Drug discovery in rheumatoid arthritis with joint effusion identified by text mining and biomedical databases

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Background: Rheumatoid arthritis is a long-term systemic disease that primarily affects multiple synovial joints throughout the body. Some patients with severe joint effusion even require repeated arthrocentesis or arthroscopic debridement to relieve symptoms, which causes them much suffering mentally and physically. This text-mining study was designed to find potential drugs that target key genes in this disease.

Methods: Firstly, we performed text mining by two keywords (“rheumatoid synovitis” and “joint effusion”) to get a common set of genes. Secondly, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis performed on these genes, and protein-protein interaction (PPI) network was constructed. Subsequently, the significant genes clustered in the PPI network were chose to execute gene-drug interaction analysis for potential drug discovery.

Results: Through text mining, 68 overlapping genes were identified as an initial set of key genes. Construction of the initial gene set’s PPI network showed that 25 genes clustered in a significant gene module. Ultimately, 8 out of 25 genes could be targetable by a total of 19 drugs.

Conclusions: The final 8 genes (PTGS2, TNF, VEGFA, IL1B, CCL2, VWF, IL6, and ESR1) and 19 drugs may provide significant therapeutic value for rheumatoid arthritis patients with joint effusion.

Keywords: Rheumatoid arthritis; joint effusion; drug discovery; text mining; bioinformatics analysis

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Introduction

Rheumatoid arthritis (RA) is a long-term systemic disease that primarily affects multiple synovial joints throughout the body. The prevalence of RA is approximately similar between different regions globally, ranging from 0.5% to 1% in adults (1-3). RA most often strikes in middle age, and is 2.5 times more common in women than in men (4,5). It usually causes joint pain, stiffness, swelling, or joint effusion, accompanied by extra-articular manifestations such as anemia, respiratory, or nervous system lesions. RA was responsible for approximately 38,000 deaths in 2013, placing a massive health management burden on various countries (6-8). The exact causes of RA are unclear today. Still, research has shown that both genetic [such as shared epitope (SE) of HLA-DR] and environmental (such as infection, tobacco) factors play a significant role (9,10). The primary pathogenic mechanism is the human immune system attacking the joints, resulting in inflammation and hyperplasia of the joint capsule, which usually affects bone and cartilage. A variety of cells, including T lymphocytes, B lymphocytes, macrophage-like synoviocytes (MLS),
and fibroblast-like synoviocytes (FLS) exhibit abnormal behavior that induces the production of multiple pro-inflammatory factors. And multiple inflammatory cascade responses, including overexpression of tumor necrosis factor, are involved in the development of rheumatoid arthritis. Typically, the inflammatory response mediated by TNF and IL6 can lead to severe joint destruction, making these two genes two key therapeutic targets (11,12).

In the management of RA, a crucial principle is that disease-modifying treatment should be given early after diagnosis to delay the progression of this disease or even achieve complete remission (13). NSAIDs are no longer first-line drugs because of their adverse effect profile and their inability to improve long-term prognosis of the disease. And early administration of no more than 10 mg of prednisone equivalent glucocorticosteroids has been shown to slow radiographic progression within six months (14). Overall, DMARDs (such as methotrexate) and the burgeoning biologic agents (such as TNF inhibitors) have their own pharmacological characteristics, mechanisms of action, and clinical indications (15,16). However, there are few studies on which drugs should be chosen in RA patients with severe joint effusion. Some patients even require repeated arthrocentesis or arthroscopic debridement to relieve symptoms, which causes physical and mental suffering.

Although drug development has a standard and rigorous process, it is sometimes more efficient to explore new indications for existing drugs, which can significantly reduce costs (17). One example is the successful treatment of erectile dysfunction with sildenafil. The rapid development of bioinformatics has brought new progress in the field of biomedicine. Based on the combination of text mining and data analysis, it will be more efficient to identify gene targets or signal pathways and to explore further the treatment model of the disease. Particularly in drug discovery, text mining can provide compelling evidence from a new perspective (18-20).

