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Integrated Assessment of Macrophage Lipids Homeostasis Omics Data: Identification of Potential Genes and Pathways in Atherosclerosis

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Abstract: Atherosclerosis is a chronic inflammatory disease characterized by the formation of lipid-rich plaques within the arterial wall. Increasing evidences have shown that cellular senescence may contribute to the progression of atherosclerosis, but the mechanism remains unclear. Hence, the present study aimed to identify potential therapeutic biomarkers for atherosclerosis by analyzing the gene expression profiles of macrophages incubated with total lipoproteins. The microarray dataset no. GSE84791 obtained from Gene Expression Omnibus (GEO) database was used for this study. In the comparison of two groups: (i) THP-1 macrophage models incubated with non-LPL hydrolysed products and (ii) LPL hydrolysed products, a total of 283 differentially expressed genes (DEGs) were identified. The Gene Ontology (GO) analysis indicated that the upregulated DEGs gene set were mainly enriched in cellular response to inflammation, stress, substance uptake and intracellular transport. Besides, upregulated DEGs were significantly enriched in PPAR signalling pathway by the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. Notably, GO analysis revealed that the downregulated DEGs were mainly enriched in cellular proliferation, while the KEGG analysis showed that the gene set was significantly enriched in cell cycle process. The top 10 hub genes including *KIF2C*, *NCAPG*, *BUB1*, *TOP2A*, *CENPF*, *TTK*, *CCNA2*, *PLK4*, *CDC6*, and *KIF11*, was identified from the Protein-Protein Interaction (PPI) network, which constructed using STRING and further analysed using the Network Analyzer, MCODE and cytoHubba. The present study indicated that the downregulation of these genes which involved in the process of cell cycle may have an implication on atherosclerosis development.

Keywords: Atherosclerosis; Cellular Senescence; Microarray Analysis; Gene Expression; Macrophage; Lipoproteins

1. Introduction

Atherosclerosis is regarded as a condition where passive fat deposition occurs in blood vessel walls. Lipid peroxidation, hyperlipidemia, injury response, and inflammation, cell senescence and thrombosis are evidence of pathogenesis of atherosclerosis[1]. The development of atherosclerosis lesions is mainly caused by interactions between few cell types, including the endothelial cells, smooth muscle cells, macrophages, and T lymphocytes[2]. Macrophage produces a range of cytokines and several growth-stimulating factors, leading to phenotypic changes in the blood vessels[2]. Numerous studies have demonstrated that macrophages are associated in the development of atherosclerosis[3–5]. Macrophages promote atherosclerosis by avidly taking up deposited lipoprotein and eliciting local inflammation[4].

Recently, cell senescence has gained prominence in playing a critical role in the progression of atherosclerosis[1]. Cellular senescence is a physiological process and hallmark of aging characterized by irreversible cell cycle arrest in response to various cellular stressors[1,6]. The accumulation of senescent cells drives aging and age-related diseases. For instance, the increased secretion of pro-inflammatory cytokines of aged monocytes were detected, which provided a direct evidence that aging/ senescence of monocytes/macrophages promotes pro-inflammatory changes that are relevant to atherosclerosis[7]. Hence, increased morbidity and mortality rates in various chronic diseases such as cardiovascular diseases, metabolic diseases, and cognitive diseases were seen in elder people[8]. Cellular senescence can be induced by various intrinsic and extrinsic factors as a stress response[9], and cell death in atherosclerosis can happen through multiple processes (necrosis, autophagy, apoptosis). However, the association between senescence and atherosclerotic progression remains unknown. Hence, identification of senescence biomarkers associated with atherosclerosis is essential for facilitating its clinical diagnosis.

The microarray dataset no. GSE84791 from the Gene Expression Omnibus database (GEO; https://www.ncbi.nlm.nih.gov/geo/) has been utilized to reveal variations in gene expression based on analysis of human macrophages exposed to lipoprotein lipase (LPL) hydrolysis products. The present study used the microarray dataset GSE84791 to identify differentially expressed genes (DEGs) associated with atherosclerosis using comprehensive bioinformatics methods. Then, the molecular mechanisms underlying the development of arteriosclerotic macrophages were researched by enrichment and protein–protein interaction (PPI) network analyses. In summary, 283 DEGs and 10 hub genes were conclusively authenticated. This study aimed to employ bioinformatics tools for screening and identifying molecular targets in arteriosclerotic macrophages.

2. Materials and Methods

2.1 Microarray Data Information

The GEO database from https://www.ncbi.nlm.nih.gov/geo/ searched with keywords, 'Atherosclerosis' and 'Macrophage'. Dataset GSE84791, which generated using GPL16686 [Affymetrix Human Gene 2.0 ST Array, transcript (gene) version] was selected for the analysis. The dataset GSE84791 (submission year, 2016; year of last update, 2019) included PMA-differentiated THP-1 macrophages incubated with non-hydrolysis products (n=3) and PMA-differentiated THP-1 macrophages incubated with hydrolysis products (n=3). Series Matrix File containing the raw data were downloaded as TXT format. The microarray probes were transformed into official gene symbols by using the annotation data provided by the platform.

2.2 Data Pre-Processing and Identification of DEGs

Series matrix of macrophages incubated with non-hydrolysis products and macrophages incubated with hydrolysis products were extracted. Data matrix was converted to normal scale from Log_2 scale. Fold change and p-value were determined. The cut-off criteria for DEGs (Differentially Expressed Genes) was set at |logFC|>1 and p-value <0.05. Then, a volcano plot of LogFC vs -Log10(p-value) was generated.

2.3 Gene Ontology and KEGG Enrichment Analysis

GO analysis and KEGG pathway enrichment of the DEGs was performed using the DAVID database (https://david.ncifcrf.gov/tools.jsp) with a significance threshold of p<0.05. The enrichment of the DEGs in GO terms of the categories biological process (BP), cellular component (CC) and molecular function (MF) were determined. Besides, KEGG enriched pathways with p<0.05 regarded as significant.

2.4 Construction of PPI Network and Hub Genes Identification

PPI network was constructed by mapping the DEGs to the STRING database (https://string-db.org/)[10]. The interacting nodes were filtered and selected for inclusion in the PPI network according to the criteria of 'combine score >0.5'[11]. Resulting PPI network was then exported in .TSV file format and was edited in Cytoscape software[12]. Cytoscape tool Network Analyzer was used to determine the network centrality and screen for key genes in the network[13]. Molecular Complex Detection (MCODE; version 1.5.1) of Cytoscape was used to discover tightly coupled modules on the basis of topological principles. Important modules of the PPI network map were identified in the following the criteria for MCODE analysis were as follows: degree cut off, 2; MCODE scores, > 5; max depth, 100; k-score, 2;

and node score cut off, 0.2. Top 10 hub genes were identified from the module using Cytohubba (v0.1), a plug-in Cytoscape software[14].

3. Results

3.1 Data Pre-processing and Identification of DEGs

The identified DEGs in the macrophages between non-hydrolysis products and hydrolysis products incubated cells are identified in dataset GSE84791. A total of 283 DEGs were recognised after consolidation and normalisation, followed by filtering with the cut-off criteria of |logFC|>1 and *p*-value <0.05. Among them, 143 genes were upregulated and 140 genes were downregulated as shown in Figure 1, Figure 2, and supplementary data (Supplementary Table 1 and 2).

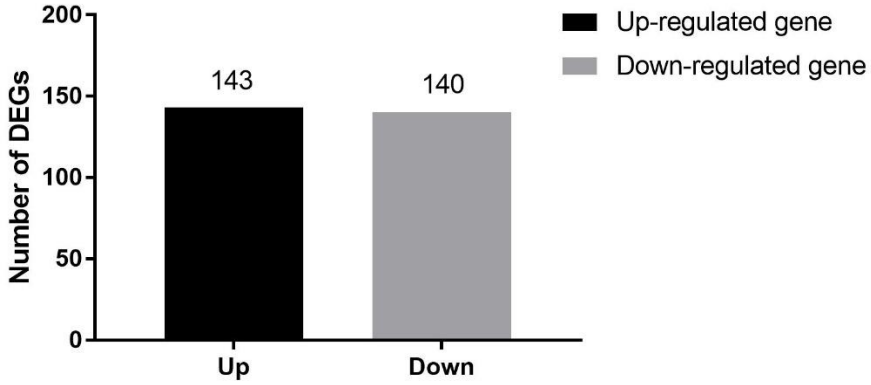

Figure 1. Number of DEGs for GSE84791. The Y-axis represents the number of identified DEGs whereas the X-axis represents up- and down-regulated genes.

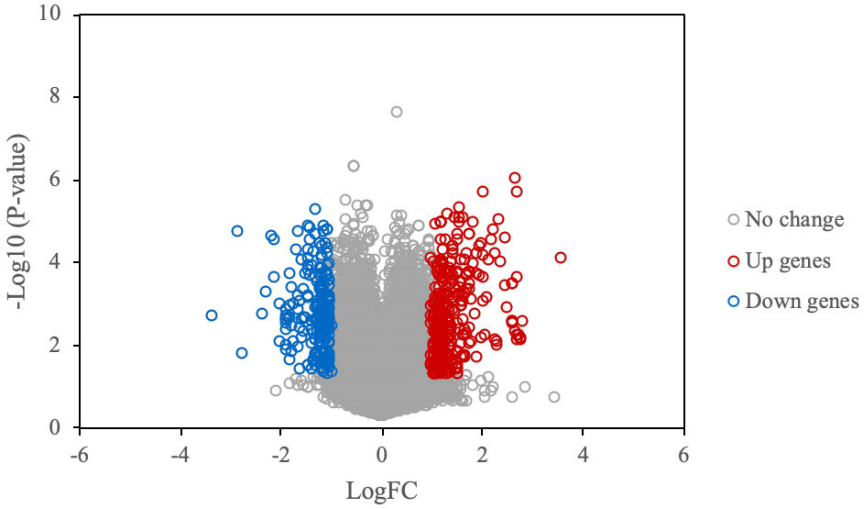

Figure 2. Volcano plot [Log2FC vs -Log10(*p*-value)] of upregulated and downregulated DEGs for GSE84791. Red colour represents upregulated genes; blue colour represents down regulated genes. The grey data-points represent genes with no significant difference in expression. DEGs cut-off criterion: |logFC|>1, *p*-value <0.05.

