Published in final edited form as:
Neurobiol Dis. 2011 August ; 43(2): 305–311. doi:10.1016/j.nbd.2011.04.015.

The role of IκB kinase complex in the neurobiology of Huntington's disease

Ali Khoshnan[*] and **Paul H. Patterson**

Abstract

The IκB kinase β (IKKβ) is a prominent regulator of neuroinflammation, which is implicated in the pathogenesis of Huntington's disease (HD). Inflammatory mediators accumulate in the serum and CNS of premanifest and manifest HD patients, and cytokine levels correlate with disease progression. IKKβ may also directly regulate the neurotoxicity of huntingtin (Htt). Activation of IKKβ by DNA damage triggers caspase-dependent cleavage of WT and mutant Htt and enhances the accumulation of oligomeric fragments. Moreover, the N-terminal fragments of mutant Htt (HDx1) directly bind to and activate IKKβ. Thus, the IKKβ-dependent cleavage of full-length mutant Htt and the buildup of HDx1 could form a deleterious feed-forward loop. Elevated IKKβ activity is present throughout the CNS in a symptomatic mouse model of HD expressing HDx1, whereas in asymptomatic mice with full-length mutant Htt, it is confined to the striatum. IKKβ could also influence the phosphorylation of Htt at Ser13 and Ser16, which is linked to HD pathology. IKKβ inhibitors ameliorate the toxicity of mutant Htt in striatal neurons and prevent DNA damage-induced Htt cleavage. Inhibition of IKKβ in the CNS also reduces neuroinflammation and imparts neuroprotection in a chemical model of HD. These findings support an active role for IKKβ in HD pathogenesis and represent an example of how gene–environment (exemplified by DNA damage and inflammation) interactions can influence Htt neurotoxicity. We will summarize these findings and describe the therapeutic potentials of IKKβ for HD.

Keywords

Huntington's disease; IKKβ; Neuroinflammation; Htt cleavage; DNA damage

Introduction

Huntington's disease and IKKβ

HD is an inherited neurodegenerative disorder caused by expansion of a CAG repeat,which is translated into a polyglutamine (polyQ) stretch in exon-1 (HDx1) of Htt. (The Huntington's Disease Collaborative Research Group (1993). In most animal and cellular models of HD, the neurotoxicity of mutant Htt is enhanced by the cleavage and production of N-terminal fragments, which are generated by various enzymes including caspases and calpains. The fragments containing expanded polyQ aberrantly bind to various proteins, impair cellular machinery, and promote neurotoxicity. The N-terminal mutant Htt fragments also form amorphous intracellular aggregates and accumulate in the HD brain. The role of these aggregates in the pathobiology of HD remains a contentious area of investigation. Wild type Htt is also cleaved by similar proteases, which can lower its level and interfere with its vital function in neurons. Therefore, both the loss of WT Htt and the gain of toxic

[*]Corresponding author at: Biology Division, 216-76, California Institute of Technology, Pasadena CA 91125, USA. Khoshnan@caltech.edu (A. Khoshnan).

functions by mutant Htt contribute to HD. Studies on the neurobiology of HD were extensively reviewed recently (Zuccato and Cattaneo, 2010). Although expansion of polyQ is a determinant of HD, the age of disease onset is variable among patients with similar polyQ length (Wexler et al., 2004). Thus, other genetic or environmental factors may regulate the onset and progression of HD.

Two potential modifiers of HD pathogenesis are neuroinflammation and the accumulation of DNA damage in the brain. A prominent pathway regulating the effects of these environmental insults is the IκB kinase (IKK) complex. The core IKK has two kinases, IKKα and IKKβ, and a regulatory subunit, IKKγ. IKK is induced by various stimuli including cytokines, oxidative stress and DNA damage, and it phosphorylates the inhibitors of κB (IκB), a family of proteins that sequesters NF-κBs in the cytoplasm (Hacker and Karin, 2006). Phosphorylation of IκBs initiates their degradation by the ubiquitin–proteasome pathway, which liberates NF-κB and allows its binding to the promoter of many genes such as cytokines (Fig. 1). IKKβ is the predominant kinase responsible for inflammatory responses (Hacker and Karin, 2006). The IKKs are ubiquitously expressed but their functions in the CNS are poorly understood. While regulated IKK/NF-κB signaling is thought to promote neuronal survival, growth and plasticity, chronic activation of IKKβ contributes to neurodegeneration (Mattson and Meffert, 2006). Excessive IKKβ activity, which coincides with elevated cytokines, has been detected in Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), ischemia, and HD (Khoshnan et al., 2004; Herrmann et al., 2005; Mattson and Meffert, 2006; Van Loo et al., 2006; Ghosh et al., 2007). On the other hand, inhibition of IKKβ activity is neuroprotective in animal models of PD, ischemia, and MS (Herrmann et al., 2005; Van Loo et al., 2006; Ghosh et al., 2007). Recent studies demonstrate that the nuclear orphan receptor Nurr-1, which is mutated in certain familial cases of PD, is an inhibitor of NF-κB pathway (Saijo et al., 2009). Moreover, optineurin, a negative regulator of IKK assembly, is mutated in familial cases of amyotrophic lateral sclerosis (ALS) and is the underlying cause of elevated levels of IKK/NF-κB in these patients (Zhu et al., 2007; Maruyama et al., 2010). Thus, dysregulation of IKK/NF-κB may contribute to the pathology of major CNS diseases.