In our study, we carried out literature mining through keywords retrieval so as to preliminarily screen for the target genes. Next, we performed enrichment analyses of the target genes and further generated a set of relevant genes with a higher interconnection level by constructing protein-protein interaction (PPI) networks. With in-depth analysis of drug-gene interaction, a list of potential candidate drugs that specifically act on one of the focused genes was identified. Compared with bioinformatics in the cancer field, there are fewer researchers working on rheumatoid arthritis via text mining and data analysis. In summary, we explored potential drugs for the RA patients associated with severe joint effusion, which provided a brand new perspective and theoretical basis for the prevention and treatment of rheumatoid arthritis. We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/apm-20-2631b).

**Methods**

**Data acquisition**

The open-access database pubmed2ensembl (http://pubmed2ensembl.ls.manchester.ac.uk) was used as a tool to mine associated genes. Based on existing biological literature, pubmed2ensembl can filter and extract the genes associated with the keywords entered (21). We selected “rheumatoid synovitis” (RS) and “joint effusion” (JE) as keywords respectively for text mining. Then unique gene symbols were extracted from each result. The overlapping genes were the intersection of two gene sets, and then for the next further analysis.

**Functional and signal pathway enrichment analysis**

The Gene Ontology (GO) analysis can analyze and annotate genes in terms of cellular components, biological processes, and molecular function. The Kyoto Encyclopedia of Genes and Genomes (KEGG) (22) was created in 1995 by the Kanehisa laboratory to provide insight into advanced functional and biological systems using genome sequencing and other high-throughput experimental techniques. The web-based enrichment analysis tool (https://david.ncifcrf.gov/) was selected for GO and KEGG enrichment analysis of the gene set corresponding to the RS and JE intersection.

**PPI analysis and gene module analysis**

PPI networks consist of individual proteins that interact with each other to participate in various aspects of life processes such as biological signaling, regulation of gene expression, energy and material metabolism, and cell cycle. The well-known online analysis tool STRING (23) (http://string-db.org/) was used to analyze the PPI network for the selected genes. The STRING (Version 11) covers more than five thousand species and contains 24.6 million proteins and about three billion PPIs. Interactions in STRING derived from five primary sources: genomic
context predictions, high-throughput lab experiments, co-expression, automated text mining and previous knowledge in databases (24). As the input set, all overlapping gene symbols were uploaded into STRING and analyzed through “Multiple Protein” mode. In order to obtain more detailed data for drug mining, we set the interaction score threshold at 0.400. Besides, we downloaded the result file in TSV format and rebuilt the PPI network of target genes via Cytoscape (Version 3.7.1) (25). The STRING app in Cytoscape was used to visualize and embellish the PPI network. MCODE, an app that can calculate topological parameters of every node in the PPI network, was used to classify the significant nodes and to select highly relevant gene modules. The Degree Cutoff and the Node Score Cutoff were set at 2 and 0.2, respectively. Subsequently, the genes in highly interconnected gene modules were chosen to performed final drug discovery.

**Drug-gene interaction and functional analysis of potential genes**

DGIdb (http://www.dgidb.org) (26) contains over 40,000 genes and 10,000 drugs involved in over 100,000 drug-gene interactions or belonging to one of 42 potentially druggable gene categories. We uploaded module genes into the DGIdb database (Version 3.0) to search for drugs or compounds that may have therapeutic value. Besides, all drugs were approved by the FDA. Subsequently, the genes which have precise interactions with specific drugs were selected and analyzed for functional enrichment as target genes.

We just re-analyzed the open accessed datasets, and no ethical approval and informed consent were required by the local ethics committees. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

**Statistical analysis**

Fisher’s Exact test was used to analyzed GO and KEGG enrichments via online tool DAVID or R software (version 3.6.3). P<0.05 was considered statistically significant.

**Results**

**Data acquisition**

The flow chart of our study was shown in Figure 1. Based on the text mining strategy described method section, 107 genes were related to “rheumatoid synovitis”, and 410 genes were related to “joint effusion” . Besides, there were 68 overlapping genes of two gene sets.

