

Identify asthma genes across three phases based on protein–protein interaction network

ISSN 1751-8849

Received on 9th January 2015

Revised on 26th February 2015

Accepted on 21st March 2015

doi: 10.1049/iet-syb.2015.0001

www.ietdl.org

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Abstract: Asthma is a common inflammatory disease that is generally caused by genetic mutations or environmental factors. Recently, the emerging of omics data provides an alternative way to understand asthma. In this study, the authors present a new framework to detect asthma disease genes based on protein–protein interaction network (PPIN) and gene expression. Specifically, they construct PPINs for different stages of asthma, and detect those interactions occurred in the specific stages. By investigating the proteins in these stage-specific interactions, they find they are more likely related to asthma, and the functional enrichment analysis indicate that the pathways enriched in the differential interactions are related to the progress of asthma. Moreover, some proteins in the differential interactions have been previously reported to be related to asthma in the literature, implying the usefulness of the proposed approach.

1 Introduction

Asthma is a common inflammatory disease affecting over 300 million people worldwide [1, 2], with ~250 000 annual deaths attributed to the disease [3, 4], whereas most deaths could be avoided with timely intervention or prevention. It is estimated that the number of people affected by the disease will grow by more than 100 million by 2025. It is found that some asthma were caused by environmental factors, for example, exposure to fumes, gases or dust, and the environmental factors are responsible for 11% of asthma cases worldwide [4]. Unlike chronic obstructive pulmonary disease, asthma may result in eosinophils in tissues and sputum, thickening of the mucous membrane and bronchial muscle hypertrophy. Asthma may lead to the disability of patients, and greatly influences their life quality. Unfortunately, the precise pathologies of asthma are still poorly understood and effective therapies are demanded.

In the literature, some genes have been found to be related to asthma. For example, Immunoglobulin E (IgE), cytokines (interleukins and interleukin receptors (IL) [IL]-4, IL-3 and IL-5) and TH2 have been reported to be related to asthma, and were used as biomarkers [5–7]. Accordingly, some drugs have been developed for the disease based on the invaluable knowledge. For instance, Omalizumab is a recombinant humanised monoclonal immunoglobulin G1 antibody (Ab) that prevents the attachment of IgE to the Fcε receptor of mast cells, basophils and dendritic cells by binding to the Fc portion of IgE, which in turn represses the expression of IgE. There are also some antibodies that have been designed for asthma by targeting IL-13, for example, CAT-354 that is undergoing clinical trials [5]. However, asthma is a common heterogeneous disease characterised by variable airflow obstruction, airway inflammation and bronchial hyper responsiveness [8], which makes it necessary to identify the asthma-related genes and design effective therapies.

Recently, the advances of biotechnologies produce a huge amount of omics data, for example, microarray gene expression and

sequencing data. These omics data enables us to investigate the molecular mechanisms underlying the development and progression of asthma from a systematic perspective. For example, with the transcriptome data, ADAM8 was found to be involved in the progress of asthma [9] and STAT6 was found to be associated with asthma [10]. With the knowledge that distinct microRNAs regulating the expression level of genes may be related to asthma disease development, some related works have been done by profiling the microRNAs to predict novel asthma associated genes [11–13]. For example, the gene AQP4 was predicted as the target of microRNA-203 [11]. It has been noted that complex diseases, such as asthma, are generally caused by the dysfunction of certain pathways instead of by the mutations of single gene [14], where pathway play more important roles in biology and are more easy to explain [15]. In addition, many diseases are caused because of the dysfunction of multiple genes, and these genes tend to interact with each other in a functionally distinguishable module [16]. In this paper, we adopted the differential interaction idea proposed by Liu *et al.* [17] to identify asthma-related genes. We constructed protein–protein interaction networks (PPINs) for different stages of asthma, and detected those interactions that occur differentially in different stages of asthma. By investigating the proteins in these stage-specific interactions, we find they are more likely related to asthma, and the functional enrichment analysis indicate that the pathways enriched in the differential interactions are related to the progress of asthma. Moreover, some proteins in the differential interactions have been previously reported to be related to asthma in the literature, implying the usefulness of the proposed approach.

