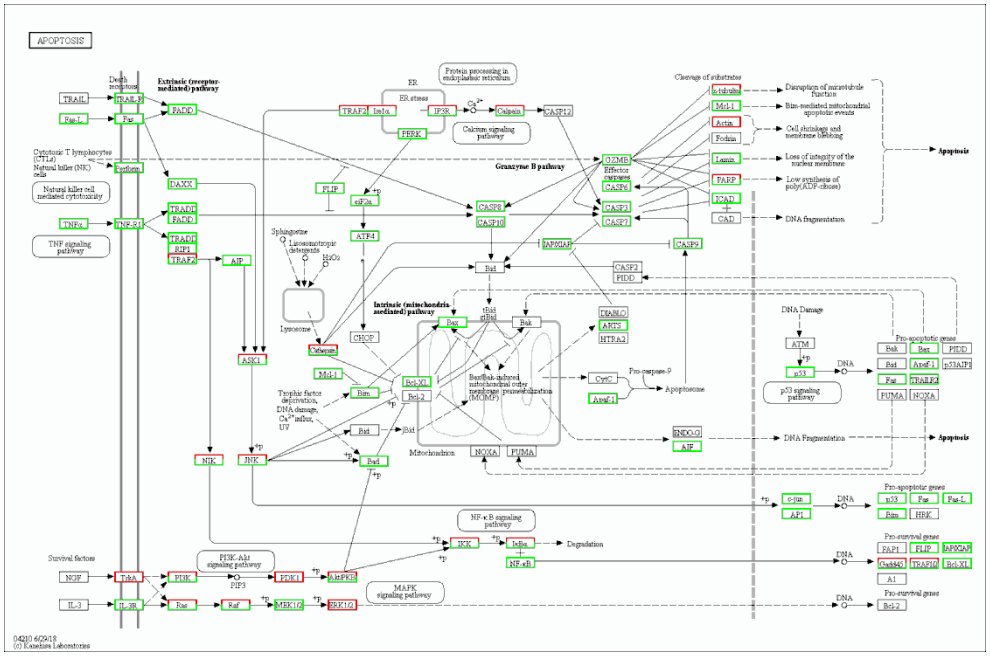
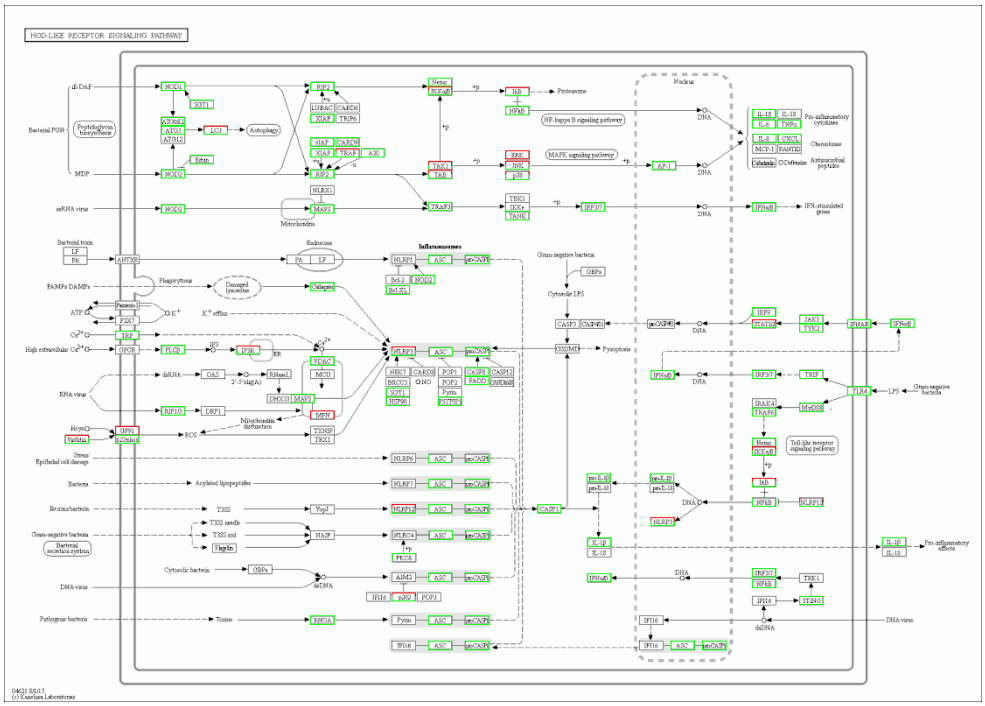
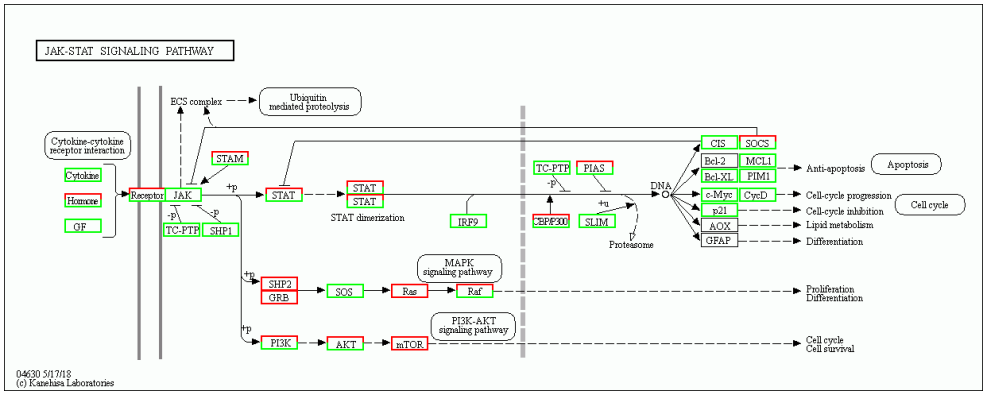
A