IKK/NF-κB signaling and inflammation in HD

Neuroinflammation, signified by activated microglia and elevated levels of proinflammatory cytokines, is a component of major neurodegenerative disorders including AD, PD, ALS, and HD (Björkqvist et al., 2008; Glass et al., 2010). While the role of inflammation in these disorders is not well characterized, the accumulation of amyloid proteins, which is a hallmark of these disorders, may be causal. HD patients express increased levels of the inflammatory cytokine IL-6 in the serum and CNS ~ 16 years before the onset of symptoms, and its level correlates with disease development. Other cytokines, including IL-1β, IL-8 and TNF-α are also abundant in the symptomatic HD patients as well as in HD animal models (Björkqvist et al., 2008). Studies of postmortem HD brains also indicate abnormal level of several inflammatory mediators, including CCL2, IL-10, IL-6, IL-8 and MMP9 in various brain regions (Silvestroni et al., 2009). The IKK/NF-κB pathway is major inducer of these inflammatory mediators and is dysregulated in HD (Khoshnan et al., 2004; Hacker and Karin, 2006). Elevated IKKβ activity is widespread in the CNS of R6/2 a genetic mouse model of HD, which expresses a toxic N-terminal fragment of mutant Htt (HDx1) (Khoshnan et al., 2004; Zuccato and Cattaneo, 2010). These animals also express high levels of inflammatory cytokines including IL-6, IL-1β and TNF-α in the serum and CNS, which is consistent with a deregulated IKKβ/NF-κB pathway (Björkqvist et al., 2008). Activated microglia, which are a likely source of elevated cytokines in the CNS, are detected in preclinical HD brains and their accumulation coincides with striatal neuronal dysfunction (Tai et al., 2007). Interestingly, inhibition of caspase-mediated maturation of IL-1β

ameliorates neuroinflammation and neurotoxicity in a R6/2 mouse model (Ona et al., 1999). Moreover, knockdown of IKKβ in microglia reduces inflammation and neurotoxicity in a kainic acid-induced excitotoxicity model of HD (Cho et al., 2008). These studies support a role for IKKβ in neuroinflammation and highlights that imbalances in IKKβ activity may be the underlying cause of elevated cytokines in the CNS of HD patients. Aberrant activity of IKKβ/NF-κB may also be responsible for the abnormal level of inflammatory mediators in the serum of HD patients. Immune cells of HD patients are hypersensitive to immunological challenges and produce various cytokines to significantly higher levels than those from control subjects (Björkqvist et al., 2008). Moreover, striatal neurons expressing full-length mutant Htt display exaggerated IKKβ/NF-κB activity when stimulated with cytokines known to activate IKKβ (Khoshnan et al., 2004). Thus, mutant Htt may increase the cellular responses to stimuli that activate IKKβ. Considering the prominent role of IKKβ in cytokine biology, it will be interesting to investigate how deregulation of IKKβ promotes inflammation in HD patients many years before the onset of motor symptoms.

Mutant HDx1 activates IKKβ

One factor, which may activate the IKK/NF-κB, is the accumulation of amyloidogenic peptides such as the Aβ fragment of the amyloid precursor protein (Kaltschmidt et al., 2005). We have shown that mutant HDx1, which has amyloidogenic properties, directly associates with the IKKγ subunit of the IKK complex. The binding of mutant HDx1 to IKKγ requires expanded polyQ as well as the proline motifs in HDx1. This interaction promotes the assembly and activation of the IKK complex and is disrupted by recombinant intrabodies targeting the polyproline motifs of HDx1 (Khoshnan et al., 2002, 2004). Trimerization of IKKγ is a prerequisite for IKK activation (Agou et al., 2002). We find that soluble mutant HDx1 promotes the assembly of an SDS-resistant IKKγ trimer in a human neuronal model (Fig. 2, Khoshnan et al., 2009). Binding of HDx1 to IKKγ may act as a nucleation signal to recruit other IKK subunits to form an active complex. Thus, the ability of mutant HDx1 to directly activate the IKK complex may be the underlying cause of widespread IKKβ activity and neuroinflammation observed in the CNS of R6/2 HD mice (Ona et al., 1999; Khoshnan et al., 2004; Björkqvist et al., 2008). On the other hand, in a presymptomatic knock-in mouse model of HD (HdhQ150), which expresses full-length mutant Htt, elevated IKKβ activity is only detected in the striatum, a primary target of mutant Htt toxicity. Full-length mutant Htt is incapable of activating the IKKβ, however HDx1 accumulates gradually in the brain of HdhQ150 (Khoshnan et al., 2004; Landles et al., 2010). Selective sensitivity of the striatum to environmental insults may trigger the generation of HDx1 and activate IKKβ locally in HdhQ150. HDx1 also accumulates in various parts of HD brains and potentially other tissues (Kim et al., 2001), which may aberrantly activate IKKβ. While acute and regulated activation of IKKβ may be protective and essential for physiological homeostasis, chronic stimulation by the gradual build up of HDx1 could lead to abnormalities such as neuroinflammation and potentially neurodegeneration in HD.

IKKs regulate the cleavage of Htt

The cleavage of Htt by proteolytic enzymes is a pivotal step in the pathogenesis of HD. N-terminal fragments with the expanded polyQ repeat are more toxic than full-length mutant Htt in cellular and animal models of HD and cleavage of full-length mutant Htt is a prerequisite for the onset of symptoms in certain models. For example, inactivation of the caspase-6 cleavage site of mutant Htt abrogates neuropathology in YAC-128 HD mice (Graham et al., 2006). However, other caspases and calpains are also known to cleave Htt and potentially produce neurotoxic N-terminal fragments (Zuccato and Cattaneo, 2010). Factors that induce the cleavage of Htt are not well characterized, however both genetic and environmental modifiers are expected to play a role. One potential environmental factor,

which may influence HD progression, is the gradual accumulation of DNA damage in aging brain (Katyal and McKinnon, 2008). Indeed, HD patients contain abnormal levels of DNA damage in the brain and reduction of WT Htt levels as occurs in HD patients, lowers neuronal resiliency to DNA damaging agents (Butterworth et al., 1998; Bae et al., 2005; Anne et al., 2007). In search of factors that could trigger the cleavage of Htt, we discovered that exposure of human neurons to DNA damaging agents promotes caspase-dependent cleavage of both WT and mutant Htt (Khoshnan et al., 2009). Interestingly, Htt cleavage induced by DNA damage is IKKβ-dependent. Knockdown of IKKβ expression with shRNAs or blocking its activity with small molecule inhibitors reduces caspase activation and subsequent Htt cleavage (Khoshnan et al., 2009). IKKβ phosphorylates Bcl-xL, which promotes its degradation in neurons exposed to DNA damaging agents. The reduction of Bcl-xL triggers caspases that can cleave Htt (Fig. 3). WT Htt is also cleaved in cells exposed to inflammatory cytokines (Zhang et al., 2006; Thompson et al., 2009). In neurons, WT Htt regulates many important functions including cell survival, BDNF expression, neurogenesis and protection from genotoxic stress (Godin et al., 2010; Zuccato and Cattaneo, 2010). IKKβ may therefore contribute to neurodegeneration by lowering and inactivating WT Htt. At the same time, IKKβ-dependent cleavage of mutant Htt can produce substrates for further processing that generates neurotoxic oligomeric species (Ratovitski et al., 2009). Thus, IKKβ may trigger some of the earliest events in HD pathology in mouse models.