2 Materials and methods

2.1 Data source

The gene expression profiles of asthmatic bronchial epithelial cells were obtained from Gene Expression Omnibus with accession

number GSE43696 [18], involving 20 normal control (NC) samples, 50 mild-moderate asthmatic (MMA) samples and 38 severe asthmatic (SA) samples. Probe sets were mapped to their corresponding gene symbols, the expression values of replicated probe sets corresponding to one gene were averaged. The gene expression profiles were normalised as follows

$$X'_{ij} = \frac{(X_{ij} - \bar{X}_j)}{\text{Std}_j} \quad (1)$$

where X'_{ij} is the normalised expression value of gene i in sample j , X_{ij} is the original expression value of gene i in sample j and $\bar{X}_j$ and Std_j , respectively, denote the mean and standard deviation of expression values for genes within sample j .

The protein–protein interaction data were retrieved from the human protein reference database [19]. The above obtained gene expression data were then superimposed on the PPIN, and only the proteins whose encoding genes express were considered here. As a result, 9284 genes that can be found in both the PPIN and the gene expression profiles were kept for further analysis, including 37 599 protein–protein interactions.

2.2 Detection of differentially expressed genes

In general, the genes that are differentially expressed in disease are assumed to be related to the corresponding disease. In this paper,

to see the effectiveness of the differential interactions, we compared them with the differentially expressed genes (DEGs). Here, the genes differentially expressed (DEGs) between different stages, that is, NC against MMA and MMA against SA, were detected with Student's t -test. The genes were determined to be differentially expressed if their corresponding p -values are smaller than 0.01.

To further investigate how the genes in the differential interactions detected above, functional enrichment analysis was conducted for these genes with [20], and the function information can help understand the roles of these genes in asthma.

2.3 Identification of asthma-related genes with differential interactions

Although the DEGs detected above provide valuable information and are potentially asthma genes, a recent paper by Liu *et al.* demonstrated that differential interactions can result in more reliable and biologically meaningful predictions, based on the combination of the gene expression and the protein–protein interaction [14]. In this paper, the gene expression data were divided into three subsets according to the category of samples, that is, NC, MMA and SA. Subsequently, the protein–protein interactions that occur differentially between sample categories were detected. For example, the protein interactions occur in NC but miss in MMA or vice versa were differential interactions

