

Review

Kinase Signalling in Huntington's Disease

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Abstract. Alterations in numerous signal transduction pathways and aberrant activity of specific kinases have been identified in multiple cell and mouse models of Huntington's disease (HD), as well as in human HD brain. The balance and integration of a network of kinase signalling pathways is paramount for the regulation of a wide range of cellular and physiological processes, such as proliferation, differentiation, inflammation, neuronal plasticity and apoptosis. Unbalanced activity within these pathways provides a potential mechanism for many of the pathological phenotypes associated with HD, such as transcriptional dysregulation, inflammation and ultimately neurodegeneration. The characterisation of aberrant kinase signalling regulation in HD has been inconsistent and may be a result of failure to consider integration between multiple signalling pathways, as well as alterations that may occur over time with both age and disease progression. Collating the information about the effect of mHTT on signalling pathways demonstrates that it has wide ranging effects on multiple pro- and anti-apoptotic kinases, resulting in the dysregulation of numerous complex interactions within a dynamic network.

Keywords: Huntington's disease, kinase signalling, inflammation, pro-survival, pro-apoptotic, AKT, MEK/ERK, CDK5/P35, MAPKs, P53, IKK

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant monogenic neurodegenerative disorder caused by an expanded CAG repeat in the *huntingtin* (*HTT*) gene, resulting in a mutant HTT (mHTT) protein carrying an expanded polyglutamine (polyQ) repeat on exon1. HD is characterised primarily by motor disturbances, but is commonly accompanied by cognitive impairments and psychiatric abnormalities [1–5]. Progressive striatal neurodegeneration is a hallmark of HD that can be identified prior to motor symptom onset, however there is evidence for widespread neuropathology in HD brain, including degeneration of cortical and subcortical structures [4, 6–8]. mHTT neuronal intranuclear inclusions (NIIs) can be found throughout vulnerable neuronal populations in HD brain [9, 10], however whether these may play a protective or damaging role within the cell remains to be elucidated [11, 12].

Protein kinases have the ability to phosphorylate other proteins in order to regulate their function, and are responsible for the mediation of signal transduction as well as regulating multiple downstream effects [13, 14]. Numerous kinase signalling pathways are thought to contribute to HD pathophysiology. They are known to counter toxic metabolic changes induced by mHTT and help to maintain neuronal survival [15, 16]. Alterations in kinase signalling are also likely to have implications for the maintenance of the chronic neuroinflammation observed in HD [17–19], and the regulation of transcription, a central mechanism contributing to HD pathogenesis [20–25], either by direct regulation or through the phosphorylation of other proteins [26–36]. mHTT is able to alter signalling events both upstream and downstream of multiple pro-survival and pro-apoptotic pathways, and therefore predicting patterns of signal transduction and cell fate is challenging [37]. Furthermore, a single pathway can elicit multiple effects, and may have both pro-survival and pro-apoptotic functions, dependent on tissue and cell type, subcellular localisation, the intensity and duration of its activation, and the presence of additional signalling mediators [38]. To date,

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the characterisation of kinase signalling in models of HD has been inconsistent, which may be a result of variability in experimental design or technique and the consideration of individual pathways in isolation away from integrative signalling networks. The kinase signalling pathways most commonly investigated in HD are discussed in this review; a representation of how they interact to form a broader, more complex signalling network can be found in Fig. 1, and a schematic detailing the overlapping effects of mHTT on pro-survival and pro-apoptotic pathways can be found in Fig. 8.

PRO-SURVIVAL PATHWAYS

MEK/ERK pathway

The mitogen activated protein kinase/extracellular signal-related kinase (MEK/ERK) pathway is a strong mediator of anti-apoptotic and pro-survival signalling [39] and is part of the mitogen activated protein kinase (MAPK) signalling cascade (Fig. 2). RAS- guanosine diphosphate (GDP) is converted into its active form RAS- guanosine triphosphate (GTP) by activation of receptor tyrosine kinases. RAS-GTP then activates MAPK kinase members of the RAF kinase family, which phosphorylates the dual specificity kinase MEK1/2 (a MAPK kinase), which in turn phosphorylates threonine and tyrosine residues in ERK1/2 (a MAPK) [32, 40]. Activated ERKs are present in the cytoplasm, where they may regulate the activity of additional kinases, receptors and signalling pathways, or may translocate to the nucleus in order to phosphorylate transcription factors [31, 32].

ERK signalling mediates neuroprotection following diverse neuronal insults, such as excitotoxicity, DNA damage and hypoxia [41, 42]. The phosphorylation of ERK activates neuroprotective factors [26, 33, 43] and inactivates pro-apoptotic mediators by phosphorylation [44] or by targeting for ubiquitin-mediated proteolysis [45]. Correct regulation of this pathway is also critical for neuronal development: [46–48] and for the regulation of gliogenesis in the developing cortex [49]. Inhibition of MEK1/2 and ERK has been found to block the induction of brain derived neurotrophic factor (BDNF)-regulated genes [50], thus implicating this pathway as an important regulator of BDNF-induced transcriptional regulation. MEK inhibition was found to abrogate the protective effect of BDNF stimulation in the *StHdh^{Q111}* immortalised cell model of HD [16], and ERK signalling has been identified as an integra-

tion point for BDNF and glutamate signalling [37]. The MEK/ERK pathway is therefore likely to act as a key downstream modulator of BDNF activity.

The MEK/ERK signalling pathway is typically considered to be neuroprotective; consistent with this idea is the observation of its downregulation in neurodegenerative conditions such as ischemia [51] and traumatic spinal cord injury [52]. However, the role of MEK and ERK signalling in neuronal protection may depend on cellular context, such as cell type, tissue, the trigger of cellular insult and interactions with other signalling pathways [53, 54]. The activation of ERK has been demonstrated to be detrimental to neurons in models of Alzheimer's disease (AD) and Parkinson's disease (PD) [55, 56], therefore MEK/ERK pathway activation may be able to facilitate apoptosis in particular cellular contexts, and the duration of activation may influence whether neurons enter a pro-survival or pro-apoptotic program [57, 58].

MEK & ERK in models of HD

As MEK and ERK activity plays a role in striatal transcriptional regulation and regulation of the BDNF-mediated cellular response [16, 33, 37, 50], these pathways have been investigated as potential neuroprotective modulators of HD pathology [26, 59]. Overexpression of constitutively active MEK and subsequently enhanced ERK activity has been correlated with the reduction of caspase-3 activation in a PC12 model of HD [26], which is likely to be protective due to the predicted attenuation of caspase-regulated cleavage of mHTT into toxic fragments [60–62]. Reduced ERK phosphorylation due to mHTT-associated mechanisms has also been found to decrease ERK-dependent expression of glutamate transporters in *Drosophila*, increasing glutamate signalling and toxicity in neighbouring cells [63]. In addition, ERK has been implicated in synaptic plasticity and memory, which may be relevant to the deficits seen in HD transgenic mouse models [64–68].

Despite the evidence suggesting a significant neuroprotective effect of enhanced MEK/ERK activity in HD, there is disagreement about whether there is enhanced basal activity within this pathway in models of HD, or whether there is a reduction in activity in this pathway as a consequence of mHTT-induced cellular disruption. Table 1 summarises the disparity in the characterisation of MEK and ERK phosphorylation between multiple models of HD. Whether this inconsistency results from differences between the expression of full length or truncated forms of mHTT remains unclear; full length HTT

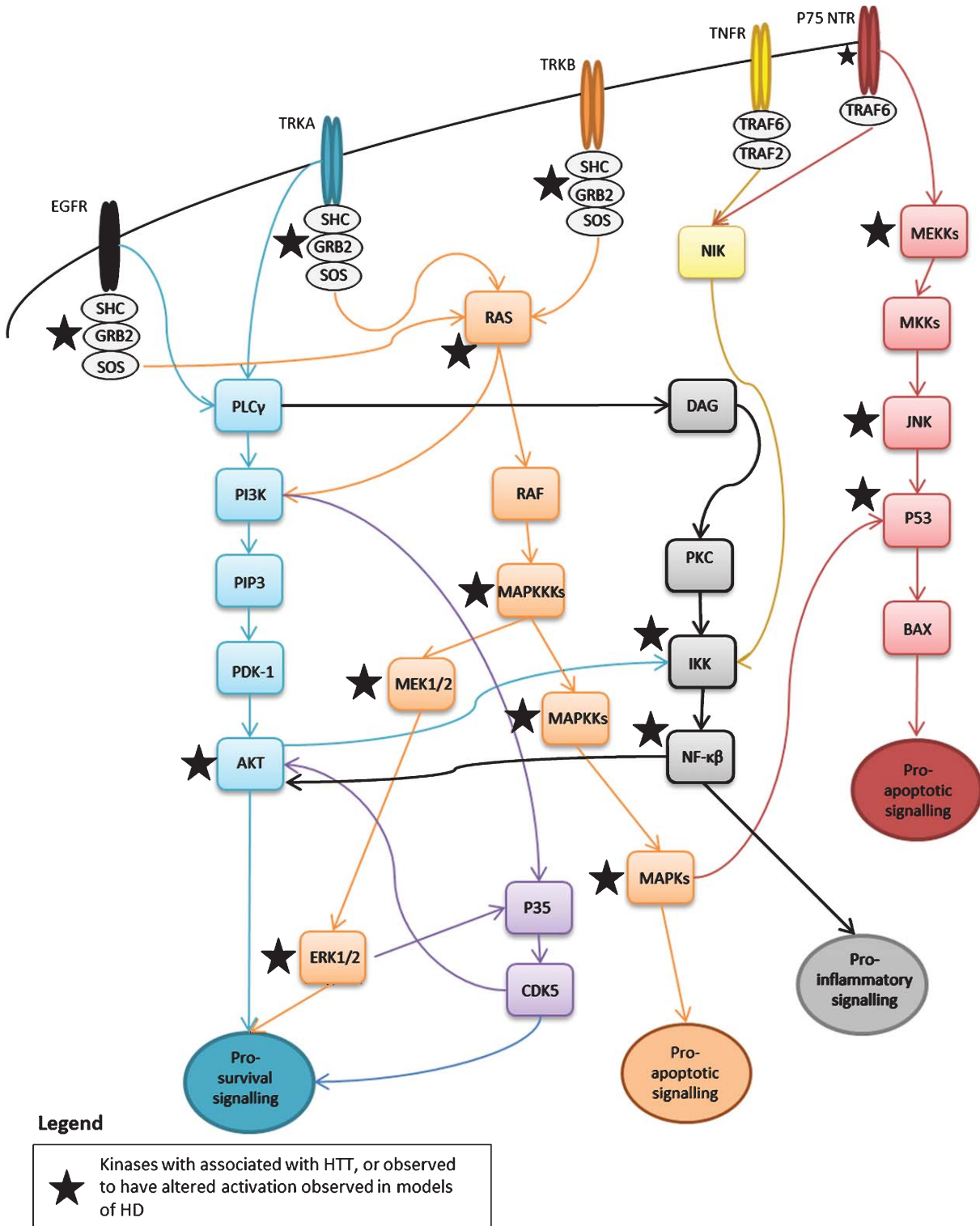


Fig. 1. A cartoon depicting the network of kinase signalling pathways downstream of growth factor receptor stimulation that have been most commonly investigated in HD. Black stars indicate points within these signalling cascades that have altered activation in models of HD, or have been found to associate with mHTT.