Knockdown of IKKβ expression also reduces the toxic effects of DNA damage and enhances neuronal survival. IKKβ is a key regulator of the DNA-damage response and a determinant of cell survival (Wu et al., 2006; Wu and Miyamoto, 2008). In ischemia and genotoxic stress, the IKK/NF-κB activation promotes the expression apoptotic genes such as Noxa and Bim (Inta et al., 2006; Wu and Miyamoto, 2008). DNA damage also promotes the production of the inflammatory cytokine IL-6, which is likely to be IKKβ-dependent and is elevated early in presymptomatic HD (Björkqvist et al., 2008; Rodier et al., 2009). While proliferating cells are equipped to repair DNA damage, post-mitotic neurons undergo cell cycle activation and apoptosis when exposed to DNA damaging agents (Kruman et al., 2004; Kim and Tsai, 2009). It is intriguing that knockdown expression of IKKβ in post-mitotic human neurons prevents DNA damage-induced incorporation of BrdU, a marker of DNA synthesis (Fig. 4). Reduction of IKKβ also inhibits the activation of pro-apoptotic caspases (Khoshnan et al., 2009). Thus, IKKβ represents an interesting target to prevent neuronal loss by DNA damage as it may occur with aging brain.

While IKKβ promotes Htt cleavage, IKKα has the opposite effect. DNA damage lowers the activity of IKKα in human neurons and elevating IKKα prevents DNA damage-induced caspase activation and Htt cleavage (Khoshnan et al., 2009). IKKα is known to inhibit the activity of IKKβ in various models (Chariot, 2009). For example, knockdown of IKKα enhances the IKKβ-dependent expression of proinflammatory cytokines in immune cells (Li et al., 2005). Thus, we predict that the protective effect of IKKα on Htt cleavage may involve inhibition of IKKβ. However, IKKα also influences other signaling pathways that are neuroprotective. IKKα phosphorylates and promotes the activity of CREB binding protein (CBP) and histone-3 (Anest et al., 2003; Huang et al., 2007). The ability of IKKα to modify histone-3 and CBP activity is important in memory reconsolidation and thus synaptogenesis in the hippocampus (Lubin and Sweatt, 2007). CBP regulates the expression of important neuronal genes including BDNF, which is induced by IKKα (Greer and Greenberg, 2008; Khoshnan and Patterson, in preparation). Considering that both CBP activity and BDNF expression are reduced in HD brains (Zuccato and Cattaneo, 2010), factors that enhance IKKα activity may have neuroprotective properties. This is contrary to the effects IKKβ on Htt cleavage and promotion of inflammation in the CNS. Thus, changes in the homeostasis of the IKKs may be critical determinants of Htt cleavage, neuroinflammation, and neuronal survival in paradigms such as DNA damage.

The role of IKK in Htt phosphorylation

The N-terminal 17 amino acid motif of Htt is essential for intracellular localization, turnover, and neurotoxicity (Zuccato and Cattaneo, 2010). Recent studies indicate that IKK can phosphorylate two Ser residues (S13 and S16) of Htt and potentially enhance the turnover of WT HDx1 in culture models. Moreover, overexpression and cytokine-induced activation of IKKβ in rat striatal precursor cells promote the cleavage of WT Htt and generate phosphorylated fragments of various lengths, which may be eliminated by autophagy (Thompson et al., 2009). Abnormal IKKβ-mediated phosphorylation and turnover of WT Htt may become detrimental, however, since WT Htt is important for neuronal survival and BDNF expression (Zuccato and Cattaneo, 2010). An example is the DNA damage-induced activation of IKKβ, which promotes cleavage and depletion of WT Htt (Khoshnan et al., 2009; Fig. 3). Interestingly, IKKβ has no effect on the turnover of mutant HDx1 and indeed phosphorylated mutant HDx1 accumulates in the nucleus, which could promote neurotoxicity (Thompson et al., 2009). Recent studies indicate that mutant HDx1 phosphorylated at Ser16 selectively accumulates in the nucleus of striatal neurons, impairs nuclear export, and correlates with disease progression (Havel et al., 2011). Thus, IKKβ-mediated phosphorylation of mutant Htt may contribute to disease progression.

On the contrary, Truant et al. (personal communication) recently reported that inhibition of IKKβ by small molecules or shRNAs enhances the phosphorylation of Htt at its N-terminus without affecting its turnover. While these opposing effects of IKKβ on Htt phosphorylation requires further clarification, it is intriguing that phospho-mimetic of Ser13 and Ser16 in full-length mutant Htt imparts neuroprotection and ameliorates symptoms in HD mice (Gu et al., 2009). However, it is unclear whether IKKβ affects the phosphorylation of Htt *in vivo* or if these mutations affect Htt stability, intracellular transport, cleavage and oligomerization. The rescue of pathology by mimicking phosphorylation and the findings that IKKβ inhibition could promote the phosphorylation of Htt further support the notion that IKKβ activation may be detrimental (Gu et al., 2009, Truant et al., unpublished data). IKKβ induced by elevated cytokines and abnormal levels of DNA damage could accelerate the cleavage and turnover of WT Htt and deplete neurons of this pro-survival protein (Khoshnan et al., 2009; Thompson et al., 2009). On the other hands if IKKβ phosphorylates mutant Htt, it may promote the nuclear accumulation of HDx1and induce pathology (Thompson et al., 2009; Havel et al., 2011). Thus, further studies such as generating HD mice with deleted IKKβ in the CNS should reveal important information about the role of IKKβ in Htt phosphorylation and HD pathology.