3.2 GO and KEGG Enrichment Pathway Analysis

GO and KEGG enrichment analysis were performed to identify gene sets with statistical difference between non-hydrolysis products incubated and hydrolysis products incubated macrophages. The enrichment of 143 upregulated DEGs was performed using the DAVID database (https://david.ncifcrf.gov/tools.jsp) with a significance threshold of $p<0.05$[15]. Results of GO and KEGG enrichment analysis was shown in Figure 3 and Figure 4, respectively. Results from Gene Ontology – Biological Process (GO-BP) analysis suggested that these enriched DEGs were mainly involved in the process of inflammation, response to cellular stress/external stimuli, and substance uptake and intracellular transport such as positive regulation of inflammatory response (GO:0050729), cellular response to heat (GO:0034605), IRE1-mediated unfolded protein response (GO:0036498), cellular response to unfolded protein (GO:0034620), cellular response to mechanical stimulus (GO:0071260), negative regulation of transcription from RNA polymerase II promoter in response to stress (GO:0097201), and long-chain fatty acid transport (GO:0015909). The most gene set of DEGs in the CC of GO was enriched in nucleolus (GO:0005730). Results from Gene Ontology – Molecular Function (GO-MF) analysis suggested that DEGs also enriched mainly in lipid binding and transfer such as phospholipid binding (GO:0005543) and organic anion transmembrane transporter activity (GO:0008514). Moreover, the enriched KEGG pathways mainly were PPAR signaling pathway (hsa03320), phagosome (hsa04145), and protein processing in endoplasmic reticulum (hsa04141), which indicated that the uptake of hydrolysis products by the cells has induced inflammatory response.

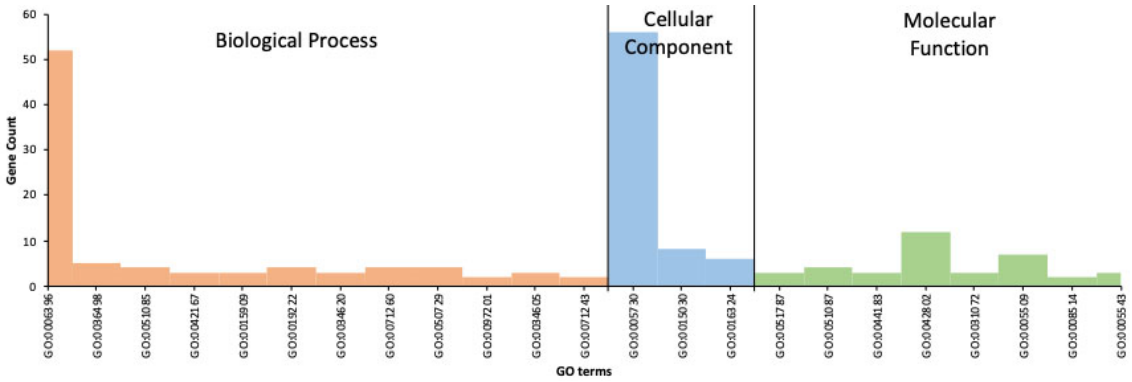

Figure 3. GO enrichment analysis of up-regulated genes of macrophage samples.

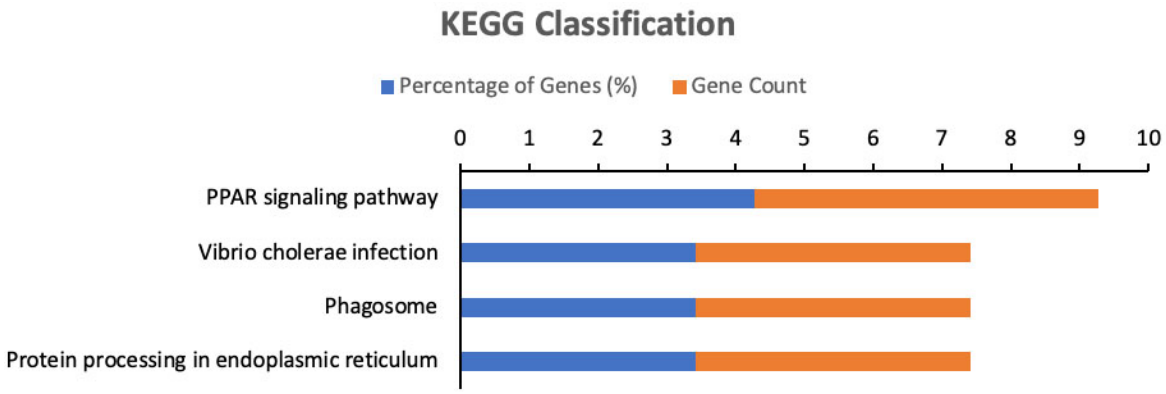

Figure 4. KEGG enrichment analysis of up-regulated genes of macrophage samples.

The analysis was repeated with the downregulated DEGs, and the results of GO and KEGG enrichment analysis were shown in Figure 5 and Figure 6, respectively. The GO-BP analysis of DEGs was shown to enrich mainly in process of cellular proliferation such as cell division (GO:0051301), DNA replication (GO:0006260), mitotic spindle organization (GO:0007052), mitotic cell cycle (GO:0000278), cell proliferation (GO:0008283), DNA replication initiation (GO:0006270). In addition, the KEGG pathways analysis of the enriched DEGs were involved in cell cycle (hsa04110) and DNA replication (hsa03030).

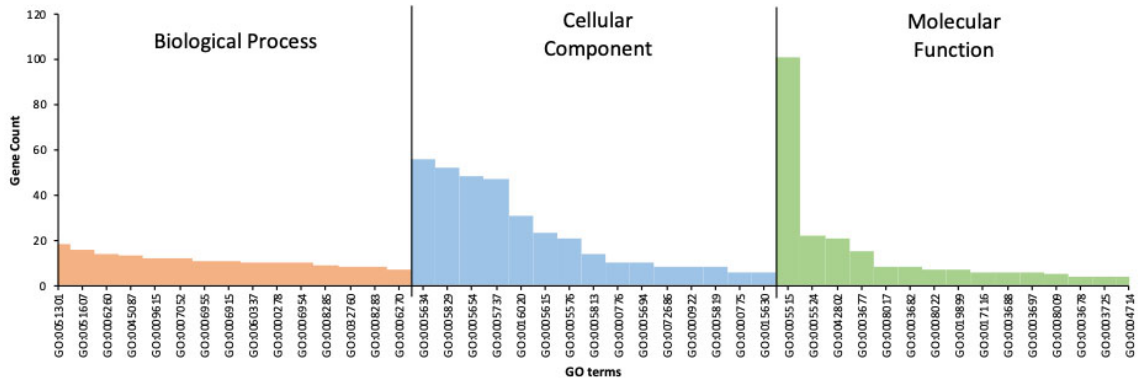

Figure 5. GO enrichment analysis of down-regulated genes of macrophage samples.

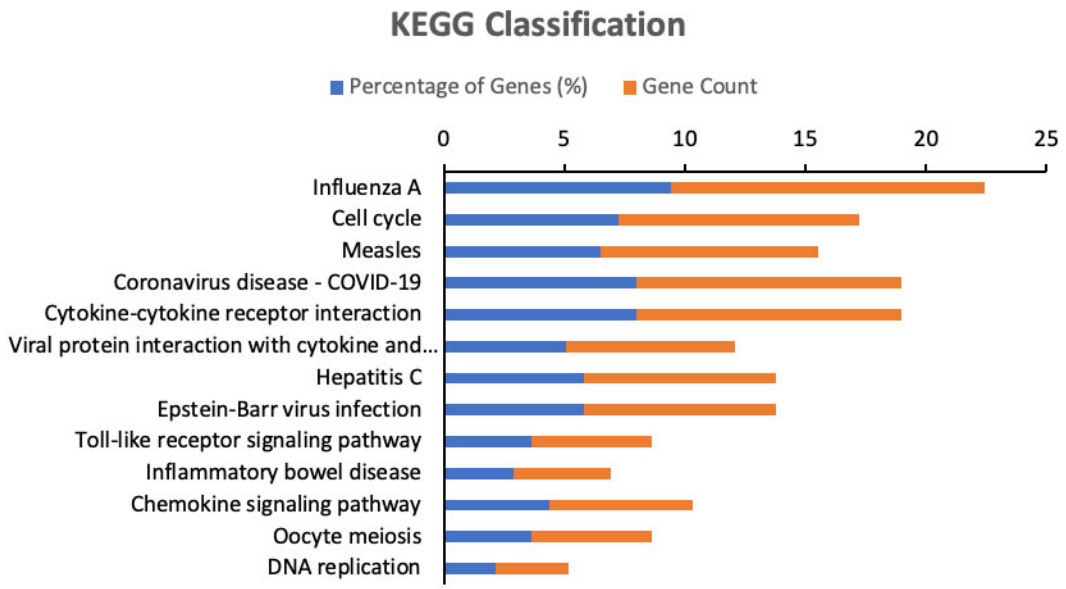

Figure 6. KEGG enrichment analysis of down-regulated genes of macrophage samples.

3.3 PPI Construction and Hub Genes Identification

The PPI network of the DEGs was constructed using the STRING database and Cytoscape software with 151 nodes and 1278 edges identified. The two most significant modules, Module A (score = 39.7) and Module B (score = 16.9) in the PPI network were identified using MCODE (Figure 7). Module A consisted 43 nodes and 834 edges, whereas Module B consisted 19 nodes and 152 edges. The clustered module networks of the two modules were displayed in Figure 8. Top 10 hub genes were identified from the most significant module (Module A), and listed in Table 1.

Table 1. Top 10 hub genes identified by Cytohubba.