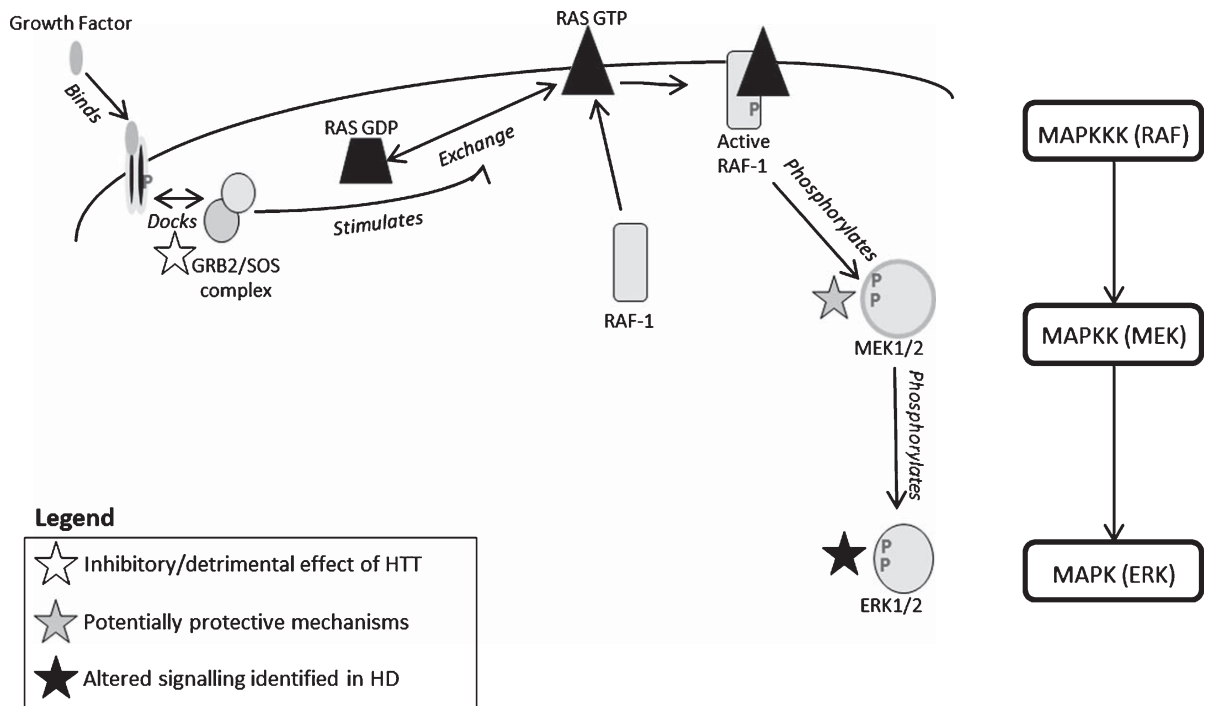


Fig. 2. Simplified cartoon of the MEK/ERK signalling pathway and flow diagram indicating its elements within the MAPK cascade. Stimulation of the phosphotyrosine kinase receptor initiates docking with the GRB2 adaptor protein/ SOS nucleotide exchange factor complex. The signal is transduced to stimulate the exchange of inactive RAS-GDP to active RAS-GTP. This prompts a conformational change in RAS, which recruits RAF-1 to the cell membrane, leading to its phosphorylation and activation. Active RAF-1 then phosphorylates and activates MEK1/2, which in turn phosphorylates and activates ERK1/2 (see [40] for a detailed review). Stars indicate points within the pathway that have been identified as being altered in models of HD, have been found to interact with mHTT, or have alterations that may be protective. White stars represent inhibitory or detrimental effects of mHTT; blue/grey stars represent potentially protective mechanisms in HD; black stars mark where altered kinase signalling has been identified in HD, but the evidence for the nature of the effect has been mixed.

models tend to exhibit suppressed ERK activation [69, 70], although two truncated models, R6/1 and R6/2, show widespread variation in the activation status of ERK that is age, brain region and cell type dependent [33, 59, 71–73]. *Drosophila* carrying a truncated exon1 fragment also exhibit suppressed ERK phosphorylation [63], similar to the full-length HD models. The available transgenic mouse data suggests that an increase in ERK activity may be a progressive striatal phenotype: such progression would not be apparent in immortalised and embryonic cell cultures. This progression may not be exclusive to medium spiny neurons (MSNs); Fusco et al. (2012) suggest that in R6/2 MSNs, although ERK activation increases from 8–13 weeks of age, it remains either lower, or comparable, to the level of activation in wild type mice. However, in striatal cholinergic and somatostatinergic interneurons, although active ERK is reduced with age, it remains higher in these cells than in their wild type counterparts. As cholinergic and somatostatinergic interneurons are relatively spared in HD,

enhanced ERK phosphorylation may be a mechanism for their improved survival. The reduction of ERK activity over time in R6/2 cortical neurons compared with the enhancement in striatal neurons [72] also suggests neuronal subtype specificity, as well as a potential mechanism for a loss of BDNF trophic support from cortical to striatal neurons typical of HD pathogenesis [74–76]. Apostol et al. (2006) suggest that as the expression of BDNF is a downstream target of ERK activity, reduced cortical ERK in HD models leads to increased cell death and suppressed BDNF expression. In turn, less trophic support is available to striatal neurons, which consequently mount a compensatory response including increased ERK activation.

MEK1 overexpression was found to be protective against cell death in PC12 cell models of HD [26], consistent with the anti-apoptotic effects of increasing downstream ERK activity (Figs. 1 and 2). However, MEK overexpression and increased ERK activation were found to have no protective effect on neuronal dysfunction or survival in *Drosophila* models of HD

Table 1
Investigation of phosphorylated MEK and ERK levels in various models of HD

Model	mHTT transgene	Repeat length	Brain region	Age	Phosphorylated ERK/MEK	Direction of effect compared to wild type	Additional information	Ref.	
Transgenic cell models	Inducible Htt14A2.5	103	-	-	ERK	Increased	Increase over time following mHTT induction, reaching maximum activation at 24 hours	[26]	
	Inducible Htt ^{Q103}	103	-	-	ERK	Increased	Increase over 48 hours, but to a lesser extent than in the truncated model	[26]	
	N548mu	120	-	-	ERK	Increased	Only observable at permissive temperature	[26]	
Knock-in cell models	Inducible PC12/Htt ^{Q103}	103	-	-	ERK	Increased	Could be further enhanced with treatment with ERK-activator Fisetin	[79]	
	<i>StHdh^{Q111}</i>	111	-	-	MEK	Decreased	Reduced response to BDNF stimulation	[16]	
	<i>StHdh^{Q111}</i>	111	-	-	ERK	Decreased	Reduced response to BDNF stimulation, but deficit in response to EGF stimulation	[16]	
	<i>StHdh^{Q111}</i>	111	-	-	ERK	Decreased	Could be ameliorated with overexpression of <i>Grb2</i>	[70]	
	<i>Drosophila</i>	Exon1	93	Whole head	-	ERK	Decreased	Suppressed response to expression of constitutively active EGFR	[63]
	<i>Drosophila</i>	Exon1	93	Whole head	-	ERK	Increased	Could be further enhanced with treatment with ERK-activator Fisetin	[79]

Table 1
(Continued)

Model	mHTT transgene	Repeat length	Brain region	Age	Phosphorylated ERK/MEK	Direction of effect compared to wild type	Additional information	Ref.
Transgenic mouse models	R6/1	116	Striatum	20–30 weeks	ERK	Increased	ERK phosphorylation response also more prolonged and resistant at 12 weeks following administration of QUIN	[59]
	R6/1	116	Hippocampus	5 weeks	ERK	No change		[71]
	R6/2	150	Striatum	8–12 weeks	ERK	Increased	Progressive increase with age, but progressive decrease in cortex	[72]
	R6/2	150	Striatum	10–11 weeks	ERK	No change		[73]
	R6/2	150	Striatum	12 weeks	ERK	Increased	Total ERK remained unchanged	[33]
R6/2	150	Striatum (MSNs)	8–13 weeks	ERK	Decreased	Phosphorylation was progressive with age, but remained below the level of WT mice until 13 weeks, where ERK phosphorylation was comparable	[58]	
R6/2	Human exon 1	150	Striatum (cholinergic and somatostatin-ergic interneurons)	8–13 weeks	ERK	Increased	Progressively reduced with age	[58]
Knock-in mouse models	R6/2	150	Striatum	10 weeks	ERK	Decreased	Highly variable	[151]
	Hdh ^{Q111}	111	Striatum	E15	ERK	Decreased	Reduced response to BDNF stimulation in embryonic primary cell cultures	[69]
Human models	Fibroblasts	39–44	–	–	ERK	Decreased	Weaker and more transient response following EGF stimulation	[90]

Table 2
Investigation of total and phosphorylated AKT levels in various models of HD

Model	mHTT transgene	Repeat length	Brain region	Age	AKT activation status	Direction of effect compared to wild type	Additional information	Ref.
Transgenic cell models	PC12	Full length	-	-	Phosphorylated	Decrease	Attenuated at baseline and in response to EGF and NGF stimulation.	[85]
	PC12	Full length	-	-	Total	No difference	At baseline and following EGF and NGF stimulation	[85]
	Inducible Htt14A2.5 HEK293	Truncated exon 1 - EGFP 1-1212a.a	-	-	Phosphorylated	No difference		[26]
	HEK293	1-1212a.a	-	-	Phosphorylated/ total ratio	No change		[146]
Knock-in cell models	Hdh ^{Q140} Neural Stem cells	Chimeric human/mouse exon1 knocked into endogenous mouse gene	-	-	Phosphorylated/ total ratio	Increase	At baseline and following BDNF stimulation	[147]
	<i>ShHtt^{Q111}</i>	Chimeric human/mouse exon1 knocked into endogenous mouse gene	-	-	Phosphorylated	Increase	Associated with pro-survival signalling via inactivation of GSK3 β	[15]
Lentiviral infection models	<i>ShHtt^{Q111}</i>	Chimeric human/mouse exon1 knocked into endogenous mouse gene	-	-	Phosphorylated	Increase	Results in increased phosphorylation and inactivation of FKHL1	[29]
	Rat	171a.a	Striatum	9-13 weeks post infection	Phosphorylated	Decrease	Evident during neuronal dysfunction and prior to neuronal loss	[86]
Transgenic animal models	R6/1	Human exon1	Striatum	6 months	Phosphorylated	Decrease	Deficiency was reversed in R6/1 mice crossed with BDNF-overexpressing transgenic mice	[148]
	R6/1	Human exon1	Striatum	12-30 weeks	Phosphorylated	Increase	Associated with a reduction in PHLPP1. Specific to MSNs	[149]
R6/1	Human exon1	Hippocampus	12 weeks	Total & phosphorylated	Decrease	Total AKT reduced in female R6/1 and running-induced AKT phosphorylation in females was suppressed	[150]	

Table 2
(Continued)

Model	mHTT transgene	Repeat length	Brain region	Age	AKT activation status	Direction of effect compared to wild type	Additional information	Ref.
R6/2	Human exon 1	150	Whole brain	4–10 weeks	Phosphorylated/ total ratio	No change		[146]
R6/2	Human exon 1	150	Striatum	12 weeks	Phosphorylated	Increase	Associated with a reduction in PHLPP1. Specific to the striatum	[149]
R6/2	Human exon 1	150	Striatum	11–12 weeks	Phosphorylated	Decrease	Deficit could be ameliorated with LM22A-4 small molecule ligand for TRKB	[151]
YAC128	Human full length	128	Whole brain	6–8 months	Phosphorylated/ total ratio	No change		[146]
YAC128	Human full length	128	Cerebral cortex & striatum	16 months	Total & phosphorylated	No change	Total and phosphorylated AKT increased in cortex and striatum in YAC128 mice crossed with BDNF-overexpressing transgenic mice	[152]
Tet-HD94	Chimeric human/mouse exon 1	94	Striatum	22 months	Phosphorylated	Increase	Partial reduction of the phosphorylated/total AKT ratio following inactivation of the transgene	[149]
HdhQ111	Chimeric human/mouse exon 1 knocked into endogenous mouse gene	111	Striatum	2–18 months	Phosphorylated	Increase		[15]
Human	Post-mortem	–	Striatum, cortex & cerebellum	–	Total	Decrease	Reduced full length HTT, but increased accumulation of shorter caspase 3-generated products	[137]
Lymphoblasts	–	40–66	–	–	Phosphorylated/ total ratio	Decrease	Total AKT was twice as high in HD patient derived cells, but levels of phosphorylated AKT did not differ from controls	[86]

