Int J Clin Exp Med 2016;9(5):7986-7995
www.ijcem.com /ISSN:1940-5901/IJCEM0019172

Original Article

A database and functional annotation of NF-κB target genes

Yang Yang, Jian Wu, Jinke Wang

The State Key Laboratory of Bioelectronics, Southeast University, Nanjing 210096, People's Republic of China

Received November 4, 2015; Accepted February 10, 2016; Epub May 15, 2016; Published May 30, 2016

Abstract: Backgrounds: The previous studies show that the transcription factor NF-κB always be induced by many inducers, and can regulate the expressions of many genes. The aim of the present study is to explore the database and functional annotation of NF-κB target genes. Methods: In this study, we manually collected the most complete listing of all NF-κB target genes identified to date, including the NF-κB microRNA target genes and built the database of NF-κB target genes with the detailed information of each target gene and annotated it by DAVID tools. Results: The NF-κB target genes database was established (http://tfdb.seu.edu.cn/nfkb/). The collected data confirmed that NF-κB maintains multitudinous biological functions and possesses the considerable complexity and diversity in regulation the expression of corresponding target genes set. The data showed that the NF-κB was a central regulator of the stress response, immune response and cellular metabolic processes. NF-κB involved in bone disease, immunological disease and cardiovascular disease, various cancers and nervous disease. NF-κB can modulate the expression activity of other transcriptional factors. Inhibition of IKK and IκBα phosphorylation, the decrease of nuclear translocation of p65 and the reduction of intracellular glutathione level determined the up-regulation or down-regulation of expression of NF-κB target genes. Conclusion: Through the analysis of 1667 distinct NF-κB target genes, it can further perfect the NF-κB signaling pathways and provide the data for building the gene expression regulatory networks and the clinical targets of diagnosis and treatment.

Keywords: NF-κB signaling pathway, target gene, database, regulatory network

Introduction

In the post-genomic era, the word for illuminating the rule of gene expression and regulation, and following revealing the mysteries of life from exploring human genome sequence, have become the focus of life science research in the recent years. Meanwhile, studies of gene expression regulatory networks are one of the important tasks of systems biology [1-3]. Transcription factors (TFs) are proteins that bind to specific DNA sequences (cis-elements), and play the crucial roles in regulation of gene expressions. Almost all of the genes in the expression must be regulated by transcription factors. The collection of target genes of a transcription factor is the primary work for uncovering its functions in cells and building its transcriptional regulatory network.

NF-κB is a transcription factor first identified in lymphocyte and exists in most cell types [4]. NF-κB can recognize and bind to a specific κB regulatory sequences in the promoter of target genes, which promotes the expression of the target genes [5]. Meanwhile, NF-κB is a typically inducible transcription factor involved in regulating the expression of many genes. NF-κB is expressed and plays a role in many cells. NF-κB is the main regulator of the organism's immune response and inflammation, and is also involved in embryonic development, apoptosis, cell cycle regulation, and so on [6-9]. The pathogenesis of various diseases is associated with abnormal activation of NF-κB [10]. NF-κB is also currently an important target for transcription therapeutic drugs. Therefore, the literature of NF-κB has resulted in a vast number of publications every year on the transcription factor since 1986.

NF-κB family contains five members, including RelA (p65), c-Rel, RelB, NF-κB1 (p50), and NF-κB2 (p52), which can act as heterodimers or homodimers in gene transcription regulation

[11]. The heterodimer of p50/p65 is the most common form of NF-κB in mammalian cells. NF-κB is sequestered in the cytoplasm as an inactivated form by its inhibitory protein IκB [11]. All the genes that are bound and regulated by NF-κB constitute the NF-κB target genes spectrum. However, currently limited by the understanding of the biological functions and the building of NF-κB regulatory networks, the spectrum of NF-κB target genes is not complete.

In recent years, with the development of biology experiments technology and sequencing technology, there have a lot of high-throughput identification technologies of DNA-binding sites and target genes of transcription factors and biology experiments and bioinformatics analysis and forecasting techniques; such as: ChIP-chip [12], ChIP-PET [13], ChIP-seq [14]. These high-throughput experiments technologies can obtain hundreds of NF-κB target genes and a large number of DNA-binding sites each experiment [15-17]. The conventional experimental methods include: gene knockout, overexpression of the transcription factor, ChIP-PCR, EMSA, mutagenesis of the promoter/enhancer, DNA footprinting, and so on. These experimental methods usually identify one or several target genes each experiment.

Collection of NF-κB target genes is vital to reveal the biological functions of NF-κB. NF-κB target genes are numerous, and there are several tools to predict these genes. However, due to no formula to recognize NF-κB target genes accurately, these computer-aided prediction are usually not right and cannot be verified by experiment. So it is necessary to collect NF-κB target genes by manually and build a database. Though there are already several databases for collecting NF-κB target genes, these databases are usually primitive, lack of detail, out of data and not full enough.

In this study, we manually collected the NF-κB direct target genes identified by the high-throughput experiments technologies and conventional experiment technologies after 1999 as full as possible and built the database with the specific information. Recently, microRNA (miRNA) has been demonstrated to play the important roles in gene expression regulation, we also collected the NF-κB microRNA target genes. Moreover, we performed a functional annotation of these NF-κB target genes.

Materials and methods

Collection of NF-κB target genes

We manually collected the direct target genes of NF-κB reported in publications through the searching engines of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://scholar.google.com.hk/schhp?hl=zh-CN) with the key words of NF-κB and ChIP (Chromatin Immunoprecipitation). Briefly, NF-κB activation binds to the promoter/enhancer regions of the given genes in vivo, and NF-κB can regulate the expression of the given genes; and then they are the direct target genes of NF-κB. Because NF-κB is an inducible transcription factor, we simultaneously collected the specific inducers, cell types, expression quantity of target genes, experiment methods, references, as well as NF-κB binding domain: GGGRNNTYCC from TRANSFAC [18], GGRRNNYYCC [19], NGGRNTTYCC [16], RGGRNNHHYY, DGGGGGTTTY, GGKRRWKBHB, GKRVTTYCCV, GKVNWTYCCV, RGGGGRWKTW and NGGGGRWDDY [20].

Building the database of NF-κB target genes

We employed the free, mature platform of Linux+Apache+MySQL+PHP to build NF-κB target genes database. Briefly, Linux (CentOS V5.5) as the operating system and Apache (version, 2.2.17) as the server software, we write the data of NF-κB target genes in MySQL (5.0.77) with Perl script. We used PHP (version, 5.1.6; Hypertext Preprocessor) program to operate the MySQL database and published it on the Internet.

Gene annotation analysis

We employed the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7 [21] to proceed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways analysis of NF-κB target genes. And the KEGG pathways analysis also was employed by WEB-based GEneSeTAnaLysisToolkit [22]. Gene Ontology for Biological Processes, Cellular Components and Molecular Function, as well as KEGG pathways analysis were considered significantly enriched when p value less than 0.05.

