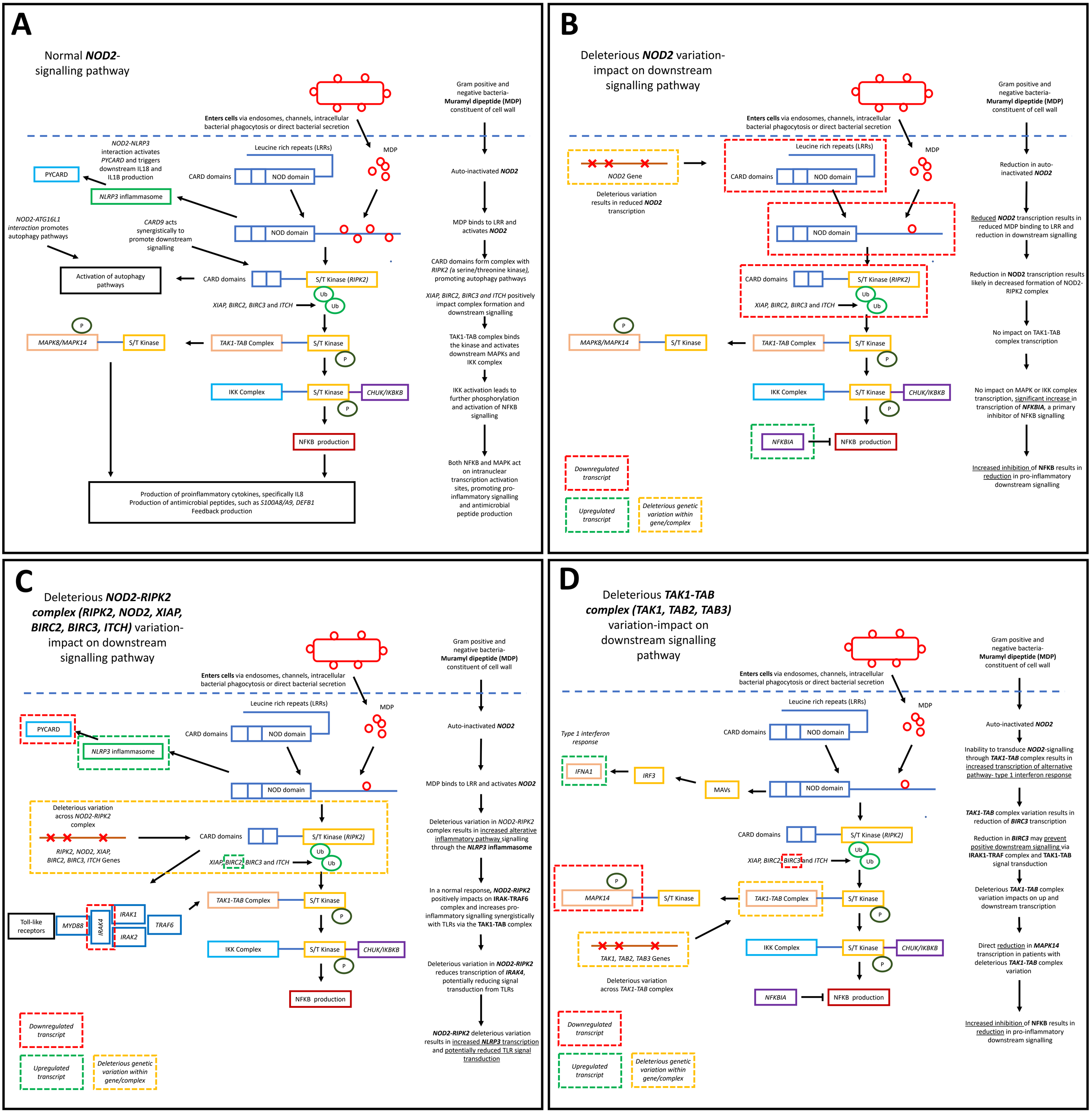
A
Normal NOD2-signalling pathway
Enters cells via endosomes, channels, intracellular bacterial phagocytosis or direct bacterial secretion
Gram positive and negative bacteria- Muramyl dipeptide (MDP) constituent of cell wall
NOD2-NLRP3 interaction activates PYCARD and triggers downstream IL18 and IL1B production
PYCARD
NLRP3 inflammasome
Leucine rich repeats (LRRs)
MDP
CARD domains
NOD domain
Auto-inactivated NOD2
NOD2-ATG16L1 interaction promotes autophagy pathways
CARD9 acts synergistically to promote downstream signalling
MDP binds to LRR and activates NOD2
Activation of autophagy pathways
CARD domains form complex with RIPK2 (a serine/threonine kinase), promoting autophagy pathways
S/T Kinase (RIPK2)
Ub
XIAP, BIRC2, BIRC3 and ITCH
XIAP, BIRC2, BIRC3 and ITCH positively impact complex formation and downstream signalling
P
MAPK8/MAPK14
S/T Kinase
TAK1-TAB Complex
TAK1-TAB complex binds the kinase and activates downstream MAPKs and IKK complex
IKK Complex
CHUK/IKBKB
IKK activation leads to further phosphorylation and activation of NFKB signalling
NFKB production
Both NFKB and MAPK act on intranuclear transcription activation sites, promoting pro-inflammatory signalling and antimicrobial peptide production
Production of proinflammatory cytokines, specifically IL8
Production of antimicrobial peptides, such as S100A8/A9, DEFB1
Feedback production
B
Deleterious NOD2 variation-impact on downstream signalling pathway
NOD2 Gene
Deleterious variation results in reduced NOD2 transcription
Reduction in auto-inactivated NOD2
Reduced NOD2 transcription results in reduced MDP binding to LRR and reduction in downstream signalling
Reduction in NOD2 transcription results likely in decreased formation of NOD2-RIPK2 complex
No impact on TAK1-TAB complex transcription