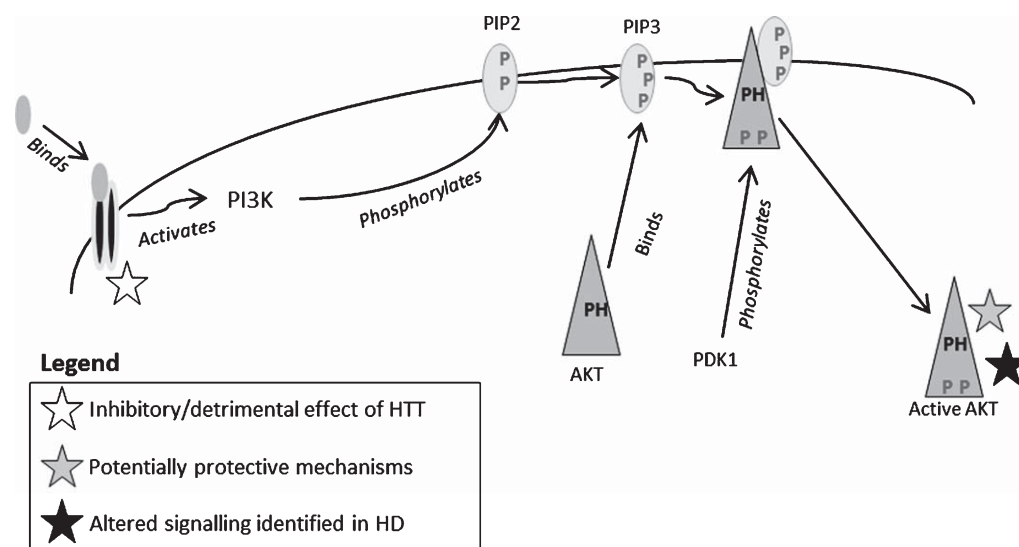


Fig. 3. Simplified cartoon depicting AKT activation. Growth factor binding to a receptor tyrosine kinase recruits PI3K to the plasma membrane where it is also activated. This initiates the phosphorylation of PIP2, creating PIP3. AKT is then anchored to PIP3 at the plasma membrane through its PH-domain. This alters the conformation of AKT, therefore allowing its activation by phosphorylation of its tyrosine and serine residues by PDK1. (See [141] for a review). Stars indicate points within the pathway that have been identified as being altered in models of HD, or have been found to interact with mHTT. White stars represent an inhibitory or detrimental effect of mHTT; blue/grey stars represent potentially protective mechanisms in HD; black stars mark where altered kinase signalling has been identified in HD, but the evidence for the nature of the effect has been mixed.

[77, 78]. In contrast, in a more recent *Drosophila* model of HD, genetic reduction of the *Drosophila Erk* gene 'rolled' by 50% had no effect on fly survival or neurodegeneration; however reduction of the *Mek* gene 'dsor' significantly decreased survival [79]. Additionally, although ERK phosphorylation was found to be required for the neuroprotective effect of cannabinoid receptor agonists in a PC12 model of HD, the number of additional surviving cells was less than 10%, and not all cells exhibited the ERK phosphorylation response correlated with rescue [80]. These models suggest that ERK activation alone may not be sufficient for neuroprotection; targeting multiple signalling pathways may be required in order to form an effective neuroprotective response.

Mechanisms for MEK/ERK alterations and neuronal protection

Increased phosphorylation of ERK-activated transcription factors, such as ELK1 and CREB has been correlated with increased ERK phosphorylation in R6/2 striatum [33]. However, the expression of *C-fos*, an immediate-early gene associated with regulating neuronal survival [81], was downregulated in these mice [82]. It was suggested that attenuated expression of *C-fos* may be a result of mHTT-associated down-

regulation of mitogen- and stress-activated kinase 1 (MSK1) activity [33], which is also a downstream target of ERK [83, 84]. Accordingly, the overexpression of MSK1 was able to restore *C-fos* transcription and was neuroprotective [33]. *MSK1* expression is also decreased in human HD post-mortem caudate, but not in the cerebral cortex [33], therefore indicating tissue-specific effects of mHTT on the regulation of downstream targets of ERK.

MEK/ERK signalling is one of the multiple pathways downstream of epidermal growth factor receptor (EGFR) activation (Fig. 1), and the reductions in ERK phosphorylation that have been observed in several models of HD have been attributed to direct antagonism of the EGFR by mHTT [63, 85, 86] (Fig. 8). The EGFR complex interacts with both HTT and mHTT via the interaction of HTT proline rich motifs with SH3 domain-containing molecules [26, 78, 85, 87]. This association can be strengthened with EGF stimulation [87]. The EGFR complex includes growth factor receptor-bound protein 2 (GRB2), and aberrant association between mHTT and GRB2 can attenuate downstream signalling, including MEK/ERK and protein kinase B (AKT) phosphorylation [85, 87, 88]. Elevated expression of *Grb2* has been observed in *StHdh^{Q111}* cells, despite suppressed ERK

phosphorylation [70]. It has been argued that GRB2 also plays a role in the autophagic removal of mHTT, and that aberrant interactions between the two occur on vesicular structures and eventually activate autophagy, independent of EGFR activation. Excess GRB2 in *StHdh^{Q111}* cells may therefore be directed towards autophagic removal of mHTT rather than to the regulation of growth factor-stimulated signalling [70]. The redistribution of the EGFR to the late endosomal compartment is thought to be a prerequisite for EGF-dependent ERK signalling [89], and inhibition of this process by the expanded polyQ on mHTT has been proposed as a contributing factor in the suppression of ERK phosphorylation observed in human HD fibroblasts [90].

ERK phosphorylation can also be induced by BDNF stimulation [50, 69] (Fig. 1). As such, impairment of the BDNF-associated receptors P75 neurotrophin receptor (NTR) and tyrosine kinase B (TRKB) have been investigated as mechanisms for reduced ERK phosphorylation in several models of HD. Transfection of *StHdh^{Q111}* cells with P75 NTR did not improve levels of BDNF-induced ERK phosphorylation [91], therefore reduced TRKB expression may be responsible for the attenuation of the BDNF-associated ERK response [91, 92] (Fig. 8). However, Ginés et al. (2010) found no alterations in TRKB phosphorylation in *StHdh^{Q111}* cell lines, and suggested that diminished levels of P52/P46 SHC scaffolding proteins that couple the activated TRKB receptor to the RAS/MEK/ERK pathway (Figs. 1 and 2) may account for reduced ERK activation. Indeed, transfection of these cells with constitutively active RAS restored BDNF-associated ERK activation [16].

The accumulation of phosphorylated ERK and the pro-apoptotic kinase P38 MAPK in R6/1 striatum has been attributed to disruption of the brain-specific striatal-enriched protein tyrosine phosphatase (STEP) by phosphorylation [59] (Fig. 8). STEP activation has been associated with excitotoxic-induced cell death, and its activation can be enhanced by injection with the neurotoxin quinolinic acid (QUIN) [59]. In hippocampal cells, STEP inactivation leads to ERK phosphorylation and attenuated cell death [93], and in R6/1 striatum, increased STEP phosphorylation correlates with enhanced phosphorylation of ERK and P38 MAPK in 20–30 week old animals [59]. Furthermore, ERK phosphorylation was more prolonged and neurons were more resistant to cell death following a QUIN injection in 12 week old R6/1 striata, indicating that progressive STEP inactivation may be a neuroprotective mechanism that mediates neuronal responses to

excitotoxicity through maintenance of the ERK pathway [59].

Increased MEK/ERK signalling may also confer neuroprotective effects in models of HD via direct interactions with the HTT protein that reduce expanded polyQ-associated toxicity. The presence of mHTT in a cell model of HD increased the expression of the lys-asg-glu-leu motif receptor (KDELRL), which plays a role in endoplasmic reticular (ER) stress and activation of autophagy [94]. In this model, the autophagic removal of mHTT was enhanced by increased KDELRL expression, but was prevented by inhibition of MEK [94]. The neuroprotective clearance of mHTT proteins in response to ER stress and KDELRL expression may therefore occur via MEK/ERK pathway activation (Fig. 8). The phosphorylation of HTT is typically considered to be a neuroprotective mechanism by mediating its subcellular localisation [95–101], cleavage [60, 62, 102] and interaction with other proteins [74, 103, 104]. MEK1 activation has been identified as a mechanism for enhancing HTT phosphorylation, whereas MEK inhibition reduced general HTT serine phosphorylation [105].

CDK5/P35 signalling

Cell division protein kinase 5 (CDK5) is a member of the serine/threonine CDK family, and is associated with a wide range of cellular functions including neural development, neuromuscular development and hippocampal neurogenesis (see [106] for a review). Expression of CDK5 is highest in neurons due to the specific neuronal expression of its activators P35 or P39 [107], which can be regulated by nerve growth factor (NGF) and BDNF stimulation via activation of the MEK/ERK and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signalling cascades [108–111]. It forms a negative feedback loop within the MEK/ERK pathway [111–113], inactivates c-jun N-terminal kinase (JNK) [114] and activates the AKT signalling pathway [115] (Figs. 1 and 8), implicating CDK5 in neuronal survival. CDK5 activity has been found to be crucial for neuronal survival during development and disease [116], although excessive CDK5 has been implicated in cell death induced by oxidative stress and neurotoxicity [116]. Calpain cleavage of P35 results in a truncated isoform, P25, which is associated with neurodegenerative diseases such as PD and AD [116]. This may be due to the mislocalisation of CDK5 by P25 activation [117], and the longer half-life of P25 leading to aberrantly prolonged CDK5 activation [118].

CDK5/P35 in HD

CDK5 activity is consistently found to suppress mHTT toxicity [119]. It interacts and co-localises with HTT *in vitro* and phosphorylates HTT on serine 434 [60]. Phosphorylation of this serine on mHTT reduces its caspase cleavage, diminishing the presence of toxic amino-terminal fragments, attenuating aggregate formation and preventing cell death [60]. CDK5 activity has been observed to be reduced in N171-82Q transgenic mouse brain, and consequently the neuroprotective phosphorylation of HTT on serine 434 was also suppressed in these mice [60]. As CDK5 was not present in any inclusion bodies, it was concluded that mHTT may be altering the interaction between CDK5 and its activator P35 [60].

The dysregulation of CDK5 occurs with aging and increased DNA damage. Acute DNA damage triggers enhanced CDK5 phosphorylation which results in the neuroprotective phosphorylation of HTT on serines 1181 and 1201 [119]. However, long term accumulation of DNA damage is associated with CDK5 downregulation [120]. Downregulation of CDK5 and P35 protein has been identified in post-mortem human HD brain [121, 122], however although total CDK5 is also suppressed in *StHdh^{Q111}* cells and in 9 month *Hdh^{Q111}* mouse striata, the phosphorylated to total CDK ratio was substantially higher, suggesting enhanced activation within this pathway [122]. This was attributed to substantially higher P25 expression in these models [122] which may be pushing CDK5 activity towards a pro-apoptotic function rather than a neuroprotective one. Increased CDK5 activity also sensitised neuronal cells to stimulation with a dopamine receptor agonist, therefore enhancing vulnerability to excitotoxicity [122].

The neuroprotective potential of CDK5 is therefore likely to be dependent on factors such as age and disease progression, or any other cellular insult resulting in DNA damage. CDK5 could be initially high in models of HD, where it may act as either a compensatory protective mechanism by phosphorylating mHTT or as a pro-apoptotic mechanism by enhancing excitotoxic vulnerability, dependent on the ratio of P25 to P35 activators present. With the accumulation of mHTT toxicity and DNA damage over time, CDK5 may become suppressed, as observed in the N171-82Q mouse model of HD and in human brain. Reduced CDK5 activity stabilises microtubules, which are required for mHTT inclusion formation [123–126]. Microtubules are major targets of CDK5 [127]; CDK5 activation disrupts microtubule formation in primary cortical neuronal cultures, attenuating mHTT aggre-

gation and toxicity [126]. Reduced CDK5 over time may therefore be a pathogenic mechanism contributing to mHTT inclusion formation. Due to the dependence of CDK5-associated neuroprotective mechanisms on multiple factors such as age and extent of DNA damage, this pathway should not be considered in isolation in models of HD (Fig. 8).

AKT pathway

The AKT signalling pathway is one of the most comprehensively characterised pathways in HD models, and its activation is universally considered to be anti-apoptotic and neuroprotective in both acute and chronic models of neurodegeneration [15, 128–132]. A primary mechanism of AKT-mediated neuroprotection is by its phosphorylation and inactivation of pro-apoptotic machinery, such as glycogen synthase kinase 3 β (GSK3 β), BCL-2 associated death promoter (BAD), BIM, histone deacetylase 3 (HDAC3), I kappa β kinase (IKK) forkhead family proteins and pro-caspase-9 [15, 28, 88, 133–139].