Table 1. The list of NF-κB target genes

Acute phase proteins	C4A, DEFB1, DEFB4A, F3, PTX3, SAA1
Cell Adhesion Molecules	ACAP2, AMIGO2, ANKIB1, ANKRD10, ANKRD46, ANKRD57, ANTXR2, ASB7, CD200, CD44, CD53, CD59, CDH1, FN1, ICAM1, ITGA5, NCAM2, NEXN, PCDH7, SELE, SELL, SELP, TNC, VCAM1
Cell Surface Receptors	ADAM12, ADAM19, ADORA2A, ADORA3, AGER, CD69, CREB3L4, EGFR, EMR1, ERBB2, FPR1, GALR2, GRIN1, GRM5, KLKB1, LDLR, LEPROT, OLR1, OPRD1, OPRM1, OXTR, PIGT, PTAFR, RABEP1, SCAMP1, SCN5A, SLCO1C1, THBD, TREM2, VLDLR
Cytokines/Chemokines and their modulators	CCL1, CCL11, CCL15, CCL17, CCL19, CCL2, CCL20, CCL21, CCL22, CCL23, CCL24, CCL3, CCL4, CCL5, CCL6, CCR1, CCRL2, CX3CL1, CX3CR1, CXCL1, CXCL10, CXCL11, CXCL12, CXCL16, CXCL2, CCL28, CXCL6, CXCL8, CXCL9, CXCR4, CXCR4, CXCR5, EBI3, ICOS, IFNAB, IFNAR1, IFNB1, IFNE, IFNG, IFNGR1, IFNGR2, IFNK, IFNL1, IIGP1, IL10, IL10RA, IL10RB, IL11, IL12A, IL12B, IL12RB1, IL13, IL13RA1, IL15, IL15RA, IL1A, IL1B, IL1R1, IL1R2, IL1RAP, IL1RN, IL2, IL21, IL23A, IL27, IL32, IL4, IL4I1, IL4R, IL6, IL6ST, IL7R, IL8, IL9, LIFR, LTA, LTB, TFF3, TNF, TNFRSF10B, TNFSF10, TNFSF11, TNFSF13B, TNFSF14, TNFSF4, XCL1
Early response genes	TNFAIP2, TNFAIP6, TNFAIP8
Enzymes	ACADM, ACAS2L, ACO2, ACSL3, ADAMDEC1, ADAMTS6, ADSSL1, AGPS, AHCYL2, AK2, AKAP13, AKAP9, AKR1C1, ALAS1, ALG9, ALOX12B, ALOX5AP, AMPD2, AMPD3, AOAH, ARHGAP4, ARHGEF7, ARHH, ASS1, ATM, ATP10D, ATP11B, ATP1B1, ATP2C1, ATP5G1, B3GALNT1, B3GALT2, B3GNT5, B4GALT3, B4GALT4, B4GALT5, B4GALT6, BCAP, BCKDHB, BGALT15, BHMT, BLK, BLVRA, CAMK2D, CARD11, CASP3, CASP8, CAT, CBR4, CDK2, CDK6, CHD7, CHEK1, CHST11, CHST15, CHSY1, CKB, CPD, CSNK1G3, CTDSPL2, CTSK, CTSL, DAPK1, DBT, DGUOK, DHRS2, DHX9, DIO2, DNASE1L2, DUSP1, DUSP10, DUSP16, DUSP2, DUSP4, DUSP5, DUSP6, EARS2, TYMP, ECHDC1, EME1, ENPP2, ENTPD4, EXT1, EXTL2, FDXR, FGR, FLT3, FLT4, FMO5, FUCA1, FUT4, FUT7, G2E3, GALNT1, GALNT7, GBGT1, GCNT1, GFPT1, GFPT2, GGT1, GLDC, GMDS, GNB2L1, GNRH2, GPD2, GRK5, GZMB, HCK, HDAC3, HDAC5, HIPK2, HMGCR, HMGCS1, PRMT1, HS2ST1, HS3ST3A1, HS3ST3B1, HS6ST1, HSD11B1, HSD11B2, HTRA1, HTRA2, IDH1, IDH3A, IDO1, IRAK2, IRAK3, ITPKB, JAK1, JARID1B, KAT2B, KHK, KIDINS220, KLK3, KYNU, LATS2, LIMK1, LIPE, LIPG, LONP1, LTC4S, LYN, MAN1A, MAN2A1, MAP2K3, MAP3K14, MAP3K5, MAP3K7, MAP3K8, MAPK1, MAPK1IP1L, MAPK6, MAPK8, MAT2A, ME3, MGAT4A, MGLL, MKNK1, MMP1, MMP13, MMP19, MMP2, MMP3, MMP9, MOCOS, MOXD1, MPO, MPST, MTR, NAGK, NAMPT, NCF2, NDST1, NEK1, NEK2, NEK6, NEK7, NOS1, NOS2, NOX4, NUAK2, OAS2, OAS3, OTUD1, PADI1, PADI4, PAPOLG, PCK1, PDE1A, PDE4B, PELI2, PFKFB4, PGAP1, PGD, PGM2L1, PHACTR2, PHEX, PHGDH, PI4KA, PIK3CA, PIK3CB, PIK3CG, PIK3R1, PIK3R5, PIKFYVE, PIM1, PIM3, PIP4K2C, PKN2, PLA2G4C, PLA2G4C, PLA2G7, PLA2G7, PLAU, PLK1, POFUT1, POLK, POLR2A, PPAP2A, PPAT, PPIF, PPIG, PPM1E, PPP1R13L, PPP1R14C, PPP1R15A, PPP1R15B, PPP1R3B, PPP3CA, PPP3CC, PPP6C, PREPL, PRKAA1, PRKAA2, PRKAB1, PRKACB, PRKAG2, PRKCD, PRKCE, PRKD3, PSPH, PTGES, PTHLH, PTK2, PTGDS, PTPRJ, PYROXD1, QPCT, RIPK1, RIPK2, RND1, ROR2, RPS6KA4, RRAS2, RRM2B, SAT1, SENP6, SGK1, SLFN2, SLK, SMARCAD1, SMG1, SNRK, SPPL2B, SPTLC2, SRC, SRD5A1, SSH-3, ST3GAL1, ST3GAL2, ST3GAL4, ST3GAL5, ST3GAL6, ST6GAL1, ST6GALNAC6, ST8SIA1, STK17B, SUCLA2, SYNJ2, TBXAS1, TGM1, TGM2, TJP2, TLK1, TNK1, TPMT, TPO, TRPM7, TST, UBE2D2, UBE2H, UGCG, UGGT2, UGT1A1, USP31, USP34, USP36, USP38, USP47, UXS1, WARS2, XYLT2, YES1, ZAK
Growth Factors, Ligands and their Modulators	ACVR2A, BCAP29, BDNF, BLNK, BMP2, CSF1, CSF1R, CSF2, CSF3, CSF3R, CTGF, EGF, EGFR, EGR4, EREG, FGF2, FGF8, FGF16, FSTL3, HGF, HGFAC, IGF1, IGF1R, IGFBP1, MET, NOL8, OGFRL1, PDGFA, PDGFB, PDGFC, PDGFRA, RICTOR, SPP1, TGFA, TGFB1, TGFBR1, TGFBR2, THBS1, VEGFA, VEGFB, VEGFC
Immunoreceptors	ALCAM, B2M, BCAP29, BDKRB1, CAMP, CCR2, CCR5, CCR7, CCR8, CD14, CD1D1, CD27, CD33, CD36, CD38, CD3G, CD40, CD40LG, CD48, CD7, CD74, CD81, CD82, CD83, CD86, CD9, CMRF35, CR2, CTLA4, CXCR1, FCGR2B, FCGR3, FCGR4, FCGRT, GNLY, HLA-A, HLA-B, HLA-DRA, HLA-E, HLA-F, ICOSL, IGHA2, IGHG3, IGHG4, IGHMBP2, IGKC, IGLL1, CADM1, IL2RA, IL8RB, LILRB2, MEFV, MHC CLASS I, MICA, MR1, MYD88, NOD2, SLC25A46, SLC39A3, SLC3A2, TLR2, TLR4, TLR8, TNFRSF10B, TNFRSF1A, TNFRSF21, TNFRSF9, TREM1
Miscellaneous	ABL2, AC005005.6, ACAP2, ACPP, ACSL3, ADCYAP1R1, ADFP, ADM, AFP, AHSG, AIG1, AKAP11, AKAP2, AKAP9, ALS2, AMH, AMOTL2, AMPH, ANK3, ANKH, ANKIB1, ANKRD15, ANKRD46, ANLN, ANTXR2, ANXA2, AP000557.3, AP1B1, AP1S2, AP4E1, APBB3, APOC3, APOE, APPBP2, AQP2, AREG, ARFGAP3, ARFGEF2, ARGLU1, ARHGAP15, ARHGAP18, ARHGAP29, ARHGAP4, ARHGEF10, ARHGEF7, ARL1, ARRB2, ASB7, ASCC3, ASE-1, ASPH, ATG7, ATP1A1, AVL9, AVP, AXIN2, AXUD1, B4GALT1, BA247113.2, BAA09484, BAA19121, BBS2, BCL10, BICD1, BICD1, BIRC5, BLM, BRAF, BTBD19, BZRAP1, C11ORF13, C14ORF106, C15ORF39, C1ORF29, C1ORF9, C20ORF103, C20ORF160, C21ORF45, C21ORF5, C3ORF52, C4ORF21, C5ORF13, C5ORF42, C5ORF51, C6ORF33, C6ORF89, C6ORF96, C9ORF100, C9ORF45, C9ORF72, C9ORF89, CABC1, CACHD1, CACNA1D, CACNA1E, CACNA2D3, CACNB2, CACNB4, CAMSAP1L1, CANX, CAPN1, CAPN2, CASC5, CBL, CCDC132, CCDC90B, CCND1, CCND2, CCND3, CCNF, CCNG2, CCPG1, CDC27, CDC42SE2, CDCA2, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CEB1, CENPA, CENPC1, CENPF, CEP120, CEP152, CEP350, CEP70, CFP, CFP1, CGI-143, CHD1, CHD2, CHD9, CHI3L1, CHM, CIAS1, CKAP2, CLIC4, CLN5, CLSTN2, CLUAP1, COL1A1, COL1A2, COL2A1, COL4A3BP, COL6A2, COL9A1, COP, CPNE8, CPNE9, CREB3L1, CRIM1, CRMP1, CROC4, CSF1R, CSPG6, CUGBP2, CXADR, CXXC5, CYBB, CYCS, CYLD, CYLN2, DAAM1, DAB2, DAF, DBF4, DCP1A, DDB1, DDX18, DDX21, DENND1B, DENND3, DENND4C, DENND5A, DHX57, DHX58, DISC1, DJ756G23.3, DKFZP434F091, DKFZP564K0822, DMXL1, DMXL2, DNAJC13, DNAJC21, DNAJC5B, DNAPTP6, DOCK4, DOCK7, DPY19L2P2, DPY19L3, DPY19L4, DPYSL2, DRAM1, DSCR1, DST, DTR, EBRP, EDEM3, EDN1, EDN2, EEFSEC, PSD3, EFHC1, EFHD2, EFNA1, EHD1, EHZF, EIF1, EIF4E, EIF4G3, EMB, EMP3, EMR2, ENAH, ENC1, EPB41L3, EPHA2, EPHRINA, EPM2AIP1, ERCC1, EREG, ERRFI1, ERVW-1, EXOC2, FAM105B, FAM126B, FAM13C, FAM171B, FAM208A, FAM208B, FAM69A, FAM69B, FAM73A, FAM76B, FAM91A1, FBXO8, FBXW2, FEM1B, FEZ1, FIGN, FKBP5, FLJ00058, FLJ10199, FLJ10815, FLJ11259, FLJ11712, FLJ12439, FLJ12598, FLJ12903, FLJ13909, FLJ14129, FLJ20035, FLJ20485, FLJ20489, FLJ21148, FLJ22344, FLJ23231, FLJ23436, FLJ23749, FLJ25124, FLJ31818, FLJ33620, FLJ33641, FLJ35681, FLJ43663, FLJ45459, FLJ90440, FLJ90709, FLNA, FLOT1, FNBP1L, FNIP2, FOXP3, FPR1, FRAG1, FRAS1, FRY, FXYD2, FZD1, FZD4, FZD8, GAB2, GAB3, GABRG1, GADD45A, GADD45B, GAST, GBP1, GDAP1, GEM, GJA1, GJB3, GLCCI1, GNA13, GNAI1, GNAQ, GNG12, GOLGA8B, GPR124, GPR132, GPR137B, GABBR2, GPR64, GRAP2, GULP1, GYPC, HAUS6, HCST, HECA, HECTD1, HECTD2, HELZ, HERC1, HINT3, HIST2H2BE, HLX1, HMGN1, HMGN4, HOMER1, HSPC049, TMEM138, HSU79266, HSU79274, HYOU1, HYPOTH. PROT., RNF217, IFI27, IFI44,