The therapeutic potential of IKKβ in HD

The prevailing evidence indicates that suppressing IKKβ activity may impede disease progression in HD. Inhibition of IKKβ may lower neuroinflammation and the production of inflammatory cytokines, which are considered as important modifiers of HD progression (Björkqvist, et al., 2008). IKKβ-dependent neuroinflammation is also implicated in PD and AD and is mediated by caspases known to cleave Htt (Khoshnan et al., 2009; Burguillos et al., 2011). Thus, lowering IKKβ activity may dampen the toxic effects of neuroinflammation, which is a component of several neurodegenerative disorders (Glass et al., 2010). For HD, blocking of IKKβ activity should also decrease the cleavage of WT and mutant Htt and slow down the accumulation of oligomeric toxic fragments and neuronal death induced by genotoxic insults (Khoshnan et al., 2009; Thompson et al., 2009). Moreover, inhibitors of IKKβ reduce the neurotoxicity of HDx1 in a brain slice culture model of HD by yet an unknown mechanism (D. Lo et al. personal communication; Khoshnan et al., 2004). Elevation of IKKβ activity appears to promote nuclear localization of HDx1 an event, which enhances neurotoxicity (Khoshnan et al., 2004; Thompson et al.,

2009; Zuccato and Cattaneo, 2010). Thus, exploring the effects of IKKβ inhibitors in animal models of HD could lead to development of novel therapeutics.

While numerous IKKβ inhibitors are available, their neuroprotective effects in disease models are not well understood. Encouraging results have been obtained with a NEMO Binding Domain (NBD) peptide, which corresponds to the C-terminus of IKKβ and disrupts the binding of IKKγ to IKKβ, preventing the assembly of an active complex (Madge and May, 2009). Systemic administration of NBD blocks neurodegeneration, impedes microglial activation in the substantia nigra, and improves motor function in a chemical mouse model of PD (Ghosh et al., 2007). Subcutaneous injection of a selective inhibitor of IKKβ also protects dopaminergic neurons from LPS-induced neurotoxicity (Zhang et al., 2010). Moreover, CNS delivery of a small molecule inhibitor of IKKβ (BMS-345541) impedes neurodegeneration in an ischemia model (Herrmann et al., 2005). NBD, chemical, and genetic inhibition of IKKβ prevents degeneration of medium-sized spiny neurons induced by a mutant HDx1 (Khoshnan et al., 2004, D. Lo et al., personal communication). We have identified IKKβ inhibitors including the NBD peptide, which block DNA damage-induced Htt cleavage, and improve survival in a human neuronal model (A. Khoshnan et al., unpublished data). Interestingly, these IKKβ inhibitors also block caspase-6 activation, which is a prominent enzyme in the pathogenesis of HD (Graham et al., 2006; Khoshnan et al., 2009). These findings warrant the evaluation of IKKβ inhibitors in HD animal models. Several IKK inhibitors have entered clinical trials for their effects on malignancy (Lee and Hung, 2008). These studies should reveal their safety and potency in human subjects and potentially facilitate their application in HD patients. Considering the elevated levels of inflammatory cytokines in the serum and CNS of pre-symptomatic HD patients (Björkqvist et al., 2008), it will be interesting to see whether early systemic delivery of IKKβ inhibitors could affect the age of onset and disease progression in HD animal models.

The long-term systemic application of IKKβ inhibitors however, may produce undesired side effects considering the importance of IKKβ in immune cell development and survival (Hacker and Karin, 2006). Thus, strategies should be developed to selectively inhibit IKKβ in the brain. An interesting therapeutic strategy is to knockdown the expression of IKKβ in the CNS by delivery of shRNAs, synthetic miRNAs, or anti-sense oligonucleotides (Boudreau and Davidson, 2010). It is notable that deleting IKKβ in the CNS of mice has no visible effect on neurodevelopment, growth, and indeed ameliorates neurodegeneration in ischemia and MS models (Herrmann et al., 2005; Van Loo et al., 2006). Moreover, reduction of IKKβ in the CNS prevents demylination induced by neurotoxic agents (Raasch et al., 2011). Thus, long-term inhibition of IKKβ in the CNS may not carry major deleterious side effects. Silencing IKKβ expression is protective in human neurons exposed to toxic agents and prevents the activation of caspases, which cleave WT Htt (Khoshnan et al., 2009; Thompson et al., 2009). Testing such strategies in animal models of HD are worthy of investigation for efficacy, delivery and potential side effects.

Conclusions

While the role of IKKβ in regulating NF-κB and promoting inflammation is well characterized, elucidating NF-κB-independent functions of IKKβ in the CNS and their effects on neurodegeneration remains an important area of investigation. For HD, future studies should focus on ablating IKKβ in the CNS of animal models and observing disease progression. This will elucidate whether disrupting the local activity of IKKβ in the CNS will affect the age of onset and HD progression. The presence of systemic inflammation in HD years before the onset of symptoms is indicative of deregulated IKKβ in the immune cells and possibly other organs. Characterizing the role of IKKβ in the immune system of HD patients may provide insights into the complex nature of IKKβ/Htt interaction and how

dysregulation in this molecular switch may contribute to the development of early systemic inflammation. The role of IKKβ in regulating the phosphorylation of Htt is intriguing and further studies are needed to unravel this aspect of IKKβ in the neurobiology of Htt. Truant et al. (personal communication), find that phospho-mimetics of Ser13 and Ser16 in the mutant HDx1 induce a conformation that is less amenable to oligomerization and thus, less toxicity. Further studies should uncover novel targets and a more efficacious route for therapy and early intervention.

While these studies will take several years to accomplish, it is feasible to immediately implement behavioral changes in HD patients, which could reduce IKKβ activity systemically and possibly lower the level of pro-inflammatory cytokines. One possible avenue for therapy involves diet. It is known that daily food intake is substantially higher in HD patients than in the normal population (Trejo et al., 2004). Moreover, excess food intake, particularly high fat diet, is associated with IKKβ-dependent neuroinflammation, insulin tolerance, hypothalamic deregulation, and abnormal production of inflammatory mediators in the CNS (Zhang et al., 2008). Thus, formulating diets enriched in natural compounds with anti-inflammatory properties may help HD patients. Such modifications are risk-free and may help to delay the onset and progression of HD.