AKT levels are typically low in adult brain [128]; however its activation rises following stress and injury [140]. AKT activation generally occurs via the PI3K pathway following growth factor or cytokine signalling [134, 141] (Fig. 3). The active form can then translocate to cell nuclei and directly phosphorylate transcription factors [34], and inactivation of AKT occurs via the action of phosphatases [142, 143]. There are three highly homologous AKT isoforms; there is evidence that despite their similarities, the different AKTs may have some non-overlapping functions [144, 145], however AKT1 has been most thoroughly investigated in models of HD, and further references to 'AKT' in this review will refer to 'AKT1.'

AKT in models of HD

Activation of the AKT pathway has been determined in several cell and mouse models of HD [15, 26, 29, 85, 86, 146–152], as well as in human post-mortem brain [137], a summary of which can be found in Table 2. Similar to MEK/ERK signalling, there are many inconsistencies in AKT regulation both between and within models. Enhanced AKT signalling has been attributed to the striatal-specific reduced expression of its inhibitor PHLPP1 in several mouse models of HD, which is also reduced in human putamen [149]. However, despite reduced expression of PHLPP1 in R6/2, R6/1 and HD94 striatum, AKT activation in transgenic models of HD is much more variable (Table 2). However, with the exception of

one study [146], AKT phosphorylation has not been investigated longitudinally in transgenic mouse models, preventing the characterisation of any progressive phenotype. Early developmental-stage models and more slowly progressing knock-in models of HD tend to exhibit enhanced AKT activation, which may be an initial compensatory response that inhibits other pro-apoptotic stress-activated pathways such as JNK and P38 [141]. However, with disease progression, AKT activation becomes suppressed and less efficient, therefore no longer protecting against cell death. Suppression of AKT may be more prevalent in transgenic models due to the increased neurotoxicity of the truncated mutant fragment and accelerated progression of the motor and neuronal phenotype. This is consistent with suppressed AKT phosphorylation that is observed in human HD post-mortem brain [137]. This suppression was attributed to reduced full-length 60 kDa AKT species in human post-mortem HD brain, and increased accumulation of a short 49 kDa caspase-3 generated product that may prevent AKT phosphorylation and activation [137].

Regardless of its activation in different models of HD, increasing AKT phosphorylation has consistently been found to be a protective mechanism. For example, activation of AKT in *Drosophila* alleviated mHTT-induced toxicity in the retina, although it did not prevent fly lethality [78], and expression of AKT in glia improved *Drosophila* locomotor activity [78]. AKT activation may directly alter the toxicity of mHTT by phosphorylation on serine 421 [88, 137]. The phosphorylation of mHTT on serine 421 has been associated with reduced mHTT toxicity and accumulation of fragments, as well as the restoration of BDNF axonal transport in neurons [62, 78, 104, 153–155]. However, as AKT activation in amino-terminal models lacking this serine is still protective, it is likely that additional mechanisms, such as the inactivation of pro-apoptotic machinery, may also underlie the neuroprotective effect of AKT phosphorylation [146, 156].

AKT and growth factor signalling

AKT phosphorylation is downstream of the activation of multiple growth factor receptors (Fig. 1): for example, EGF and insulin-like growth factor 1 (IGF-1) stimulation of immortalised rat cells caused transient and sustained activation of AKT, respectively, which also increased cell viability [157]. AKT activation shares multiple upstream growth factor receptors with MEK/ERK signalling, and its alteration in models of HD has been attributed to similar mechanisms as alterations in MEK/ERK activation, namely inter-

ference of GRB2 at the EGFR and tyrosine kinase A (TRKA) by mHTT [85, 87]. However, this interference does not explain the substantially augmented AKT response that is observed in many models of HD [15, 29, 147, 149]. AKT has been identified as an integration point for several growth factor pathways, and therefore synergism between multiple pathways may be a mechanism for altered AKT observed in models of HD; for example, IGF-1, BDNF, NGF and transforming growth factor β (TGF β) signalling have all been associated with modulating AKT activation [50, 91, 104, 110, 134, 137, 158–165].

IGF-1 stimulation in amino-terminal models of HD ameliorates mHTT toxicity and reduces nuclear inclusions, which is thought to be mediated by the direct phosphorylation of mHTT on serine 421 as a result of AKT activation [137]. IGF-1-induced AKT phosphorylation can restore the anterograde and retrograde transport of BDNF-containing vesicles that is lost in a mouse neuronal cell model of HD [104], therefore enhancing striatal BDNF neurotrophic support. Stimulation with IGF-1 was unable to fully rescue cells that carried an mHTT fragment with a phosphoresistant mutation on serine 421 [137]; however, there was still some IGF-1-associated survival in these cells, strengthening the probability that the neuroprotective effects of AKT act via multiple mechanisms in addition to direct mHTT phosphorylation.

Although AKT activation plays a role in enhancing the vesicular transport and release of BDNF [104], BDNF stimulation is also able to phosphorylate AKT [50, 91] and AKT activation has been found to contribute to BDNF-induced dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP32) expression in MSNs [110]. The BDNF receptor, TRKB, is downregulated in several models of HD and in human HD brain [16, 91, 92, 148, 166], and may account for suppressed AKT activation in response to BDNF [148]. However, increased expression of the BDNF-responsive P75 NTR in models of HD and human HD brain may facilitate TRKB-mediated AKT activation following stimulation with BDNF [91]. The modulation of AKT activation is likely to rely on the integration of multiple input signals, therefore attempts to characterise and manipulate this pathway by targeting a single kinase may prove ineffective.

AKT has been identified as a point of convergence between EGF, IGF-1 and TGF β signalling pathways [162, 165, 167]. TGF β is a versatile regulator of cell growth, proliferation and apoptosis [164, 168]; mothers against decapentaplegic homolog (SMAD) proteins

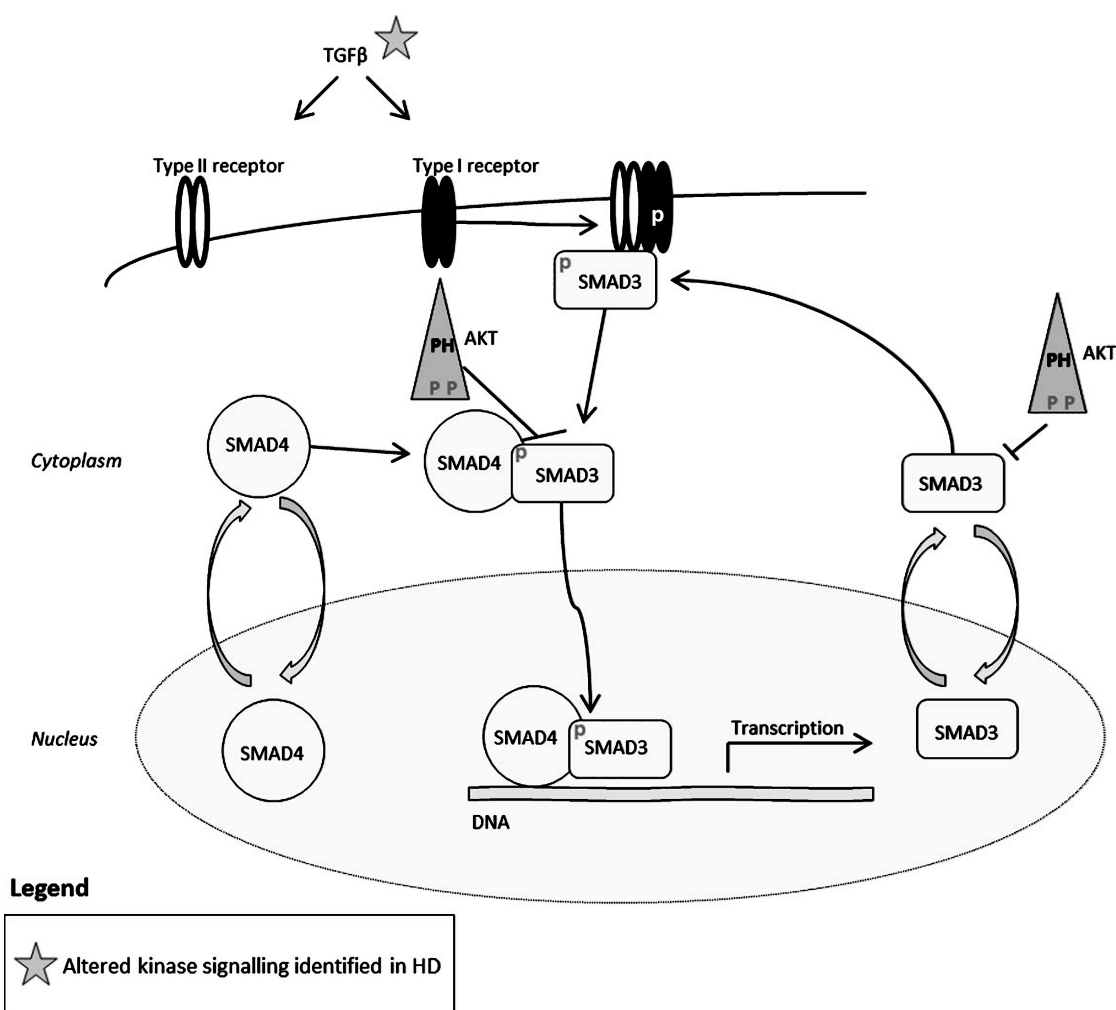


Fig. 4. Simplified cartoon depicting the basic mechanism of SMAD3 signalling in the TGF β pathway and inhibition by AKT. TGF β stimulates its Type I and Type II receptors, creating a hetero-tetrameric receptor complex. The Type II receptor phosphorylates the Type I receptor, which then allows the phosphorylation of receptor-regulated SMAD3, which is constantly shuttling between the nucleus and cytoplasm until anchor proteins recruit them to the active Type I receptor. Phosphorylated SMAD3 can bind to the Co-SMAD4, which is also consistently shuttling between nuclear and cytoplasmic compartments. The resulting SMAD3-SMAD4 complex then translocates to the nucleus where it may either bind directly to DNA to stimulate transcription, or will incorporate DNA binding cofactors (see [164, 193] for a review). Activated AKT binds to SMAD3 and sequesters it in the cytoplasm, thus preventing its phosphorylation, binding to SMAD4 and nuclear translocation; this effect is enhanced with IGF-1 stimulation, and attenuated with TGF β stimulation [162, 163]. The blue/grey star marks where altered kinase signalling has been identified in HD, but the evidence for the nature of the effect has been mixed.

and their interactions with AKT are key mediators of this pathway [162, 163] (Fig. 4), which can also be modulated by stimulation of the EGFR [169]. TGF β can upregulate AKT and ERK [167] as well as proapoptotic members of the MAPK family [170]. As TGF β signalling overlaps substantially with targets implicated in the pathogenesis of HD, this pathway may contribute to altered kinase signal transduction and downstream effects such as transcriptional dysregulation. However, investigation of this pathway in the context of HD remains sparse. A reduction in circu-

lating TGF β in the blood of asymptomatic HD patients has been observed, and its presence had an inverse correlation with CAG repeat length [171]. A small reduction of serum TGF β was identified in female R6/1 mice [150], but despite reduced cortical TGF β 1 in YAC128 and R6/2 mice, there was a slight increase in striatal TGF β 1 in these animals [171]. A human induced pluripotent stem cell (iPSC) model of HD was also found to have an upregulation of the TGF β pathway, which could be restored to normal levels by replacing the expanded HTT CAG repeat with one of

a non-pathogenic length [172]. In addition, increased TGF β signalling has been identified in the hippocampus of a transgenic rat model of HD and in R6/2 mice, where it had an inverse effect on neural stem cell proliferation [173]. Given their association with the AKT pathway and evidence of dysregulation in models of HD, the TGF β signalling pathway and the regulation of SMAD transcription factors may prove to be an interesting new mechanism contributing to transcriptional dysregulation and molecular pathogenesis in HD.