No impact on MAPK or IKK complex transcription, significant increase in transcription of NFKBIA, a primary inhibitor of NFKB signalling
NFKBIA
Increased inhibition of NFKB results in reduction in pro-inflammatory downstream signalling
Downregulated transcript
Upregulated transcript
Deleterious genetic variation within gene/complex
C
Deleterious NOD2-RIPK2 complex (RIPK2, NOD2, XIAP, BIRC2, BIRC3, ITCH) variation-impact on downstream signalling pathway
Deleterious variation across NOD2-RIPK2 complex
RIPK2, NOD2, XIAP, BIRC2, BIRC3, ITCH Genes
Toll-like receptors
MYD88
IRAK4
IRAK1
IRAK2
TRAF6
Deleterious variation in NOD2-RIPK2 complex results in increased alterative inflammatory pathway signalling through the NLRP3 inflammasome
In a normal response, NOD2-RIPK2 positively impacts on IRAK-TRAF6 complex and increases pro-inflammatory signalling synergistically with TLRs via the TAK1-TAB complex
Deleterious variation in NOD2-RIPK2 reduces transcription of IRAK4, potentially reducing signal transduction from TLRs
NOD2-RIPK2 deleterious variation results in increased NLRP3 transcription and potentially reduced TLR signal transduction
D
Deleterious TAK1-TAB complex (TAK1, TAB2, TAB3) variation-impact on downstream signalling pathway
Type 1 interferon response
IFNA1
IRF3
MAVs
Auto-inactivated NOD2
Inability to transduce NOD2-signalling through TAK1-TAB complex results in increased transcription of alternative pathway- type 1 interferon response
TAK1-TAB complex variation results in reduction of BIRC3 transcription
Reduction in BIRC3 may prevent positive downstream signalling via IRAK1-TRAF complex and TAK1-TAB signal transduction
Deleterious TAK1-TAB complex variation impacts on up and downstream transcription
Direct reduction in MAPK14 transcription in patients with deleterious TAK1-TAB complex variation
TAK1, TAB2, TAB3 Genes
Deleterious variation across TAK1-TAB complex