules and 9 core genes for IFX treated RA patients. The findings might give great insights to reveal the molecular mechanism underlying IFX, and provide potential biomarkers for treatment and prognosis of this progression.

RECOMMENDATIONS

However, some deficiencies is existent in the researchers' analysis. Firstly, sample size extracted from databases is small. Second, the results summarized in this paper have not been clinically verified. Therefore, further clinical trial verification is necessary.

ACKNOWLEDGMENTS

This research received no specific grants from any funding agency in public, commercial, or not-for-profit sectors.

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Paper received for publication on March 2018
Paper accepted for publication on May 2018