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Review

Signaling via NF-κB in the nervous system

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Abstract

Nuclear factor kappa B (NF-κB) is an inducible transcription factor present in neurons and glia. Recent genetic models identified a role for NF-κB in neuroprotection against various neurotoxins. Furthermore, genetic evidence for a role in learning and memory is now emerging. This review highlights our current understanding of neuronal NF-κB in response to synaptic transmission and summarizes potential physiological functions of NF-κB in the nervous system. This article contains a listing of NF-κB activators and inhibitors in the nervous system, furthermore specific target genes are discussed. Synaptic NF-κB activated by glutamate and Ca^{2+} will be presented in the context of retrograde signaling. A controversial role of NF-κB in neurodegenerative diseases will be discussed. A model is proposed explaining this paradox as deregulated physiological NF-κB activity, where novel results are integrated, showing that p65 could be turned from an activator to a repressor of anti-apoptotic genes.

Keywords: Transcription factor; Neuron; Neuroprotection; Memory; Tumor necrosis factor; Calcium; Synapse; Retrograde; Inhibitor; Activator; Target gene; NF-κB; IκB

1. NF-κB activation via tumor necrosis factor (TNF)

Nuclear factor kappa B (NF-κB) was discovered by David Baltimore's laboratory as an inducible transcription factor in lymphocytes [1]. The so-called canonical pathway of NF-κB activation via tumor necrosis factor (TNF) [2,3] will be presented to summarize part of the general knowledge on activation mechanisms (see Fig. 1). The TNF pathway is one of the best characterized NF-κB-dependent pathways with more than 70 000 references in PubMed. Therefore, we have chosen this so-called canonical pathway, which is also operating in the nervous system, to introduce the NF-κB activation.

Within the nervous system, TNF (a 17 kDa protein) can bind to TNF receptors (TNF-Rs) expressed on both glia and neurons [4]. The expression of the TNF-α gene is subject to autoregulation via activated NF-κB [5]. Two different receptors, p55 (TNF-R1) and 75 (TNF-R2), have been identified. The p55 receptor is thought to be the major NF-κB activating TNF-R [6].

Central to NF-κB activation seems to be the IκB kinase complex (IKK), which is catalyzing the signal-dependent phosphorylation of the NF-κB inhibiting IκB. Thus, the IKK complex initiates NF-κB activation via phosphorylation of IκB, which is a signal for polyubiquitination and subsequent degradation. An amazing wealth of information has been accumulated, describing how receptor activation might be connected to IKK activation. There are themes of ubiquitination after the activation of the trimeric TNF receptor. The binding of soluble or cell-bound TNF leads to the activation of the latent trimerized TNF receptors. These receptors share an intracellular so-called death domain (DD) with several other TNF receptors such as TRAIL receptors or DR3, DR6 and various other receptors with non-TNF ligands such as the CD 95 (Apo/Fas) receptor or the p75 low-affinity nerve growth factor receptor. TNF-RI is unique in its composition of intracellular interaction proteins [7]. The genetic ablation of TNF-R1 (p55) exacerbates traumatic brain injury and correlated with a reduced NF-κB activation [4]. Recent data suggest that the TNF-R2 is responsible for a persistent NF-κB activation and neuroprotection [8,9].

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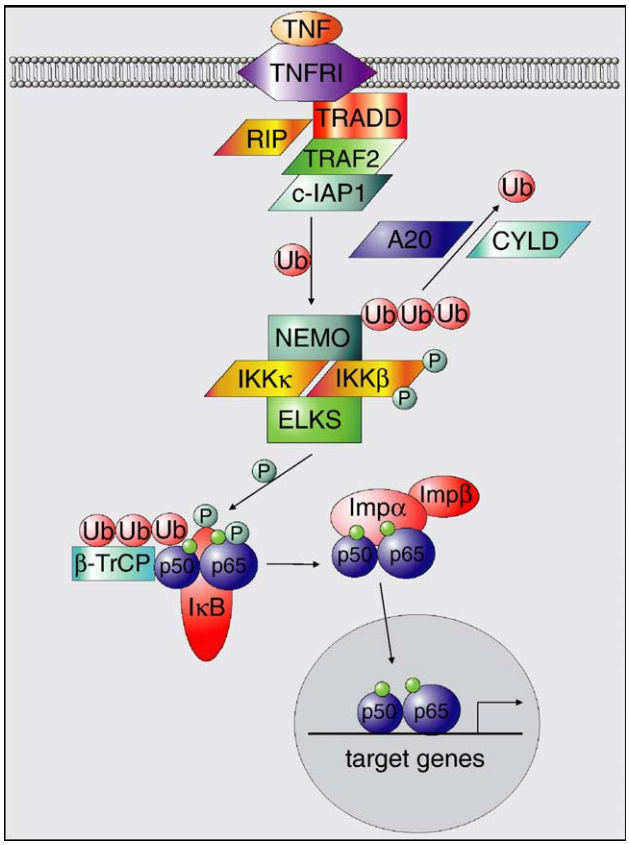