Gene	Gene description	Degree	LogFC
KIF2C	kinesin family member 2C	42	-1.15
NCAPG	non-SMC condensin I complex subunit G	40	-1.49
BUB1	BUB1 mitotic checkpoint serine/threonine kinase	42	-1.24
TOP2A	DNA topoisomerase II alpha	42	-1.38
CENPF	centromere protein F	42	-1.12
TTK	TTK protein kinase	42	-1.16
CCNA2	cyclin A2	42	-1.48
PLK4	polo like kinase 4	42	-1.07
CDC6	cell division cycle 6	42	-1.03
KIF11	kinesin family member 11	42	-1.14

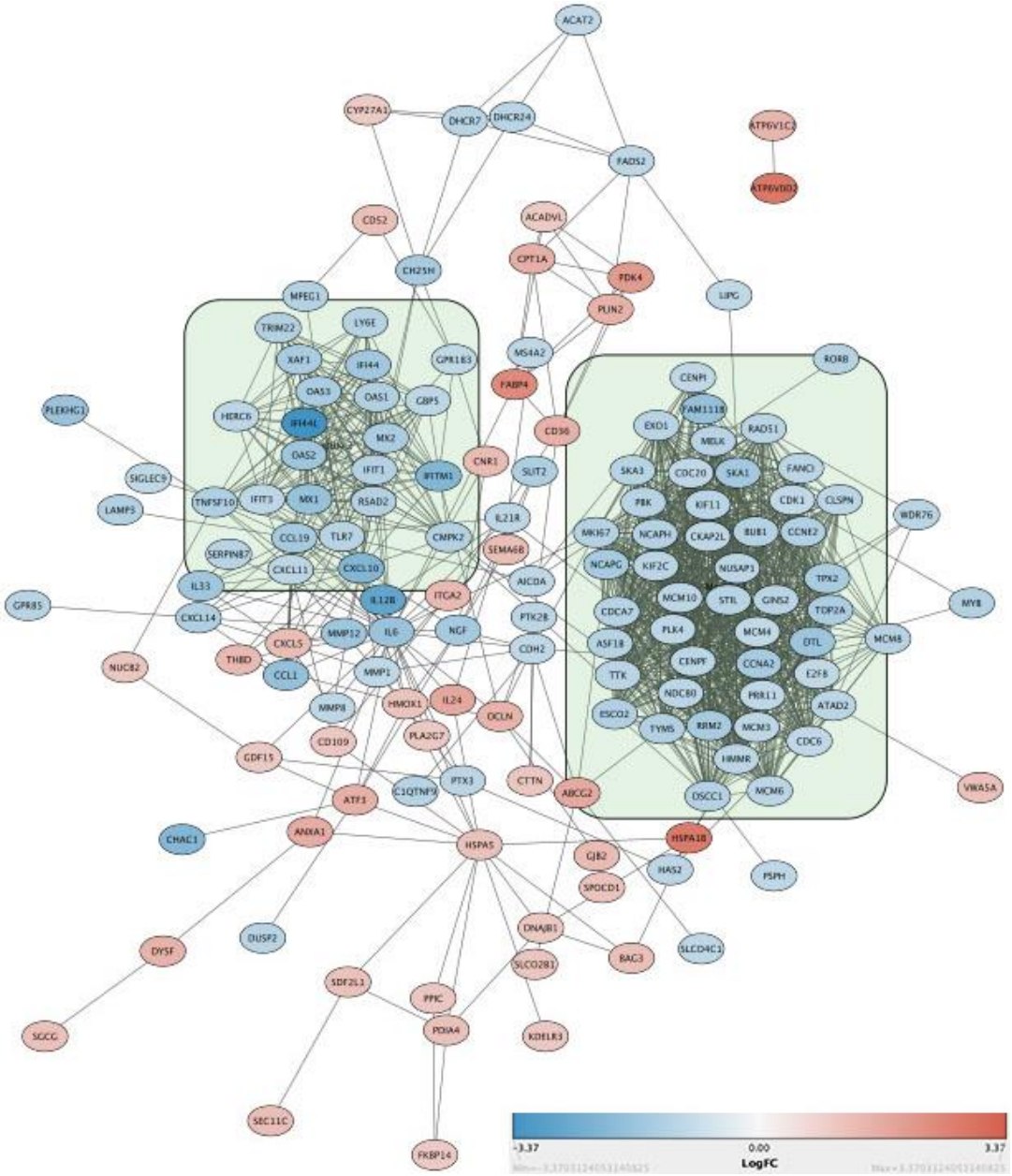

Figure 7. Protein–protein interaction network of the enriched DEGs. The different colours indicate the different level of degree centralities. A and B denotes the two most significant modules of the PPI network using MCODE.

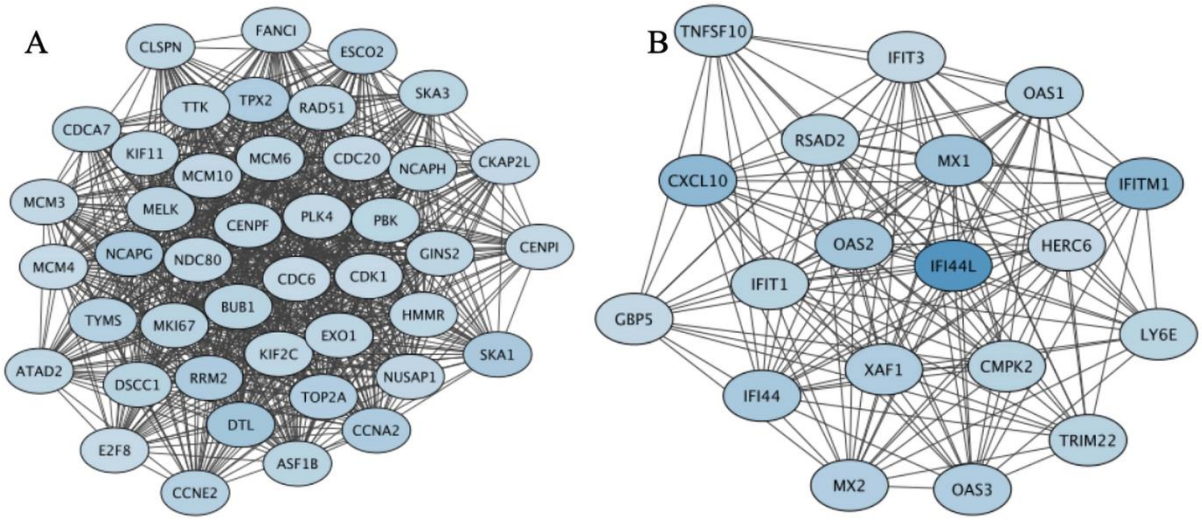

Figure 8. Cluster network of Module A (**A**) and Module B (**B**).

4. Discussion

An increasing number of studies have revealed that cellular senescence also contributed to the development of atherosclerosis. For instance, senescent vascular endothelial cells which exhibited senescence-associated phenotypes were detected in atherosclerotic lesions[16], and associated with increased atherosclerosis and formation of necrotic core[17]. In addition, localized expression of senescence markers which include *p16INK4a* was detected within $CD68^+$ macrophages residing in atherosclerotic lesions[18]. Since macrophages take part in all stages of atherosclerosis, it is essential to identify the relationship between the senescence of macrophages and atherogenesis. It is plausible that senescent foamy macrophages drive lesion growth by increasing the expression of inflammatory cytokines and monocyte chemotactic factors[19], however, the actual mechanisms has not been fully elucidated.

In the present study, various bioinformatic tools were used to analyse critical genes and pathways between macrophages that were incubated with non-LPL hydrolysed products and LPL hydrolysed products. A total of 283 DEGs were identified from the dataset where 143 DEGs were upregulated and 140 DEGs were downregulated. Through the GO and KEGG enrichment analysis of the upregulated DEGs, a total of 12 BP, 3 CC, 8 MF, and 4 KEGG pathways function were enriched (Figure 3 and Figure 4). The results from GO-BP analysis demonstrated that the upregulated DEGs mainly enriched in the process of inflammation, response to cellular stress/external stimuli, and substance uptake and intracellular transport. The fatty acid-inflammation interactions was described in detail elsewhere[20,21]. For instance, the saturated fatty acids (SFAs) — an essential structural

component of endotoxins, contribute to the proinflammatory activity of lipopolysaccharide (LPS)[21]. Besides, SFAs also directly involved in the stimulation of inflammatory genes via the TLR4 signaling pathway[22]. Most gene set of DEGs in Gene Ontology – Cellular Component (GO-CC) analysis was enriched in nucleolus (GO:0005730). The nucleolus is a membraneless compartment located within the nucleus of eukaryotic cells which involved in various aspects of cell physiology including genome organization, stress responses, senescence and lifespan[23]. Stress induces alteration of nucleolar morphology, and persistent stress causes the delocalisation of nucleolar proteins (e.g. nucleolin, nucleostamin, and nucleophosmin) that involved in the regulation of cell cycle and proliferation[24]. GO-MF analysis showed that the DEGs were mostly enriched in protein binding (GO:0042802), suggesting that the protein-protein interaction of two or more proteins played a crucial role in the inflammation (e.g. *MCEMP1*), lipid transport and metabolism (e.g. *ACADVL*, *CPT1A*, and *ANXA1*), and stress responses (e.g. *TNFSF14* and *ATF3*). Upregulation of *MCEMP1* was associated to increased inflammation response by increasing expression of proinflammatory cytokines such as interleukin 6 (IL-6), IL-1β, IL-10, and tumor necrosis factor-α (TNF-α)[25]. Acyl-CoA Dehydrogenase Very Long Chain (*ACADVL*) and Carnitine Palmitoyltransferase 1A (*CPT1A*) gene both involved in lipid metabolism via the fatty acid beta-oxidation pathway[26,27], whereas *ANAXA1* take part in mediating cholesterol transportation[28]. TNF Superfamily Member 14 (*TNFSF14*) gene involved in the apoptosis process via the LIGHT–LTβR signalling pathway[29]. On the other hand, Activating Transcription Factor 3 (*ATF3*) gene plays a critical role in reconstructing chromatin accessibility to promote cellular senescence[30]. Moreover, the KEGG analysis demonstrated that the DEGs were mainly enriched in PPAR signaling pathway (hsa03320), where the key transcriptional factors like the PPAR regulates CD36 and take part in the cholesterol internalisation[31].

The GO-BP analysis of down-regulated DEGs was shown to enrich mainly in process of cell division, which included 18 DEGs. Cell division is the process of division and partitioning of cell components for the purpose of forming more cells. When cells were damaged from extrinsic stimuli such as oxidative stress, the process of undergoing cell division stopped and triggered the cellular senescence process. Senescence is defined as stable growth arrest accompanied by characteristics of phenotypic alterations including chromatin remodelling, increased autophagy and the release of a complex proinflammatory secretome[32]. The growth arrest is induced primarily by the activation of p16INK4a/Rb and p53/p21 signaling pathways[8]. Several studies have linked senescence to atherosclerosis[33–35]. A study from Childs *et al*.[19] showed that foam cell macrophages with senescence markers

accumulate and initiate the development of atherosclerosis by inducing expression of atherogenic cytokines and chemokines.