APOPTOSIS
Extrinsic (receptor-mediated) pathway
Intrinsic (mitochondria-mediated) pathway
Granzyme B pathway
Protein processing in endoplasmic reticulum
Calcium signaling pathway
Cytotoxic T lymphocyte (CTL)
Natural killer (NK) cells
Natural killer cell mediated cytotoxicity
TNF signaling pathway
Sphingosine
Lysosomotropic detergents
Lysosome
Cathepsins
Trophic factor deprivation, DNA damage, Ca2+influx, UV
Mitochondrion
Bcl-2 induced mitochondrial outer membrane permeabilization (MOMP)
Pro-caspase-9
Apoptosome
Cleavage of substrates
Disruption of microtubule function
Bim-mediated mitochondrial apoptotic events
Cell shrinkage and membrane blebbing
Loss of integrity of the nuclear membrane
Low synthesis of poly(ADP-ribose)
DNA fragmentation
Apoptosis
DNA Damage
Pro-apoptotic genes
Pro-survival genes
p53 signaling pathway
NF-κB signaling pathway
MAPK signaling pathway
PI3K-Akt signaling pathway
Survival factors
Degradation
04210 6/29/18
(c) Kanehisa Laboratories

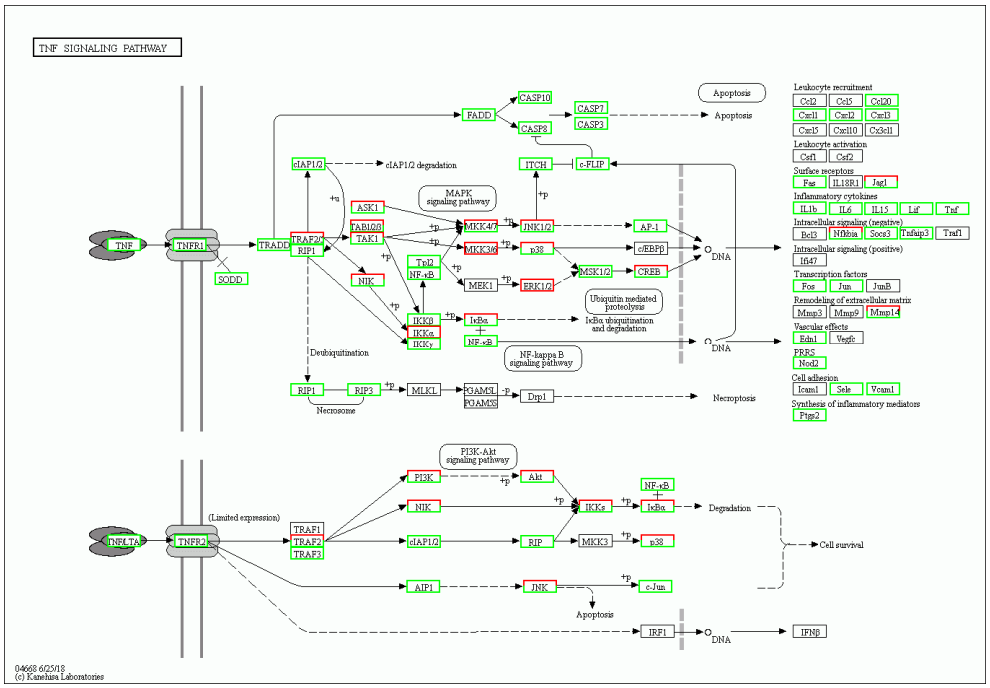
B


NOD-LIKE RECEPTOR SIGNALING PATHWAY
Nucleus
Inflammasomes
Mitochondria
Endosome
Phagosome
Gram-negative bacteria
Cytosolic LPS
Pyroptosis
Toll-like receptor signaling pathway
Pro-inflammatory cytokines
Chemokines
Antimicrobial peptides
IFN-stimulated genes
Pro-inflammatory effects
04621 8/6/17
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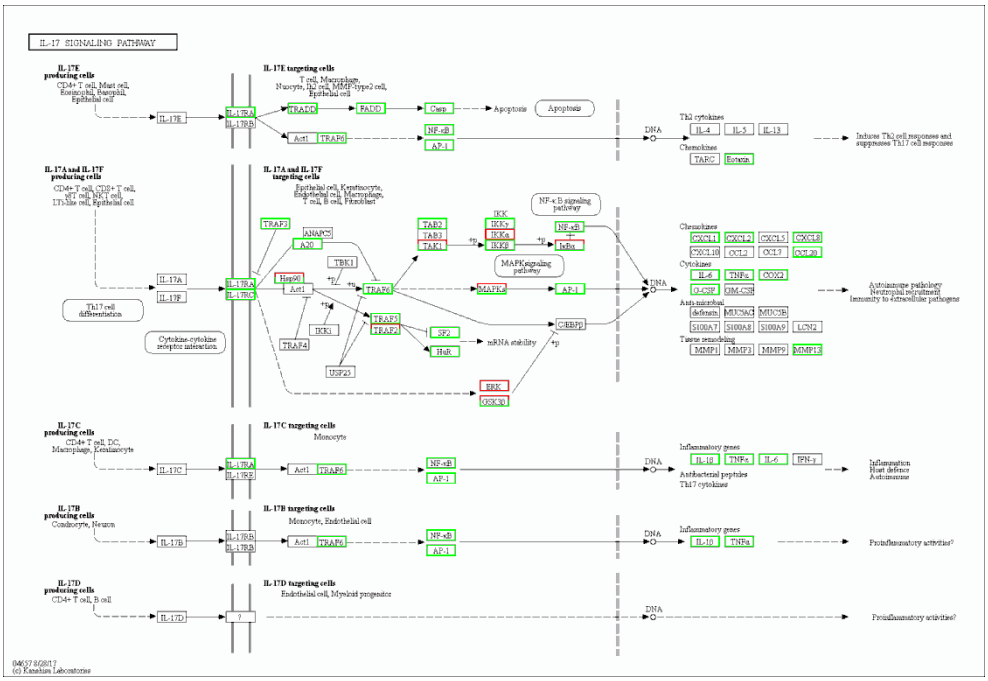
C


JAK-STAT SIGNALING PATHWAY
ECS complex
Ubiquitin mediated proteolysis
Cytokine-cytokine receptor interaction
Cytokine
Hormone
GF
STAM
Receptor
JAK
TC-PTP
SHP1
STAT
STAT dimerization
IRF9
CBP/P300
SLIM
Proteasome
TC-PTP
PIAS
DNA
CIS
SOCS
Bcl-2
Bcl-XL
MCL1
PIM1
c-Myc
CyrcD
p21
AOX
GFAP
Anti-apoptosis
Apoptosis
Cell-cycle progression
Cell-cycle inhibition
Cell cycle
Lipid metabolism
Differentiation
MAPK signaling pathway
SHP2
GRB
SOS
Ras
Raf
Proliferation
Differentiation
PI3K-AKT signaling pathway
PI3K
AKT
mTOR
Cell cycle
Cell survival
04630 5/17/18
(c) Kanehisa Laboratories