	IFI44L, IFIH1, IFITM1, IFT80, INSR, IPO7, IQGAP2, IREB2, IRS2, ISG15, ITGB8, ITPR2, ITSN2, JMY, JUND, KCNH2, KCNH5, KCNJ12, KCNJ2, KCNN4, KCNQ3, KIAA0089, KIAA0140, KIAA0146, KIAA0182, KIAA0711, KIAA0776, KIAA0999, KIAA1012, KIAA1078, KIAA1377, KIAA1533, KIAA1539, KIAA1712, KIAA1731, KIAA2026, KIDINS220, KIF14, KIF15, KIF18A, KIF23, KIF3A, KIRREL2, KIT, KLHDC10, KL, KRAS, KRT34, KRT5, KRTAP1-3, KRTCAP2, LAMB1, LAMB3, LATS2, LBP, LCN2, LCP2, LGALS2, LGALS3, LHFPL2, LITAF, LMNA, LMO7, LOC100294020, LOC113655, LOC140095, LOC153364, LOC220929, LOC221710, LOC348840, LOC56920, LOC643837, LOC647979, LOC89958, LPAR1, LPP, LRBA, LRG1, LRRC17, LRRC40, LRRC8C, LRWD1, LSP1, LUM, MAC30, MADHIP, MAP2, MAPK1AP, MAPRE2, MARCKS, MAT1, MDM1, MEFV, MEK5C, MFSD8, MGC10854, MGC13010, MGC16075, MGC16664, MGC20262, MGC20446, MGC21854, MGC27085, MGC27434, MGC3113, MGC34680, MGC34695, MGC35206, MID1IP1, MKLN1, MLLT2, MLLT4, MOBKL3, MPA2L, MPHOSPH9, MS4A14, MS4A7, MT3, MTA1, MTERFD2, MTRF1, MUC1, MUC5AC, MUC5B, MX2, MYBPC3, MYBPH, MYO10, MYO5A, NAV3, NBEA, NBPF1, NDFIP1, NEK1, NEK2, NEK6, NEXN, NF1, NGB, NICAL, NIN, NINJ1, NIPBL, NKIR, NOLA1, NOTCH 1, NPAP1, NPHS1, NPTX1, NT5DC3, NTN1, NUFIP2, NUMA1, NUP98, NUPL1, OLFM4, OPRS1, OPTN, OSBPL1A, OSBPL5, ORAI1, OSBPL8, OXR1, OXSR1, P2RX4, P2RX7, P2RY8, PANX1, PAPPA, PBF, PCGF5, PCLO, PCMTD1, PCNX, PDCD6IP, PDS5B, PEO1, PGAP1, PHEMX, PHLDA1, PHLDB2, PI3, PIAS1, PIGK, PIM2, PJA2, PKM2, PLCXD3, PLDN, PLEC1, PLEKHA3, PLEKHG6, PLK1, PNKD, POMC, PPP1R9A, PRAM-1, PREPRO UPA, PRF1, PROSTEIN, PSCD4, PSEI7, PSMA2, PSTPIP2, PTGER2, PTGER4, PTPRN2, PURB, R3HCC1, RAB18, RAB3GAP2, RABEP1, RABEPK, RABL2B, RABL3, RALGAPA1, RAP1A, RAPGEF1, RAPGEF2, RAPGEF6, RAPH1, RARA, RARG, RARRES1, RASSF2, RB1CC1, RBBP6, RC3H2, RCAN1, RCN1, RFTN1, RGL1, RGMA, RGS12, RGS14, RGS16, RGS3, RHOB, RICH1, RIPK1, RIPK2, RMND5A, RNF13, RNF145, RNF44, ROR2, RPS15A-PS4, RPUSD2, RRAS, RRS1, RSPO3, S100A10, S100A12, S100A6, S100A9, SAMD4A, SAMD9, SAMSN1, SASH1, SBF1, SCAMP1, SCAPER, SCARB1, SCF, SCLT1, SCNN1A, SDC4, SDCBP, SEC24A, SECISBP2L, SELB, SELPLG, SEMA6D, SERPINA1, SERPINB10, SERPINB2, SERPINB8, SERPINB9, SERPINE1, SERPINE2, SFI1, SFN, SFPI1, SFRS12IP1, SGOL2, SH2B3, SH3BP1, SHCBP1, SHH, SHROOM3, SIKE1, SIPA1L1, SIRT1, SKP2, SLA, SLC11A2, SLC12A7, SLC15A3, SLC16A1, SLC17A5, SLC19A2, SLC1A2, SLC1A3, SLC22A16, SLC22A4, SLC25A10, SLC25A30, SLC25A46, SLC26A9, SLC27A3, SLC2A1, SLC2A13, SLC2A3, SLC2A5, SLC2A6, SLC37A2, SLC39A11, SLC5A5, SLC6A6, SLC7A2, SLC7A5, SLC9A2, SLC9A8, SLPI, SMARCA2, SMARCA3, SMARCAD1, SMC1B, SMC2, SND1, SNTB1, SNX1, SNX13, SNX20, SOCS2, SOCS3, SOCS4, SORBS2, SOS1, SPIRE1, SPSB1, SQSTM1, STAG1, STARD4, STC2, STIM1, STRBP, STX11, STX4, SUMO4, SUSD3, SUV420H1, SYNCRIP, T3JAM, TACC2, TAGAP, TARBP2, TAZ, TBC1D14, TBC1D23, TBL1XR1, TBL2, TCN1, TDRD7, TENS1, TET3, TFPI2, TGS, THOC1, THRAP3, TIMELESS, TIMM44, TLE1, TM7SF2, TM9SF3, TMEM106B, TMEM158, TMEM161B, TMEM176B, TMEM177, TMEM214, TMEM38B, TMPRSS2/ERG FUSION GENE, TMTC4, TMX3, TNFBBC3, TNIP1, TNPO1, TOM1, TPD52L1, TPPP, TPRA1, TRA1, TRAF1, TRAF3, TRIM33, TRIM35, TRIM5, TRIM63, TRIP10, TROVE2, TRP73, TSPAN5, TTLL1, TTYH2, TUBB2A, TUBB2A, TUSC4, TXN2, UBE2M, UBE3A, UBR3, UBXN4, UCHL1, UPK1B, VDR, VILL, VPREB, VPS13A, VPS13C, VPS37B, VPS53, VSTM2L, WDR19, WDR36, WDR4, WDR7, WDR72, WNT1, WNT10A, WNT5A, WTAP, YIPF5, YTHDC2, ZDHHC17, ZDHHC8, ZFAND3, ZFAS1, ZFP36, ZMYND8, ZNF342, ZNF450
Proteins Involved in Antigen Presentation	C2, C3, C5, CD24A, CFB, DCNP1, EEA1, ITGAX, MGEA5, NEMF, PALM, PSMB9, STEAP4, TAP1, TAPBP, UACA