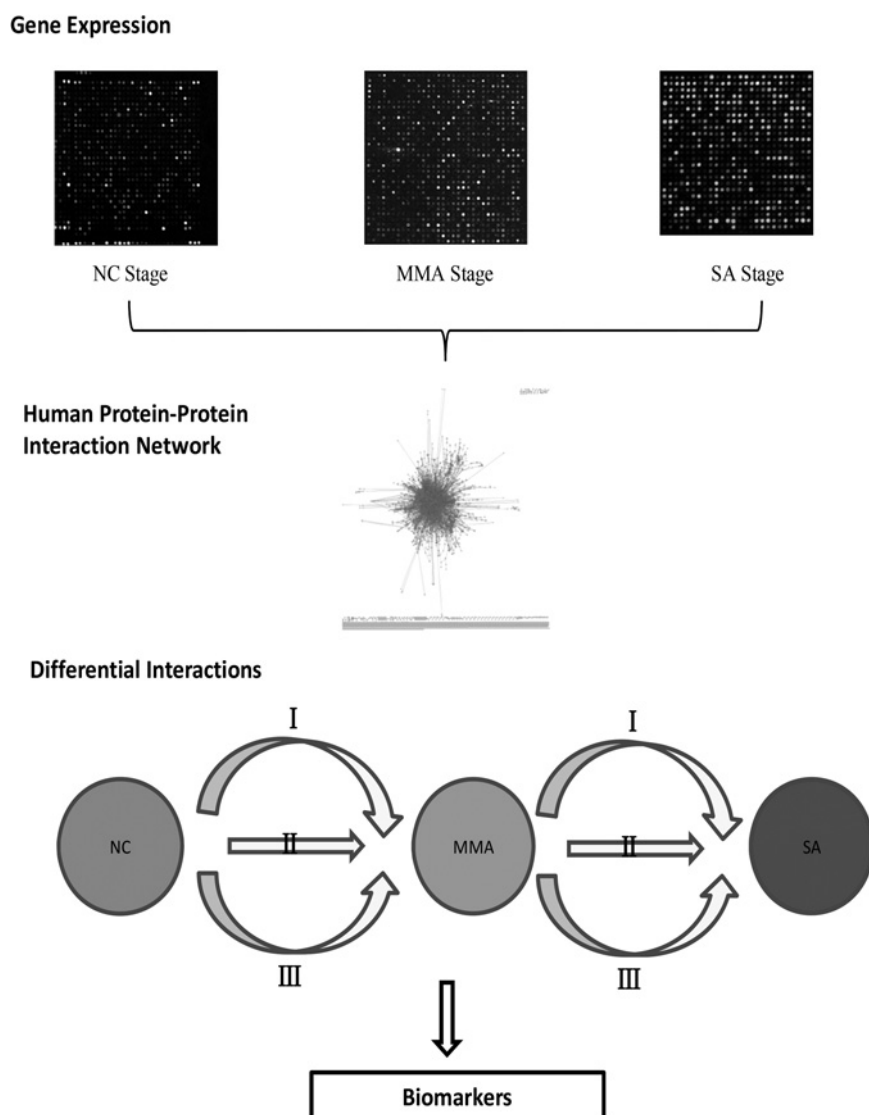


Fig. 1 Flowchart of detecting differential interactions between different stages of asthma

Table 1 Differential interactions detected in NC against MMA

Differential interactions type	Detected differential interactions	Genes
I	GTF3C2---GTF3C4, GNB2L1---NFATC1, NFASC---SCN3B, BRAP---CNKSR1, MND4---TP53, FMOD---TGFB1, GNB3---GNG4, SMURF2---TXNIP, RXRG---THRA, CD4---CXCL12, SMURF1---SQSTM1, CSF1R---INPPL1, DHX30---SKIL, MAD2L1---TSC22D4, CDK5---CDK5RAP1	NFATC1, MAD2L1, TGFB1, CSF1R, CD4, GTF3C2, GTF3C4, TXNIP, SMURF1, SMURF2, INPPL1, CNKSR1, THRA, GNB2L1, FMOD, MND4, RXRG, TSC22D4, GNB3, NFASC, SKIL, CXCL12, SQSTM1, BRAP, TP53, DHX30, GNG4, CDK5, CDK5RAP1, SCN3B
III	PAR3---SMAD7, CACNA1E---EFHC1, BRCA1---SMAD2, CS---DYNLL1, AR---GTF2H1, GIGYF1---GRB10, HSPA4---PRSS23, KIAA1377---RBM23, ARF1---INSR, ALOX5---TGFB1, DTX2---UBQLN4, CASP1---FGF2, JAK3---STAM2, TRIM23---ZNF581, COX17---PPBP, EPS15---SNAP91, DNMT3B---SUMO1, EPN1---ZBTB16, CRYAA---CS, LPXN---PHF21A, GAL---GALR2, DAZAP2---ZFYVE9, CYFIP2---FMR1, CSNK2A1---JUN, C7ORF64---PSMD11, GNAI1---IGF1R, SERPINB9---UNC119, HSP90AB1---IKBK	DNMT3B, DYNLL1, GIGYF1, DTX2, HSPA4, SUMO1, SMAD7, PHF21A, SMAD2, CRYAA, SNAP91, ZFYVE9, INSR, IKBK, FMR1, GNAI1, EPS15, ZBTB16, UNC119, ARF1, CYFIP2, JUN, CACNA1E, UBQLN4, FGF2, HSP90AB1, PPBP, GAL, JAK3, GTF2H1, BRCA1, IGF1R, C7ORF64, ALOX5, EPN1, TRIM23, ZNF581, AR, CS, EFHC1, TGFB1, CSNK2A1, SERPINB9, DAZAP2, PAR3, CASP1, GRB10, PSMD11, GALR2, RBM23, LPXN, PRSS23, KIAA1377, STAM2, COX17

between NC and MMA. In this way, the differential interactions were detected for NC against MMA and MMA against SA. Fig. 1 shows the workflow for differential interaction detection, where the differential interactions were detected by comparing the gene expression data from different stages of asthma. To detect the differential interactions, an interaction score was defined for each protein–protein interaction (PPI). Here, the scores for differential interactions of NC against MMA ($PPI_{cm(i,j)}$) and MMA against SA ($PPI_{ms(i,j)}$) were separately defined as follows