References

Agou F, Ye F, Goffinont S, Courtois G, Yamaoka S, Israël A, et al. NEMO trimerizes through its coiled-coil C-terminal domain. J. Biol. Chem. 2002; 277:17464–17475. [PubMed: 11877453]

Anest V, Hanson JL, Cogswell PC, Steinbrecher KA, Strahl BD, Baldwin AS. A nucleosomal function for IkappaB kinase-alpha in NF-kappaB-dependent gene expression. Nature. 2003; 423:659–663. [PubMed: 12789343]

Anne SL, Saudou F, Humbert S. Phosphorylation of huntingtin by cyclin-dependent kinase 5 is induced by DNA damage and regulates wild type and mutant huntingtin toxicity in neurons. J. Neurosci. 2007; 27:7318–7328. [PubMed: 17611284]

Bae BI, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, et al. p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. Neuron. 2005; 47:29–41. [PubMed: 15996546]

Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, et al. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J. Exp. Med. 2008; 205:1869–1877. [PubMed: 18625748]

Boudreau RL, Davidson BL. RNAi therapeutics for CNS disorders. Brain Res. 2010; 1338:112–121. [PubMed: 20307511]

Burguillos MA, Deierborg T, Kavanagh E, Persson A, Hajji N, Garcia-Quintanilla A, et al. Caspase signaling controls microglia activation and neurotoxicity. Nature. 2011 Mar 9. [Epub ahead of print].

Butterworth NJ, Williams L, Bullock JY, Love DR, Faull RL, Dragunow M. Trinucleotide (CAG) repeat length is positively correlated with the degree of DNA fragmentation in Huntington's disease striatum. Neuroscience. 1998; 87:49–53. [PubMed: 9722140]

Chariot A. The NF-kappaB-independent functions of IKK subunits in immunity and cancer. Trends Cell Biol. 2009; 19:404–413. [PubMed: 19648011]

Cho IH, Hong J, Suh EC, Kim JH, Lee H, Lee JE, et al. Role of microglial IKK beta in kainic acid-induced hippocampal neuronal cell death. Brain. 2008; 131:3019–3033. [PubMed: 18819987]

Ghosh A, Roy A, Liu X, Kordower JH, Mufson EJ, Hartley DM, et al. Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 2007; 104:18754–18759. [PubMed: 18000063]

Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010; 140:918–934. [PubMed: 20303880]

Godin JD, Colombo K, Molina-Calavita M, Keryer G, Zala D, et al. Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis. Neuron. 2010; 67:392–406. [PubMed: 20696378]

Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. Cell. 2006; 125:1179–1191. [PubMed: 16777606]

Greer PL, Greenberg ME. From synapse to nucleus: calcium-dependent gene transcription in the control of synapse development and function. Neuron. 2008; 59:846–860. [PubMed: 18817726]

Gu X, Greiner ER, Mishra R, Kodali R, Osmand A, Finkbeiner S, et al. Serines 13 and 16 are critical determinants of full-length human mutant huntingtin induced disease pathogenesis in HD mice. Neuron. 2009; 64:828–840. [PubMed: 20064390]

Hacker H, Karin M. Regulation and function of IKK and IKK-related kinases. Sci. STKE. 2006; 357:re13. [PubMed: 17047224]

Havel LS, Wang CE, Wade B, Huang B, Li S, Li XJ. Preferential accumulation of N-terminal mutant huntingtin in the nuclei of striatal neurons is regulated by phosphorylation. Hum. Mol. Genet. 2011; 20:1424–1437. [PubMed: 21245084]

Herrmann O, Baumann B, de Lorenzi R, Muhammad S, Zhang W, Kleesiek J, et al. IKK mediates ischemia-induced neuronal death. Nat. Med. 2005; 11:1322–1329. [PubMed: 16286924]

Huang WC, Ju TK, Hung MC, Chen CC. Phosphorylation of CBP by IKKalpha promotes cell growth by switching the binding preference of CBP from p53 to NF-kappaB. Mol. Cell. 2007; 26:75–87. [PubMed: 17434128]

Inta I, Paxian S, Maegele I, Zhang W, Pizzi M, Spano P, et al. Bim and Noxa are candidates to mediate the deleterious effect of the NF-kappa B subunit RelA in cerebral ischemia. J. Neurosci. 2006; 26:12896–12903. [PubMed: 17167080]

Kaltschmidt B, Widera D, Kaltschmidt C. Signaling via NF-kappaB in the nervous system. Biochim. Biophys. Acta. 2005; 1745:287–299. [PubMed: 15993497]

Katyal S, McKinnon PJ. DNA strand breaks, neurodegeneration and aging in the brain. Mech. Ageing Dev. 2008; 129:483–491. [PubMed: 18455751]

Khoshnan A, Patterson PH. IKKα regulates MeCP2 activity and the expression of BDNF. in preparation.

Khoshnan A, Ko J, Patterson PH. Effects of intracellular expression of anti-huntingtin antibodies of various specificities on mutant huntingtin aggregation and toxicity. Proc. Natl. Acad. Sci. U. S. A. 2002; 99:1002–1007. [PubMed: 11792860]

Khoshnan A, Ko J, Watkin EE, Paige LA, Reinhart PH, Patterson PH. Activation of the IkappaB kinase complex and nuclear factor-kappaB contributes to mutant huntingtin neurotoxicity. J. Neurosci. 2004; 24:7999–8008. [PubMed: 15371500]

Khoshnan A, Ko J, Tescu S, Brundin P, Patterson PH. IKKα and IKKβ regulation of DNA damage-induced cleavage of huntingtin. PLoS One. 2009; 4:e5768. [PubMed: 19488402]

Kim D, Tsai LH. Linking cell cycle reentry and DNA damage in neurodegeneration. Ann. N.Y. Acad. Sci. 2009; 1170:674–679. [PubMed: 19686210]

Kim YJ, Yi Y, Sapp E, Wang Y, Cuiffo B, Kegel KB, et al. Caspase 3-cleaved N-terminal fragments of wild-type and mutant huntingtin are present in normal and Huntington's disease brains, associate with membranes, and undergo calpain-dependent proteolysis. Proc. Natl. Acad. Sci. U. S. A. 2001; 98:12784–12789. [PubMed: 11675509]

Kruman II, Wersto RP, Cardozo-Pelaez F, Smilenov L, Chan SL, Chrest FJ, et al. Cell cycle activation linked to neuronal cell death initiated by DNA damage. Neuron. 2004; 41:549–556. [PubMed: 14980204]