Regulators of apoptosis	ATG5, BAD, BAX, BBC3, BCL2, BCL2A1, BCL2L1, BID, BIK, CASP1, CD274, CFLAR, FADD, FAS, FASLG, FEM1B, GSTP1, XAF1, IER3, MCL1, MKL1, NR4A1, NUAK2, PAWR, PDCD1, PDCD5, PLAGL2, PMAIP1, SERPINB9, SH3GLB1, TNFAIP3, TNFAIP8, TNFRSF10A, TNFRSF10B, TNFSF10, XIAP
Stress response genes	COX2, CYP7B1, FTH1, GADD45A, GADD45B, GADD45G, GCLC, GCLM, HSP90AA1, HSPA1A, MX1, NQO1, PKIB, PLA2G4A, PTGS2, PTPN1, PTPN7, PTPRJ, PTPRN2, RGS3, SESN3, SOD2, SPRY2
Transcription Factors and their Modulators	ACAP2, AFF3, AKAP13, ANKIB1, ANTXR2, AR, ARAP3, ARFGAP3, ARHGAP15, ARHGAP29, ARID3B, ARNT2, ATF3, ATM, B4GALT3, B4GALT4, B4GALT5, BATF, BBX, BCL3, BCL6, BCL9L, BDP1, BIRC2, BIRC3, BLM, BMP2, BNC2, BRCA2, BTG2, C14ORF106, C19ORF2, C4ORF21, C5ORF41, CBFA2T3, CBL, CBX5, CCNL1, CCRN4L, CDX1, CEBPB, CEBPD, CENPC1, CITED2, CPEB4, CREB1, CREB3L1, CREB3L4, CREB5, CREM, CSRNP1, CTNND1, CXXC5, CYP7B1, DBF4, DDHD1, DHX57, DHX9, DIDO1, DLX1, DLX2, DMBX1, DMP1, DNAJC21, DTX4, E2F1, E2F3, E2F5, E2F7, EFHD2, EGLN1, EGLN3, EGR1, EGR2, EIF2C2, ELF2, ELF3, EOMES, EP300, ETV3, ETV5, ETV6, EWSR1, FOS, FOSL2, FOXE1, FOXL1, FOXN3, FOXO1, FOXO3, FRY, FRYL, FST, FTSJ3, G2E3, GALT, GATA3, GATA6, GTF21, HDAC11, HDAC4, HECTD1, HELZ, HIF1A, HIVEP1, HLTF, HLX, HMGN1, HMGN4, HMOX1, HNRNPA3, HOXA13, HOXA5, HOXA9, HOXC4, ID2, IER2, IER5, IFI16, IGHMBP2, IKBKE, IMPA2, IRF1, IRF2, IRF4, IRF5, IRF7, JMJD1C, JMY, JUN, JUNB, JUND, KDM6B, KIT, KLF12, KLF13, KLF5, KLF6, LARP1B, LARP4, LCORL, LEF1, LEO1, LMO7, LPP, LPXN, LUC7L3, LYL1, LZTFL1, MAFB, MAFG, MAFK, MBTD1, MECOM, MED31, MEIS1, MGA, MIER1, MITF, MKL1, MLLT3, MOBKL3, MSX2, MT1F, MT2A, MXD3, MXD4, MYC, MYCBP2, NAB1, NAB2, NCOA1, NCOA7, NEBL, NFATC1, NFE2, NFE2L2, NFE2L3, NFIL3, NFKB1, NFKB2, NFKBIA, NFKBIB, NFKBIE, NFKBIZ, NKX3.1, NLRP3, NR1D2, NR2C2, NR2F6, NR4A1, NR4A2, NR5A1, NRF1, NRIP1, NUFIP2, NUMA1, NUP153, OLIG2, PAPOLG, PATZ1, PAX8, PCDH7, PCGF5, PDZD8, PER1, PHF20L1, PHF7, PHLDA1, PIAS1, PJA2, PLAGL2, PLEKHG6, PML, PNRC1, POLB, POLR1A, POLR2C, POU2F2, PPARG, PPP3CC, PPP6C, PRDM1, PRPF31, PSPH, PURB, QPCT, RB1CC1, RBAK, RBBP6, RBL1, RBM15, RBMS3, RBPJ, RC3H1, RC3H2, REL, RELB, REV3L, RFX7, RNF13, RNF145, RNF44, RRS1, RSF1, RTN4IP1, RUNX1, RUNX3, S100A10, S100A12, SCAPER, SERTAD2, SETDB2, SFPQ, SFRS12, SFRS12IP1, SFRS13A, SFRS2, SFRS2IP, SIN3A, SIX5, SLC39A11, SLC39A3, SMAD3, SMAD7, SMARCA2, SMG1, SNAI1, SNAPC3, SNTB1, SORBS2, SOX9, SP110, SPEN, SPI1, SPIB, SQSTM1, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STEAP4, TAF4B, TANK, TBL1XR1, TCF12, TCF7L2, TERT, TET3, TFB2M, TFDP1, TFE3, TFEB, TGM1, THOC2, THRAP3, TINF2, TLE1, TNFAIP3, TNFSF10, TNIP3, TNRC6A, TP53, TP63, TRAF1, TRAF3, TRIM2, TRIM22, TRIM31, TRIM33, TRIM35, TRIM45, TRIM5, TRIM56, TTC3, TWIST1, TWISTNB, TXNIP, UBR3, UPB1, UPF2, WDR4, WHSC1L1, WTAP, XIAP, YY1, ZBED1, ZBTB10, ZBTB26, ZBTB44, ZC3H12A, ZC3HAV1, ZCCHC7, ZDHHC17, ZDHHC8, ZEB1, ZFC3H1, ZFP64, ZIC2, ZMYM1, ZMYM2, ZMYM4, ZNF217, ZNF239, ZNF366, ZNF439, ZNF521, ZNF529, ZNF589, ZNF638, ZNF644, ZNF678, ZNF765, ZNF770, ZNRF2
Viruses	bovine foamy virus, HIV-1, the polyomavirus JC
miRNA	miR-125B, miR-125B-1, miR-125B-1-3P, miR-1276, miR-1286, miR-130A, miR-143, miR-145, miR-146A, miR-150, miR-155, miR-16, miR-17-92, miR-193B, miR-199, miR-21, miR-210, miR-219-1-3P, miR-223, miR-224, miR-23A, miR-23B, miR-23B-27B-24-1, miR-2467-5P, miR-301A, miR-30B, miR-30B-3P, miR-3200-3P, miR-340-3P, miR-34A, miR-3620-5P, miR-425, miR-4454, miR-448, miR-4485, miR-449C-5P, miR-451, miR-502-5P, miR-548D-5P, miR-9-1, miRLET7A3, miRLET7I