PRO-APOPTOTIC PATHWAYS

The MAPKs

The co-ordination of pro-survival and pro-apoptotic signalling networks regulates cell growth and differentiation [149], and contributes to cell fate following neuronal insult. MAPKs are a superfamily of serine/threonine protein kinases that mediate diverse cellular responses to external stimuli, such as proliferation, differentiation and apoptosis [174–176]. MEK/ERK signalling is the pro-survival branch of this family, whereas P38 and JNK are more strongly associated with a pro-apoptotic response. The phosphorylation of P38 and JNK occurs through a multi-tiered kinase cascade analogous to the phosphorylation of ERK, with different upstream activators (Fig. 5), and their localisation following activation is likely to determine the target substrate and consequent cell response [177].

JNK signalling

JNK signalling regulates transcription associated with the cell death response [178], and is activated in response to stimuli such as heat shock, ER stress and oxidative stress [88, 179–181]. JNK activation in turn phosphorylates and increases the activation of the transcription factor C-JUN [182]; as C-JUN is a part of the transcription complex activator protein 1 (AP1), the dysregulation of its activity via altered JNK signalling has widespread consequences for the regulation of many pro-apoptotic genes [183–185]. Increased JNK activation may also cause an impairment of axonal transport; JNK phosphorylates kinesin-1, reducing its binding affinity to microtubules and blocking axonal transport [186]. Chronic activation of JNK has been observed in both AD and PD as a major regulator of cell death [187, 188]. In addition, mice lacking the CNS-expressed JNK3 have exhibited some neuroprotection against kainic acid-induced excitotoxicity [189, 190],

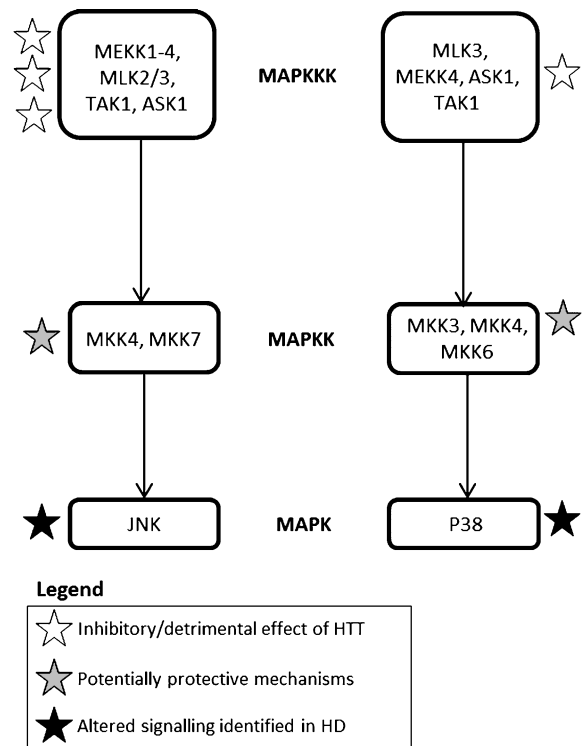


Fig. 5. The MAPK multi-tiered cascade. MAPKKKs upstream of JNK phosphorylate MKK4 and MKK7, which catalyse the phosphorylation and activation of JNK. Upstream activators of P38 phosphorylate MKK3 and MKK6, which in turn activate P38; MKK4 acts as a point of convergence between the two pathways and is able to phosphorylate both JNK and P38 (for a review, see [31]). Stars indicate points within the pathway that have been identified as being altered in models of HD, have been found to interact with HTT, or have alterations that may be protective. White stars represent inhibitory or detrimental effects of mHTT; blue/grey stars represent potentially protective mechanisms in HD; black stars mark where altered kinase signalling has been identified in HD, but the evidence for the nature of the effect has been mixed.

although they do not appear to be protected against 3-nitropropionic acid (NP) neurotoxicity [139]. JNK3 signalling has an antagonistic relationship with the AKT signalling pathway [141]; JNK3 null mice have increased PI3K activity and enhanced AKT phosphorylation [191].

JNK has also been associated with several other growth factor-stimulated pathways and kinases (Fig. 1). For example, JNK can be phosphorylated by both EGF [192] and TGF β [193–196], and both JNK and P38 can be enhanced by aberrant CDK5 activation in response to beta-amyloid (A β) [197, 198]. However, in non-pathogenic contexts, CDK5 can promote survival via JNK inactivation [114]. JNK has also been found to stabilise P53 by phosphorylation, thus increasing its pro-apoptotic activity [199], and may

also modulate other MAPKs (Fig. 8); JNK3 null mice had a suppressed P38 response to a kainic acid injection, and a less persistent ERK phosphorylation effect [189].

JNK in HD

The majority of investigations into JNK signalling in models of HD have detected an upregulation of this pathway in response to mHTT (Table 3), and protein-protein networks constructed from published data have demonstrated a gain of function in the JNK pathway in HD [200]. These studies have focused primarily on transgenic cell lines and transgenic mice and the finding of increased JNK phosphorylation is fairly consistent. However, this is not the case for the *StHdh^{Q111}* knock-in cell line. As an immortalised embryonic model, the *StHdh^{Q111}* cell line may be more representative of very early developmental stages in HD pathogenesis, and the initial activation of compensatory pro-survival signalling pathways, such as AKT, may be attenuating pro-apoptotic JNK responses. Although increased JNK activity has been observed in YAC128 and YAC72 mice at relatively young ages [201], the equivalent has not yet been investigated in knock-in models of HD. It would therefore be of interest to longitudinally examine the activation of JNK over the life-span of a knock-in mouse model in order to determine whether increased JNK phosphorylation is a disease-development specific phenotype, or is a result of truncated or overexpressed HTT.

Enhanced JNK phosphorylation is accompanied by increased caspase-3 activation, which can be suppressed with JNK inhibition [26]. The cleavage of mHTT by caspases has been associated with increased cellular toxicity and neurodegeneration [9, 61, 62, 105, 202], and the inhibition of JNK phosphorylation has consistently been found to be protective against apoptosis and neurodegeneration in models of HD [26, 79, 203–205]. Targeting upstream activators of JNK has proven to be effective for JNK suppression and neuroprotection; for example, expression of a dominant negative form of MAPK-kinase 4 (MKK4) (Fig. 4) attenuated cell death in an immortalised murine hippocampal cell line [204]. The activation of the upstream regulator of JNK, MAPK-kinase-kinase 1 (MEKK1) (Fig. 4), reduces the solubility of polyQ peptides in a transgenic cell model of HD, and therefore stimulates the formation of mHTT intranuclear inclusions [206] (Fig. 8). However, in this model constitutively active MEKK1 did not activate JNK, and MAPK inhibitors had no effect on inclusion formation [206]. In addition, the overexpression of dominant

negative mutants of MEKK1 and JNK-interacting protein 1 (JIP1) in a rat lentiviral model rescued the loss of DARPP-32 expression [207], but had no effect on intracellular mHTT inclusions or the expression of *c-Jun* [207]. Therefore MEKK1 activation is likely to be altering mHTT pathology via multiple mechanisms and signalling pathways in addition to JNK activation, and the targeting of multiple signalling pathways may be required to modulate a more substantial neuroprotective response.

Mechanisms of increased JNK signalling in models of HD

The impairment of JNK kinase signalling by mHTT is complex due to its occurrence at multiple points within the JNK signal transduction cascade (Fig. 5), including the inhibition of negative regulators, the phosphorylation of upstream activators, and the modification of cellular responses due to alterations in receptor expression. MLKs are a family of serine/threonine protein kinases that function as MAPKKKs to activate MAPKKs, which consequently activate JNK and P38 (Fig. 5) [35, 208, 209]. MLK2 is predominantly expressed in brain [210], and is specifically associated with activation of the JNK cascade [31, 35, 211–214]. MLK2 has an SH3 domain that is homologous to the SH3 domain of GRB2 [210]; HTT binds to MLK2 in a manner similar to its interaction with GRB2, and this association is lost with the presence of an expanded polyQ on mHTT [88, 205]. As MLK2 is constitutively active in its free form [215], HTT acts as an inhibitor of its activity and suppresses JNK activation; when this inhibitory association is lost due to the presence of mHTT, MLK2 is free to enhance pro-apoptotic JNK activation [88]. Expression of a dominant negative form of MLK2 could attenuate apoptosis in a hippocampal neuron-derived cell model (HN33) expressing expanded mHTT, and overexpression of amino-terminal HTT could partially rescue toxicity induced by MLK2 activation [205]. mHTT has also been found to enhance pro-apoptotic signalling via ER stress-dependent activation of apoptosis signal-regulating kinase 1 (ASK1) [216, 217]; another MAPKKK upstream of JNK signalling [31].

In addition to the hyperactivation of upstream kinases, Merienne et al. 2003 proposed that the expanded polyQ of mHTT alters the solubility of the JNK dual specificity phosphatase M3/6, therefore rendering it inactive and unable to attenuate JNK phosphorylation. Additionally, heat shock protein 70 (HSP70) activity is able to prevent the aggregation of M3/6 and reduce JNK activation; however

Table 3
Investigation of phosphorylated P38 and JNK levels in various models of HD

Model	mHTT transgene	Repeat length	Brain region	Age	P38/JNK	Direction of effect compared to wild type	Additional information	Ref.
Transgenic cell lines								
PC12	Full length	48 & 89	-	-	JNK	Decrease	Activity induced by NGF or EGF reduced by 80–90%. Total JNK also reduced by 30%	[85]
Inducible Htt14A2.5	Truncated exon1 - EGFP	103	-	-	JNK	Increase	Parallel with progressive increase in caspase 3 activity	[26]
Inducible Htt14A2.5	Truncated exon1 - EGFP	103	-	-	P38	No change		[26]
Inducible Htt ^{Q103}	Exon1 - EGFP	103	-	-	JNK	Increase	Phosphorylated JNK remained at a 15-fold increase 48 hours following mHTT induction	[26]
N548mu	1–548a.a	120	-	-	JNK	Increase	Correlates with increased caspase-3 activation	[26]
Inducible PC12/Htt ^{Q103}	Exon1 - EGFP	103	-	-	JNK	Increase	Activation could be reduced by treatment with ERK-activator Fisetin	[79]
PC6.3	Exon1 - EGFP	53–120	-	-	P38	Increase	Correlated with a reduction in NFκβ	[287]
PC6.3	Exon1 - EGFP	120	-	-	JNK	Increase	Correlated with a reduction in NFκβ	[287]
HN33	Full length	48 & 89	-	-	JNK	Increase	Activation of JNK precedes apoptosis. Co-expression of dominant negative mutant SEK1 blocked JNK activation	[204]
COS	133a.a	125	-	-	JNK	Increase		[218]
COS	133a.a	125	-	-	P38	No change		[218]
NG108	80a.a	125	-	-	JNK	Increase		[218]
Mouse primary cultures	Exon1	103	Striatum	E14	JNK	Increase	Hyperphosphorylation occurred 7-8 hours post mHTT transfection	[203]
Knock-in cell lines								
<i>StHdh^{Q111}</i>	Chimeric human/mouse exon1 knocked into endogenous mouse gene	111	-	-	JNK	No change	Larger increase in activated JNK in <i>StHdh^{Q111}</i> cells could be identified following increased expression of P75 NTR	[91]
<i>StHdh^{Q111}</i>	Chimeric human/mouse exon1 knocked into endogenous mouse gene	111	-	-	JNK	Decrease		[70]

Table 3
(Continued)

Model	mHTT transgene	Repeat length	Brain region	Age	P38/JNK	Direction of effect compared to wild type	Additional information	Ref.
<i>StHdh^{Q111}</i>	Chimeric human/mouse exon1 knocked into endogenous mouse gene	111	-	-	P38	No change		[70]
Fly models	<i>Drosophila</i>	93	Whole head	-	JNK	Increase	No effect of Fisetin on JNK activation despite a reduction seen in an inducible PC12 model	[79]
Lentiviral infection models	Rat	82	Striatum	4 weeks post infection	JNK	Increase	Persisted for 13 weeks following lentiviral expression of mHTT	[207]
	Rat	82	Striatum	12 weeks post infection	JNK	Increase	Not present in neurons co-expressing MKP-1	[223]
	Rat	82	Striatum	12 weeks post infection	P38	Increase	Not present in neurons co-expressing MKP-1	[223]
Transgenic mouse models	YAC128	128	Striatum	1-2 months	P38	Increase		[201]
	YAC128	128	Striatum	1-2 months	JNK	Increase		[201]
	YAC72	72	Striatum	1-2 months	JNK	Increase	Milder than YAC128, positive correlation between JNK activation and polyQ length	[201]
	R6/1	116	Retina	8 months	JNK	Increase	Hyperphosphorylation also in mice expressing mutant ataxin-7 from 1 month	[218]
	R6/1	116	Striatum	20-30 weeks	P38	Increase	Progressive with age, and correlates with increased STEP phosphorylation	[59]
	R6/2	150	Striatum	10-11 weeks	P38	Increase	Correlated with striatal damage. No difference observed in the cingulate cortex	[73]
Knock-in mouse models	Hdh ^{Q111}	111	Cortico-striatal slices	8 months	JNK	Increase	Following BDNF treatment	[91]

its expression is downregulated by mHTT, preventing its protective function [218]. Finally, the imbalance of P75 NTR and TRKB BDNF-responsive receptors has been proposed as a mechanism for enhanced JNK activation by altering the nature of cellular responses to BDNF [91]. Reducing the expression of P75 NTR in Hdh^{Q111} mice attenuated JNK phosphorylation, whereas its overexpression in *StHdh*^{Q111} cells enhanced JNK activation and decreased cell survival [91].