$$PPI_{cm(i,j)} = \frac{\min(W_{ij(m)}, W_{ij(c)})}{\max(W_{ij(m)}, W_{ij(c)})} \quad (2)$$

$$PPI_{ms(i,j)} = \frac{\min(W_{ij(s)}, W_{ij(m)})}{\max(W_{ij(s)}, W_{ij(m)})} \quad (3)$$

where c , m and s , respectively, denote NC, MMA and SA, and W_{ij} is the weight defined for the interaction between protein i and protein j and was defined as the Pearson correlation coefficient based on their transcriptional expression profiles as follows

$$W_{ij} = \frac{|\text{cov}(X, Y)|}{\sigma_X \sigma_Y} \quad (4)$$

where X and Y are expression values of genes i and j , respectively.

In this paper, according to their interactions scores, the differential interactions were grouped into three different types: (i) type I, interactions emerging during disease progress; (ii) type II, interactions that are not significantly different between distinct stages; and (iii) type III, interactions missing during disease progress. We can see that types I and III interactions are more likely related to diseases, and the proteins associated with these interactions are more possibly related to the disease progress. The interactions score thresholds for these two types of interactions were set to 0.001, where the interactions with score <0.001 and

$W_{ij(c)} < W_{ij(m)}$ were grouped into type I, whereas those with scores <0.001 and $W_{ij(c)} > W_{ij(m)}$ were grouped into type III. For type II interactions, those interactions with $PPI_{cm(i,j)}$ or $PPI_{ms(i,j)}$ score larger than 0.001 were grouped into type II.

With the differential interactions defined above, we detected the differential interactions that happen between different stages, that is, NC against MMA and MMA against SA. Moreover, to check whether differential interactions exist through the whole stages of asthma progress or not, we investigated the differential interactions that occur across the three different stages of asthma. These differential interaction can be grouped into the following four classes: type I in NC against MMA and type I in MMA against SA (I–I), type I in NC against MMA and type III in MMA against SA (I–III), type III in NC against MMA and type I in MMA against SA (III–I) and type III in NC against MMA and type III in MMA against SA (III–III). Since these differential interactions happen across the three different stages, they may play important roles in asthma.

3 Results

3.1 Detection of differential interactions between NC and MMA

In this section, we first detected the differential interactions that happen between NC and MMA stages of asthma. As a result, 43 differential interactions were detected in total, where 85 proteins were involved in the interactions. Among the differential interactions, 15 interactions among 30 genes were from type I interactions, whereas 28 interactions among 55 genes were from type III. Table 1 lists the detailed information about the detected interactions as well as involved genes.

By investigating the genes involved in the differential interactions, we want to see whether these genes are related to asthma. We investigated the pathways enriched in these genes with functional

Table 2 Pathways enriched in the genes of the differential interactions (NC against MMA)

Enriched pathways	Genes	P-value
hsa05200: pathways in cancer	HSP90AB1, IGF1R, AR, JUN, IKBK, TP53, RXRG, SMAD2, ZBTB16, FGF2, TGFB1, CSF1R	1.7700213533575657×10 ⁻⁴
hsa04350: TGF-beta signalling pathway	SMAD7, ZFYVE9, SMAD2, SMURF2, SMURF1, TGFB1	0.0012535833719909783
hsa04144: endocytosis	EPS15, IGF1R, PAR3, STAM2, SMURF2, SMURF1, EPN1, CSF1R	0.0015169347252279087
hsa04062: chemokine signalling pathway	PAR3, PPBP, GNAI1, IKBK, JAK3, GNB3, GNG4, CXCL12	0.0016658632214587746
hsa04520: adherens junction	IGF1R, PAR3, CSNK2A1, SMAD2, INSR	0.005711858266611148
hsa05210: colorectal cancer	IGF1R, JUN, TP53, SMAD2, TGFB1	0.007761511876274679
hsa05215: prostate cancer	HSP90AB1, IGF1R, AR, IKBK, TP53	0.009490198668201532
hsa05212: pancreatic cancer	IKBK, TP53, SMAD2, TGFB1	0.02988545084346355
hsa05340: primary immunodeficiency	IKBK, CD4, JAK3	0.042609175460902135
hsa04914: progesterone-mediated oocyte maturation	HSP90AB1, IGF1R, MAD2L1, GNAI1	0.04682232678221617
hsa04310: WNT signalling pathway	CSNK2A1, JUN, TP53, SMAD2, NFATC1	0.05300538176324243
hsa04660: T cell receptor signalling pathway	JUN, IKBK, CD4, NFATC1	0.0810409682133598