The target genes were represented using the official gene symbols.

Table 2. The fields used in our database

Fields	Meaning
Gene ID	The identifier of a gene indexed by our database.
Gene Symbol	The official symbol of a gene defined by Gene Bank.
Description	Description of the gene.
Species	Species of the gene sources.
Inducer	The material that induce NF-κB regulating the target gene.
Cell Type	Cell model used to identify the target gene.
Experimental Method	The experimental method for identifying the target gene.
Regulation	The change of expression of the target gene.
Reference ID	The identifier of the reference that report the target gene.

Table 3. The main databases for NF-κB target genes

	Dr. Gosselin's database	Dr. Gilmore's database	Our database
Records	128	482	2267
Creation time	2004	2008	2014
Last update	2004	2008	2014
Inducer	Not recorded	Not recorded	Recorded
Condition	Not recorded	Not recorded	Recorded
Cell model	Not recorded	Not recorded	Recorded
Method	Not recorded	Not recorded	Recorded
Site location	Recorded	Not recorded	Recorded
Binding motif	Recorded	Not recorded	Recorded
Up or Down	Not recorded	Not recorded	Recorded
MicroRNA	Not collected	Collected	Collected
Reference	Indicated	Indicated	Indicated
Updated	Never	Never	Updated continuously
Interface	None	None	Designed

Results

Built NF-κB target genes database

We used the searching engines of PubMed and Google Scholar obtained 274 and 994 relevant articles, respectively. We finally found 382 articles that contained the NF-κB direct target genes identified by experiment methods and obtained 2267 target genes and 1667 distinct target genes after removing the duplications. All the target genes were classified by their functions and were shown in **Table 1**.

Then we established the database of NF-κB target genes and published them in our web server (http://tfdb.seu.edu.cn/nfkb/). The web site mainly included 3 pages: home page to introduce information and instruction of the database, browse page to list and detail all target genes collected by this database, search page to convenient for reader to find an interested target genes in our database.

All fields in database and their meanings were described in **Table 2**. Briefly, our database recorded the official gene symbols of NF-κB target genes, the specific inducers, cell model, the change of expression of target genes and detection methods, as well as the concentration of inducer, induction time, detection mean, NF-κB binding domain and the counts of the specific binding motifs and the references. Clicking the hyperlink of Gene ID of the specific NF-κB target gene exhibits the expression quantity of the specific NF-κB target gene with the specific inducer, concentration, induction time and detection mean. Meanwhile, the PCR amplified object region or ChIP (Chromatin Immunoprecipitation) region is also exhibited with the counts of the specific binding motifs in the region. Clicking the hyperlink of Reference ID of the specific NF-κB target gene exhibits the specific reference.

For convenient to use, we programmed the retrieval interfaces that can search the relevant NF-κB target genes according to the gene symbol, cell types and subordinate species (http://tfdb.seu.edu.cn/nfkb/searchgene.php). The retrieval supports the fuzzy search for easy use.

As is known that the Rel/NF-kappaB target genes database created by Dr. Gosselin et al. (http://bioinfo.lifl.fr/NF-κB/) and the NF-κB Ta-

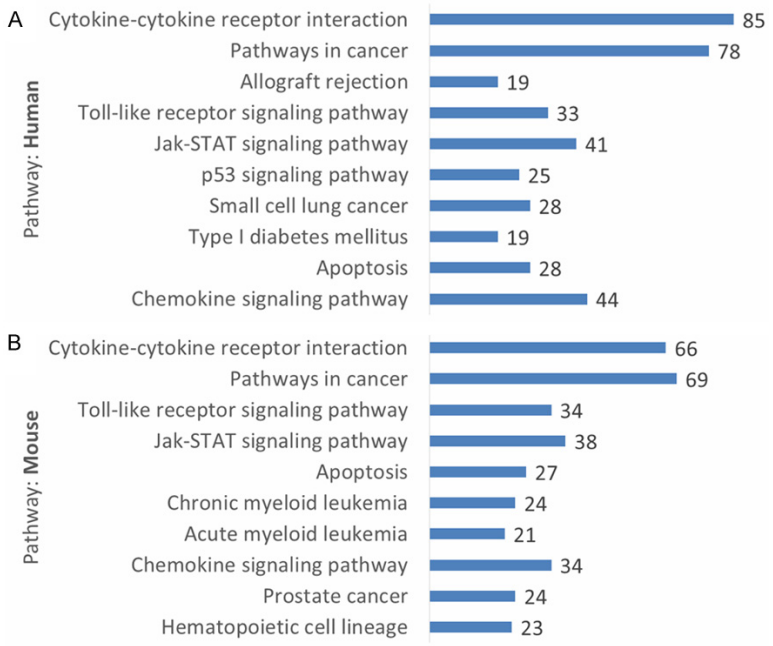

Figure 1. Top 10 KEGG significant pathways enriched by NF-κB target genes with the species of human (A) and mouse (B), respectively. The *p* values of all pathways were less than 0.05 (for details, please see the Additional files 1 and 2). In each plot, the pathways were aligned from top to bottom according to their *p* values from low to high. The count of genes that participated in related pathway was displayed next to the bars.