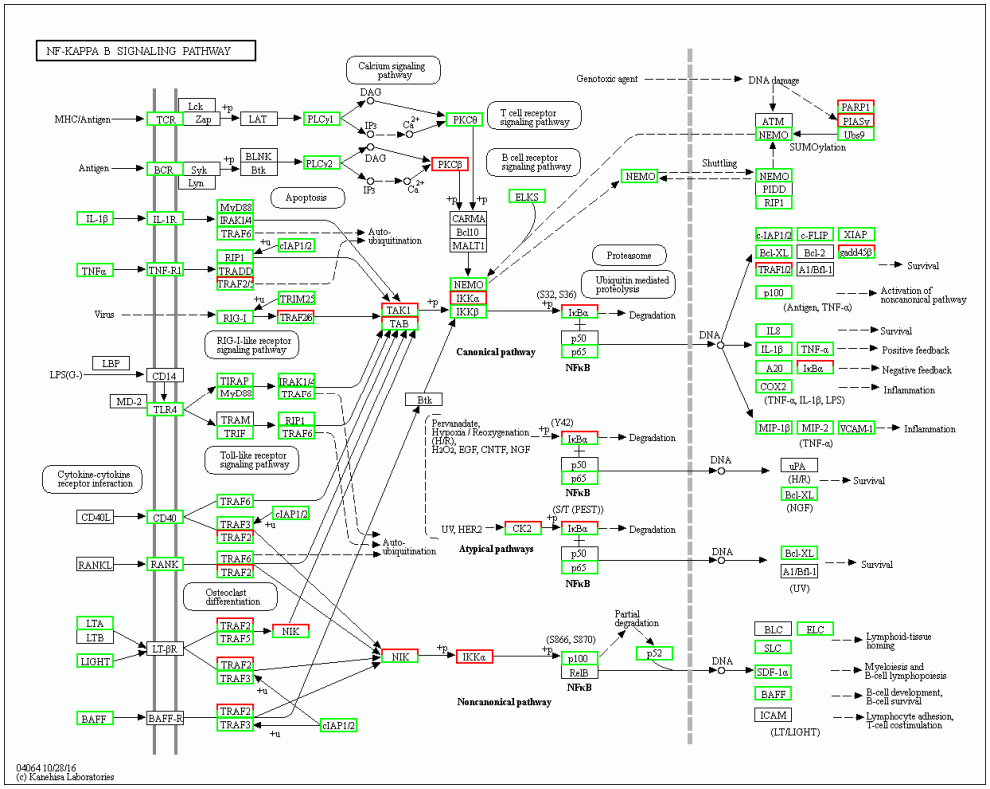
D


TNF SIGNALING PATHWAY
FADD
CASP10
CASP8
CASP7
CASP3
Apoptosis
Apoptosis
cIAP1/2
cIAP1/2 degradation
ITCH
c-FLIP
MAPK signaling pathway
ASK1
TAB1/2/3
TAK1
MKK4/7
JNK1/2
AP-1
MKK3/6
p38
C/EBPβ
DNA
TNF
TNFR1
SODD
TRADD
TRAF2/5
RIP1
Tpl2
NF-κB
MEK1
ERK1/2
MSK1/2
CREB
NIK
IKKβ
IKKα
IKKγ
IκBα
NF-κB
Ubiquitin mediated proteolysis
IκBα ubiquitination and degradation
DNA
NF-kappa B signaling pathway
Deubiquitination
RIP1
RIP3
MLKL
GSDMD
FOXM1
Dnp1
Necroptosis
Necrosome
Leukocyte recruitment
Ccl2
Ccl5
Ccl20
Cxcl1
Cxcl2
Cxcl3
Cxcl5
Cxcl10
Cx3cl1
Leukocyte activation
Csf1
Csf2
Surface receptors
Fas
IL15R1
Jag1
Inflammatory cytokines
IL1b
IL6
IL15
Lif
Tnf
Intracellular signaling (negative)
Bcl3
Nfkbia
Socs3
Tnfaip3
Traf1
Intracellular signaling (positive)
Ifi47
Transcription factors
Fos
Jun
JunB
Remodeling of extracellular matrix
Mmp3
Mmp9
Mmp14
Vascular effects
Edn1
Vegfc
PRRS
Nod2
Cell adhesion
Icam1
Sele
Vcam1
Synthesis of inflammatory mediators
Ptgs2
PI3K-Akt signaling pathway
PI3K
Akt
NF-κB
NIK
IKKs
IκBα
Degradation
(Limited expression)
TNFSF13B
TNFR2
TRAF1
TRAF2
TRAF3
cIAP1/2
RIP
MKK3
p38
Cell survival
AIP1
JNK
c-Jun
Apoptosis
IRF1
DNA
IFNB
04668 6/25/18
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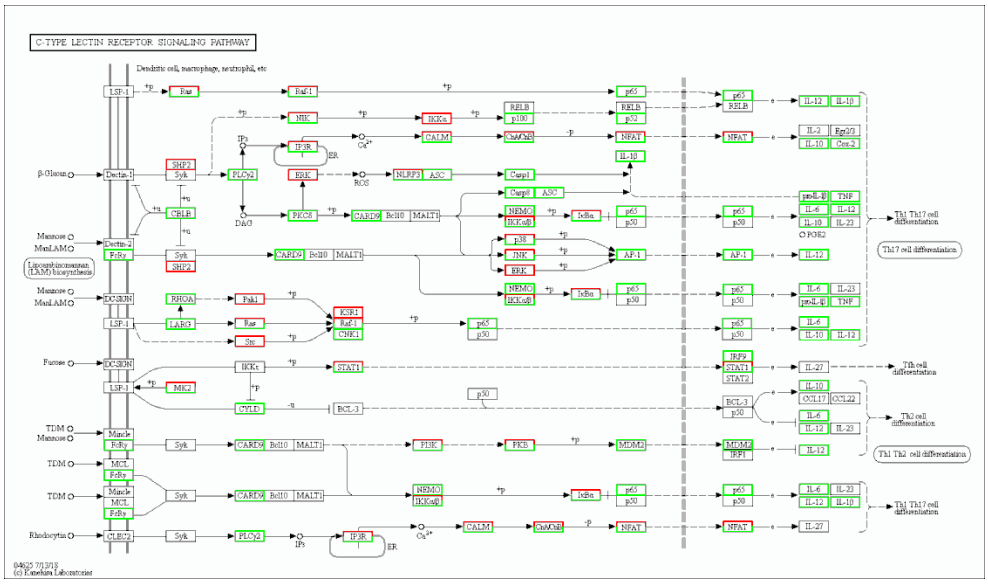
E


