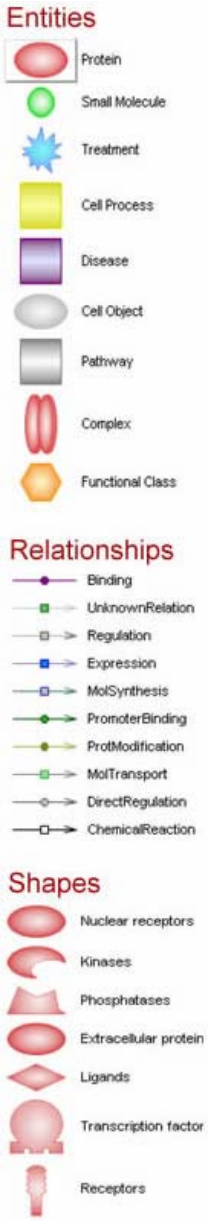
Nuclear Factor Kappa B signaling pathway



Description

Nuclear Factor Kappa B (NF-kB) signaling pathway is essential for the proper functioning of the immune system. NF-kB pathway regulates the expression of cytokines, growth factors and other regulatory proteins in response to the activation of upstream ligand-receptor signaling pathways. The mammalian NF-kB family of transcription factors is composed of five members that can form homo- or heterodimers. The presence of Rel homology domain (RHD) which underlies several functionalities is a characteristic feature shared by all members. Dimers are kept inactive through their association to one of the inhibitory IkB proteins. Ligand mediated activation of receptors and subsequent interactions with various adapter proteins leads to the activation of the IkB kinases (IKK). The IKK complex is composed of Chuk (known as Ikkα or 1), Ikbkb (known as Ikkβ or 2) and the regulatory subunit Ikbkg (Ikkγ or Nemo). In the canonical (classical) NF-kB pathway, activation of Ikbkb/Ikbkg leads to phosphorylation of the inhibitory IkBs, best exemplified by Nfkbia (IkBα). Phosphorylated Nfkbia is targeted for degradation and the released NF-kB dimer, primarily the RelA (p65)/Nfkb1(p50) complex, translocates to the nucleus to induce the activation of many target genes. Amongst them is Nfkbia which thus provides a negative regulatory feedback loop. The non-canonical (alternative) pathway is independent of Ikbkg (Nemo) but dependent on Map3k14 (Nik or NF-kB inducing kinase) upstream of Chuk (Ikkα). Activated Chuk phosphorylates the Nfkb2 (p100) member of the NF-kB family which is then processed to p52, followed by the translocation of the Nfkb2(p52)/RelB complex to the nucleus. The two and probably not the only NF-kB pathways are elicited by ligand-receptor subsets of the tumor necrosis factor (Tnf) superfamilies of ligands and receptors, respectively. The canonical NF-kB pathway downstream but not exclusively of tumor necrosis factor signaling through receptor 1 is regarded as a paradigm of NF-kB signaling. The association of ligand activated receptors with particular adapter molecules upstream of NF-kB activation coupled to the combinatorial NF-kB dimer and dimer-IkB interactions, provides for a diversity of conduits that uniquely modulate the manifestations and outcomes of NF-kB pathway.