P38 signalling

P38 activity has been associated with multiple signalling pathways (Fig. 1), and has been identified as having both pro- and anti-apoptotic functions depending on which pathway substrates are engaged. P38 activation can be induced by TGF β [194–196, 219] in order to selectively modulate gene responses dependent on P38-induced transcription factor regulation [164]. P38 activity can also be inhibited by AKT signalling [141], and can form a positive feedback loop for its activation by phosphorylation of the EGFR [220]. P38 acts in a similar way to JNK by enhancing P53 activity, albeit by a different mechanism; P38 blocks the interaction between P53 and its negative regulator, mouse double minute 2 homolog (MDM2), which would normally target P53 for degradation by the ubiquitin proteasome system [199, 221].

P38 in models of HD

P38 is commonly found to be increased in models of HD (Table 3), although several models have noted no difference in P38 phosphorylation in the presence of mHTT expression [26, 70, 218]. As the range of models that have been utilised to investigate P38 activity encompasses both transgenic and knock-in approaches as well as a variety of mHTT fragments and polyQ repeat lengths, it is difficult to determine a reason for the lack of P38 alteration in these models. However, as kinase signalling responses can be modulated by a variety of factors, such as cellular context, tissue type and environment, inconsistencies between laboratories and conditions may be unsurprising.

The increased activation of P38 identified in transgenic mouse models of HD correlates with the extent of striatal damage in these animals [59, 73] and contributes to the enhanced glutamate excitotoxicity observed in YAC128 mice [201]. Although P38 is increased in animal models of HD, the time point at which this occurs and its function remains under debate: alterations in P38 are observed in YAC128 mice from a relatively early age (1–2 months) [201]

and at an early pre-pathogenic time point (8 months) in Hdh^{Q111} knock-in mice [91]. However, Saavedra et al. (2011) suggest that in R6/1 mice, P38 accumulates with age and is not significantly enhanced until the advanced stages of disease in these animals (20–30 weeks). This progressive accumulation was correlated with the progressive inactivation of STEP [59]. Although enhanced P38 activation is considered to be pro-apoptotic, and its inhibition has shown to increase neuronal survival in several models of HD [222, 223], it has also been argued that P38 activation may be neuroprotective. R6 mouse models demonstrate neuronal dysfunction rather than substantial neuronal loss [224, 225], and this anti-apoptotic effect has been attributed to its co-ordination with upregulated pro-survival pathways such as AKT and ERK in these models [223, 226]. In addition, P38 can regulate mHTT-induced serine/threonine protein kinase (SGK) activity, which, like AKT, has been shown to regulate HTT toxicity by promoting the neuroprotective post-translational modification of serine 421 phosphorylation [227]. However, whether P38 will support pro- or anti-apoptotic signalling is likely to be dependent on cellular context and the activation of downstream substrates, and may fluctuate with disease progression.

MKP1

MKP1 is a dual specificity phosphatase (DUSP), which is an immediate-early gene that is expressed in response to stressors such as oxidative damage or heat shock [228], and can target both JNK and P38. Its downregulation in models of HD is a potential mechanism for the enhanced P38 also observed in these models; MKP1 is reduced in R6/2 [223, 229] and in Hdh^{Q150} [230] brain, as well as in a primary cell model and in human HD post-mortem caudate [223]. Consequently, its overexpression is able to prevent mHTT-induced activation of JNK and P38, whereas ERK phosphorylation was not altered [223]. Furthermore, attenuating the activation of either JNK or P38 alone was not as effective in rescuing the neurotoxic effects of mHTT expression as the attenuation of both together [223], suggesting that the regulation of multiple signalling pathways is required to modulate cell survival in the presence of mHTT neurotoxic insult. Additional evidence for the role of MKP1 in regulating the pro-apoptotic P38 response in HD models includes its upregulation by treatment with BDNF [231] and with the histone deacetylase inhibitor, sodium butyrate, which has been shown to have neuroprotective effects in *Drosophila* and R6/2 models of HD [232, 233].

Targeting an upstream modulator of several pathways may be an efficacious approach to altering kinase signalling within multiple connected networks: however care must be taken when considering the potential long-term implications of this approach on HD neuropathology and on pro-survival signalling pathways.

P53

P53 is a key regulator of apoptotic machinery and tumour suppression through the co-ordination of cellular responses to stress [234, 235]. Upon cell stress, P53 is stabilised via several mechanisms (Fig. 6); it is deubiquitinated by ubiquitin carboxyl-terminal hydrolase 1 (USP1), thus rescuing it from degradation and increasing its activity [236], its activator peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1) can be phosphorylated by other DNA damage-activated kinases, such as ataxia telangiectasia mutated (ATM) and homeodomain-interacting protein kinase 2 (HIPK2), which then leads to a conformational change in P53 that promotes its accumulation [237–240] and its inhibitor, MDM2, is impaired, therefore preventing the promotion of P53 proteasomal degradation [36, 241]. In addition, active P53 translocates to cell nuclei where it can then enhance its own expression [36]. P53 activity can also be enhanced by JNK and P38, as previously described, and AKT signalling can also regulate P53 levels by the activation of MDM2 [242, 243] (Fig. 1). The overexpression of P53 in neuronal cultures elicits cell death, whereas P53 null mice have been shown to be mildly resistant to neurotoxicity [244, 245]. P53 therefore provides an additional pro-apoptotic target that may be dysregulated in HD, thus promoting cell death and neurodegeneration.

P53 in models of HD

Although it has been less thoroughly investigated than the other kinase pathways discussed above, P53 is consistently identified as upregulated in several cell and animal models of HD, as well as in human lymphoblasts and brain (Table 4), and genes downstream of P53 signalling are upregulated in both cell and mouse models of HD [240, 246]. High levels of P53 have been identified in human post-mortem HD brain, with high levels of P53 phosphorylation on serine 46, a post-translational mechanism associated with activation of P53 apoptotic function [239, 247] that can be induced by mHTT expression *in vitro* [240]. The role of P53 in HD-associated neurodegeneration has been

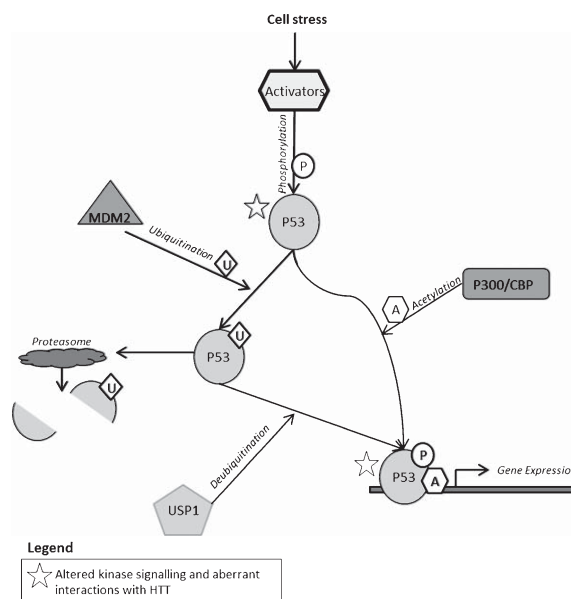


Fig. 6. Stabilisation of P53. P53 is phosphorylated by a variety of cell stress-induced kinases, such as ATM, JNK, PIN1, P38 and HIPK2. The activation of P53 by phosphorylation promotes nuclear localisation, where it acts as a transcription factor, and potentiates acetylation by P300/CBP, which augments DNA binding. MDM2 negatively regulates P53 by ubiquitination, which targets its for clearance by the proteasome. USP1 deubiquitinates P53, thus rescuing it from degradation and stabilising it for activation. Active P53 is also able to enhance its own gene expression [36, 236–240]. White stars indicate where altered kinase activation and aberrant interactions with mHTT that are detrimental to cell survival have been identified.

associated with several mechanisms including mitochondrial membrane depolarisation and cytotoxicity [248]. The binding of P53 to mitochondria is 3x higher in *StHdh*^{Q111} cell lines compared with their wild type counterparts, which may be regulated by the activity of the mitochondrial fission protein dynamin-related protein (DRP1) [249]; DRP1 inhibition reduced this association and increased the survival of R6/2 mice, and reduced the number and size of intracellular striatal aggregates [249].

P53 interacts with nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) (Fig. 8), resulting in the suppression of NF κ B expression and activity; this subsequently decreases the expression of microRNA miR-146a in *StHdh*^{Q111} cell lines and R6/2 striatum, negatively impacting transcriptional regulation [250]. The expression of negative regulators of P53, MiR-150 and MiR-125b, were also suppressed in these models, providing a mechanism for prolonged P53 activation and cellular dysfunction [250]. P53 activation has been described as providing a transient pro-survival response in MSNs following

Table 4
Investigation of phosphorylated P53 levels in various models of HD

Model	mHTT transgene	Repeat length	Brain region	Age	Direction of effect compared to wild type	Additional information	Ref.
Transgenic cell lines	Inducible PC12	148	-	5 days post induction	Increase	Protein levels are increased significantly, but changes in mRNA level were modest	[248]
	Rat primary neuronal cultures	82	Cortex	E16-18	Increase		[248]
	SH-SY5Y	150	-	-	Increase	mHTT expression was sufficient to promote interaction between endogenous P53 & PIN1	[240]
Knock-in cell lines	<i>StHdh^{Q111}</i>	111	-	-	Increase	Thought to reflect augmentation of the stress response pathway in response to immortalisation	[296]
	<i>StHdh^{Q111}</i>	111	-	-	Increase	Due to reduced miR-125b & miR-150 expression	[250]
	<i>StHdh^{Q111}</i>	111	-	-	Increase	Increased association of P53 with mitochondria and with DRP1 hyperactivation	[249]
Transgenic mouse models	N171-82Q	82	Striatum	8 months	Increase	P53 increase selective to mHTT insult, as kainate treatment enhanced P53 to a lesser extent	[248]
	R6/2	150	Striatum	-	Increase		[250]
	R6/2	150	Striatum	13 weeks	Increase	Amelioration of neurological deficits following DRP1 inhibition treatment	[249]
Knock-in mouse models	Hdh ^{Q111}	111	Striatum	12 months	Increase	Transcriptional induction of P53 target genes was dependent on PIN1 expression	[240]
Human	Brain	-	Striatum & cortex	-	Increase	Progressive accumulation with increasing HD grade. No effect in cerebellum	[248]
	Post-mortem	-	-	-	Increase	P53 more commonly phosphorylated on serine 46 in HD brain	[240]
	iPSC	-	-	-	Increase	Mitochondrial dysfunction could be ameliorated with P53 shRNA	[249]