Fig. 1. Canonical pathway of NF-κB activation by tumor necrosis factor (TNF). The activation of the TNF receptor by ligand binding is transmitted to the IKK complex which phosphorylates IκB family inhibitory molecules (see text for details). This targets IκB for polyubiquitination and subsequent degradation within the 26S proteasome. This frees nuclear localization signal on the DNA-binding p65/p50 subunits. After nuclear import, target gene transcription is initiated. Not all signaling components depicted in the canonical pathway have been investigated in the nervous system, but appear to be present in neurons and glia. Proteins are depicted as icons which illustrate a functional category (receptor, enzyme, etc.) as suggested by the Alliance for Signalling convention (www.signaling-gateway.org). Ub=ubiquitination; P=phosphorylation.

The trimerization of the non-signaling TNF-R complex is mediated by a N-terminal pre-ligand assembly domain. TNF binding activates the pre-assembled receptor trimer via release of silencer of death domains (SODD) from the intracellular death domains; see [7] for discussion. The physiological role of SODD remains unclear. The trimeric death domains seem to function as an assembly platform for further intracellular interactors such as the adapter protein TRADD. TRADD seems to enable a bifurcation in either the apoptotic pathway, leading to caspase activation, or in the anti-apoptotic NF-κB-dependent pathway, which involves the transcription of genes encoding survival factors. Apoptosis, as well as anti-apoptosis, is involving TRADD in the context of different signaling complexes [10]. The initial receptor-bound complex (see Fig. 1) might contain TRADD, RIP and TRAF2. This provides a signaling scaffold for the activation of NF-κB. An apoptotic pathway could be triggered by FADD, which might interact with RIP and TRADD in a non-receptor bound cytoplasmic complex. With its N-terminal domain, TRADD could facilitate the interactions with TRAF1 and TRAF2. Anti-apoptotic proteins are targeted to the receptor complex, e.g. cIAP-1 and cIAP-2. This might be the reason for the relative good protection of activated TNF-R1 signaling against apoptosis. Several studies with murine neuronal cultures use human TNF-α, which has been shown to activate the TNF-R1 [11,12].

The IκB kinase complex might integrate many NF-κB activating stimuli culminating on NF-κB activation within the nervous system such as TNF, LPS, IL-1, NGF or glutamate-mediated signaling; see [13] for a review.

Crucial for NF-κB activation is the phosphorylation of IκB. This is most commonly due to the interaction of activated IκB–kinase complex (IKK) with IκB. The IKK complex is composed of two catalytic subunits (IKK-α and IKK-β), a receptor targeting/oligomerization subunit NEMO and ELKS, a recently discovered IκB-α targeting subunit [14]. The activation of the IKK complex might be regulated by multiple mechanisms [2]. A classical phosphorylation of an activation loop has been reported for the main IκB phosphorylating kinase IKK-β at serines 177 and 181 [15]. This might be either due to autophosphorylation or due to upstream kinases. Surprisingly, only for the upstream kinase MEKK3 genetic evidence for an involvement in the TNF pathway could be provided [16]. Other activation mechanisms dependent on the oligomerization of the IKK complex have been described [17,18]. NEMO-mediated recruitment of the IKK complex to the T cell receptor complex has been identified as activation mechanism [19]. Surprisingly, also the membrane localization of NEMO could activate the IKK complex [19]. NEMO, the regulatory subunit of the IKK complex, is inducibly ubiquitinated. The receptor-bound complex containing TRAF2 and TRAF5 could recruit the IKK complex to the membrane-bound TNF receptor and thus lead to activation via IKK oligomerization [20]. IκB is recruited to the IKK complex via an interaction with ELKS [14]. The activated IKK complex could catalyze the phosphorylation of Ser 32 and 36 on the IκB-α molecule.

As summarized above, the activation of the IKK complex seems to rely on multimerization. The ubiquitination of NEMO might be an essential prerequisite of the activation process, since deubiquitinating enzymes such as CYLD [21,22] are essential to deactivate the IKK complex. These ubiquitination pathways seem to be independent of the proteasomal degradation but are modulating oligomeric state. Other deubiquitination and ubiquitination activity is found to be encoded in the protein A20, which could target RIP for degradation [23].

For an extensive review of the ubiquitin–proteasome system, see the special issue of BBA, Vol. 1695 (2004). Ubiquitin (Ub) is a small (86 kDa) protein used to tag proteins either for the degradation or for signaling (multimerization). Ubiquitin is conjugated to the amino groups of lysine residues on target proteins by a cascade of enzymes called E1, E2 and E3 [24]. An SCF (Skp-1/Cul/F box)-type