**Functional and signal pathway enrichment analysis**

The online tool DAVID was used to perform enrichment analysis of the target genes and to visualize the data. Figure 2 and Table 1 showed the top six items most significantly enriched in each category (biological process, BP; cellular component, CC; or molecular function, MF) during the functional enrichment analysis. In the BP category, inflammation response, regulation of inflammation response, acute inflammation response, regulation of response to stimulus or external stimulus, regulation of defense response was most dramatically enriched. In the enrichment of CC category, extracellular space, extracellular region or region part, secretory granule lumen, secretory granule was significantly enhanced. As for the MF section, cytokine receptor binding, cytokine activity, receptor binding, growth factor activity, protease binding showed a higher degree of enrichment. Figure 3 showed the 20 most prominent pathways in the KEGG pathway analysis. The five pathways in which the 68 genes were most significantly involved were cytokine-cytokine receptor interaction, rheumatoid arthritis, IL-17 signaling pathway, TNF signaling pathway, and malaria.

**PPI analysis and gene module analysis**

The original data was processed by STRING database, Cytoscape software, STRING app, and MCODE app sequentially. Then we obtained a PPI network with 60 nodes and 542 edges (Figure 4A). There were eight genes that were not involved in constructing the PPI network, so they were excluded from the gene set. According to the aforementioned screening method, we got a gene module with 25 nodes, 253 edges (Figure 4B). Twenty-five genes with high levels of interaction were as follows: ELANE, CCL2, CCL4, CCL5, PTGS2, TNFRSF11B, CRP, IL1B, MMP3, MMP1, VWF, IL10, B2M, TIMP1, TIMP2, TNF, CSF2, CXCL8, ALB, CD40LG, IL6, IL4, VEGFA, ESR1, BDNF.

**Drug-gene interaction and functional analysis of potential genes**

Through querying the DGIdb database, we found that
Figure 1 Overall data mining procedure. Text mining was used to identify genes associated with rheumatoid synovitis and joint effusion by using pubmed2ensemble. Extracted 68 common genes were then analyzed for GO/KEGG enrichment by using DAVID. Further, the data were sequentially processed by the STRING database, Cytoscape software, STRING app, and MCODE app to obtain a gene module containing 25 genes. The final drug list (19 drugs) was obtained by gene-drug interaction analysis using the DGIdb database. GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 2

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number of Drugs</th>
</tr>
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<tbody>
<tr>
<td>PTGS2</td>
<td>6</td>
</tr>
<tr>
<td>TNF</td>
<td>4</td>
</tr>
<tr>
<td>VEGFA</td>
<td>3</td>
</tr>
<tr>
<td>IL1B</td>
<td>2</td>
</tr>
<tr>
<td>CCL2</td>
<td>1</td>
</tr>
<tr>
<td>VWF</td>
<td>1</td>
</tr>
<tr>
<td>IL6</td>
<td>1</td>
</tr>
<tr>
<td>ESR1</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

Rheumatoid arthritis is one of the most common chronic autoimmune diseases worldwide today, and it causes immeasurable physical and psychological damage to the patients. Through a genome-wide association study meta-analysis, Okada et al. identified 42 novel risk loci in RA patients, which may reveal the underlying genes and pathways that contribute to the pathogenesis of RA (27).
Figure 2 The top six significant GO terms of common genes. The bar charts represent the counts of genes classified in the BP, CC and MF respectively; the orange line chart represents the significance of enrichment terms. The horizontal coordinate represents each GO term, the left vertical coordinate represents the number of enriched genes, and the right vertical coordinate represents −log(P value). GO, gene ontology; BP, biological process; CC, cellular component; MF, molecular function.