IL-17 SIGNALING PATHWAY
IL-17E producing cells
IL-17E targeting cells
IL-17A and IL-17F producing cells
IL-17A and IL-17F targeting cells
IL-17C producing cells
IL-17C targeting cells
IL-17B producing cells
IL-17B targeting cells
IL-17D producing cells
IL-17D targeting cells
IL-17E
IL-17A
IL-17F
IL-17D
IL-17RA
IL-17RB
IL-17RC
IL-17RE
Act1
TRAF6
TRAF3
TRAF5
TRAF4
TRAF2
TRAF1
TRAF3IP2
TBK1
IKKi
USP25
Hrs96
ANAPC5
A20
TAB2
TAB3
TAK1
IKK
IKKγ
IKKα
IKKβ
IκBα
NF-κB
NF-κB signaling pathway
MAPK signaling pathway
MAPK14
AP-1
C/EBPβ
SF2
HuR
mRNA stability
ERK
GSK3β
Th17 cell differentiation
Cytokine-cytokine receptor interaction
DNA
Th2 cytokines
IL-4
IL-5
IL-13
Induces Th2 cell responses and suppresses Th17 cell responses
Chemokines
TARC
Eotaxin
CXCL1
CXCL2
CXCL3
CXCL8
CXCL10
CCL2
CCL7
CCL20
Cytokines
IL-6
TNFα
COX2
G-CSF
GM-CSF
Anti-microbial
defensin
MUC5AC
MUC5B
S100A7
S100A8
S100A9
LCN2
Tissue remodeling
MMP1
MMP3
MMP9
MMP13
Autoimmune pathology
Neutrophil recruitment
Immunity to extracellular pathogens
Inflammatory genes
IL-1β
TNFα
IL-6
IFN-γ
Antibacterial peptides
Th17 cytokines
Inflammation
Host defence
Autoimmune
IL-10
Proinflammatory activities?
Monocyte
Monocyte, Endothelial cell
Endothelial cell, Myeloid progenitor
Osteoclast differentiation
Apoptosis
Gene
FADD
TRADD
NF-κB
AP-1
Th1 cytokines
IL-1
IL-18
Chemokine
IL-8
Eotaxin
Cytokine
IL-1α
IL-1β
TNFα
IL-6
IL-10
IL-12
IL-23
IFN-γ
Anti-microbial
β-defensin
Tissue remodeling
MMP1
MMP3
MMP9
MMP13
Inflammation
Host defence
Autoimmune
Proinflammatory activities?
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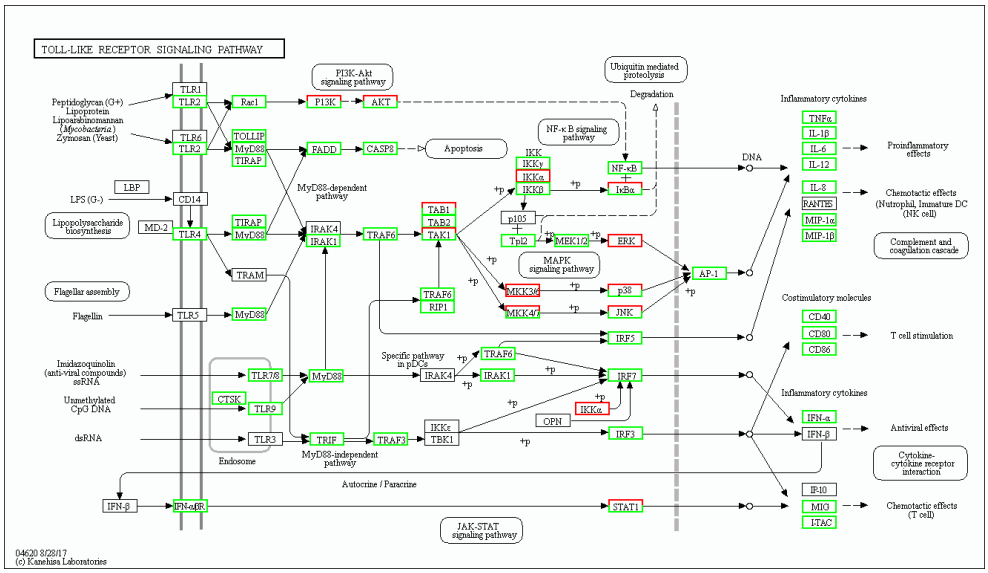
F


