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# SnapShot: NF-κB Signaling Pathways

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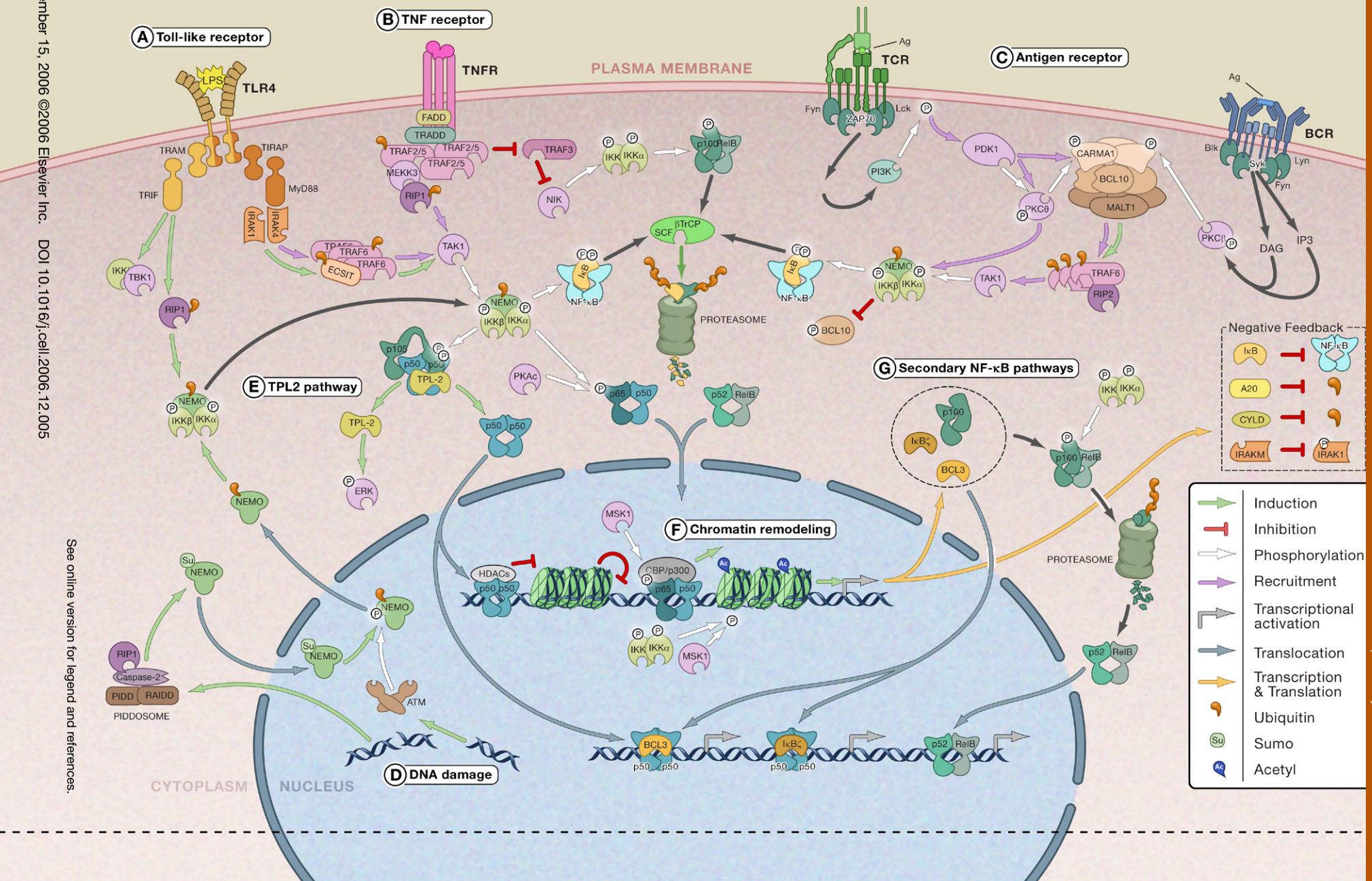
Cell