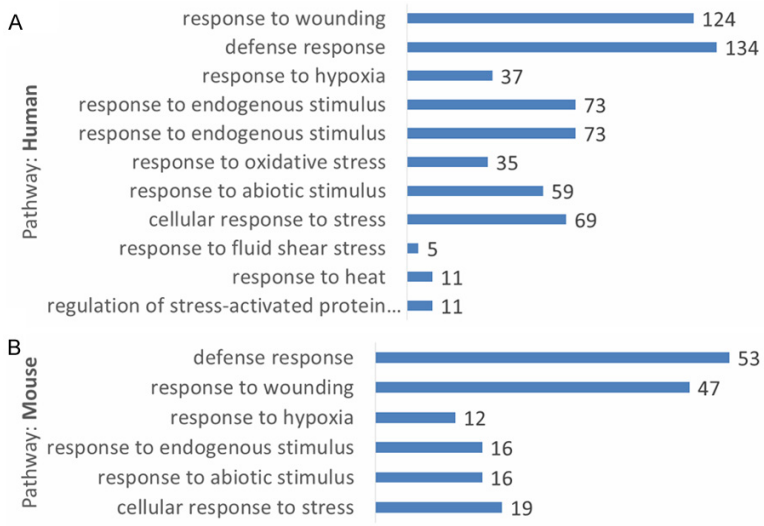

Figure 2. GO terms related to stress of the NF-κB target genes. A. NF-κB target genes with the species of human involved in the biological process of stress. B. NF-κB target genes with the species of mouse involved in the biological process of stress. The *p* values of all GO terms were less than 0.05 (for details, please see the Additional files 1 and 2). In each plot, the pathways were aligned from top to bottom according to their *p* values from low to high.

rget Genes database created by Dr. Gilmore et al. (http://www.bu.edu/nf-kb/the-gilmore-lab/the-lab/) are else two NF-κB Target Genes databases, but these databases are out of date. The database reported here has added more record of NF-κB Target Genes, updated more detail of the record and paid more attention to the data maintenance. Relative to the previous databases, the main improvement of our database were list in **Table 3**.

For understanding the biological function of these target genes, then we performed enrichment analysis of KEGG pathway, gene oncology (GO) annotation and GENETIC ASSOCIATION DB DISEASE using the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.7. Besides, we conducted analysis for the target genes that are the transcriptional factors for other genes and analyzed the inducer of the NF-κB target gene.

NF-κB acts as a central mediator of many important pathways

We carried out the KEGG analysis of NF-κB target genes. The target genes of NF-κB involved many well-known, important pathways, such as Pathways in cancer, Apoptosis, Jak-STAT signaling pathway, Acute myeloid leukemia, Prion diseases, Allograft rejection, Glioma and the other diseases (**Figure 1**). It is also consistent that NF-κB is a multifunctional transcription factor. The crosstalk between NF-κB pathway and other signaling pathways can determine the cell fate, which depends on the cellular context [23]. Meanwhile, ubiquitination possibly plays an important role in NF-κB pathway through a proteasome-independent pathway [24].

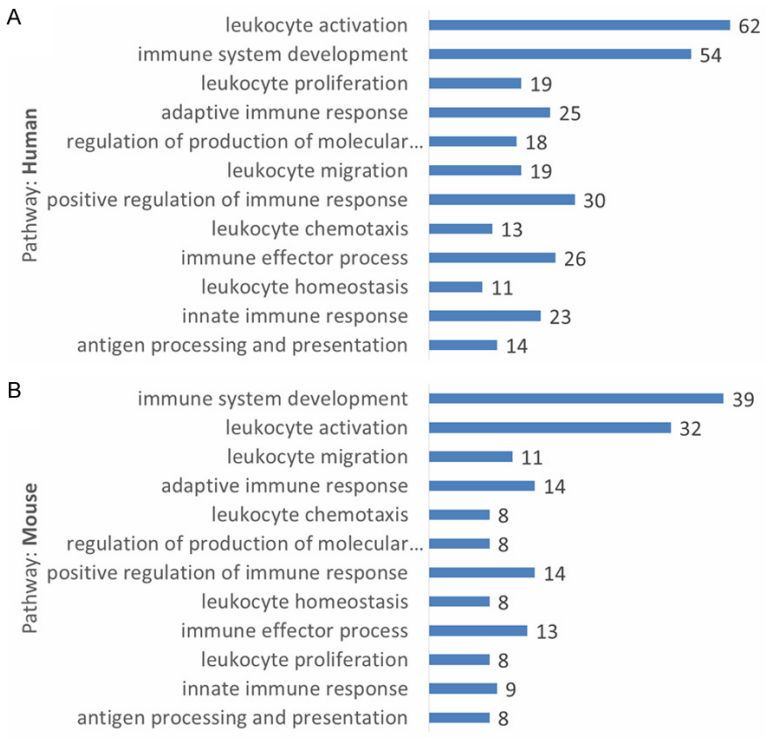

Figure 3. GO terms related to immune of the NF-κB target genes. A. NF-κB target genes with the species of human involved in the biological process of immune. B. NF-κB target genes with the species of mouse involved in the biological process of immune The *p* values of all GO terms were less than 0.05 (for details, please see the Additional files 1 and 2). In each plot, the pathways were aligned from top to bottom according to their *p* values from low to high.

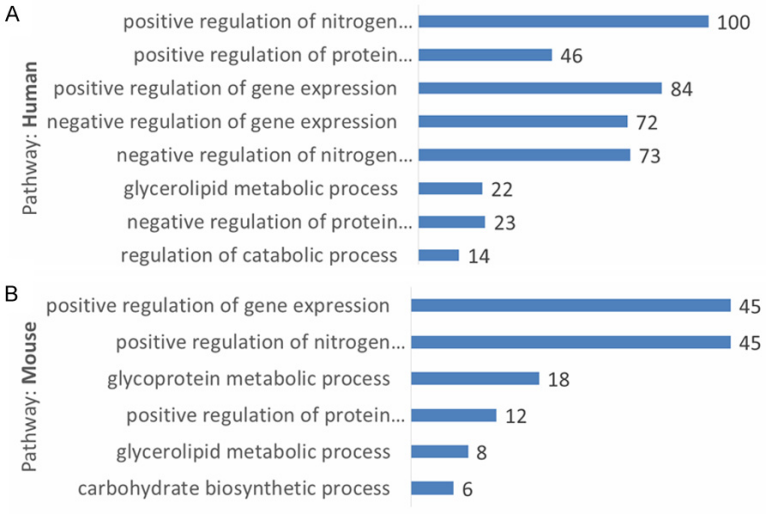

Figure 4. GO terms related to metabolic of the NF-κB target genes. A. NF-κB target genes with the species of human involved in the biological process of metabolic. B. NF-κB target genes with the species of mouse involved in the biological process of metabolic. The *p* values of all GO terms were less than 0.05 (for details, please see the Additional files 1 and 2). In each plot, the pathways were aligned from top to bottom according to their *p* values from low to high.

