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Research paper

Identifying genes related with rheumatoid arthritis via system biology analysis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that mainly attacks synovial joints. However, the underlying systematic relationship among different genes and biological processes involved in the pathogenesis are still unclear. By analyzing and comparing the transcriptional profiles from RA, OA (osteoarthritis) patients as well as ND (normal donors) with bioinformatics methods, we tend to uncover the potential molecular networks and critical genes which play important roles in RA and OA development. Initially, hierarchical clustering was performed to classify the overall transcriptional profiles. Differentially expressed genes (DEGs) between ND and RA and OA patients were identified. Furthermore, PPI networks were constructed, functional modules were extracted, and functional annotation was also applied. Our functional analysis identifies 22 biological processes and 2 KEGG pathways enriched in the commonly-regulated gene set. However, we found that number of set of genes differentially expressed genes only between RA and ND reaches up to 244, indicating this gene set may specifically accounts for processing to disease of RA. Additionally, 142 biological processes and 19 KEGG pathways are over-represented by these 244 genes. Meanwhile, although another 21 genes were differentially expressed only in OA and ND, no biological process nor pathway is over-represented by them.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that affects many tissue and organs, but mainly attacks synovial joints that ultimately leads to joint destruction (Gay et al., 1993). RA is the most common autoimmune disease, afflicting around 0.5%–2% of the human population (Kvien, 2004). RA leads to severe morbidity and disability if incorrectly treated, imposing a substantial economic burden on the affected individuals. The inflammatory process associated with RA is primarily observed in the synovial tissue. Synovial hyperplasia results from synovial outgrowths or synovial villi, composed of macrophages, synovial lining cells, lymphocytes and blood vessels (Beasley, 2012). Cartilage penetration, cartilage damage and joint erosion result in the synovial pannus producing enzymes, since joint destruction occurs (Scott and Symmons, 2008).

Osteoarthritis (OA) is a group of states associated with defective articular cartilage and changes in the underlying bone. Pathological changes in articular cartilage and subchondral bone result from chondrocyte imbalance in the extracellular matrix (Roach, 2008). In fact, OA is a degenerative disorder of the joints showing similar symptoms such as RA. Although both the diseases share similar symptoms, it has been proposed that RA follows an inflammatory pathway of pathogenesis, thus, differentiating it from OA.

Diagnosis and assessment of RA and OA is largely based on semi-quantitative methods of diagnosis, including symptoms, joint damage and physical function (Biswas et al., 2011). At present, no definite cure has been proposed for RA and OA and the management of these diseases depends upon early detection and aggressive treatment. Therefore, it is increasingly important to explore the molecular mechanisms of these diseases and analyze the associated signaling pathways, in order to uncover an effective therapeutic approach.

Microarrays (Jayapal and Melendez, 2006) have been used to study the gene expression patterns associated with various disease models in both basic and translational research in the past decade (Koh et al., 2007; Jiang et al., 2008; Dai et al., 2009; Chen et al., 2010, 2011; Choy et al., 2010; Gurung et al., 2010; Hegde et al., 2010). It helps to probe into the key genes implicated in the pathogenesis and may provide clues for the treatment of human diseases. Thus, to uncover potential genes and biological processes involved in pathogenesis of this inflammatory disorder, we studied publicly available microarray expression data of tissues collected from RA and OA patients as well as ND (normal donors). In our study, we identified 42 genes differentially expressed

Abbreviations: RA, rheumatoid arthritis; OA, osteoarthritis; ND, normal donors; DEGs, differentially expressed genes; SAM, Significance Analysis of Microarrays; PPI, protein–protein interaction; STRING, Search Tool for the Retrieval of Interacting Genes.