Similar findings were found for the KEGG pathways analysis, where the DEGs were mainly enriched in cell cycle (hsa04110) and DNA replication (hsa03030) pathways. A total of 10 genes were found enriched in cell cycle pathway (hsa04110) namely *CCNA2*, *CDC20*, *CCNE2*, *CDK1*, *MCM3*, *MCM4*, *TTK*, *CDC6*, *MCM6*, and *BUB1*. Among all, the cyclin E2 (*CCNE2*) and cyclin A2 (*CCNA2*) interacts with CDK kinases (e.g. CDK2) and take part in the Rb/E2F signaling pathway. The reduced expression of the two cyclin proteins link to arrest of cell proliferation/senescence[36]. Alternatively, the p16 of the INK4 family also known for its role in the maintenance of cellular senescence via the Rb/E2F signaling pathway[37]. Studies have shown that the increased expression of *p16INK4a* is associated to increased risk of cardiovascular disease (CVD) and atherosclerosis progression[18,38]. Hence, p16 expression in senescence macrophage is of great interest for researcher to study the effect of cellular senescence on atherosclerosis.

In the present study, 10 hub genes were identified by cytoHubba namely *KIF2C*, *NCAPG*, *BUB1*, *TOP2A*, *CENPF*, *TTK*, *CCNA2*, *PLK4*, *CDC6*, and *KIF11* (Table 1). The kinesin family member 2C (*KIF2C*) is a member of the kinesin superfamily of microtubule motor proteins that take part in the process of normal chromosome movement and segregation, and acting as a key regulator of mitotic spindle assembly[39]. *KIF2C* gene has been reported to be involved in the cellular senescence through a p53-dependent signaling pathway[39]. Besides, non-SMC Condensin I Complex Subunit G (*NCAPG*) gene responsible for encoding a subunit of the condensin complex, which take part in the condensation and stabilization of chromosomes during mitosis and meiosis[40]. The BUB1 Mitotic Checkpoint Serine/Threonine Kinase (*BUB1*) gene encodes a serine/threonine-protein kinase that promotes chromosome alignment[41]. Downregulation of *BUB1* gene is associated to replicative senescence in cells[42]. The DNA Topoisomerase II Alpha (*TOP2A*) gene is one of the important regulators of the cell cycle and a useful indicator for cellular proliferation, where its function includes regulating DNA structure, chromosome segregation, and cell cycle progression[43]. Centromere Protein F (*CENPF*) gene is a nuclear protein gene that involved in cell cycle by associating with the centromere-kinetochore complex and taking part in the G2 phase of interphase[44]. Knockdown/silencing of the *CENPF* gene was found to reduce cell proliferation in cancer cells, which has the potential to be utilised as a therapeutic cancer targets[44,45]. Subsequently, TTK protein kinase which encoded by the *TTK* gene, has the ability to phosphorylate tyrosine, serine and threonine, and this kinase play an essential role in chromosome alignment and segregation at the centromere for centrosome

duplication[46]. *CCNA2* gene that encodes one of the highly conserved cyclin family - Cyclin A2, that interacts with cyclin-dependent kinase 2 (CDK2) and cyclin dependent protein kinase 1 (CDK1) to promote the transition of G1/S and G2/M phases[47]. The Polo Like Kinase 4 encoded by *PLK4* gene responsible for the centriole duplication[48]. The inhibition of PLK4 was found to cause cell cycle arrest and senescence[48]. The Cell Division Cycle 6 (*CDC6*) protein as one of the key component of the pre-replication complex (pre-RC) is crucial for the initiation of DNA replication and the maintenance of cell cycle[49]. The last of the top 10 genes is the Kinesin Family Member 11 (*KIF11*) which encodes a motor protein belonging to the kinesin-like protein family that involves in the spindle dynamics. The protein take part in events such chromosome positioning, centrosome separation and the establishment of bipolar spindle during cell mitosis[50,51]. Therefore, the 10 hub genes identified herein are all associated with the cell cycle.

In the present study, the overall design of dataset GSE84791 focused on the effect of lipoprotein lipase (LPL) hydrolyzed products on macrophages[52], and the involvement of macrophage-secreted LPL in the pathogenesis of atherosclerosis[53–55]. Briefly, LPL hydrolysis products liberated from lipoproteins causes accumulation of cholesteryl esters in macrophages and impairs its cholesterol efflux ability. Studies have demonstrated that atherosclerosis is associated with the cells senescence in macrophages[19], vascular smooth muscle cells[56,57], and endothelial cells[16]. Interestingly, selective removal of *p16INK4a*-positive senescent cells appeared to prevent atherosclerosis progression by stabilizing plaques and reducing plaque inflammation[19], highlighting the intertwining relationship between atherosclerosis and cellular senescence. The findings from this study showed that the downregulated hub genes were all involved in the process of cell cycle. Cell cycle arrest/cellular are mainly regulated by the two well-known pathways - p16INK4a/Rb and p53/p21 signalling pathways. Among the two, the p53/p21 signaling pathway appears to play a key role in initiating cellular senescence which subsequently contributes to atherosclerosis, whereas the p16INK4a/Rb signalling pathway seems to have a central role in the maintenance of senescence[58]. It was shown that the expression of p53 has a negative correlation with the p16INK4a activity in senescent cells, indicating that the p53 activity dominated the early phase of senescence (reversible phase) while p16/Rb pathway promoted senescence in the late phase (irreversible phase)[59,60]. Hence, p16 expression in senescence macrophage is of great interest for researcher to study the effect of cellular senescence on atherosclerosis.

5. Conclusions

In this study, 283 DEGs were identified which comprised of 143 upregulated DEGs and 140 downregulated DEGs. Upregulated DEGs were found mainly involved in responses such as inflammation, stress, and lipid uptake, whereas downregulated DEGs were involved in cell cycle/apoptosis. Furthermore, the top 10 hub genes identified: *KIF2C, NCAPG, BUB1, TOP2A, CENPF, TTK, CCNA2, PLK4, CDC6,* and *KIF11* are associated to the cell cycle pathway.

The identified cell cycle-related hub genes is in line with the concept that senescent macrophages could be the contributor in the progression of atherosclerosis. Besides, it also suggests that cellular senescence might be one of the feature of macrophages transformation into foam cells. However, the potential mechanism unravelled from the bioinformatic analysis still require further studies and validation. Nevertheless, the findings may provide insights for the development of diagnostic and therapeutic biomarkers for atherosclerosis.

Author Contributions: Wei Sheng Siew, Yin Quan Tang, and Wei Hsum Yap researched literature and conceptualized the study. Wei Sheng Siew produced first original draft of the manuscript. Wei Sheng Siew, Yin Quan Tang, and Wei Hsum Yap took part in reviewing and editing the manuscript, while Wei Sheng Siew performed data analysis, result interpretation, and manuscript revision. Yin Quan Tang, and Wei Hsum Yap oversee the data analysis, interpretation of the results, and provide constructive comments for the improvement of the manuscript. All authors have read and agreed to the final version of the manuscript.

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Conflict of Interest: The authors declare no conflict of interest.

Data availability statement: The dataset used during the present study is available from the NCBI GEO repository at https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84791, The reference number to access this data are given in the manuscript.

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Supplementary Data

Supplementary Table 1. 143 upregulated DEGs between non-hydrolysis products and hydrolysis products incubated macrophages.

Gene symbol	Gene description	LogFC	p-value
CD52	CD52 molecule	1.24	0.000
RNU11|TAF12-DT	RNA, U11 small nuclear|TAF12 divergent transcript	1.99	0.000
DYNLT5	dynein light chain Tctex-type family member 5	1.10	0.005
IL24	interleukin 24	1.76	0.000
ATF3	activating transcription factor 3	1.56	0.000
SPOCD1	SPOC domain containing 1	1.15	0.000
SNORA55	small nucleolar RNA, H/ACA box 55	1.08	0.000
SNORA80E	small nucleolar RNA, H/ACA box 80E	2.65	0.000
SCARNA4	small Cajal body-specific RNA 4	2.04	0.000
SCARNA3|MIR1843	small Cajal body-specific RNA 3|microRNA 1843	1.95	0.000
SNORA36B|MIR664A	small nucleolar RNA, H/ACA box 36B|microRNA 664a	1.65	0.020
SNORA14B	small nucleolar RNA, H/ACA box 14B	2.67	0.000
OLAH	oleoyl-ACP hydrolase	2.28	0.010
AGAP11	ArfGAP with GTPase domain, ankyrin repeat and PH domain 11	1.34	0.003
BAG3	BAG cochaperone 3	1.23	0.014
ANKRD1	ankyrin repeat domain 1	1.13	0.036
SNORA3B	small nucleolar RNA, H/ACA box 3B	1.54	0.000
NUCB2	nucleobindin 2	1.10	0.014
SNORA57	small nucleolar RNA, H/ACA box 57	1.44	0.000
NEAT1	nuclear paraspeckle assembly transcript 1	1.43	0.000
CTTN	cortactin	1.07	0.005
SLCO2B1	solute carrier organic anion transporter family member 2B1	1.09	0.006
VWA5A	von Willebrand factor A domain containing 5A	1.21	0.004
SNORA54	small nucleolar RNA, H/ACA box 54	1.83	0.000
CPT1A	carnitine palmitoyltransferase 1A	1.59	0.000
SNORD14E	small nucleolar RNA, C/D box 14E	1.42	0.000
SCARNA10	small Cajal body-specific RNA 10	1.62	0.001
HSP90B1|MIR3652	heat shock protein 90 beta family member 1|microRNA 3652	1.42	0.000
SCARNA11	small Cajal body-specific RNA 11	1.22	0.002
MIR1291|SNORA2C	microRNA 1291|small nucleolar RNA, H/ACA box 2C	1.20	0.001
SNORA2A	small nucleolar RNA, H/ACA box 2A	2.26	0.000
SGCG	sarcoglycan gamma	1.21	0.003
GJB2	gap junction protein beta 2	1.33	0.001
TPT1|SNORA31B	tumor protein, translationally-controlled 1|small nucleolar RNA, H/ACA box 31B	1.21	0.000
ANG|RNASE4	angiogenin|ribonuclease A family member 4	1.00	0.001