Landles C, Sathasivam K, Weiss A, Woodman B, Moffitt H, Finkbeiner S, et al. Proteolysis of mutant huntingtin produces an exon 1 fragment that accumulates as an aggregated protein in neuronal nuclei in Huntington disease. J. Biol. Chem. 2010; 285:8808–8823. [PubMed: 20086007]

Lee DF, Hung MC. Advances in targeting IKK and IKK-related kinases for cancer therapy. Clin. Cancer Res. 2008; 14:5656–5662. [PubMed: 18794072]

Li Q, Lu Q, Bottero V, Estepa G, Morrison L, Mercurio F, Verma IM. Enhanced NF-kappaB activation and cellular function in macrophages lacking IkappaB kinase 1 (IKK1). Proc. Natl. Acad. Sci. U. S. A. 2005; 102:12425–12430. [PubMed: 16116086]

Lubin FD, Sweatt JD. The IkappaB kinase regulates chromatin structure during reconsolidation of conditioned fear memories. Neuron. 2007; 55:942–957. [PubMed: 17880897]

Madge LA, May MJ. Inhibiting proinflammatory NF-kappaB signaling using cell penetrating NEMO binding domain peptides. Methods Mol. Biol. 2009; 512:209–232. [PubMed: 19347279]

Maruyama H, Morino H, Ito H, Izumi Y, Kato H, Watanabe Y, et al. Mutations of optineurin in amyotrophic lateral sclerosis. Nature. 2010; 465:223–226. [PubMed: 20428114]

Mattson MP, Meffert MK. Roles for NF-kappaB in nerve cell survival, plasticity, and disease. Cell Death Differ. 2006; 13:852–860. [PubMed: 16397579]

Ona VO, Li M, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, et al. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. Nature. 1999; 399:263–267. [PubMed: 10353249]

Raasch J, Zeller N, van Loo G, Merkler D, Mildner A, Erny D, Knobeloch KP, et al. I{kappa}B kinase 2 determines oligodendrocyte loss by non-cell-autonomous activation of NF-{kappa}B in the central nervous system. Brain. 2011; 134:1184–1198. [PubMed: 21310728]

Ratovitski T, Gucek M, Jiang H, Chighladze E, Waldron E, D'Ambola J, et al. Mutant huntingtin N-terminal fragments of specific size mediate aggregation and toxicity in neuronal cells. J. Biol. Chem. 2009; 284:10855–10867. [PubMed: 19204007]

Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Muñoz DP, Raza SR, et al. Persistent DNA damage signaling triggers senescence-associated inflammatory cytokine secretion. Nat. Cell Biol. 2009; 11:973–979. [PubMed: 19597488]

Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, et al. A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell. 2009; 137:47–59. [PubMed: 19345186]

Silvestroni A, Faull RL, Strand AD, Möller T. Distinct neuroinflammatory profile in post-mortem human Huntington's disease. Neuroreport. 2009; 20:1098–10103. [PubMed: 19590393]

Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, et al. Microglial activation in presymptomatic Huntington's disease gene carriers. Brain. 2007; 130:1759–1766. [PubMed: 17400599]

The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72:971–983. [PubMed: 8458085]

Thompson LM, Aiken CT, Kaltenbach LS, Agrawal N, Illes K, Khoshnan A, et al. IKK phosphorylates Huntingtin and targets it for degradation by the proteasome and lysosome. J. Cell Biol. 2009; 187:1083–1099. [PubMed: 20026656]

Trejo A, Tarrats RM, Alonso ME, Boll MC, Ochoa A, Velásquez L. Assessment of the nutrition status of patients with Huntington's disease. Nutrition. 2004; 20:192–196. [PubMed: 14962685]

Van Loo G, De Lorenzi R, Schmidt H, Huth M, Mildner A, Schmidt-Supprian M, et al. Inhibition of transcription factor NF-kappaB in the central nervous system ameliorates autoimmune encephalomyelitis in mice. Nat. Immunol. 2006; 7:954–961. [PubMed: 16892069]

Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proc. Natl. Acad. Sci. U. S. A. 2004; 101:3498–3503. [PubMed: 14993615]

Wu ZH, Miyamoto S. Induction of a pro-apoptotic ATM–NF-kappaB pathway and its repression by ATR in response to replication stress. EMBO J. 2008; 27:1963–1973. [PubMed: 18583959]

Wu ZH, Shi Y, Tibbetts RS, Miyamoto S. Molecular linkage between the kinase ATM and NF-kappaB signaling in response to genotoxic stimuli. Science. 2006; 311:1141–1146. [PubMed: 16497931]

Zhang Y, Leavitt BR, van Raamsdonk JM, Dragatsis I, Goldowitz D, MacDonald ME, et al. Huntingtin inhibits caspase-3 activation. EMBO J. 2006; 25:5896–5906. [PubMed: 17124493]

Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell. 2008; 135:61–73. [PubMed: 18854155]

Zhang F, Qian L, Flood PM, Shi JS, Hong JS, Gao HM. Inhibition of IkappaB kinase-beta protects dopamine neurons against lipopolysaccharide-induced neurotoxicity. J. Pharmacol. Exp. Ther. 2010; 333:822–833. [PubMed: 20190013]

Zhu G, Wu CJ, Zhao Y, Ashwell JD. Optineurin negatively regulates TNFalpha-induced NF-kappaB activation by competing with NEMO for ubiquitinated RIP. Curr. Biol. 2007; 17:1438–1443. [PubMed: 17702576]

Zuccato C, Cattaneo E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol. Rev. 2010; 90:905–981. [PubMed: 20664076]

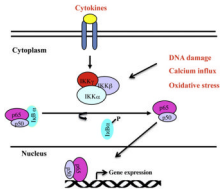

Fig. 1.

A schematic representation of canonical of IKK activation. The IKK complex is stimulated from outside by factors like cytokines binding to the cell surface receptors and internally by oxidative stress and DNA damage. Activated IKK phosphorylates IκBα, which promotes its dissociation and degradation, liberating NF-κB to enter the nucleus and regulate gene expression (Hacker and Karin, 2006).