Table 1 The gene ontology enrichment of the 68 common genes

<table>
<thead>
<tr>
<th>Category</th>
<th>ID</th>
<th>Term</th>
<th>Count</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP_FAT</td>
<td>GO:0006954</td>
<td>Inflammatory response</td>
<td>24</td>
<td>8.01E-17</td>
</tr>
<tr>
<td>BP_FAT</td>
<td>GO:0050727</td>
<td>Regulation of inflammatory response</td>
<td>18</td>
<td>2.57E-15</td>
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<tr>
<td>BP_FAT</td>
<td>GO:0002526</td>
<td>Acute inflammatory response</td>
<td>13</td>
<td>1.79E-13</td>
</tr>
<tr>
<td>BP_FAT</td>
<td>GO:0048584</td>
<td>Positive regulation of response to stimulus</td>
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<td>2.78E-13</td>
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<td>BP_FAT</td>
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<td>4.98E-13</td>
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<tr>
<td>BP_FAT</td>
<td>GO:0031347</td>
<td>Regulation of defense response</td>
<td>21</td>
<td>5.71E-13</td>
</tr>
<tr>
<td>CC_FAT</td>
<td>GO:0005615</td>
<td>Extracellular space</td>
<td>35</td>
<td>4.29E-18</td>
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<tr>
<td>CC_FAT</td>
<td>GO:0005576</td>
<td>Extracellular region</td>
<td>47</td>
<td>5.34E-11</td>
</tr>
<tr>
<td>CC_FAT</td>
<td>GO:0044421</td>
<td>Extracellular region part</td>
<td>42</td>
<td>3.98E-10</td>
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<tr>
<td>CC_FAT</td>
<td>GO:0034774</td>
<td>Secretory granule lumen</td>
<td>7</td>
<td>2.05E-06</td>
</tr>
</tbody>
</table>

Table 1 (continued)
Pathway enrichment

Pathway name

Yersinia infection
Viral protein interaction with cytokine and cytokine receptor
Toll-like receptor signaling pathway
TNF signaling pathway
Rheumatoid arthritis
PI3K-Akt signaling pathway
Pertussis
Pathways in cancer
NOD-like receptor signaling pathway
Malaria
Jak-STAT signaling pathway
Influenza A
IL-17 signaling pathway
Human cytomegalovirus infection
Hematopoietic cell lineage
Cytokine-cytokine receptor interaction
Chagas disease (American trypanosomiasis)
Asthma
Amoebiasis
AGE-RAGE signaling pathway in diabetic complications

Figure 3 Scatter plot of enriched KEGG pathways statistics. Q-value is corrected P-value ranging from 2.18E-21 to 4.00E-08. The color and size of the dots represent the range of the Q-value and the common genes mapped to the indicated pathways, respectively. Top 20 enriched pathways are shown in the figure. KEGG, Kyoto Encyclopedia of Genes and Genomes.
However, they did not identify specific drugs of potential therapeutic value. We used a bioinformatics approach to identify 19 drugs that may have improved outcomes in RA patients with severe joint effusion. These 19 drugs target the following eight genes: PTGS2 (6 drugs), TNF (4 drugs), VEGFA (3 drugs), IL1B (2 drugs), CCL2, VWF, IL6, and ESR1 (1 drug each). To some extent, these genes may play an essential role in the pathogenesis of RA.