Table 3 Pathways enriched in the genes differentially expressed between NC and MMA samples

Enriched pathways	Genes	P-value
hsa04080: neuroactive ligand–receptor interaction	CCKBR, GRIK4, AVPR1B, FSHR, HTR1F, HTR2A	0.006006307884696674
hsa04060: cytokine–cytokine receptor interaction	IFNB1, CD70, EDAR, CCL16, CXCL12	0.032411029291324576

enrichment analysis by utilising the database for annotation, visualisation and integrated discovery [20]. Consequently, we found 12 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (P -value < 0.1) were enriched in the genes of differential interactions that happen between NC and MMA. The detailed results were summarised in Table 2. From the results, we can see that there are asthma-related pathways that are enriched in the differential interactions. For example, the activation of transforming growth factor (TGF)- β signalling pathways in the airways in a mouse model of acute allergic inflammation [21, 22] has been reported to induce multiple cellular responses, including differentiation, apoptosis, survival and proliferation, and play important roles in the early stage of asthma possibly because of the high expression of IL-13 [23]. The dysfunction of chemokine signalling pathway has also been reported in allergic asthma [24]. In murine, the down-regulation of WIF1 has been assumed to lead to asthma by directly binding to the WNT ligands [25], which in turn cause the aberrant activation of the WNT signalling pathway. It is not surprising that immunodeficiency related pathways are

enriched in the differential interactions considering that asthma is an immunodeficiency disease.

We also investigated the genes that are differentially expressed between NC and MMA samples. With the Student's t -test (P -value < 0.01), there are in total 63 genes found differentially expressed between NC and MMA samples. In a similar way, we conducted functional enrichment analysis on the DEGs. There are two pathways, that is, 'neuro active ligand–receptor interaction' and 'cytokine–cytokine receptor interaction', that were found to be enriched in the DEGs. We can see that compared with the differential interactions, the pathways enriched in DEGs have no close relationship with asthma. The detailed results can be found in Table 3.

3.2 Detection of differential interactions between MMA and SA

The differential interactions were also detected between MMA and SA samples. There are in total 40 interactions among 78 genes. Among these differential interactions, 24 interactions among 47 genes were grouped into type I interactions, whereas 16 interactions among 32 genes were grouped into type III interactions. Table 4 lists the detailed information about the detected interactions as well as involved genes.

Pathway enrichment analysis was conducted on the genes involved in the differential interactions. As a result, we found there are 18 KEGG pathways that are significantly enriched in the differential interactions, and the detailed result can be found in Table 5. By investigating these pathways, we found some of them are related to the progress of asthma. For example, the nucleotide-

Table 4 Differential interactions detected in MMA against SA

Differential interactions type	Detected differential interactions	Genes
I	PARD3---SMAD7, CACNA1E---EFHC1, GTF2H1---PIK3R1, AR---GTF2H1, GIGYF1---GRB10, KIAA1377---RBM23, IRAK1---IRAK3, ALOX5---TGFB2, DTX2---UBQLN4, CASP1---FGF2, JAK3---STAM2, TRIM23---ZNF581, COX17---PPBP, EPS15---SNAP91, ACVR1---CHN1, COL4A1---NID1, PFDN1---YEATS4, CTNND1---PTPRJ, FASLG---TNFRSF6B, CBL---SLA2, C7ORF64---PSMD11, GNAI1---IGF1R, SERPINB9---UNC119, HSP90AB1---IKBK, EXOSC7---IP6K1, ATN1---WDR5, TGFB2---VTN, ESR1---RXRA, PIGK---PIGT, AURKA---UBE2N, CDK1---VIM, RASGRF1---TNK2, SH3GL3---SYNJ1, PML---RARA, KHDRBS3---RBM7, AES---GFI1B, COPS8---NFKBIA, FNBP1L---SGSM2, CUL2---NEDD8, COX17---KATNAL1	ACVR1, GIGYF1, DTX2, SMAD7, C7ORF64, SNAP91, CHN1, IKBK, CTNND1, GNAI1, EPS15, UNC119, STAM2, SLA2, CACNA1E, UBQLN4, TGFB2, PPRBP, JAK3, PIK3R1, NID1, IRAK3, IRAK1, ALOX5, PFDN1, IGF1R, GTF2H1, TRIM23, ZNF581, AR, FASLG, COL4A1, EFHC1, FGF2, SERPINB9, PARD3, CASP1, GRB10, PSMD11, CBL, TNFRSF6B, RBM23, YEATS4, KIAA1377, PTPRJ, COX17, RBM7, TGFB2, NFKBIA, AES, KHDRBS3, EXOSC7, SH3GL3, FNBP1L, RARA, GFI1B, SYNJ1, AURKA, PML, CUL2, NEDD8, WDR5, PIGK, RXRA, VTN, ATN1, SGSM2, COPS8, IP6K1, TNK2, RASGRF1, ESR1, UBE2N, VIM, CDK1, KATNAL1, PIGT, COX17
III		