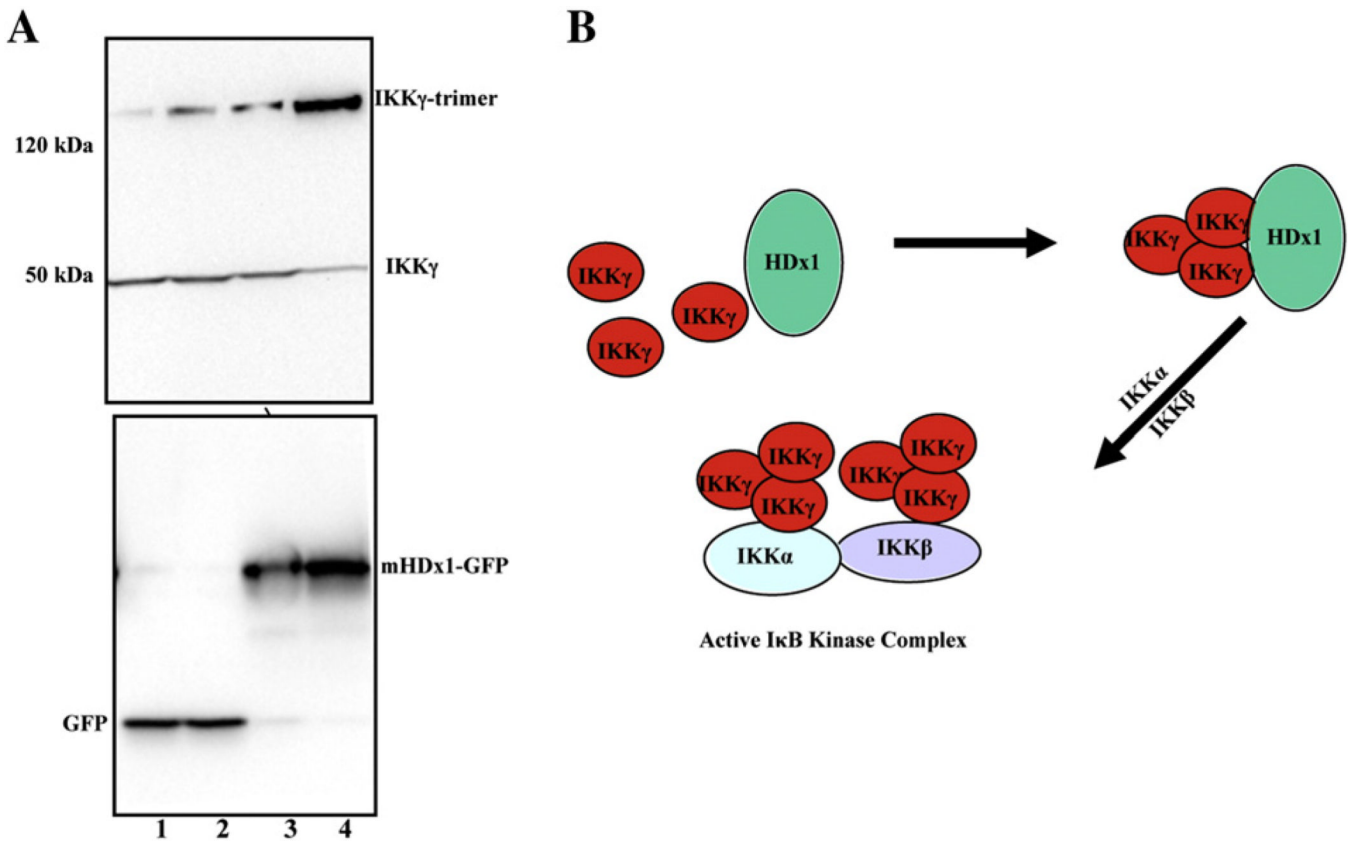

Fig. 2.

HDx1 promotes trimerization of IKKγ. (A). MESC2.10 neuroblasts (Khoshnan et al., 2009) were transduced with a lentivirus expressing EGFP or mutant HDx1-EGFP and induced to differentiate. Accumulation of HDx1-EGFP in differentiating neurons promotes the accumulation of an SDS-resistant IKKγ trimer and reduction of monomeric form (lanes 3 and 4, days 6 and 9 post-differentiation, respectively). Lanes 1 and 2 are for control neurons expressing only GFP. Part B is a schematic depicting how trimerization of IKKγ by HDx1 may induce the assembly of an active IKK complex.