**Figure 4** The PPI networks construction and significant gene module analysis. (A) The entire PPI networks of 68 common genes; (B) the significant gene module containing 25 genes.
Prostaglandin-endoperoxide synthase 2 (PTGS2), also known as COX2, can significantly promote the production of prostaglandins in synovial tissues of RA patients (28). MicroRNA-101-3p can act as an inhibitor to target COX2 and reduce the proliferation of FLS cells in a mouse model of RA, thereby alleviating joint effusion (29). In short-term studies, tumor necrosis factor (TNF) inhibitors have shown better efficacy in patients with advanced disease (3). But a meta-analysis of 1,264 patients in 16 randomized controlled trials showed that about 47 percent of patients had a relapse after discontinuation of the TNF-α inhibitor (30). In Mexican women, the lower risk of RA may be related to vascular endothelial growth factor A (VEGFA) polymorphism, and among the elderly in China, the VEGFA rs699947 CA genotype is associated with a lower risk of RA, too (31,32). Using single-cell sequencing, the team of Zhang et al. revealed the presence of a large number of IL1B+ pro-inflammatory monocytes in the synovial tissue of RA patients, which may be one of the driving cell populations of joint inflammation (33). Chemokine (C-C motif) ligand 2 (CCL2), also known as MCP1, plays a significant role in inducing monocyte infiltration and recruitment of peripheral leukocytes in synovial tissue of rheumatoid arthritis (34,35). By promoting the proliferation and invasive capacity of pro-inflammatory factors such as CCL2 and IL6, RA patients’ fibroblast-like synoviocytes can be highly sensitive to C-reactive protein (36). IL6-induced WNT5A activates canonical WNT signaling for the autocrine proliferation of human synovial fibroblasts in RA (37). Besides, a 24-week randomized controlled trial showed a better clinical benefit [achieving American College of Rheumatology (ACR) 20 response] of IL6 receptor antibodies over methotrexate (monotherapy) (38). The increase of von Willebrand factor (VWF) activity may be related to the increased risk of atherosclerosis in RA patients without cardiovascular risk factors (39,40). Estrogen receptor 1 (ESR1) encodes an estrogen receptor, a ligand-activated transcription factor composed of several domains. And ESR1 gene polymorphism may affect the efficacy of drugs and the age of onset of RA (41-43).

Some of the drugs we have found are not commonly used to treat rheumatoid arthritis. The primary indication

Figure 5 The drugs targeted to genes and functional enrichment analysis of final genes. (A) Chord plot for the connection between 19 drugs and 8 genes; (B) chord plot for functional enrichments of the final 8 genes.
Table 2: The specified information of drugs and its target genes

<table>
<thead>
<tr>
<th>Number</th>
<th>Drug</th>
<th>Gene</th>
<th>Interaction type</th>
<th>Score*</th>
<th>Drug class</th>
<th>PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DANAZOL</td>
<td>CCL2</td>
<td>Inhibitor</td>
<td>1.67</td>
<td>Anti-endometriosis agent, antineoplastic agent</td>
<td>11056242</td>
</tr>
<tr>
<td>2</td>
<td>ETORICOXIB</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>6.47</td>
<td>Anti-inflammatory agent, selective cyclooxygenase 2 inhibitors</td>
<td>17573128</td>
</tr>
<tr>
<td>3</td>
<td>CARPROFEN</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>2.77</td>
<td>Anti-inflammatory agents, non-steroidal</td>
<td>15939622</td>
</tr>
<tr>
<td>4</td>
<td>FLURBIPROFEN</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>1.08</td>
<td>Anti-inflammatory agents, non-steroidal</td>
<td>10091674</td>
</tr>
<tr>
<td>5</td>
<td>OXAPROZIN</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>1.69</td>
<td>Anti-inflammatory agents, non-steroidal</td>
<td>19338579</td>
</tr>
<tr>
<td>6</td>
<td>ETODOLAC</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>1.62</td>
<td>Anti-inflammatory agents, non-steroidal</td>
<td>12824918</td>
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<tr>
<td>7</td>
<td>SALSALETE</td>
<td>PTGS2</td>
<td>Inhibitor</td>
<td>1.62</td>
<td>Anti-Inflammatory agents, non-steroidal</td>
<td>9711054</td>
</tr>
<tr>
<td>8</td>
<td>CANAKINUMAB</td>
<td>IL1B</td>
<td>Inhibitor, binder, antibody</td>
<td>8.46</td>
<td>Therapeutic antibodies, DMARD</td>
<td>19169963</td>
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<tr>
<td>9</td>
<td>RILONACEPT</td>
<td>IL1B</td>
<td>Binder, inhibitor</td>
<td>2.01</td>
<td>Anti-inflammatory agent, DMARD</td>
<td>23319019</td>
</tr>
<tr>
<td>10</td>
<td>CAPLACIZUMAB</td>
<td>VWF</td>
<td>Inhibitor</td>
<td>14.2</td>
<td>Antithrombotic, antibody fragment</td>
<td>Not available</td>
</tr>
<tr>
<td>11</td>
<td>GOLIMUNAB</td>
<td>TNF</td>
<td>Inhibitor, antibody</td>
<td>3.87</td>
<td>Immunosuppressive agents</td>
<td>21079302</td>
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<tr>
<td>12</td>
<td>INFILXIMAB</td>
<td>TNF</td>
<td>Inhibitor</td>
<td>1.13</td>
<td>Immunosuppressive agents, DMARD</td>
<td>16720636</td>
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<td>13</td>
<td>ADALIMUNAB</td>
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<td>14</td>
<td>ETANERCEPT</td>
<td>TNF</td>
<td>Inhibitor, antibody</td>
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<td>Immunomodulatory agents, antirheumatic agents</td>
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<tr>
<td>15</td>
<td>SILTUXIMAB</td>
<td>IL6</td>
<td>Antagonist, antibody, inhibitor</td>
<td>8.61</td>
<td>Therapeutic antibodies, agents reducing cytokine levels</td>
<td>8823310</td>
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<tr>
<td>16</td>
<td>RANIBIZUMAB</td>
<td>VEGFA</td>
<td>Inhibitor</td>
<td>6.51</td>
<td>Treatment for AMD</td>
<td>18046235</td>
</tr>
<tr>
<td>17</td>
<td>PEGAPTANIB SODIUM</td>
<td>VEGFA</td>
<td>Antagonist</td>
<td>2.37</td>
<td>Treatment for AMD</td>
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<td>AFLIBERCEPT</td>
<td>VEGFA</td>
<td>Antibody, binder, inhibitor</td>
<td>1.89</td>
<td>Treatment for AMD</td>
<td>22813448</td>
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<tr>
<td>19</td>
<td>CLOMIPHENE</td>
<td>ESR1</td>
<td>Antagonist</td>
<td>0.79</td>
<td>Fertility agents</td>
<td>19761360</td>
</tr>
</tbody>
</table>