NF-KAPPA B SIGNALING PATHWAY
Calcium signaling pathway
Genotoxic agent
DNA damage
MHC/Antigen
TCR
Lck
Zap
LAT
PLCγ1
DAG
IP3
Ca2+
PKCθ
T cell receptor signaling pathway
Antigen
BCR
Syk
Lyn
BLNK
Btk
PLCγ2
B cell receptor signaling pathway
Apoptosis
IL-1β
IL-1R
MyD88
IRAK1/4
TRAF6
cIAP1/2
Auto-ubiquitination
TNFα
TNF-R1
RIP1
TRADD
TRAF2/5
Virus
RIG-I
TRIM25
TRAF25
RIG-I-like receptor signaling pathway
LBP
LPS(G-)
CD14
MD-2
TLR4
TIRAP
MyD88
IRAK1/2
TRAF6
TRAM
TRIF
RIP1
TRAF6
Toll-like receptor signaling pathway
Cytokine-cytokine receptor interaction
CD40L
CD40
TRAF6
TRAF3
TRAF2
cIAP1/2
RANKL
RANK
TRAF6
TRAF2
Osteoclast differentiation
LTA
LTB
LIGHT
LT-βR
TRAF2
TRAF5
NIK
TRAF2
TRAF3
BAFF
BAFF-R
TRAF2
TRAF3
cIAP1/2
TAK1
TAB
NEMO
IKKα
IKKβ
CARMA
Bcl10
MALT1
ELKS
Btk
Canonical pathway
NFκB
IκBα
p50
p65
(S32, S36)
Degradation
Proteasome
Ubiquitin mediated proteolysis
Pervanadate, Hypoxia / Reoxygenation (H/R), H2O2, EGF, CNTF, NGF
(Y42)
UV, HER2
CK2
(S/T (PEST))
Atypical pathways
NIK
IKKα
(S866, S870)
p100
RelB
Partial degradation
p52
Noncanonical pathway
Shuttling
PIDD
RIP1
ATM
PARP1
PIASy
Ubc9
SUMOylation
DNA
c-IAP1/2
c-FLIP
XIAP
Bcl-XL
Bcl-2
gadd45β
TRAF1/2
A1/Bfl-1
Survival
p100
Activation of noncanonical pathway
(Antigen, TNF-α)
IL8
IL-1β
TNF-α
A20
IκBα
COX2
(TNF-α, IL-1β, LPS)
Positive feedback
Negative feedback
Inflammation
MIP-1β
MIP-2
VCAM-1
(TNF-α)
uPA
(H/R)
(NGF)
(UV)
BLC
ELC
SLC
SDF-1α
BAFF
ICAM
(LT/LIGHT)
Lymphoid-tissue homing
Myelopoiesis and B-cell lymphopoiesis
B-cell development, B-cell survival
Lymphocyte adhesion, T-cell costimulation
04064 10/28/16
(c) Kanehisa Laboratories