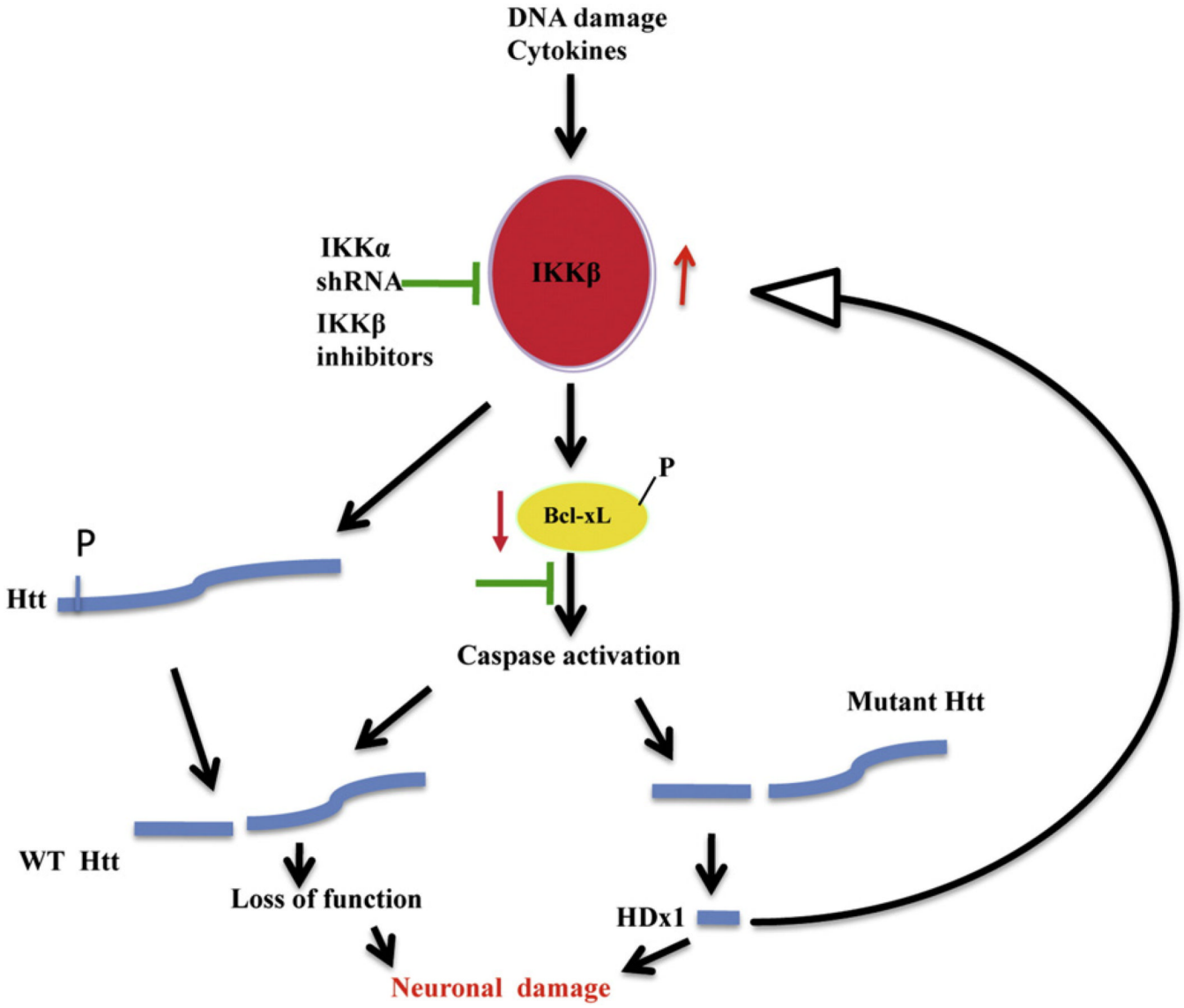

Fig. 3.

A schematic diagram illustrates the signaling pathway for IKKβ-mediated Htt proteolysis. DNA damage or cytokines activate IKKβ, which can phosphorylate Bcl-xL and reduce its level. Reduction of Bcl-xL levels triggers the activation of caspases, which cleave Htt. Inhibition of IKKβ or elevation IKKα and Bcl-xL prevent Htt proteolysis. N-terminal fragments of mutant HDx1 could further stimulate IKKβ by direct binding to the IKK complex (Khoshnan et al., 2004). These interactions could form a persistent cycle of IKK activation and Htt cleavage.

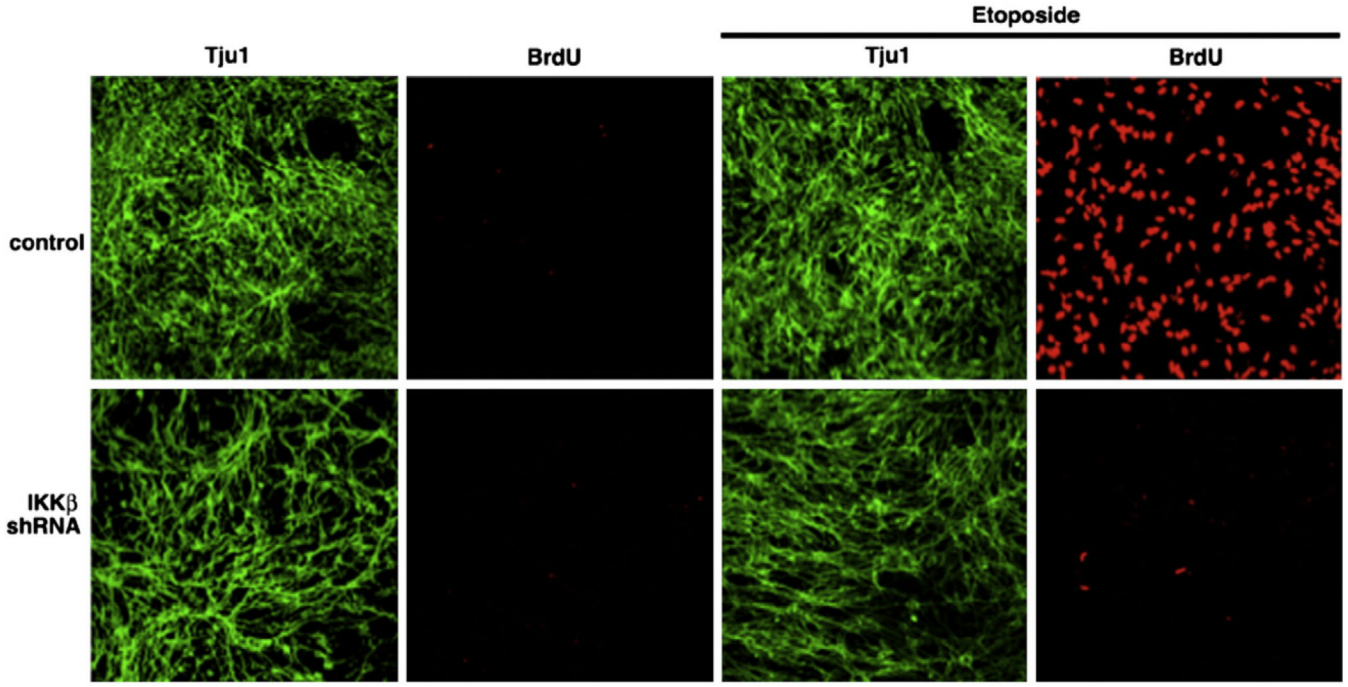

Fig. 4.

Inhibition of IKKβ prevents DNA damage-induced BrdU incorporation in MESC2.10 neurons. Day 6 differentiated neurons on coverslips were treated with 10 μM etoposide for 4 h in the presence of BrdU (1 mM). Details on these neurons are described in Khoshnan et al. (2009). BrdU incorporation was detected by immunohistochemistry (red). Neurons were stained with neuronal marker Tuj-1 (green). Pictures were captured with a confocal microscope.