*, the score is based on the evidence of an interaction, meaning that it doesn’t changed from search to search. DMARD, disease-modifying antirheumatic drug; AMD, age-related macular degeneration.

for danazol is endometriosis, but it has also been studied for the treatment of autoimmune diseases such as autoimmune progesterone dermatitis, systemic lupus erythematosus, and autoimmune thrombocytopenia associated with rheumatic diseases (44-46). Caplacizumab is a drug used to treat acquired thrombotic thrombocytopenic purpura (47). More interestingly, some drugs (ranibizumab, aflibercept and pegaptanib sodium) that target VEGFA for the treatment of age-related macular degeneration may also be useful for rheumatoid patients with joint effusion. VEGF can induce migration of vascular endothelial cells and plays a key role in angiogenesis (48,49), which is essential in the pathological process of both RA and AMD. Therefore, our findings make it possible to use existing drugs for the treatment of RA.

In addition, DMARDs and COX2 inhibitors are the more common drugs currently used in RA treatment. However, in many cases we do not know how to choose the type of them. Applying the drugs, we have found (Table 1) may give better results. As an IL1B inhibitor, Canakinumab, which has the highest interaction score in these drugs, deserves to be more explored for its therapeutic value in RA patients with joint effusion. Although NASIDs are no longer first-line drugs for rheumatoid therapy, they still have a reliable effect on the improvement of pain and stiffness (3). Interestingly, our study shows that joint effusion, one of the symptoms...
Table 3 The functional enrichments of the final 8 genes