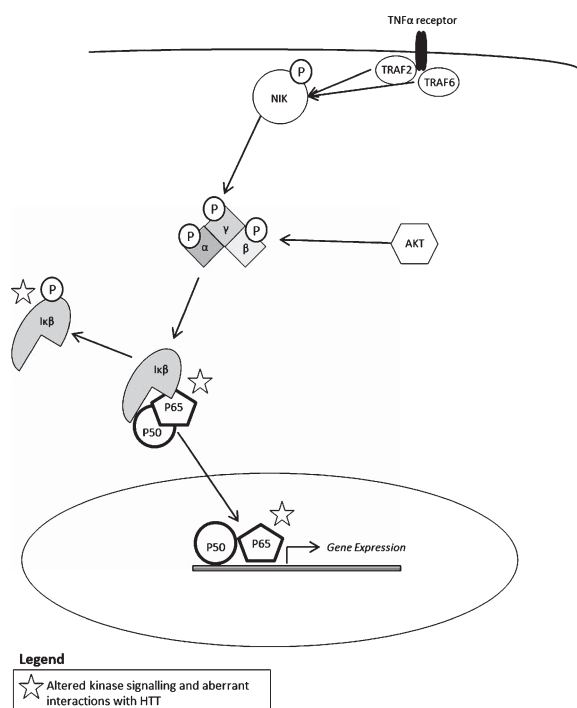


Fig. 7. IKK/NF κ B cascade. The IKK complex, consisting of α , β , and γ subunits is phosphorylated by kinases downstream of receptor activation by cytokines; the most common of which is TNF α , which phosphorylates TNF receptor associated factors, TRAF2 and TRAF6. These consequently activate NF κ B-inducing kinase (NIK), which phosphorylates the IKK complex. IKK may also be phosphorylated by AKT downstream of alternate signalling pathways, such as following EGF and platelet derived growth factor (PDGF) stimulation. NF κ B is present in the cytoplasm as a three unit complex composed of P65, P50 and I κ B subunits. Activated IKK phosphorylates I κ B, resulting in its ubiquitination and degradation. The P65 and P50 subunits are then freed for nuclear translocation and transcriptional regulation [88, 134, 250, 261, 263–267, 269]. White stars indicate where altered kinase activation and aberrant interactions with mHTT that are detrimental to cell survival have been identified.

nuclear stress due to a mHTT-associated impairment in nucleolar and ribosomal integrity [251], although prolonged P53 activity ultimately leads to cell death and neurodegeneration.

The silencing or inhibition of P53 has been shown to be neuroprotective in models of HD; silencing P53 in the *StHdh*^{Q111} cell model reduced cell death and the number of cells with fragmented mitochondria [249], and its deletion suppressed retinal degeneration in *Drosophila* and rescued behavioural abnormalities in R6/2 mice [248]. Reducing P53 also abolished neuronal death in primary striatal cell cultures and ameliorated the toxicity induced by the removal of HTT phosphorylation of serines 1181 and 1201 [121].

P53 and huntingtin

Importantly, mHTT has been shown to directly interact with P53 in a manner that alters the expression and activity of both [240, 248, 252–256] (Fig. 8). mHTT can sequester P53 within intranuclear inclusions [232, 254], and they may interact via the amino-terminal region of mHTT [248, 252, 253], which may alter P53 transcriptional activity [252]. Therefore, although P53 activity may be enhanced in HD, the mechanism by which it regulates transcription and apoptosis under normal cellular stress conditions may be aberrantly affected by mHTT, further complicating this mechanism. The *HTT* gene carries three potential P53-responsive elements, which promote the expression of HTT upon P53 activation [255, 256]. As such, the expression of *HTT* is lower in *Hdh*^{Q140} mice deficient in P53 [256]. However, although inhibition of P53 may provide a two-pronged neuroprotective mechanism by suppressing pro-apoptotic pathways and reducing the cellular level of toxic mHTT, Ryan et al. 2006 demonstrated that P53 knockout *Hdh*^{Q140} mice had considerably more striatal intracellular inclusions than those expressing P53. Whether mHTT inclusions are neurotoxic remains debatable: however, aggregation requires high levels of toxic mHTT species [257] and accumulation of aggregates over time may be disruptive to cell function. Therefore inhibition of P53 may not provide effective long-term neuroprotection. mHTT has also been proposed as an upstream inducer of P53: expression of mHTT in SH-SY5Y neuroblastoma cells was sufficient to promote the interaction between P53 and one of its inducers, PIN1, resulting in P53 phosphorylation, and increased protein levels of another P53 modulator, HIPK2 [240].

INFLAMMATORY SIGNALLING PATHWAYS

IKK & NF κ B

Neuroinflammation is a primary component of several neurodegenerative diseases [17, 258], and may promote either pro-survival or pro-apoptotic cell mechanisms depending upon the context and duration of pathway activation [19]. Both *Hdh*^{Q150} and R6/2 mouse models exhibit enhanced chronic neuronal pro-inflammatory responses to systemic inflammation that exacerbate motor and cognitive dysfunction [18], and human macrophage and monocyte cultures showed a hyper-reactive inflammatory cytokine response to lipopolysaccharide stimulation that could be attenuated with the lowering of mHTT expression [259].

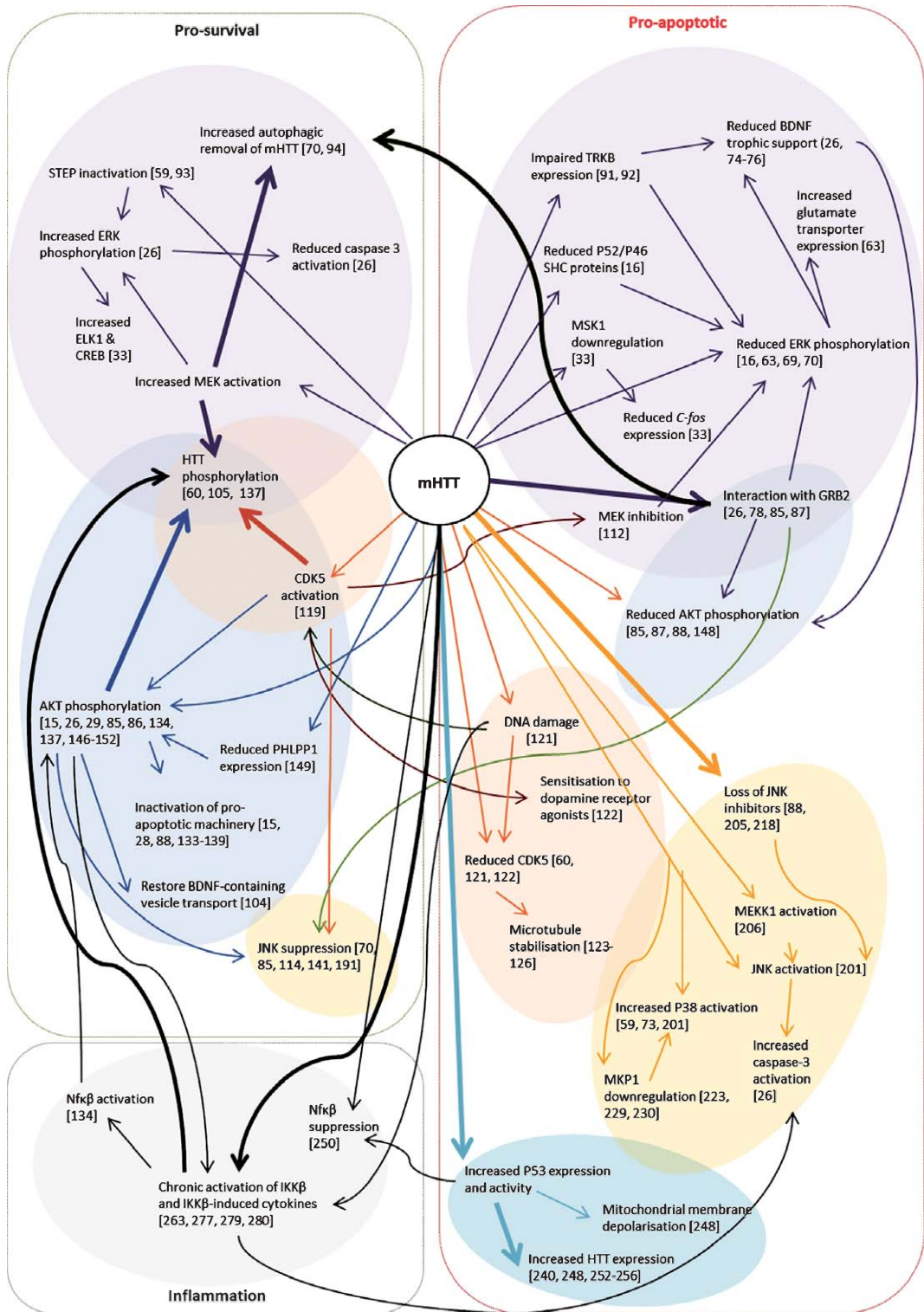


Fig. 8. Schematic displaying the interplay of mHTT with various kinase signalling pathways implicated in HD. Distinct pathways are grouped into separately shaded ellipses, which overlap where the consequences of mHTT disruption overlap. Weighted arrows indicate direct interactions with HTT or mHTT. Alterations in several signalling pathways result in both pro- and anti-apoptotic responses, depending on the model investigated, cellular context and experimental conditions employed.

However, very mild chronic inflammation had no effect on disease progression in YAC128 mice [260], indicating that the role of neuroinflammation in HD could be highly variable and dependent on the regulation of multiple factors. The IKK/NF κ B signalling pathway is a prominent regulator of neuroinflammation, and typically promotes cell survival and growth [19, 261–263]. IKK is composed of three subunits; IKK α and IKK β , which are homologous catalytic subunits, and IKK γ , a regulatory subunit [263] (Fig. 7). Phosphorylation of the IKKs has been shown to occur in response to tumour necrosis factor alpha (TNF α) stimulation, and in response to other growth factor-stimulated pathways via AKT activation [264–268] (Fig. 8). NF κ B is present in the cytoplasm as an inactive complex of P50 and P65 subunits, bound by nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (I κ B) proteins [261, 262]. The activated IKK complex phosphorylates the I κ B proteins, which targets them for ubiquitination and degradation. This subsequently frees the P50 and P65 subunits for translocation to cell nuclei where they activate transcription [88, 134, 269, 270] (Fig. 7).

Acute IKK β activation typically invokes cellular pro-survival responses, whereas chronic elevation of IKK β has been associated with neurodegenerative processes [19]. Chronic IKK β activation can be induced via DNA damage [271], and a variety of stimuli activates the NF κ B pathway, including cytokines, injury and seizure [272]. Neuronal damage as a result of chronic IKK β elevation has also been proposed to be a result of an excessive inflammatory response in adjacent astrocytes [18] as well as altering signalling in neurons themselves. Activation of the IKK α subunit is more commonly associated with neuroprotective mechanisms: for example, activation has been shown to inhibit pro-apoptotic P53 and IKK β activity [273, 274], and to regulate IKK β -dependent expression of pro-inflammatory cytokines in immune cells [275]. It is also required for the promotion of memory consolidation and synaptogenesis in the hippocampus [276].

IKK in HD

Excessive IKK β has been observed in several cell and mouse models of neurodegenerative diseases, including AD, MS, PD and HD [19, 277, 278]. HD patients also exhibit chronically increased levels of IKK/NF κ B pathway-induced inflammatory cytokines [263, 277] in blood serum and in the CNS prior to symptom onset, as well as hypersensitivity of immune cells [17, 259]. Elevated IKK β is present in HD cell culture models and in R6/2 mouse brain, which par-

allels the enhanced levels of inflammatory cytokines also detectable in these mice [277, 279]. However, increased IKK β is identified only in the striatum of Hdh^{Q150} mice [277, 280]. While exon 1 of mHTT was able to directly interact with IKK γ in an inducible PC12 cell line expressing mHTT in a manner which promoted the assembly and activation of the full IKK complex, full length mHTT was unable to activate IKK [277, 281]. The gradual accumulation of toxic amino-terminal mHTT fragments in the striatum of the full length Hdh^{Q150} model was proposed as a mechanism for the difference in IKK activation between mouse models [277, 280]. However, more recently an interaction between IKK γ and endogenous full length mHTT has been demonstrated in human-derived macrophage and monocyte cultures [259]. Consistent with a pro-apoptotic role of IKK β in models of HD, blocking IKK β activity prevented the degeneration of MSNs in cell culture and brain slice assays [277], and its knock down in microglia reduced neuroinflammatory and neurotoxic responses to kainic acid in hippocampal neurons [282].