Table 5 Pathways enriched in the genes of the differential interactions (MMA against SA)

Enriched pathways	Genes	P-value
hsa05200: pathways in cancer	HSP90AB1, AR, COL4A1, RXRA, CBL, PML, NFKBIA, FASLG, TGFB2, IGF1R, CUL2, IKBK, RARA, FGF2, PIK3R1	3.205999018975354 $\times 10^{-7}$
hsa04210: apoptosis	IRAK1, IRAK3, IKBK, NFKBIA, FASLG, PIK3R1	8.38866102456839 $\times 10^{-4}$
hsa05215: prostate cancer	HSP90AB1, IGF1R, AR, IKBK, NFKBIA, PIK3R1	9.303515940556496 $\times 10^{-4}$
hsa05220: chronic myeloid leukaemia	CBL, IKBK, NFKBIA, PIK3R1, TGFB2	0.003793149658100608
hsa04062: chemokinesignalling pathway	PARD3, PPBP, GNAI1, IKBK, NFKBIA, JAK3, PIK3R1	0.005027824056625182
hsa05222: small cell lung cancer	COL4A1, RXRA, IKBK, NFKBIA, PIK3R1	0.005691643007393315
hsa04914: progesterone-mediated oocyte maturation	HSP90AB1, CDK1, IGF1R, GNAI1, PIK3R1	0.006186181684230831
hsa05221: acute myeloid leukaemia	IKBK, PML, RARA, PIK3R1	0.013395485809049215
hsa04621: NOD-like receptor signalling pathway	HSP90AB1, IKBK, NFKBIA, CASP1	0.016030962316806494
hsa04144: endocytosis	EPS15, SH3GL3, IGF1R, PARD3, STAM2, CBL	0.020335599780616546
hsa04722: neurotrophin signalling pathway	IRAK1, IRAK3, NFKBIA, FASLG, PIK3R1	0.021562768763155802
hsa04520: adherens junction	PTPRJ, IGF1R, PARD3, CTNND1	0.028355530875454664
hsa04620: TLR signalling pathway	IRAK1, IKBK, NFKBIA, PIK3R1	0.05604190979438855
hsa04660: T cell receptor signalling pathway	CBL, IKBK, NFKBIA, PIK3R1	0.06588143090377167
hsa04114: oocyte meiosis	CDK1, IGF1R, AR, AURKA	0.06883104450379288
hsa04010: MAPK signalling pathway	RASGRF1, IKBK, FASLG, CACNA1E, FGF2, TGFB2	0.07867960355420126
hsa04623: cytosolic DNA-sensing pathway	IKBK, NFKBIA, CASP1	0.08144819188241889
hsa04510: focal adhesion	IGF1R, COL4A1, RASGRF1, VTN, PIK3R1	0.09432133358305614

Table 6 Pathways enriched in the genes differentially expressed between MMA and SA samples

Enriched pathways	Genes	P-value
hsa04080: neuroactive ligand–receptor interaction	HTR2C, HTR2A, GRID1	0.033104943504049855