<table>
<thead>
<tr>
<th>Category</th>
<th>ID</th>
<th>Term</th>
<th>Genes</th>
<th>P value</th>
</tr>
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<tr>
<td>BP_FAT</td>
<td>GO:0045429</td>
<td>Positive regulation of nitric oxide biosynthetic process</td>
<td>IL6, IL1B, PTGS2, ESR1, TNF</td>
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<td>BP_FAT</td>
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<tr>
<td>BP_FAT</td>
<td>GO:1903428</td>
<td>Positive regulation of reactive oxygen species biosynthetic process</td>
<td>IL6, IL1B, PTGS2, ESR1, TNF</td>
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<td>BP_FAT</td>
<td>GO:0032103</td>
<td>Positive regulation of response to external stimulus</td>
<td>IL6, IL1B, CCL2, PTGS2, TNF, VEGFA</td>
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<td>BP_FAT</td>
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<td>Regulation of inflammatory response</td>
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<td>4.71E-08</td>
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<td>BP_FAT</td>
<td>GO:0008284</td>
<td>Positive regulation of cell proliferation</td>
<td>IL6, IL1B, CCL2, PTGS2, ESR1, TNF, VEGFA</td>
<td>1.16E-07</td>
</tr>
<tr>
<td>BP_FAT</td>
<td>GO:0002675</td>
<td>Positive regulation of acute inflammatory response</td>
<td>IL6, IL1B, PTGS2, TNF</td>
<td>1.33E-07</td>
</tr>
<tr>
<td>CC_FAT</td>
<td>GO:0005615</td>
<td>Extracellular space</td>
<td>IL6, IL1B, CCL2, TNF, VEGFA</td>
<td>0.00265906</td>
</tr>
<tr>
<td>MF_FAT</td>
<td>GO:0005125</td>
<td>Cytokine activity</td>
<td>IL6, IL1B, CCL2, TNF, VEGFA</td>
<td>1.39E-06</td>
</tr>
<tr>
<td>MF_FAT</td>
<td>GO:0005126</td>
<td>Cytokine receptor binding</td>
<td>IL6, IL1B, CCL2, TNF, VEGFA</td>
<td>3.18E-06</td>
</tr>
<tr>
<td>MF_FAT</td>
<td>GO:0005102</td>
<td>Receptor binding</td>
<td>IL6, VWF, IL1B, CCL2, TNF, VEGFA</td>
<td>1.33E-04</td>
</tr>
</tbody>
</table>

of rheumatoid arthritis, can be relieved by selective COX2 inhibitors. Given the adverse effect profile of these drugs and their inability to slow disease progression, if necessary, the combination of COX2 inhibitors with proton-pump inhibitors, DMARDs, etc. should be considered. The levels of nitric oxide and inducible nitric oxide synthase (iNOS), which act as mediators of the inflammatory response, are significantly increased in the synovial fluid of RA patients. By interfering with the synthesis of IL12 and B-cell activating factors (BAF), nitric oxide can disrupt the normal physiological function of T and B cells (50,51). Also, studies have shown that nitric oxide plays a vital role in vascular endothelial cell dysfunction in RA (52). Serum cytokine activity in RA patients is strongly correlated with treatment effect, and multiplexed cytokine testing may be a new way of evaluation (53). Activation of the MAPK, NF-kB, JAK-STAT, and Toll signaling pathways can lead to the development of RA. In contrast, activation of the classical Wnt pathway can induce osteogenesis and promote the repair of damaged joints, which has a positive effect on the treatment of RA (54-56).

In our study, a bioinformatics strategy was used to search for drugs suitable for RA patients with joint effusion. Among the 19 drugs identified, the initial indications are not only RA but also AMD, tumor, and other diseases. As a result of our analysis, it suggests opportunities for further research in the clinical setting and give us a chance to explore new indications of these available drugs. Although our study provides new insight into drug discovery in rheumatoid arthritis, more basic experiments and clinical evaluations are needed to confirm our results in the future.

Conclusions

The final eight genes (PTGS2, TNF, VEGFA, IL1B, CCL2, VWF, IL6, and ESR1) and 19 drugs may provide significant therapeutic value for RA patients with joint effusion.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We just re-analyzed the open accessed datasets (http://pubmed2ensembl.ls.manchester.ac.uk), and no ethical approval was required by the local ethics committees. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

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References


49. Shibuya M. Vascular endothelial growth factor-dependent and -independent regulation of angiogenesis. BMB Rep 2008;41:278-86.


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