The neurotoxic effects of elevated IKK β have been associated with its role in the increased cleavage of HTT and mHTT in response to DNA damage; DNA damage accumulates with age and disease development, which activates caspases and reduces levels of anti-apoptotic protein B-cell lymphoma-extra large (BCL-XL) via activation of IKK β [271]. The creation of additional mHTT amino-terminal fragments as a result of enhanced caspase activation may then result in the prolonged activation of IKK by the interaction of mHTT with the IKK γ subunit, therefore creating a toxic feedback loop. Inhibition of IKK β or enhancement of IKK α prevented caspase activation and HTT proteolysis, which resulted in the promotion of neuronal survival [101, 271]. Deletion of IKK β from microglia reduced the extent of neurodegeneration in a chemical model of neurodegeneration [282], and astrocytes from the R6/2 mouse model exhibit higher IKK activity, which conferred a more damaging effect on adjacent neurons during inflammation [18]. Blocking IKK activity reduced the toxicity caused by R6/2 astrocytes and improved cognitive function and motor co-ordination [18].

IKK and HTT phosphorylation

The phosphorylation of HTT on serines 13 and 16 may be regulated by IKK β activity; however the mechanism by which this occurs is under debate [96, 97, 283]. Initially, Thompson et al. 2009 proposed that IKK β phosphorylates HTT on these serines, which

resulted in enhanced nuclear localisation, proteolysis and clearance by the proteasome and lysosome, and phosphorylation of mHTT by this process was less efficient. Enhanced mHTT proteolysis would firstly act as a neuroprotective mechanism by increasing the clearance of mHTT, consistent with the neuroprotective effect of acute IKK β activation. However, chronic IKK β activation and mHTT proteolysis would result in the accumulation of nuclear toxic amino-terminal fragments and the acceleration of wild type HTT turnover [96, 271]. The treatment of N171-82Q transgenic HD mice with the HDAC inhibitor 4b increased the expression of genes encoding components of the IKK complex, and increased the phosphorylation of HTT at serine 16 and threonine 3, as well as promoting the expression of genes associated with autophagy [283]. Treatment with the HDAC inhibitor also prevented the formation of mHTT aggregates, and improved motor and cognitive performance [283], therefore supporting a potentially neuroprotective role for enhancing IKK signalling.

Conversely, the inhibition of IKK β has also been found to increase the phosphorylation and nuclear localisation of HTT [97, 284]. Increased IKK β activity has been correlated with increased PP2A phosphatase activity [285], which can dephosphorylate serine 421 of HTT [286], thus increasing its nuclear accumulation. Whether IKK signalling is most likely to exert neuroprotective or neurotoxic effects remains unclear, and the nature of its activation is likely to be a result of the balance between individual contributions from the three subunits of the IKK complex, as well as the cellular context and activities within other pathways. Whether the phosphorylation of HTT on serines 13 and 16 is neuroprotective also remains under debate; it has been found to promote HTT accumulation in cell nuclei, to impair nuclear transport and it correlates with disease progression in Hdh^{Q140} mouse striatum [98], whereas in BACHD mice it appears to be neuroprotective [95].

Dysregulation of IKK signalling has therefore been consistently identified as a modulating factor in the progression of HD by influencing aberrant inflammation responses, and by direct interaction with the mHTT protein. However, the role of IKK β in HTT phosphorylation remains to be elucidated, as both its activation and inhibition are able to elicit similar neuroprotective phosphorylation of HTT [96, 97, 271, 284]. As IKK can be regulated by multiple signalling pathways, such as AKT [264, 268] and TNF α [134], model-dependent alterations in activity within these pathways may contribute to the cellular response to

IKK signalling. The individual subunits of the IKK complex appear to have differential roles for cell survival and exhibit multiple patterns in models of HD [101, 271], therefore characterisation and the specific targeting of individual IKK subunits may be required to more fully understand the role of IKK β in HD and to elicit effective neuroprotection.

Nf κ β in HD

Although formation of the inflammatory IKK complex elicits activation of NF κ β (Fig. 7), the majority of NF κ β signalling provides a pro-survival signal [134], and a lack of NF κ β signalling can be pro-apoptotic: for example, mice lacking the P50 subunit of NF κ β suffer increased 3-NP induced striatal damage and motor dysfunction [272]. As with many of the other kinase signalling pathways discussed here, the effects of mHTT on NF κ β are varied, and whether or not NF κ β generally plays a neuroprotective role in models of HD remains unclear.

A reduction in NF κ β P65 has been identified in *StHdh*^{Q111} cells and in R6/2 striatum as a result of negative regulation by increased P53 activity [250], as well as in PC6.3 cells expressing mHTT [287]. However, *StHdh*^{Q111} cells have increased responsiveness of NF κ β to stimulation by its activator interleukin 1 beta (IL-1 β) [277], and increased nuclear concentrations of NF κ β P65 have been identified in R6/2 cortex and striatum at 8 weeks of age [101]. In this context, increased NF κ β signalling was found to be pro-apoptotic; blocking NF κ β activity reduced mHTT-induced toxicity in cultured cells [277]. Aberrant NF κ β has also been observed in R6/2 mouse astrocytes as a result of increased IKK activity; however there was no difference in R6/2 neurons or microglia [18]. Increased astrocytic NF κ β was also present in human HD caudate [18]. Similar to the *StHdh*^{Q111} model, R6/2 astrocytes exhibited an increased NF κ β response following treatment with TNF α or IL-1 β , including the induction of stronger NF κ β -DNA binding [18].

Although NF κ β activity has been regarded as a pro-apoptotic inflammatory mechanism in HD, its upregulation via activation by an agonist for the ER chaperone protein, sigma 1 receptor, protected PC6.3 cells from the toxic effects of mHTT by increasing cellular antioxidants and reducing oxidative stress [288]. NF κ β activation and function may also fluctuate over time; Di Pardo et al. 2013 demonstrated that monocyte-derived macrophages from pre-symptomatic HD patients had NF κ β activation similar to controls and higher than those taken from symptomatic patients: post-mortem brain tissue exhib-

ited a similar changing profile of $\text{NF}\kappa\beta$ dependent on the stage of neurodegeneration. Activation of $\text{NF}\kappa\beta$ promotes pro-inflammatory macrophage polarisation [289], and may therefore provide neuroprotection following acute $\text{NF}\kappa\beta$ activation, which then elicits damaging neuronal effects as a result of chronic activation. The subsequent reduction in $\text{NF}\kappa\beta$ may be a result of a compensatory anti-inflammatory cascade [289]; the P50 subunit promotes the production of anti-inflammatory cytokines, which promote formation of a P50/P50 homodimer that inhibits $\text{NF}\kappa\beta$ activity [290, 291]. A reduction in P65 $\text{NF}\kappa\beta$ later in the disease course may therefore be a result of preferential P50 activation [289]. Additionally, the reduction may be due to the sequestration of $\text{NF}\kappa\beta$ into mHTT neuronal aggregates upon disease progression [250]. This phasic alteration in $\text{NF}\kappa\beta$ has also been observed in cell models of HD: upon mHTT induction, $\text{NF}\kappa\beta$ is initially enhanced, but decreases following aggregate formation during disease progression [292, 293]. Kinase activation should therefore not be considered as a static characteristic that is present over the course of a disease, but fluctuations in activation state are likely to contribute to their pro-apoptotic or pro-survival function, as well as influence the development of molecular pathogenesis.

As the $\text{IKK}/\text{NF}\kappa\beta$ pathway does not act in isolation; time-related alterations in this pathway are likely to also impact upon multiple other signalling pathways. For example, AKT has been identified as a kinase upstream of IKK activation [264, 268] (Figs. 1 and 8), however the phosphorylation of AKT has also been demonstrated as being downstream of $\text{NF}\kappa\beta$ [134], which has implications for the regulation of pro-survival signalling pathways during disease progression. The $\text{NF}\kappa\beta$ -regulated activation of macrophages also affects the number of $\text{TGF}\beta$ producing cells [289], and its activity as a transcription factor regulates the expression of inflammatory mediators, such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$ [18], and therefore may be a major regulator responsible for influencing neurotrophic signalling, and consequently cell fate.

CONCLUSION

Kinase signalling pathways are fundamental to cell death and survival and hence their operation is likely to be important in the cell dysfunction and death seen in neurodegeneration. It is notable that whilst multiple kinases and signal transduction pathways have been implicated in the regulation of neuronal survival in

HD, very few demonstrate a single coherent pattern of activation. This may be a result of kinase signalling pathways commonly being considered in isolation: multiple points within the cell signalling network are likely to contribute to cell fate and dysfunction. A lack of replication across models and techniques used to investigate kinase signalling in HD has also contributed to the difficulty in clarifying the role of kinase signalling pathways in HD. For example, differences in mouse strain and genetic background may contribute to the equilibrium and regulation of kinase signalling in different models, and different stages of HD progression may also differ with respect to their kinase signalling pathways. As complex and dynamic mechanisms that potentially alter with age and disease progression, appropriate longitudinal investigation of kinase signalling pathways in HD may prove useful.

Additionally, signalling in multiple pathways integrate downstream of a single growth factor stimulus, and multiple stimuli share similar common signalling pathways (Fig. 1). Thus different kinetics of stimulation and response, as well as different cellular contexts, are required in order to differentiate these signals [189, 294, 295]. For example, the magnitude and duration of ERK activity can determine whether or not it provides a pro-apoptotic signal [294], and the rapidity of ERK dephosphorylation has been correlated with the extent of neuroprotection that activation in this pathway may provide [189]. Consequently, treatment with the same stimulus, i.e. a growth factor or expression of mHTT, may result in different responses in different contexts, as has been commonly observed between models of HD.

The multiple stages at which kinase signalling can be altered by mHTT further adds to the complexity of signalling networks in HD: mechanisms that contribute to the dysregulation of kinase signalling pathways in HD include the disruption by mHTT at growth factor receptors [26, 63, 78, 85–87, 91], aberrant interactions with regulatory factors [33, 59, 88, 205, 216, 217, 240] and direct interaction with the mHTT protein itself [60, 240, 248, 252–256], which can in turn alter mHTT function and clearance by post-translational modifications such as phosphorylation [60, 88, 105, 121, 137].

MEK/ERK, CDK5/P35 and AKT signalling pathways are typically considered to be pro-survival pathways, although whether they are enhanced in models of HD as a compensatory response mechanism remains unclear. Activation of MEK/ERK and CDK5 has been demonstrated to be both neuroprotective and pro-apoptotic, depending on whether stimulation

is chronic or acute and the presence of additional modulating factors [116, 122]. The activation of pro-apoptotic signalling pathways in models of HD has been shown to be either upregulated, consistent with neuronal loss, or to exhibit no change. JNK activation has not yet been investigated as thoroughly as AKT or ERK signalling in HD and to date there is no evidence of its activation in human tissues or cell lines. The relationship between inflammatory kinases and additional neuroprotective or neurotoxic mechanisms is complex, and likely to be dependent on cellular context, synergistic associations with multiple signal transduction pathways and whether any inflammatory response is acute or chronic. Similar to the regulation of pro-survival and pro-apoptotic pathways, the characteristics and neuroprotective role of this pathway in HD is likely to depend on neuronal development and disease progression.

The understanding of signalling pathway networks in HD has implications for therapeutic targeting; for example, the differentiation between neuroprotective effects of acute activation and chronic inflammatory pathways would be important in order to avoid inhibiting early protective activation of these pathways. In addition, the differential activation of multiple pathways that occurs with disease progression may influence the point at which particular kinases may be targeted. Altering the activity of one kinase is likely to have effects on multiple others, thus an improved understanding of the integration of a network of pathways in different cellular contexts would be useful to construct a multi-pathway targeting approach.

In conclusion, the dysregulation of multiple kinase signalling pathways contributes to HD pathogenesis, including enhanced pro-apoptotic signalling and compensatory pro-survival mechanisms. The balance between these pathways and alterations over time may regulate disease progression and cell fate. However, inconsistencies in the pattern of kinase signalling in models of HD make any firm conclusions about individual pathways difficult to draw. The consideration of a dynamic network of multiple signalling pathways over time and in different cellular contexts may be beneficial in clarifying the role of various kinases in models of HD and to uncover new, potentially efficacious therapeutic targets.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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