SNORA28	small nucleolar RNA, H/ACA box 28	1.02	0.002
HIF1A-AS3	HIF1A antisense RNA 3	1.53	0.004
GOLGA8H|GOLGA8T|GOLGA8K|GOLGA8N|GOLGA8S|GOLGA8IP	golgin A8 family member H|golgin A8 family member T|golgin A8 family member K|golgin A8 family member N|golgin A8 family member S|golgin A8 family member I, pseudogene	1.14	0.013
GOLGA8M|GOLGA8N|GOLGA8H|GOLGA8K|GOLGA8T|GOLGA8J|GOLGA8IP|GOLGA8S	golgin A8 family member M|golgin A8 family member N|golgin A8 family member H|golgin A8 family member K|golgin A8 family member T|golgin A8 family member J|golgin A8 family member I, pseudogene|golgin A8 family member S	1.08	0.004
SNORA10	small nucleolar RNA, H/ACA box 10	1.54	0.001
SNORA46	small nucleolar RNA, H/ACA box 46	1.87	0.002
ACADVL	acyl-CoA dehydrogenase very long chain	1.00	0.000
SNORD3B-1|SNORD3D|SNORD3B-2|SNORD3C|SNORD3A	small nucleolar RNA, C/D box 3B-1|small nucleolar RNA, C/D box 3D|small nucleolar RNA, C/D box 3B-2|small nucleolar RNA, C/D box 3C|small nucleolar RNA, C/D box 3A	1.23	0.000
SNORD3B-2|SNORD3B-1|SNORD3C|SNORD3A|SNORD3D	small nucleolar RNA, C/D box 3B-2|small nucleolar RNA, C/D box 3B-1|small nucleolar RNA, C/D box 3C|small nucleolar RNA, C/D box 3A|small nucleolar RNA, C/D box 3D	1.23	0.000
SNORD104	small nucleolar RNA, C/D box 104	1.71	0.000
SNORA50C	small nucleolar RNA, H/ACA box 50C	2.38	0.000
SNORA38B	small nucleolar RNA, H/ACA box 38B	1.76	0.001
SNORD1B	small nucleolar RNA, C/D box 1B	1.28	0.008
SNORD3A|SNORD3B-2|SNORD3B-1|SNORD3D|SNORD3C	small nucleolar RNA, C/D box 3A|small nucleolar RNA, C/D box 3B-2|small nucleolar RNA, C/D box 3B-1|small nucleolar RNA, C/D box 3D|small nucleolar RNA, C/D box 3C	1.63	0.000
SCARNA20	small Cajal body-specific RNA 20	1.65	0.001
WIPI1	WD repeat domain, phosphoinositide interacting 1	1.34	0.007
ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	1.42	0.001
SEC11C	SEC11 homolog C, signal peptidase complex subunit	1.25	0.000
SNORA37	small nucleolar RNA, H/ACA box 37	1.50	0.000
MCEMP1	mast cell expressed membrane protein 1	1.01	0.003
GDF15	growth differentiation factor 15	1.02	0.003
SEMA6B	semaphorin 6B	1.27	0.001
TNFSF14	TNF superfamily member 14	1.72	0.009
DNAJB1	DnaJ heat shock protein family (Hsp40) member B1	1.03	0.002
SNORD88A	small nucleolar RNA, C/D box 88A	1.20	0.000
ATP6V1C2	ATPase H+ transporting V1 subunit C2	1.46	0.002
SNORD92	small nucleolar RNA, C/D box 92	2.00	0.000
SNORA10B|SNORA10	small nucleolar RNA, H/ACA box 10B|small nucleolar RNA, H/ACA box 10	1.26	0.000
DYSF	dysferlin	1.51	0.000
SNORD11B	small nucleolar RNA, C/D box 11B	1.07	0.002
CYP27A1	cytochrome P450 family 27 subfamily A member 1	1.01	0.000
ARMC9	armadillo repeat containing 9	1.33	0.002
SCARNA5	small Cajal body-specific RNA 5	1.40	0.000
SCARNA6	small Cajal body-specific RNA 6	1.52	0.000
LINC01920	long intergenic non-protein coding RNA 1920	1.22	0.002

SNORA75	small nucleolar RNA, H/ACA box 75	2.70	0.000
SNORA60	small nucleolar RNA, H/ACA box 60	3.56	0.000
SNORD12C	small nucleolar RNA, C/D box 12C	1.36	0.000
SNORD17	small nucleolar RNA, C/D box 17	1.24	0.001
THBD	thrombomodulin	1.37	0.000
SNORA71B	small nucleolar RNA, H/ACA box 71B	2.01	0.000
SNORA71D	small nucleolar RNA, H/ACA box 71D	1.60	0.001
SDF2L1	stromal cell derived factor 2 like 1	1.17	0.019
HMOX1	heme oxygenase 1	1.15	0.001
KDELR3	KDEL endoplasmic reticulum protein retention receptor 3	1.06	0.000
SNORA63D	small nucleolar RNA, H/ACA box 63D	1.05	0.001
SNORD66	small nucleolar RNA, C/D box 66	1.50	0.000
SCARNA7	small Cajal body-specific RNA 7	1.13	0.000
RNVU1-18|RNU1-1|RNU1-3|RNU1-4|RNU1-2	RNA, variant U1 small nuclear 18|RNA, U1 small nuclear 1|RNA, U1 small nuclear 3|RNA, U1 small nuclear 4|RNA, U1 small nuclear 2	1.64	0.006
PALLD	palladin, cytoskeletal associated protein	1.21	0.000
CXCL5	C-X-C motif chemokine ligand 5	1.30	0.001
ABCG2	ATP binding cassette subfamily G member 2 (Junior blood group)	1.71	0.000
ITGA2	integrin subunit alpha 2	1.36	0.003
OCLN	occludin	1.50	0.003
SNORA74A	small nucleolar RNA, H/ACA box 74A	1.41	0.000
VTRNA1-1	vault RNA 1-1	1.80	0.008
ABLIM3	actin binding LIM protein family member 3	1.14	0.001
SNORA74B	small nucleolar RNA, H/ACA box 74B	1.76	0.000
SCARNA18	small Cajal body-specific RNA 18	1.60	0.001
PPIC	peptidylprolyl isomerase C	1.08	0.001
HSPA1A|HSPA1B	heat shock protein family A (Hsp70) member 1A|heat shock protein family A (Hsp70) member 1B	2.73	0.006
CD109	CD109 molecule	1.05	0.001
ZNF354B	zinc finger protein 354B	1.23	0.012
SNORD100	small nucleolar RNA, C/D box 100	1.01	0.001
SNORA33	small nucleolar RNA, H/ACA box 33	2.22	0.000
SCARNA27	small Cajal body-specific RNA 27	1.19	0.000
PLA2G7	phospholipase A2 group VII	1.02	0.035
CNR1	cannabinoid receptor 1	1.33	0.000
HSPA1B|HSPA1A	heat shock protein family A (Hsp70) member 1B|heat shock protein family A (Hsp70) member 1A	2.61	0.003
HSPA1B	heat shock protein family A (Hsp70) member 1B	2.76	0.007
SNORA38	small nucleolar RNA, H/ACA box 38	1.18	0.000
TSPAN13	tetraspanin 13	1.06	0.043
SNORA14A	small nucleolar RNA, H/ACA box 14A	1.60	0.000
CD36	CD36 molecule	1.55	0.000
ZFAND2A	zinc finger AN1-type containing 2A	1.11	0.002
FKBP14	FKBP prolyl isomerase 14	1.00	0.002

SNORA9	small nucleolar RNA, H/ACA box 9	1.41	0.001
SNORA5C	small nucleolar RNA, H/ACA box 5C	1.11	0.001
PDK4	pyruvate dehydrogenase kinase 4	2.06	0.006
PDIA4	protein disulfide isomerase family A member 4	1.19	0.002
ATP6V0D2	ATPase H+ transporting V0 subunit d2	2.82	0.003
SNORA1|SNORA1B	small nucleolar RNA, H/ACA box 1|small nucleolar RNA, H/ACA box 1B	1.13	0.038
FABP4	fatty acid binding protein 4	2.44	0.000
SNORA72	small nucleolar RNA, H/ACA box 72	1.74	0.000
ANXA1	annexin A1	1.64	0.001
SCARNA8	small Cajal body-specific RNA 8	2.14	0.000
PLIN2	perilipin 2	1.54	0.000
HSPA5	heat shock protein family A (Hsp70) member 5	1.18	0.000
MIR12136	microRNA 12136	2.01	0.001
SNORA11	small nucleolar RNA, H/ACA box 11	2.35	0.000
ANKRD30BP2	ankyrin repeat domain 30B pseudogene 2	2.63	0.000
SNORA61|SNHG12	small nucleolar RNA, H/ACA box 61|small nucleolar RNA host gene 12	1.45	0.000
SNORA44|SNHG12	small nucleolar RNA, H/ACA box 44|small nucleolar RNA host gene 12	1.02	0.010
SNORA16A	small nucleolar RNA, H/ACA box 16A	1.20	0.003
SNORA19	small nucleolar RNA, H/ACA box 19	1.08	0.036
SNORA52	small nucleolar RNA, H/ACA box 52	1.40	0.000
SNORA3A	small nucleolar RNA, H/ACA box 3A	1.21	0.000
MIR612|NEAT1	microRNA 612|nuclear paraspeckle assembly transcript 1	1.20	0.007
SNORA25	small nucleolar RNA, H/ACA box 25	1.10	0.000
SNORA1B|SNORA1	small nucleolar RNA, H/ACA box 1B|small nucleolar RNA, H/ACA box 1	1.66	0.006
SNORA41	small nucleolar RNA, H/ACA box 41	1.84	0.000
SNORA51	small nucleolar RNA, H/ACA box 51	1.32	0.000
SNORA6	small nucleolar RNA, H/ACA box 6	1.91	0.000
SNORA20|SNORA20B	small nucleolar RNA, H/ACA box 20|small nucleolar RNA, H/ACA box 20B	1.72	0.000
SNORA36C|MIR664B|SNORA36A|DKC1	small nucleolar RNA, H/ACA box 36C|microRNA 664b|small nucleolar RNA, H/ACA box 36A|dyskerin pseudouridine synthase 1	1.33	0.006
SNORA56|DKC1	small nucleolar RNA, H/ACA box 56|dyskerin pseudouridine synthase 1	2.09	0.001
PDE4DIP|PDE4DIPP2	phosphodiesterase 4D interacting protein|PDE4DIP pseudogene 2	1.12	0.000
SNORA17A|SNHG7	small nucleolar RNA, H/ACA box 17A|small nucleolar RNA host gene 7	1.91	0.019

Supplementary Table 2. 140 upregulated DEGs between non-hydrolysis products and hydrolysis products incubated macrophages.