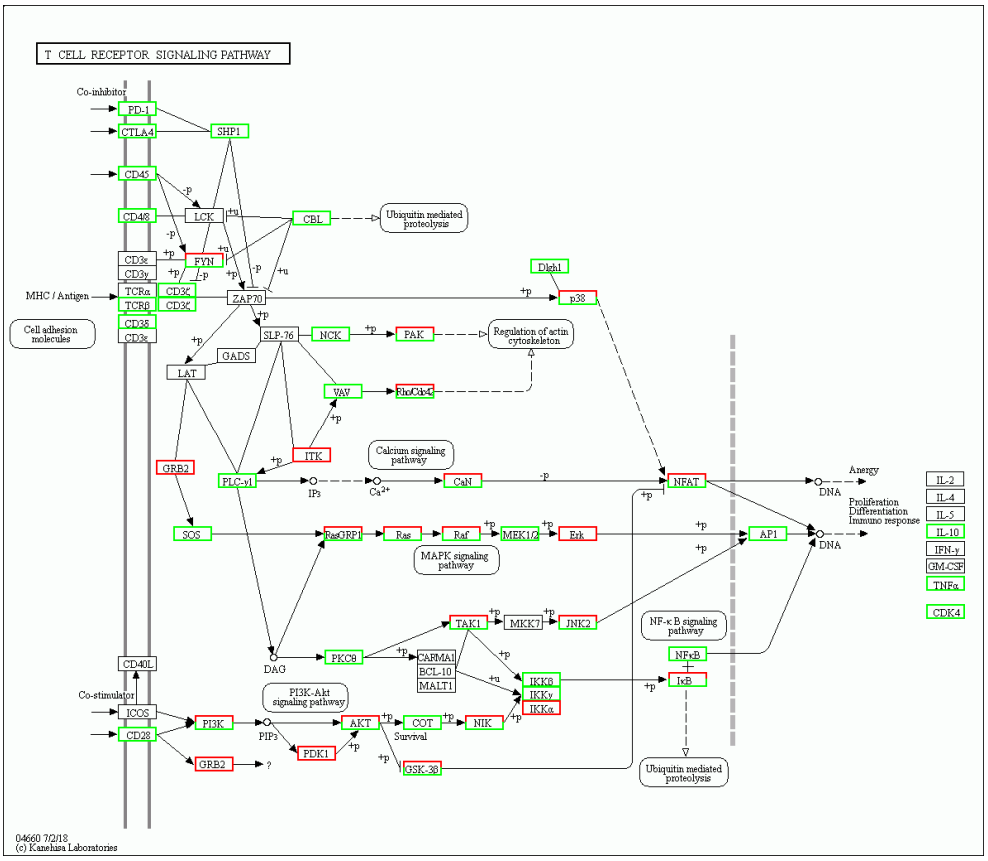
G


C-TYPE LECTIN RECEPTOR SIGNALING PATHWAY
Dendritic cell, macrophage, neutrophil, etc
β-Glucan
Mannose
ManLAM
Lipoarabinomannan (LAM) biosynthesis
Fucose
TDM
TDB
Rhodocytin
Dectin-1
Dectin-2
DC-SIGN
LSP-1
MGL
CLEC-2
SHP2
Syk
FcRγ
CARD9
Bcl10
MALT1
CLEC-2
PLCγ2
PKCδ
DAG
IP3
IP3R
ER
Ca2+
ROS
NLRP3
ASC
Casp1
IL-1β
NEMO
IKKγ/β
IκBα
p65
p50
p52
RELB
p100
CALM
CaMKII
NFAT
AP-1
p38
JNK
ERK
Raf-1
Ras
Rac1
Fak1
LAG3
Ste
KSR1
CHK1
RHOA
IKKε
STAT1
STAT2
IRF9
MIC2
CYLD
BCL-3
PI3K
PKB
MDM2
IRF1
IL-12
IL-23
IL-27
IL-10
IL-6
TNF
COX2
CCL17
CCL22
Th1 Th17 cell differentiation
Th17 cell differentiation
Tfh cell differentiation
Th2 cell differentiation
Th1 Th2 cell differentiation
04625 7/1/13
(c) Kanehisa Laboratories

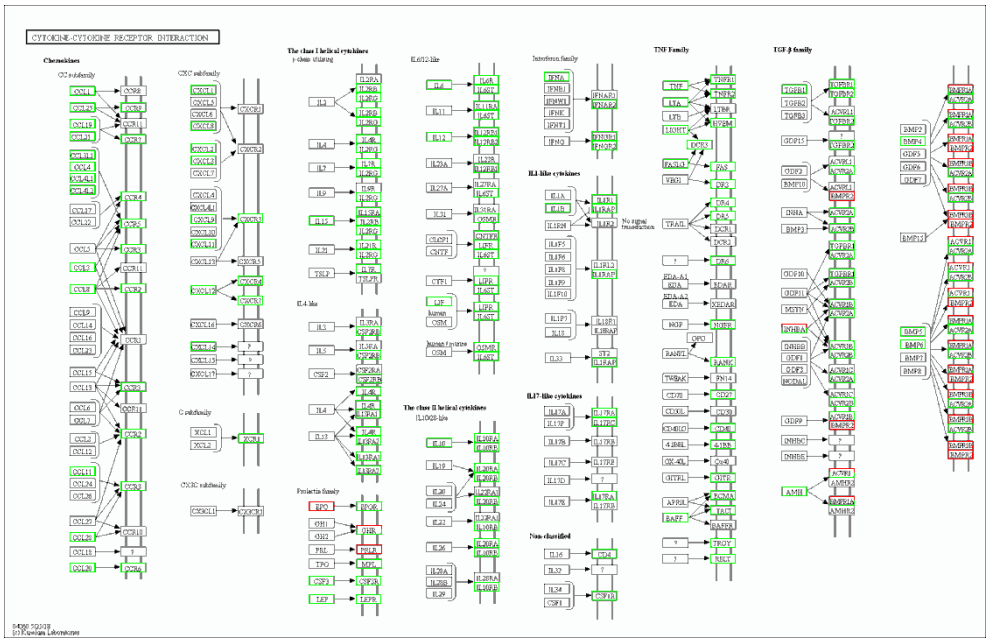
H


TOLL-LIKE RECEPTOR SIGNALING PATHWAY
Peptidoglycan (G+)
Lipoprotein
Lipoarabinomannan (Mycobacteria)
Zymosan (Yeast)
LPS (G-)
LBP
CD14
MD-2
Lipopolysaccharide biosynthesis
Flagellar assembly
Flagellin