Table 7 Genes for differential interaction type III–I

SERPINB9---UNC119	AR---GTF2H1
JAK3---STAM2	KIAA1377---RBM23
C7ORF64---PSMD11	EPS15---SNAP91
TRIM23---ZNF581	COX17---PPBP
DTX2---UBQLN4	PARD3---SMAD7
HSP90AB1---IKBKKG	CACNA1E---EFHC1
GIGYF1---GRB10	GNAI1---IGF1R
CASP1---FGF2	ALOX5---TGFBRA1

binding and oligomerisation domain (NOD)-like receptor has been reported to play important roles in asthma, and mutations in NOD1 are frequently found in asthma and atopic eczema [26, 27]. It was also found that the release of neurotrophin in growth factor caused by IgE cross-linking contributes to the development of asthma [28]. The Toll-like receptor (TLR) genes were also found to be related to childhood asthma [29], and it is not surprising that the TLR signalling was enriched in differential interactions detected by us. The MAPK pathway has also been reported to be associated with asthma [30, 31].

The genes that are differentially expressed between MMA and SA samples were also detected with the Student's *t*-test, there are in total 14 DEGs were detected in total. Pathway enrichment analysis was performed over the DEGs, and only one pathway, that is, 'neuro active ligand–receptor interaction', was found to be significantly enriched in the DEGs. It seems that there are no any obvious

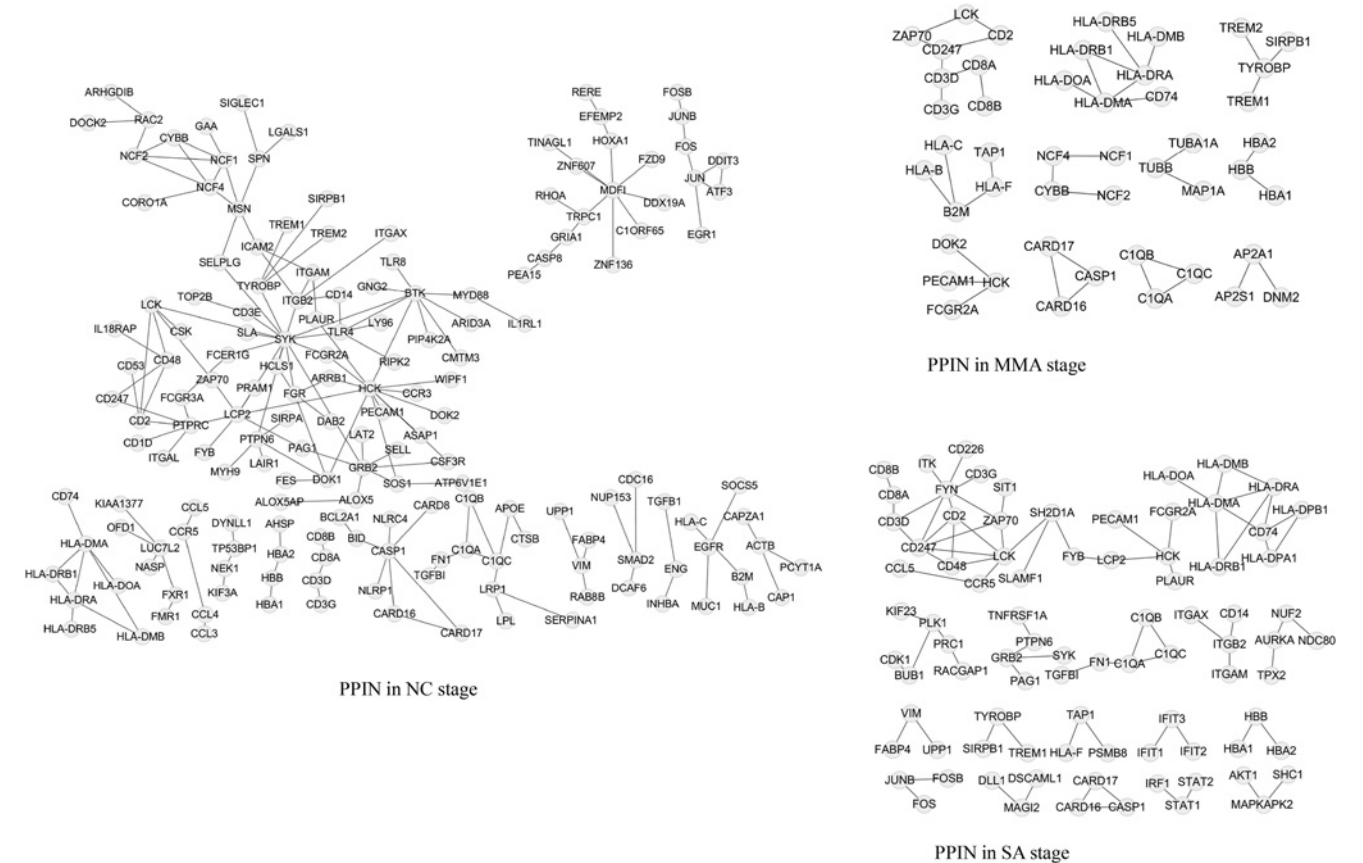
associations between this pathway and asthma. The detail result was shown in Table 6.