Gene Symbol	Gene description	LogFC	p-value
CDC20	cell division cycle 20	-1.05	0.030
KIF2C	kinesin family member 2C	-1.15	0.004
IFI44L	interferon induced protein 44 like	-3.37	0.002
IFI44	interferon induced protein 44	-1.58	0.002
DTL	denticleless E3 ubiquitin protein ligase homolog	-1.68	0.000
CENPF	centromere protein F	-1.12	0.007
EXO1	exonuclease 1	-1.18	0.000
CLSPN	claspin	-1.13	0.002
STIL	STIL centriolar assembly protein	-1.19	0.000
DHCR24	24-dehydrocholesterol reductase	-1.15	0.000
GBP5	guanylate binding protein 5	-1.08	0.000
NGF	nerve growth factor	-1.52	0.000
LOC101927851	uncharacterized LOC101927851	-1.13	0.004
MCM10	minichromosome maintenance 10 replication initiation factor	-1.10	0.001
CDK1	cyclin dependent kinase 1	-1.04	0.001
IFIT3	interferon induced protein with tetratricopeptide repeats 3	-1.09	0.015
IFIT1	interferon induced protein with tetratricopeptide repeats 1	-1.26	0.001
KIF11	kinesin family member 11	-1.14	0.003
OLMALINC	oligodendrocyte maturation-associated long intergenic non-coding RNA	-1.01	0.002
CH25H	cholesterol 25-hydroxylase	-1.48	0.000
MKI67	marker of proliferation Ki-67	-1.26	0.000
IFITM1	interferon induced transmembrane protein 1	-2.16	0.000
TRIM22	tripartite motif containing 22	-1.28	0.005
FAM111B	FAM111 trypsin like peptidase B	-1.81	0.000
MS4A2	membrane spanning 4-domains A2	-1.05	0.048
FADS2	fatty acid desaturase 2	-1.04	0.000
E2F8	E2F transcription factor 8	-1.02	0.000
MPEG1	macrophage expressed 1	-1.24	0.019
DHCR7	7-dehydrocholesterol reductase	-1.19	0.000
MMP8	matrix metallopeptidase 8	-1.05	0.000
MMP1	matrix metallopeptidase 1	-1.05	0.001
MMP12	matrix metallopeptidase 12	-1.66	0.012
OAS1	2'-5'-oligoadenylate synthetase 1	-1.33	0.000
OAS3	2'-5'-oligoadenylate synthetase 3	-1.42	0.000
OAS2	2'-5'-oligoadenylate synthetase 2	-1.66	0.000
AICDA	activation induced cytidine deaminase	-1.04	0.016
LINC02384	long intergenic non-protein coding RNA 2384	-1.66	0.001
SLC9A7P1	solute carrier family 9 member 7 pseudogene 1	-1.03	0.001
C1QTNF9	C1q and TNF related 9	-1.19	0.028
SKA3	spindle and kinetochore associated complex subunit 3	-1.19	0.000

GPR183	G protein-coupled receptor 183	-1.02	0.036
KNL1	kinetochore scaffold 1	-1.30	0.000
RAD51	RAD51 recombinase	-1.16	0.001
DLL4	delta like canonical Notch ligand 4	-1.24	0.000
CHAC1	ChaC glutathione specific gamma-glutamylcyclotransferase 1	-2.14	0.000
NUSAP1	nucleolar and spindle associated protein 1	-1.13	0.000
WDR76	WD repeat domain 76	-1.15	0.000
FANCI	FA complementation group I	-1.15	0.000
IL21R	interleukin 21 receptor	-1.08	0.002
MMP2-AS1	MMP2 antisense RNA 1	-2.36	0.002
GINS2	GINS complex subunit 2	-1.15	0.002
XAF1	XIAP associated factor 1	-1.44	0.000
TMEM97	transmembrane protein 97	-1.24	0.000
CDC6	cell division cycle 6	-1.03	0.002
PRR11	proline rich 11	-1.06	0.002
CCL1	C-C motif chemokine ligand 1	-1.82	0.001
TOP2A	DNA topoisomerase II alpha	-1.38	0.003
TYMS	thymidylate synthetase	-1.31	0.000
NDC80	NDC80 kinetochore complex component	-1.12	0.001
LIPG	lipase G, endothelial type	-1.02	0.001
SKA1	spindle and kinetochore associated complex subunit 1	-1.58	0.000
SERPINB7	serpin family B member 7	-1.18	0.000
HMSD	histocompatibility minor serpin domain containing	-1.89	0.012
CDH2	cadherin 2	-1.06	0.029
SIGLEC9	sialic acid binding Ig like lectin 9	-1.02	0.004
ASF1B	anti-silencing function 1B histone chaperone	-1.21	0.000
RSAD2	radical S-adenosyl methionine domain containing 2	-1.27	0.003
RRM2	ribonucleotide reductase regulatory subunit M2	-1.48	0.000
NCAPH	non-SMC condensin I complex subunit H	-1.24	0.000
CDCA7	cell division cycle associated 7	-1.23	0.002
NRIR	negative regulator of interferon response	-1.16	0.013
CMPK2	cytidine/uridine monophosphate kinase 2	-1.27	0.001
CYRIA	CYFIP related Rac1 interactor A	-1.11	0.013
LRRTM1	leucine rich repeat transmembrane neuronal 1	-1.01	0.009
DUSP2	dual specificity phosphatase 2	-1.19	0.001
BUB1	BUB1 mitotic checkpoint serine/threonine kinase	-1.24	0.002
CKAP2L	cytoskeleton associated protein 2 like	-1.07	0.004
MCM6	minichromosome maintenance complex component 6	-1.12	0.000
MCM8	minichromosome maintenance 8 homologous recombination repair factor	-1.20	0.000
TPX2	TPX2 microtubule nucleation factor	-1.44	0.001
CPXM1	carboxypeptidase X, M14 family member 1	-1.38	0.000
MX2	MX dynamin like GTPase 2	-1.40	0.000
MX1	MX dynamin like GTPase 1	-1.80	0.000

PTX3	pentraxin 3	-1.10	0.004
SGO1	shugoshin 1	-1.20	0.003
TNFSF10	TNF superfamily member 10	-1.32	0.017
LAMP3	lysosomal associated membrane protein 3	-1.28	0.002
P3H2	prolyl 3-hydroxylase 2	-1.17	0.001
NCAPG	non-SMC condensin I complex subunit G	-1.49	0.000
SLIT2	slit guidance ligand 2	-1.37	0.009
SLC4A4	solute carrier family 4 member 4	-1.02	0.001
HERC6	HECT and RLD domain containing E3 ubiquitin protein ligase family member 6	-1.06	0.000
PLK4	polo like kinase 4	-1.07	0.000
LINC02562	long intergenic non-protein coding RNA 2562	-1.27	0.001
CXCL10	C-X-C motif chemokine ligand 10	-2.15	0.000
CXCL11	C-X-C motif chemokine ligand 11	-1.11	0.007
DKK2	dickkopf WNT signaling pathway inhibitor 2	-2.00	0.008
CCNA2	cyclin A2	-1.48	0.000
LOC102467226	uncharacterized LOC102467226	-1.60	0.006
HMMR	hyaluronan mediated motility receptor	-1.14	0.004
CD180	CD180 molecule	-1.03	0.001
SLCO4C1	solute carrier organic anion transporter family member 4C1	-1.04	0.002
CXCL14	C-X-C motif chemokine ligand 14	-1.33	0.025
IL12B	interleukin 12B	-2.76	0.016
H2BC14	H2B clustered histone 14	-1.16	0.016
HLA-DQA2	major histocompatibility complex, class II, DQ alpha 2	-1.88	0.002
SCAT8	S-phase cancer associated transcript 8	-1.25	0.020
TTK	TTK protein kinase	-1.16	0.003
VGLL2	vestigial like family member 2	-1.09	0.003
MYB	MYB proto-oncogene, transcription factor	-1.28	0.001
PLEKHG1	pleckstrin homology and RhoGEF domain containing G1	-1.73	0.008
ACAT2	acetyl-CoA acetyltransferase 2	-1.03	0.000
MAS1	MAS1 proto-oncogene, G protein-coupled receptor	-1.20	0.000
SERPINB9	serpin family B member 9	-1.09	0.026
H3C8	H3 clustered histone 8	-1.02	0.008
H1-5	H1.5 linker histone, cluster member	-1.17	0.001
MCM3	minichromosome maintenance complex component 3	-1.07	0.000
HLA-DQA2|HLA-DQA1	major histocompatibility complex, class II, DQ alpha 2|major histocompatibility complex, class II, DQ alpha 1	-1.92	0.004
IL6	interleukin 6	-1.72	0.001
IL6-AS1	IL6 antisense RNA 1	-2.00	0.001
PSPH	phosphoserine phosphatase	-1.04	0.001
GPR85	G protein-coupled receptor 85	-1.17	0.002
PTK2B	protein tyrosine kinase 2 beta	-1.11	0.002
ESCO2	establishment of sister chromatid cohesion N-acetyltransferase 2	-1.31	0.000
MCM4	minichromosome maintenance complex component 4	-1.01	0.001
LY6E	lymphocyte antigen 6 family member E	-1.22	0.000

PBK	PDZ binding kinase	-1.19	0.004
CCNE2	cyclin E2	-1.30	0.001
DSCC1	DNA replication and sister chromatid cohesion 1	-1.23	0.002
HAS2	hyaluronan synthase 2	-1.11	0.002
ATAD2	ATPase family AAA domain containing 2	-1.12	0.000
IL33	interleukin 33	-1.63	0.004
MELK	maternal embryonic leucine zipper kinase	-1.20	0.001
RORB	RAR related orphan receptor B	-1.21	0.006
CCL19	C-C motif chemokine ligand 19	-1.51	0.002
TLR7	toll like receptor 7	-1.21	0.005
CENPI	centromere protein I	-1.04	0.000
ANKRD20A8P|ANKRD20A4-ANKRD20A20P	ankyrin repeat domain 20 family member A8, pseudogene|ANKRD20A4-ANKRD20A20P readthrough	-1.18	0.001
ZNF730	zinc finger protein 730	-1.08	0.000
LOC285889	uncharacterized LOC285889	-1.14	0.040

Supplementary Table 3. GO and KEGG enrichment analysis of up-regulated genes of macrophage samples.