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0378-1119/

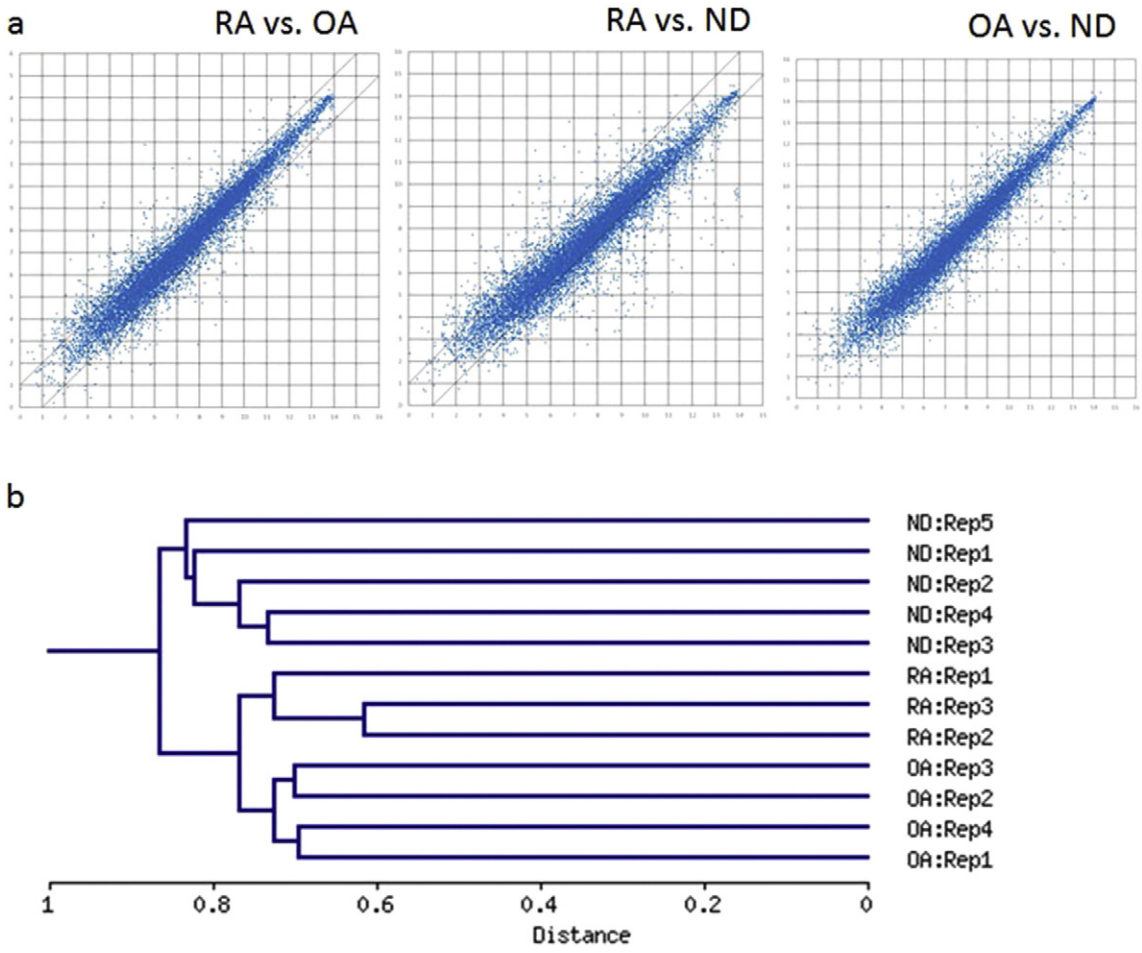

Fig. 1. (a) Scatter plots compare the average signal values for all probe sets of RA vs. OA, RA vs. ND or OA vs. ND. (b) Hierarchical clustering of replications for global gene expression. ND: normal donor; RA: rheumatoid arthritis; OA: osteoarthritis.

between OA and ND, and 228 genes are up-regulated in RA while 36 genes are down-regulated in RA using differentially expressed gene (DEG) analysis. We identified 22 biological processes and 2 KEGG pathways enriched in the commonly-regulated gene set of RA and OA patients.

2. Materials and methods

2.1. Collection of data

To identify genes and biological pathways and signaling networks that are involved in the RA and/or OA, we searched Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) using "rheumatoid arthritis" and "osteoarthritis" as key words. Microarray datasets that were produced via commercial platforms and had enough

Table 1
Number of genes significantly differentially expressed between RA and ND and OA and DN.

FDR < 0.05; fold change >2		
	Gene number	Common gene number
RA over OA	0	0
RA under OA	0	
OA over ND	22	11
RA over ND	228	
OA under ND	20	10
RA under ND	36	

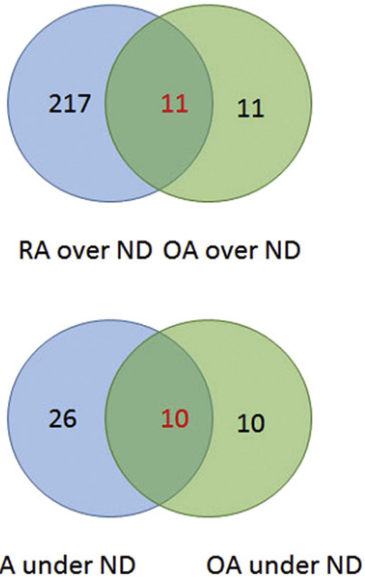

Fig. 2. Venn diagram indicates the number of overlapping genes differentially expressed between normal and arthritic tissues. We identified 42 genes differentially expressed between OA and ND, of which 22 are up-regulated and 20 are down-regulated. Meanwhile, we obtained differential expression between RA and ND, showing that 228 genes are up-regulated in RA while 36 genes are down-regulated.