Imidazoquinolin (anti-viral compounds) ssRNA
Unmethylated CpG DNA
dsRNA
CTSK
Endosome
TLR1
TLR2
TLR4
TLR5
TLR6
TLR7/8
TLR9
TLR3
TOLLIP
MyD88
TIRAP
TRAM
TRIF
Rac1
PI3K
AKT
PI3K-Akt signaling pathway
FADD
CASP8
Apoptosis
MyD88-dependent pathway
IRAK4
IRAK1
TRAF6
TAB1
TAB2
TAK1
TRAF6
RIP1
MyD88-independent pathway
TRAF3
IKKε
TBK1
Specific pathway in pDC
IRF7
IRF5
IRF3
IKKα
OPN
Ubiquitin mediated proteolysis
Degradation
NF-κ B signaling pathway
IKK
IKKγ
IKKα
IKKβ
NF-κB
IκBα
p105
Tpl2
MEK1/2
ERK
MAPK signaling pathway
MKK3/6
MKK4/7
p38
JNK
AP-1
DNA
Inflammatory cytokines
TNFα
IL-1β
IL-6
IL-12
Proinflammatory effects
IL-8
RANTES
MIP-1α
MIP-1β
Chemotactic effects (Nutrophil, Immature DC (NK cell)
Complement and coagulation cascade
Costimulatory molecules
CD40
CD80
CD86
T cell stimulation
Inflammatory cytokines
IFN-α
IFN-β
Antiviral effects
Cytokine-cytokine receptor interaction
IP-10
MIG
ITAC
Chemotactic effects (T cell)
Autocrine / Paracrine
IFN-β
IFN-αβR
STAT1
JAK-STAT signaling pathway
04620 8/28/17
(c) Kanehisa Laboratories