Category	Term	Count	%	p-value
GOTERM_BP_DIRECT	GO:0006396~RNA processing	52	44.44	4.03E-49
GOTERM_BP_DIRECT	GO:0036498~IRE1-mediated unfolded protein response	5	4.27	2.51E-04
GOTERM_BP_DIRECT	GO:0051085~chaperone mediated protein folding requiring cofactor	4	3.42	8.92E-04
GOTERM_BP_DIRECT	GO:0042167~heme catabolic process	3	2.56	3.52E-03
GOTERM_BP_DIRECT	GO:0015909~long-chain fatty acid transport	3	2.56	3.97E-03
GOTERM_BP_DIRECT	GO:0019222~regulation of metabolic process	4	3.42	4.18E-03
GOTERM_BP_DIRECT	GO:0034620~cellular response to unfolded protein	3	2.56	1.06E-02
GOTERM_BP_DIRECT	GO:0071260~cellular response to mechanical stimulus	4	3.42	1.12E-02
GOTERM_BP_DIRECT	GO:0050729~positive regulation of inflammatory response	4	3.42	2.00E-02
GOTERM_BP_DIRECT	GO:0097201~negative regulation of transcription from RNA polymerase II promoter in response to stress	2	1.71	2.76E-02
GOTERM_BP_DIRECT	GO:0034605~cellular response to heat	3	2.56	3.54E-02
GOTERM_BP_DIRECT	GO:0071243~cellular response to arsenic-containing substance	2	1.71	4.91E-02
GOTERM_CC_DIRECT	GO:0005730~nucleolus	56	47.86	3.13E-36
GOTERM_CC_DIRECT	GO:0015030~Cajal body	8	6.84	1.53E-07
GOTERM_CC_DIRECT	GO:0016324~apical plasma membrane	6	5.13	4.84E-02
GOTERM_MF_DIRECT	GO:0051787~misfolded protein binding	3	2.56	3.37E-03
GOTERM_MF_DIRECT	GO:0051087~chaperone binding	4	3.42	4.33E-03
GOTERM_MF_DIRECT	GO:0044183~protein binding involved in protein folding	3	2.56	6.65E-03
GOTERM_MF_DIRECT	GO:0042802~identical protein binding	12	10.26	1.09E-02
GOTERM_MF_DIRECT	GO:0031072~heat shock protein binding	3	2.56	1.71E-02
GOTERM_MF_DIRECT	GO:0005509~calcium ion binding	7	5.98	2.30E-02
GOTERM_MF_DIRECT	GO:0008514~organic anion transmembrane transporter activity	2	1.71	3.81E-02
GOTERM_MF_DIRECT	GO:0005543~phospholipid binding	3	2.56	4.84E-02
KEGG_PATHWAY	hsa03320:PPAR signaling pathway	5	4.27	2.25E-04
KEGG_PATHWAY	hsa05110:Vibrio cholerae infection	4	3.42	1.06E-03
KEGG_PATHWAY	hsa04145:Phagosome	4	3.42	2.33E-02
KEGG_PATHWAY	hsa04141:Protein processing in endoplasmic reticulum	4	3.42	3.16E-02

Supplementary Table 4. GO and KEGG enrichment analysis of down-regulated genes of macrophage samples.

Category	Term	Count	%	p-value
GOTERM_BP_DIRECT	GO:0006260~DNA replication	14	10.14	1.32E-11
GOTERM_BP_DIRECT	GO:0051607~defense response to virus	16	11.59	1.46E-11
GOTERM_BP_DIRECT	GO:0009615~response to virus	12	8.70	1.92E-10
GOTERM_BP_DIRECT	GO:0051301~cell division	18	13.04	4.06E-10
GOTERM_BP_DIRECT	GO:0007052~mitotic spindle organization	12	8.70	5.68E-10
GOTERM_BP_DIRECT	GO:0060337~type I interferon signaling pathway	10	7.25	5.99E-10
GOTERM_BP_DIRECT	GO:0006270~DNA replication initiation	7	5.07	2.41E-07
GOTERM_BP_DIRECT	GO:0000278~mitotic cell cycle	10	7.25	4.01E-07
GOTERM_BP_DIRECT	GO:0045071~negative regulation of viral genome replication	7	5.07	4.88E-07
GOTERM_BP_DIRECT	GO:0032760~positive regulation of tumor necrosis factor production	8	5.80	5.34E-06
GOTERM_BP_DIRECT	GO:0007059~chromosome segregation	7	5.07	9.01E-06
GOTERM_BP_DIRECT	GO:0006268~DNA unwinding involved in DNA replication	5	3.62	1.34E-05
GOTERM_BP_DIRECT	GO:0098586~cellular response to virus	6	4.35	2.79E-05
GOTERM_BP_DIRECT	GO:0008283~cell proliferation	8	5.80	4.99E-05
GOTERM_BP_DIRECT	GO:0000727~double-strand break repair via break-induced replication	4	2.90	5.55E-05
GOTERM_BP_DIRECT	GO:0060700~regulation of ribonuclease activity	3	2.17	2.46E-04
GOTERM_BP_DIRECT	GO:0045087~innate immune response	13	9.42	5.46E-04
GOTERM_BP_DIRECT	GO:0007094~mitotic spindle assembly checkpoint	4	2.90	6.87E-04
GOTERM_BP_DIRECT	GO:0036388~pre-replicative complex assembly	5	3.62	8.29E-04
GOTERM_BP_DIRECT	GO:0006955~immune response	11	7.97	1.09E-03
GOTERM_BP_DIRECT	GO:0070098~chemokine-mediated signaling pathway	5	3.62	1.10E-03
GOTERM_BP_DIRECT	GO:0031640~killing of cells of other organism	5	3.62	1.10E-03
GOTERM_BP_DIRECT	GO:0006267~pre-replicative complex assembly involved in nuclear cell cycle DNA replication	3	2.17	1.13E-03
GOTERM_BP_DIRECT	GO:0060333~interferon-gamma-mediated signaling pathway	5	3.62	1.22E-03
GOTERM_BP_DIRECT	GO:0006954~inflammatory response	10	7.25	1.23E-03
GOTERM_BP_DIRECT	GO:0071222~cellular response to lipopolysaccharide	7	5.07	1.48E-03
GOTERM_BP_DIRECT	GO:0010389~regulation of G2/M transition of mitotic cell cycle	5	3.62	1.97E-03
GOTERM_BP_DIRECT	GO:0035455~response to interferon-alpha	3	2.17	2.19E-03
GOTERM_BP_DIRECT	GO:0032728~positive regulation of interferon-beta production	4	2.90	2.51E-03
GOTERM_BP_DIRECT	GO:0007076~mitotic chromosome condensation	4	2.90	2.51E-03
GOTERM_BP_DIRECT	GO:0034501~protein localization to kinetochore	3	2.17	2.62E-03
GOTERM_BP_DIRECT	GO:0051983~regulation of chromosome segregation	3	2.17	2.62E-03
GOTERM_BP_DIRECT	GO:0006271~DNA strand elongation involved in DNA replication	3	2.17	3.08E-03
GOTERM_BP_DIRECT	GO:0051310~metaphase plate congression	3	2.17	3.08E-03
GOTERM_BP_DIRECT	GO:0008608~attachment of spindle microtubules to kinetochore	3	2.17	3.58E-03
GOTERM_BP_DIRECT	GO:0070106~interleukin-27-mediated signaling pathway	3	2.17	4.11E-03
GOTERM_BP_DIRECT	GO:0010818~T cell chemotaxis	3	2.17	4.11E-03
GOTERM_BP_DIRECT	GO:0006915~apoptotic process	11	7.97	4.63E-03
GOTERM_BP_DIRECT	GO:0061844~antimicrobial humoral immune response mediated by antimicrobial peptide	5	3.62	5.48E-03
GOTERM_BP_DIRECT	GO:0060339~negative regulation of type I interferon-mediated signaling pathway	3	2.17	7.29E-03
GOTERM_BP_DIRECT	GO:0046597~negative regulation of viral entry into host cell	3	2.17	9.59E-03
GOTERM_BP_DIRECT	GO:0008285~negative regulation of cell proliferation	9	6.52	9.70E-03