NF-κB was a central regulator of the stress response

There were 205 inducers that can activate NF-κB, such as environmental hazards, therapeutic drugs, and ect. Meanwhile, the physiological stress conditions and physical stresses, such as, irradiation and oxidative stress, can also activate NF-κB [25]. Furthermore, the phosphorylation of the α subunit of eukaryotic initiation factor 2 (eIF2α) is necessary for induction of NF-κB transcriptional activity in response to cellular stresses [26]. Furthermore, the functions of its target genes extend beyond the immediate immune response. Therefore, NF-κB perhaps represented a central regulator of stress responses (**Figure 2**).

NF-κB was a central mediator of the immune response

From the analysis, NF-κB may be a central mediator of the human immune response. It can be seen from **Figure 3**, both in human and mouse, NF-κB target genes participate in various inflammatory response, included leucite activation, proliferation, migration, chemotaxis and homeostasis, immune system development, innate and adaptive immune response, regulation of production of molecular mediator of immune response, antigen processing and presentation, immune effector process, etc.

NF-κB was a central moderator of cellular metabolic processes

There were 626 NF-κB target genes involved in various metabolic processes (data not

Table 4. The NF-κB target genes with the species of human involved in the remarkable diseases

Term	Count	%	*P*-value	Fold Enrichment	FDR
Systemic lupus erythematosus	43	0.276118924	6.1648E-12	3.002652031	1.08E-08
COPD	26	0.166955628	6.31094E-09	3.46300695	1.11E-05
Bladder cancer	35	0.224747961	9.42986E-08	2.568713946	1.65E-04
Bone density	34	0.218326591	1.97575E-06	2.328967311	3.47E-03
Colorectal cancer	60	0.385282219	2.38286E-09	2.146984791	4.18E-06
Multiple sclerosis	56	0.359596738	1.79618E-11	2.4862614	3.15E-08
Myocardial infarct	35	0.224747961	2.61553E-05	2.06339317	0.045872569
HIV	37	0.237590702	1.00333E-12	3.501562695	1.76E-09
Longevity	29	0.186219739	5.92027E-08	2.937740457	1.04E-04
Lung cancer	46	0.295383035	3.30042E-06	1.981139858	0.005789551
Lymphoma	20	0.128427406	2.54328E-06	3.1966218	0.004461406
Ovarian cancer	29	0.186219739	3.36599E-06	2.483090148	0.005904572
Pancreatic cancer	14	0.089899184	0.003245766	2.39746635	5.543515638
Prostate cancer	43	0.276118924	7.08816E-05	1.819253877	0.124269985
Stomach cancer	41	0.263276183	8.9583E-12	3.071753761	1.57E-08

Abbreviation: COPD, chronic obstructive pulmonary disease. Legend: By importing NF-κB target genes with the species of human into the Functional Annotation tool of DAVID, the diseases showing significant relevance to the imported genes were identified with the GENETIC_ASSOCIATION_DB_DISEASE. They were listed with *p* values corrected by Bonferroni's multiple comparison test, false discovery rate (FDR), and fold enrichment (FE).

Table 5. The 98 transcription factors belonged to the NF-κB target genes

Class	Transcription factors
Beta-Hairpin-Ribbon	*EOMES*
Helix-Loop-Helix	*DLX1, DLX2, DMBX1, HLX, HOXA13, HOXA5, HOXA9, MEIS1, MSX2, POU2F2, TFE3, TFEB*
Lg-fold	*NFKB1, NFKB2, REL, STAT1*
Leucine zipper	*CREB3L4*
Leucine zipper factors	*ATF3, TAF4B*
RHR	*BCL3, RELB*
Tryptophan clusters	*IRF7*
Winged helix	*E2F7*
Winged Helix-Turn-Helix	*E2F1, ELF2, ELF3, EWSR1, FOXL1, IRF1, IRF2, IRF4, MGA, SPI1, SPIB*
Zinc finger	*EGR4*
Zinc-coordinating	*AR, BCL6, EGR1, EGR2, GATA6, KLF5, NR2C2, PPARG, PRDM1, YY1, ZEB1*
Zipper-Type	*BATF, CEBPB, CREB1, FOSL2, JUN, JUNB, JUND, MAFB, MAFK, MYC, NFE2L2, NFIL3, TCF12*
Other Alpha-Helix	*SOX9*
Other	*C5ORF41, CBFA2T3, CCRN4L, CDKN2A, CITED2, CSRNP1, EP300, ETV3, ETV5, ETV6, FOXE1, FOXN3, KLF12, KLF6, MITF, NFATC1, NFE2L3, NR1D2, NR2F6, NR4A1, NR5A1, NRF1, OLIG2, PLAGL2, PURB, RBPJ, RCAN1, SIX5, SMAD7, SPEN, STAT2, STAT4, STAT5A, TFDP1, TRIM22, TWIST1, ZNF217*

shown) and 153 NF-κB target genes involved in the metabolic disorders (data not shown). Therefore, NF-κB maybe is a central moderator of cellular metabolic processes (**Figure 4**). The data showed these target genes can participate in gene expression, nitrogen compound metabolic process, protein metabolic process and carbohydrate biosynthetic process.

NF-κB involved in bone disease, immunological disease and cardiovascular disease

It is remarkable that *immunological disease,* bone density, longevity, chronic obstructive pulmonary disease, systemic lupus erythematosus, multiple sclerosis, myocardial infarct and many cancers associated with NF-κB (**Table 4**).

NF-κB can modulate the expression activity of other transcriptional factors

There were 98 transcription factors belonged to the NF-κB target genes (**Table 5**), such as fosl2, elf2, elf3, stat5a, e2f7 et al. NF-κB may play the crucial roles in the organism's transcriptional regulatory network.

Discussion

In this study we established a most complete and most quality database of NF-κB target genes. From the related analysis for the database, we concluded that NF-κB acts as a central mediator of many important pathways, was a central regulator of the stress response, immune response, cellular metabolic processes and gene regulation, and was involved in many diseases. The database is useful for the NF-κB researchers, biologists and medical scientists.

The database shows inducer sometimes determined the up-regulation or down-regulation of the expression of NF-κB target genes. In human astrocytic glial cell line U-87MG, the multiple sclerosis-detrimental cytokines (TNFα, IL-1β, IL-6, and IFNγ) and PMA up-regulated the expression of syncytin-1 gene; but the multiple sclerosis-beneficial cytokine IFNβ down-regulated the expression of syncytin-1 gene [27]. In mouse NIH-3T3 cells, the inducers doxorubicin, daunorubicin and UV-C down-regulated the expression of DMP1 gene [28]; but the inducer TNFα up-regulated the expression of DMP1 gene. Therefore, inducers determined the up-regulation or down-regulation of the expression of NF-κB target genes through various mechanisms, including: inhibition of IKK and IκBα phosphorylation and the decrease of nuclear translocation of p65 [29], reduction of intracellular glutathione level [30].

The regulation pattern of NF-κB target genes in the diseased cells of patients and normal cells is different. And the understanding of the role of NF-κB in human diseases will contribute to the development of inhibitors of this pathway for the disease treating through their effects on IKK and NF-κB signaling [31, 32]. Meanwhile, the understanding of the NF-κB pathway integrated with other cell-signalling pathways also possesses the pivotal clinical significance. To sum up, it should establish the gene transcriptional regulatory network according to the various circumstances including the various pathological conditions.

Acknowledgements

This work was partially supported by the grants from the National Important Science Research Program of China (2011CB933503, 2006CB933205), the National Natural Science Foundation of China (61171030) and the Technology Support Program of Jiangsu (BE2012741).

Disclosure of conflict of interest

None.

Address correspondence to: Jinke Wang, The State Key Laboratory of Bioelectronics, Southeast University, Nanjing 210096, People's Republic of China. E-mail: wangjinke@seu.edu.cn

References

[1] Cooper SJ, Trinklein ND, Anton ED, Nguyen L, Myers RM. Comprehensive analysis of transcriptional promoter structure and function in 1% of the human genome. Genome Res 2006; 16: 1-10.