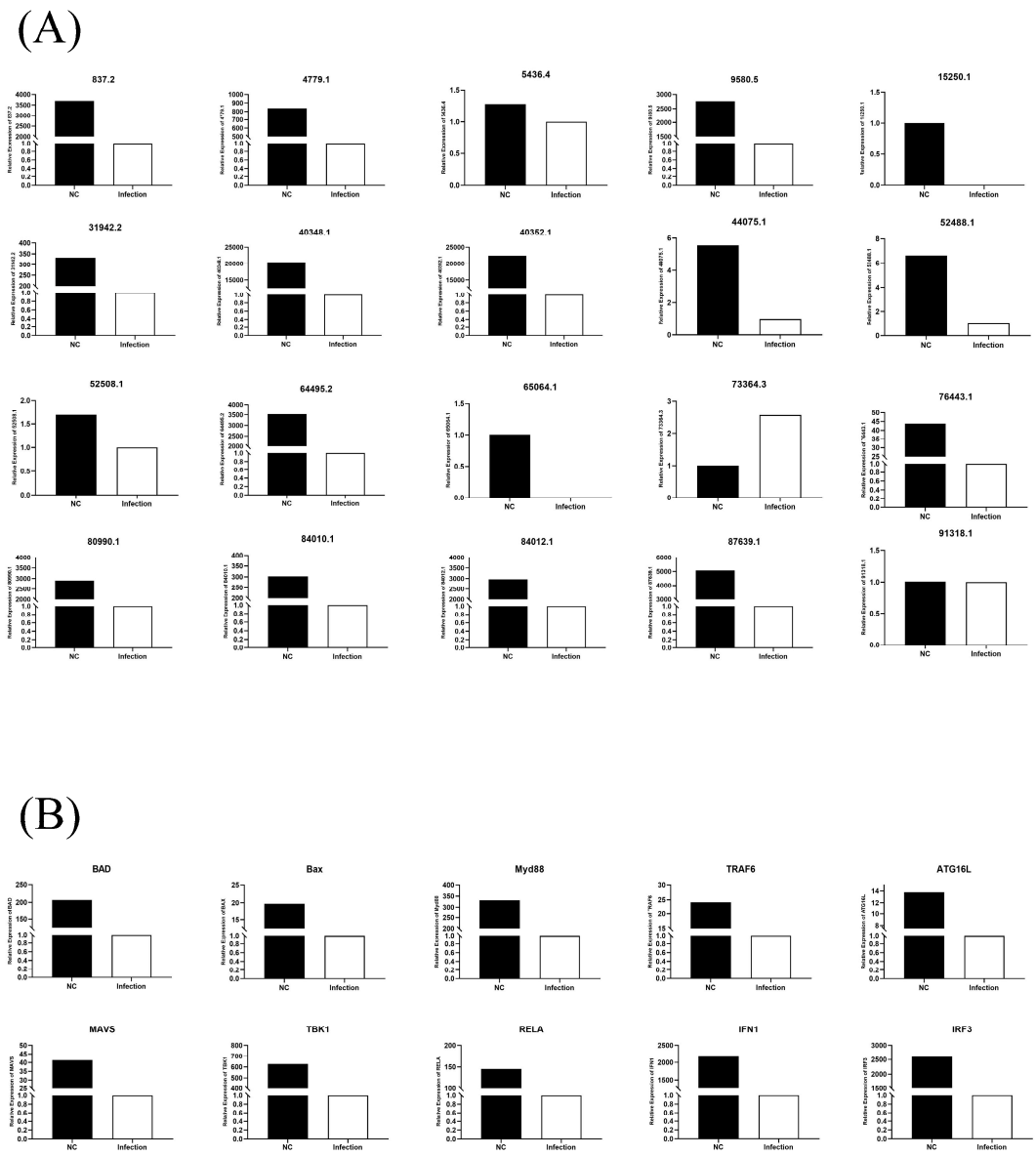
I



J



Supplementary Figure S1. Differentially expressed genes in immune signaling pathways.



Supplementary Figure S2. RT-qPCR results of randomly selected 10 DEmRNAs and 20 lncRNAs.