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## Figure Legend

(A) Toll-like receptor signaling. A Toll-like receptor (TLR) bound to ligand recruits TIR-containing adaptor molecules, MyD88 and/or TRIF, which bind to downstream effectors IRAK1-4 and RIP1, respectively. Active IRAKs bind to TRAF6 and TAK1, which subsequently activate the IKK complex. Ubiquitination of TRAF and the regulatory subunit of the IKK complex, NEMO, facilitates activation of the catalytic IKKβ subunit. This results in the phosphorylation and proteasomal degradation of IκB and the release of heterodimers of the master transcription factor NF-κB.
(B) TNF receptor signaling. Signaling via members of the TNF receptor superfamily, such as TNFR1, leads to recruitment of the adaptor proteins FADD and TRADD, several TRAF family members (TRAF2, 5, and 6), and the kinase RIP1. The TRAF/RIP complex recruits and activates TAK1, which induces activation of the IKK complex and downstream signaling via the NF-κB pathway. When stimulated, a subset of TNFR superfamily members that bind to TRAF3 (CD40, LTβR, BAFFR) induce TRAF3 degradation resulting in accumulation of the kinase NIK, which undergoes constitutive degradation in the absence of stimulation. Accumulated NIK phosphorylates and activates IKKα. IKKα, in turn, induces processing of the NF-κB family member p100 into p52 and, thus, activation of p52-containing NF-κB complexes (prototypically RelB:p52).
(C) Antigen receptor signaling. Signaling via the T cell receptor (TCR), or analogously through the B cell receptor (BCR), recruits the Src family tyrosine kinases, ZAP70 and Syk, leading to production of inositide-3-phosphate (IP3) and diacylglycerol (DAG). Activation of PI3K induces activation of PDK1, which recruits and activates protein kinase C (PKC) family members and the CARMA1/BCL10/MALT1 (CBM) complex. PKC phosphorylates CARMA1 resulting in activation and oligomerization of the CBM complex, recruitment of TRAF6, and stimulation of the classical TAK1 to IKK signaling pathway. Active IKK may also exert negative feedback through phosphorylation of BCL10.
(D) DNA damage response. DNA damage triggers activation of the PIDDosome (containing RIP1/PIDD/RAIDD) leading to sumoylation of NEMO and its translocation to the nucleus. DNA damage also activates the kinase ATM, leading to phosphorylation and ubiquitination of NEMO, which returns to the cytoplasm and mediates IKK activation.
(E) TPL2 pathway. Active IKK phosphorylates p105 resulting in the release of p50 homodimers, which translocate to the nucleus and active TPL2, which then activates the ERK signaling pathway.
(F) Chromatin remodeling. NF-κB activation leads to expression of target genes by regulating chromatin structure. Unphosphorylated p65-containing NF-κB heterodimers or p50 homodimers bind to repressive histone deacetylases (HDACs) and suppress transcription. In the cytoplasm, p65 can be phosphorylated by IKK and protein kinase A (PKA), and in the nucleus by MSK1. This enables recruitment of histone acetyl transferases (HATs) including CBP/p300 resulting in the acetylation of histones, relaxing of chromatin structure and activation of gene expression. Phosphorylation of histones by IKKα or MSK1 directly may also promote transcription.
(G) Secondary NF-κB pathways. Active NF-κB induces expression of components of the NF-κB signaling pathway including p100, BCL3, and IκBζ. IκBζ forms transcriptionally active complexes with p50 homodimers. BCL3 may form either repressive or active complexes with p50 and p52 dimers, depending on posttranslational modifications of BCL3. Transcription of p100 allows full activation of the alternate NF-κB pathway through IKKα-induced processing of p100 to p52. NF-κB also induces negative feedback through expression of IκB, deubiquitinating enzymes A20 and CYLD, and IRAKM, which blocks phosphorylation of IRAK1.

## Abbreviations

CARMA1, caspase recruitment domain-membrane associated guanylate kinase 1; CBP/p300, cyclic-adenosine monophosphate response element binding protein/p300; CYLD, cylindromatosis; ECSIT, evolutionarily conserved signaling intermediate in Toll/IL1R pathways; ERK, extracellular signal-regulated kinase; FADD, Fas-associated death domain protein; IKK, inhibitor of kappa B kinase; IκB, inhibitor of kappa-B; IRAK, interleukin-1 receptor-associated kinase; LPS, lipopolysaccharide; MALT1, mucosal-associated lymphoid tissue; MEKK, mitogen-activated protein/ERK kinase kinase; MSK1, mitogen and stress-activated kinase-1; NEMO, nuclear factor kappa B essential modifier; NF-κB, nuclear factor-kappa B; NIK, nuclear factor kappa B inducing kinase; PI3K, phosphatidylinositol 3-kinase; PIDD, p53-induced protein with a death domain; PKAc, protein kinase A catalytic subunit; RAIDD, RIP-associated ICH-1 homologous protein with a death domain; RIP, receptor-interacting protein; SCF, Skp1 cullin F box; SUMO, small ubiquitin-related modifier; TAK1, transforming growth factor-β-activated kinase 1; TBK1, TANK binding kinase-1; TICAM, TIR-containing adaptor molecule; TIR, Toll/IL1 resistance; TIRAP, TIR-containing adaptor protein; TLR, Toll-like receptor; TNFR, tumor necrosis factor receptor; TPL, tumor progression locus; TRADD, TNF receptor-associated death domain-containing protein; TRAF, tumor necrosis factor receptor-associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-containing adaptor inducing interferon β.

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