[2] Blanchette M, Bataille AR, Chen X, Poitras C, Laganière J, Lefèbvre C, Deblois G, Giguère V, Ferretti V, Bergeron D, Coulombe B, Robert F. Genome-wide computational prediction of transcriptional regulatory modules reveals new insights into human gene expression. Genome Res 2006; 16: 656-668.

[3] Kim TH, Ren B. Genome-wide analysis of protein-DNA interactions. Annu Rev Genomics Hum Genet 2006; 7: 81-102.

[4] Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell 1986; 46: 705-716.

[5] Sen R, Baltimore D. Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism. Cell 1986; 47: 921-928.

[6] Tripathi P, Aggarwal A. NF-κB transcription factor: a key player in the generation of immune response. Current Science 2006; 90: 519-531.

[7] Nishikimi A, Mukai J, Yamada M. Nuclear translocation of nuclear factor kappa B in early 1-cell mouse embryos. Biol Reprod 1999; 60: 1536-1541.

[8] Chen X, Kandasamy K, Srivastava RK. Differential roles of RelA (p65) and c-Rel subunits of nuclear factor κB in tumor necrosis factor-related apoptosis-inducing ligand signaling. Cancer Res 2003; 63: 1059-1066.

[9] Biswas DK, Cruz AP, Gansberger E, Pardee AB. Epidermal growth factor-induced nuclear factor κB activation: a major pathway of cell-cycle progression in estrogen-receptor negative breast cancer cells. Proce Natl Acad Sci U S A 2000; 97: 8542-8547.

[10] Baldwin AS Jr. Series introduction: the transcription factor NF-κB and human disease. J Clin Invest 2001; 107: 3-6.

[11] Ghosh S, May MJ, Kopp EB. NF-{kappa} B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol 1998; 16: 225-60.
[12] Ren B, Robert F, Wyrick JJ, Aparicio O, Jennings EG, Simon I, Zeitlinger J, Schreiber J, Hannett N, Kanin E, Volkert TL, Wilson CJ, Bell SP, Young RA. Genome-wide location and function of DNA binding proteins. Science 2000; 290: 2306-2309.
[13] Wei CL, Wu Q, Vega VB, Chiu KP, Ng P, Zhang T, Shahab A, Yong HC, Fu Y, Weng Z, Liu J, Zhao XD, Chew JL, Lee YL, Kuznetsov VA, Sung WK, Miller LD, Lim B, Liu ET, Yu Q, Ng HH, Ruan Y. A global map of p53 transcription-factor binding sites in the human genome. Cell 2006; 124: 207-219.
[14] Robertson G, Hirst M, Bainbridge M, Bilenky M, Zhao Y, Zeng T, Euskirchen G, Bernier B, Varhol R, Delaney A, Thiessen N, Griffith OL, He A, Marra M, Snyder M, Jones S. Genome-wide profiles of STAT1 DNA association using chromatin immunoprecipitation and massively parallel sequencing. Nat Methods 2007; 4: 651-657.
[15] Martone R, Euskirchen G, Bertone P, Hartman S, Royce TE, Luscombe NM, Rinn JL, Nelson FK, Miller P, Gerstein M, Weissman S, Snyder M. Distribution of NF-κB-binding sites across human chromosome 22. Proc Natl Acad Sci U S A 2003; 100: 12247-12252.
[16] Lim CA, Yao F, Wong JJ, George J, Xu H, Chiu KP, Sung WK, Lipovich L, Vega VB, Chen J, Shahab A, Zhao XD, Hibberd M, Wei CL, Lim B, Ng HH, Ruan Y, Chin KC. Genome-wide mapping of RELA (p65) binding identifies E2F1 as a transcriptional activator recruited by NF-κB upon TLR4 activation. Mol Cell 2007; 27: 622-635.
[17] Xing Y, Zhou F, Wang J. Subset of genes targeted by transcription factor NF-κB in TNFα-stimulated human HeLa cells. Funct integr genomics 2013; 13: 143-154.
[18] Matys V, Fricke E, Geffers R, Gössling E, Haubrock M, Hehl R, Hornischer K, Karas D, Kel AE, Kel-Margoulis OV, Kloos DU, Land S, Lewicki-Potapov B,Michael H, Münch R, Reuter I, Rotert S, Saxel H, Scheer M, Thiele S, Wingender E. TRANSFAC®: transcriptional regulation, from patterns to profiles. Nucleic Acids Res 2003; 31: 374-378.
[19] Nijnik A, Mott R, Kwiatkowski DP, Udalova IA. Comparing the fine specificity of DNA binding by NF-κB p50 and p52 using principal coordinates analysis. Nucleic Acids Res 2003; 31: 1497-1501.
[20] Wong D, Teixeira A, Oikonomopoulos S, Humburg P, Lone IN, Saliba D, Siggers T, Bulyk M, Angelov D, Dimitrov S, Udalova IA, Ragoussis J. Extensive characterization of NF-κB binding uncovers non-canonical motifs and advances the interpretation of genetic functional traits. Genome Biol 2011; 12: R70.
[21] Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2008; 4: 44-57.
[22] Wang J, Duncan D, Shi Z, Zhang B. WEB-based GEne SeT AnaLysis Toolkit (WebGestalt): update 2013. Nucleic Acids Res 2013; 41 (Web Server issue): W77-83.
[23] Perkins ND. Integrating cell-signalling pathways with NF-κB and IKK function. Nat Rev Mol Cell Biol 2007; 8: 49-62.
[24] Chen ZJ. Ubiquitin signalling in the NF-κB pathway. Nat Cell Biol 2005; 7: 758-765.
[25] Pahl HL. Activators and target genes of Rel/NF-kappaB transcription factors. Oncogene 1999; 18: 6853-6866.
[26] Jiang HY, Wek SA, McGrath BC, Scheuner D, Kaufman RJ, Cavener DR, Wek RC. Phosphorylation of the α subunit of eukaryotic initiation factor 2 is required for activation of NF-κB in response to diverse cellular stresses. Mol Cell Biol 2003; 23: 5651-5663.
[27] Mameli G, Astone V, Khalili K, Serra C, Sawaya BE, Dolei A. Regulation of the syncytin-1 promoter in human astrocytes by multiple sclerosis-related cytokines. Virology 2007; 362: 120-130.
[28] Taneja P, Mallakin A, Matise LA, Frazier DP, Choudhary M, Inoue K. Repression of Dmp1 and Arf transcription by anthracyclins: critical roles of the NF-κB subunit p65. Oncogene 2007; 26: 7457-7466.
[29] Xu C, Shen G, Chen C, Gélinas C, Kong AN. Suppression of NF-κB and NF-κB-regulated gene expression by sulforaphane and PEITC through IκBα, IKK pathway in human prostate cancer PC-3 cells. Oncogene 2005; 24: 4486-4495.
[30] Liu YC, Hsieh CW, Weng YC, Chuang SH, Hsieh CY, Wung BS. Sulforaphane inhibition of monocyte adhesion via the suppression of ICAM-1 and NF-κB is dependent upon glutathione depletion in endothelial cells. Vascul Pharmacol 2008; 48: 54-61.
[31] Kim HJ, Hawke N, Baldwin AS. NF-κB and IKK as therapeutic targets in cancer. Cell Death Differ 2006; 13: 738-747.
[32] Karin M, Yamamoto Y, Wang QM. The IKK NF-κB system: a treasure trove for drug development. Nat Rev Drug Discov 2004; 3: 17-26.