GOTERM_BP_DIRECT	GO:0032740~positive regulation of interleukin-17 production	3	2.17	1.04E-02
GOTERM_BP_DIRECT	GO:0044772~mitotic cell cycle phase transition	3	2.17	1.04E-02
GOTERM_BP_DIRECT	GO:1901224~positive regulation of NIK/NF-kappaB signaling	4	2.90	1.05E-02
GOTERM_BP_DIRECT	GO:0043154~negative regulation of cysteine-type endopeptidase activity involved in apoptotic process	4	2.90	1.18E-02
GOTERM_BP_DIRECT	GO:0048511~rhythmic process	4	2.90	1.41E-02
GOTERM_BP_DIRECT	GO:0007166~cell surface receptor signaling pathway	7	5.07	1.50E-02
GOTERM_BP_DIRECT	GO:0030593~neutrophil chemotaxis	4	2.90	1.56E-02
GOTERM_BP_DIRECT	GO:0000083~regulation of transcription involved in G1/S transition of mitotic cell cycle	3	2.17	1.60E-02
GOTERM_BP_DIRECT	GO:0009410~response to xenobiotic stimulus	6	4.35	1.89E-02
GOTERM_BP_DIRECT	GO:0071659~negative regulation of IP-10 production	2	1.45	1.93E-02
GOTERM_BP_DIRECT	GO:0034421~post-translational protein acetylation	2	1.45	1.93E-02
GOTERM_BP_DIRECT	GO:0000070~mitotic sister chromatid segregation	3	2.17	2.03E-02
GOTERM_BP_DIRECT	GO:0007095~mitotic G2 DNA damage checkpoint	3	2.17	2.14E-02
GOTERM_BP_DIRECT	GO:1903978~regulation of microglial cell activation	2	1.45	2.56E-02
GOTERM_BP_DIRECT	GO:0033489~cholesterol biosynthetic process via desmosterol	2	1.45	2.56E-02
GOTERM_BP_DIRECT	GO:0006235~dTTP biosynthetic process	2	1.45	2.56E-02
GOTERM_BP_DIRECT	GO:0033490~cholesterol biosynthetic process via lathosterol	2	1.45	2.56E-02
GOTERM_BP_DIRECT	GO:0051726~regulation of cell cycle	6	4.35	2.58E-02
GOTERM_BP_DIRECT	GO:0006695~cholesterol biosynthetic process	3	2.17	2.63E-02
GOTERM_BP_DIRECT	GO:0071346~cellular response to interferon-gamma	4	2.90	2.64E-02
GOTERM_BP_DIRECT	GO:0032755~positive regulation of interleukin-6 production	4	2.90	2.85E-02
GOTERM_BP_DIRECT	GO:0006974~cellular response to DNA damage stimulus	6	4.35	2.85E-02
GOTERM_BP_DIRECT	GO:0090307~mitotic spindle assembly	3	2.17	2.88E-02
GOTERM_BP_DIRECT	GO:0007049~cell cycle	7	5.07	2.88E-02
GOTERM_BP_DIRECT	GO:0050729~positive regulation of inflammatory response	4	2.90	2.92E-02
GOTERM_BP_DIRECT	GO:0030574~collagen catabolic process	3	2.17	3.15E-02
GOTERM_BP_DIRECT	GO:0046601~positive regulation of centriole replication	2	1.45	3.19E-02
GOTERM_BP_DIRECT	GO:1905821~positive regulation of chromosome condensation	2	1.45	3.19E-02
GOTERM_BP_DIRECT	GO:0002548~monocyte chemotaxis	3	2.17	3.42E-02
GOTERM_BP_DIRECT	GO:0032722~positive regulation of chemokine production	3	2.17	3.42E-02
GOTERM_BP_DIRECT	GO:0009617~response to bacterium	4	2.90	3.53E-02
GOTERM_BP_DIRECT	GO:0006275~regulation of DNA replication	3	2.17	3.70E-02
GOTERM_BP_DIRECT	GO:1902975~mitotic DNA replication initiation	2	1.45	3.81E-02
GOTERM_BP_DIRECT	GO:2000342~negative regulation of chemokine (C-X-C motif) ligand 2 production	2	1.45	3.81E-02
GOTERM_BP_DIRECT	GO:0061470~T follicular helper cell differentiation	2	1.45	3.81E-02
GOTERM_BP_DIRECT	GO:0042493~response to drug	6	4.35	3.82E-02
GOTERM_BP_DIRECT	GO:0045429~positive regulation of nitric oxide biosynthetic process	3	2.17	3.85E-02
GOTERM_BP_DIRECT	GO:0006334~nucleosome assembly	4	2.90	4.37E-02
GOTERM_BP_DIRECT	GO:0051574~positive regulation of histone H3-K9 methylation	2	1.45	4.44E-02
GOTERM_BP_DIRECT	GO:0016185~synaptic vesicle budding from presynaptic endocytic zone membrane	2	1.45	4.44E-02
GOTERM_BP_DIRECT	GO:0000079~regulation of cyclin-dependent protein serine/threonine kinase activity	3	2.17	4.45E-02
GOTERM_BP_DIRECT	GO:0006935~chemotaxis	4	2.90	4.55E-02
GOTERM_CC_DIRECT	GO:0000776~kinetochore	10	7.25	2.12E-07
GOTERM_CC_DIRECT	GO:0005654~nucleoplasm	48	34.78	1.26E-06

GOTERM_CC_DIRECT	GO:0072686~mitotic spindle	8	5.80	8.83E-06
GOTERM_CC_DIRECT	GO:0000922~spindle pole	8	5.80	1.51E-05
GOTERM_CC_DIRECT	GO:0042555~MCM complex	4	2.90	1.95E-05
GOTERM_CC_DIRECT	GO:0005694~chromosome	10	7.25	1.96E-05
GOTERM_CC_DIRECT	GO:0005813~centrosome	14	10.14	3.34E-05
GOTERM_CC_DIRECT	GO:0005819~spindle	8	5.80	3.40E-05
GOTERM_CC_DIRECT	GO:0071162~CMG complex	4	2.90	3.79E-05
GOTERM_CC_DIRECT	GO:0000775~chromosome, centromeric region	6	4.35	4.63E-05
GOTERM_CC_DIRECT	GO:0000940~condensed chromosome outer kinetochore	4	2.90	5.03E-05
GOTERM_CC_DIRECT	GO:0016020~membrane	31	22.46	3.10E-04
GOTERM_CC_DIRECT	GO:0005634~nucleus	56	40.58	3.16E-04
GOTERM_CC_DIRECT	GO:0005829~cytosol	52	37.68	5.73E-04
GOTERM_CC_DIRECT	GO:0000793~condensed chromosome	4	2.90	6.24E-04
GOTERM_CC_DIRECT	GO:0000777~condensed chromosome kinetochore	5	3.62	2.45E-03
GOTERM_CC_DIRECT	GO:0005876~spindle microtubule	4	2.90	2.62E-03
GOTERM_CC_DIRECT	GO:0005615~extracellular space	23	16.67	3.57E-03
GOTERM_CC_DIRECT	GO:0015630~microtubule cytoskeleton	6	4.35	5.24E-03
GOTERM_CC_DIRECT	GO:0005737~cytoplasm	47	34.06	9.02E-03
GOTERM_CC_DIRECT	GO:0031012~extracellular matrix	6	4.35	2.24E-02
GOTERM_CC_DIRECT	GO:0000781~chromosome, telomeric region	5	3.62	2.25E-02
GOTERM_CC_DIRECT	GO:0000307~cyclin-dependent protein kinase holoenzyme complex	3	2.17	2.47E-02
GOTERM_CC_DIRECT	GO:0000942~condensed nuclear chromosome outer kinetochore	2	1.45	2.48E-02
GOTERM_CC_DIRECT	GO:0098844~postsynaptic endocytic zone membrane	2	1.45	3.09E-02
GOTERM_CC_DIRECT	GO:0005576~extracellular region	21	15.22	3.94E-02
GOTERM_CC_DIRECT	GO:0000228~nuclear chromosome	3	2.17	4.34E-02
GOTERM_CC_DIRECT	GO:0000796~condensin complex	2	1.45	4.89E-02
GOTERM_MF_DIRECT	GO:0017116~single-stranded DNA-dependent ATP-dependent DNA helicase activity	6	4.35	1.92E-07
GOTERM_MF_DIRECT	GO:0003688~DNA replication origin binding	6	4.35	3.14E-07
GOTERM_MF_DIRECT	GO:0005515~protein binding	101	73.19	6.51E-05
GOTERM_MF_DIRECT	GO:0001730~2'-5'-oligoadenylate synthetase activity	3	2.17	2.45E-04
GOTERM_MF_DIRECT	GO:0008009~chemokine activity	5	3.62	3.01E-04
GOTERM_MF_DIRECT	GO:0003697~single-stranded DNA binding	6	4.35	7.93E-04
GOTERM_MF_DIRECT	GO:0005524~ATP binding	22	15.94	8.05E-04
GOTERM_MF_DIRECT	GO:0008017~microtubule binding	8	5.80	1.63E-03
GOTERM_MF_DIRECT	GO:0008022~protein C-terminus binding	7	5.07	2.25E-03
GOTERM_MF_DIRECT	GO:0042802~identical protein binding	21	15.22	6.16E-03
GOTERM_MF_DIRECT	GO:0003678~DNA helicase activity	4	2.90	7.17E-03
GOTERM_MF_DIRECT	GO:0003725~double-stranded RNA binding	4	2.90	1.17E-02
GOTERM_MF_DIRECT	GO:0003682~chromatin binding	8	5.80	2.95E-02
GOTERM_MF_DIRECT	GO:0016628~oxidoreductase activity, acting on the CH-CH group of donors, NAD or NADP as acceptor	2	1.45	3.18E-02
GOTERM_MF_DIRECT	GO:0048248~CXCR3 chemokine receptor binding	2	1.45	3.18E-02
GOTERM_MF_DIRECT	GO:0003677~DNA binding	15	10.87	3.35E-02
GOTERM_MF_DIRECT	GO:0019899~enzyme binding	7	5.07	3.74E-02
GOTERM_MF_DIRECT	GO:0004714~transmembrane receptor protein tyrosine kinase activity	4	2.90	3.92E-02

KEGG_PATHWAY	hsa05164:Influenza A	13	9.42	1.37E-08
KEGG_PATHWAY	hsa04110:Cell cycle	10	7.25	8.99E-07
KEGG_PATHWAY	hsa05162:Measles	9	6.52	1.89E-05
KEGG_PATHWAY	hsa05171:Coronavirus disease - COVID-19	11	7.97	2.05E-05
KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	11	7.97	1.56E-04
KEGG_PATHWAY	hsa04061:Viral protein interaction with cytokine and cytokine receptor	7	5.07	1.78E-04
KEGG_PATHWAY	hsa05160:Hepatitis C	8	5.80	3.21E-04
KEGG_PATHWAY	hsa05169:Epstein-Barr virus infection	8	5.80	1.43E-03
KEGG_PATHWAY	hsa04620:Toll-like receptor signaling pathway	5	3.62	1.11E-02
KEGG_PATHWAY	hsa05321:Inflammatory bowel disease	4	2.90	1.70E-02
KEGG_PATHWAY	hsa04062:Chemokine signaling pathway	6	4.35	2.21E-02
KEGG_PATHWAY	hsa04114:Oocyte meiosis	5	3.62	2.39E-02
KEGG_PATHWAY	hsa03030:DNA replication	3	2.17	3.63E-02