By comparing the differential interactions with the DEGs detected by traditional approaches, we can see that the differential interactions can help enumerate asthma-related genes which otherwise may be failed to be detected. The pathway enrichment analysis results indicate that the genes involved in differential interactions are indeed related to asthma and can help understand the pathogenesis underlying the disease.

3.3 Differential interactions across different stages of asthma

As described above, the enriched pathways for genes in the differential interactions of NC against MMA and MMA against SA are related with asthma development. There are also some differential interactions that only occur in one stage but not in another. For example, there are some differential interactions existing in MMA against SA but not in NC against MMA, and the genes from the interactions are enriched in pathways including 'apoptosis', 'focal adhesion', which are consistent with the development mechanism of asthma in later stage.

After checking the differential interactions that occur between different stages of asthma, we also investigated the differential interactions that happen across the three stages of asthma. Therefore, considering the four types of differential interactions, we grouped them into four types: type I in NC against MMA and type I in MMA against SA (I–I), type I in NC against MMA and type III in MMA against SA (I–III), type III in NC against MMA and type I in MMA against SA (III–I) and type III in NC against MMA and type III in MMA against SA (III–III). As a result, only III–I type was detected, there are in total 16 interactions involving 32 genes as shown in Table 7, and these differential interactions changing from lower to higher are much more likely associated with asthma progress.



By investigating the 32 genes involved in the 16 differential interactions listed in Table 7, we found that some of them have been reported to be related to asthma. For example, the gene SMAD7 has been found to be aberrantly expressed in bronchial epithelial cells and was assumed to be related to the development of airway remodelling and airway hyper responsiveness in asthma. The genes ALOX5 and GNAI1 have been reported to be associated with asthma in the GeneCards database [32]. Pathway enrichment analysis was also performed over the genes involved in the differential interactions. Some pathways have been found to be related to asthma directly or indirectly. For example, the pathways 'chemokine signalling pathway' and 'NOD-like receptor signalling pathway' have been found to be associated with asthma [24, 26, 27].

4 Conclusions

Traditional bioinformatics analysis generally detects DEGs and regards these genes as related to the trait of interest. However, the expression of some genes may not change significantly in diseases even they play important roles in the development of diseases. In fact, some molecular interactomes rewired when the disease happens, where the expression of corresponding genes do not change significantly and will not be detected by conventional approaches [33]. In this paper, with the idea of differential interactions proposed by Liu *et al.* [14], we present a new pipeline to identify asthma-related genes. The differential interactions that may play important roles in the development of asthma were detected. In particular, we detected the differential interactions occurring between and across different stages of asthma. By investigating the genes in the differential interactions, we found that some genes have already been reported to be related to asthma, and the pathways enriched in these genes were also found to be related to the development of the disease. These results demonstrate that the differential interaction detected in this paper are indeed related to asthma, and provide new insights into the pathogenesis of asthma.

Another advantage of the differential interactions is that they can help investigate the topology structure of the PPINs in different stages of asthma. Fig. 2 shows the PPINs of the three different stages, where an interaction was regarded to be positive in the stage of interest if their corresponding coding genes are significantly co-expressed (here, the Pearson correlation coefficient calculated is above 0.7). For clearness, the isolated interaction pairs were discarded. From the three networks, we can see that the topologies of the three PPINs corresponding to the three different stages changed according to the progress of asthma, from which we can see that the molecular interactome was indeed rewired in different stages of diseases. These findings can help us understand how the asthma disease develops.

5 References

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