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Apoptosis in Neurodegeneration: Programmed Cell Death and its Role in Alzheimer's and Huntington's Diseases

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Summary

Chronic neurodegenerative diseases are characterized by progressive, irreversible neuronal cell loss. Since neurons have minimal regenerative potential, preventing their degeneration is vital to preventing disease progression; however, few effective therapies currently exist. Research in the last two decades has focused on uncovering neuronal cell loss mechanisms in hopes of devising new treatment strategies. These studies have evaluated the potential role of apoptosis within neurodegenerative diseases. Investigations of programmed cell death and its role in neurodegenerative disease has shed light on the possible apoptotic mechanisms employed by these disorders. This article will review general mechanisms of apoptosis and their implications within Alzheimer's and Huntington's diseases.

The Apoptotic Machinery

Cell death: necrosis versus apoptosis
Cell death occurs in one of two ways: necrosis is a pathological process in which death signals are the direct cause of cellular destruction; apoptosis a is programmed process in which death signals initiate a cascade of activities that eventually result in cell death (Mattson 2006). The latter process, also known as programmed cell death, has important implications in neurodegenerative disorders. Although physiological apoptosis is a feature of normal development, aberrant apoptosis may become rampant in these diseases (Friedlander 2003).

Processes of programmed cell death
Apoptosis occurs through two pathways: the death-receptor pathway and the mitochondrial pathway (Hengartner 2000). In the death-receptor pathway, death signals activate neuronal cell membrane receptors, prompting a cascade of events that eventually results in cell death (Hengartner 2000). The mitochondrial pathway, on the other hand, occurs when proapoptotic molecules respond to cell death signals by converging at the mitochondria (Hengartner 2000). These molecules cause mitochondrial release of proteins that carry out the cell death cascade (Hengartner 2000). Both pathways involve the activation of molecules called caspases, which degrade necessary proteins and ultimately lead to apoptosis (Liu 1997; Hengartner 2000).

Cells undergoing apoptosis display cytoplasmic and nuclear condensation, chromatin aggregation, and aggregation of mitochondria and ribosomes (Liu 1997; Hengartner 2000). After death, these cells exist as fragments and their DNA undergoes further cleavage (Liu 1997; Hengartner, 2000). This review will convey the potential roles of the death-receptor and mitochondrial apoptotic pathways within Alzheimer's and Huntington's diseases.

Treatment development for these and other neurodegenerative disorders demands a thorough understanding of the apoptotic mechanisms that contribute to neuronal cell death. Just 15 years ago, the general mechanism of apoptosis was largely illusive. However, studies published throughout the 1990's shed light on the genes controlling developmental apoptosis in Caenorhabditis elegans. These findings fostered later investigations of programmed cell death in mammalian subjects.

C. elegans: a model for the study of apoptotic mechanisms
In the early 1990's, a series of studies on apoptosis in C. elegans uncovered several genes involved in the programmed cell death pathway. In this organism, apoptotic events require ced-3 and ced-4 genes, but are inhibited by the nematode's ced-9 gene (Yuan et al. 1993). Mammalian gene product homologues have since been discovered. The C.elegans ced-3, ced-4 and ced-9 genes respectively correspond to the following mammalian gene products: caspases, Apaf-1 adaptor proteins and Bcl-2 proteins (Miura et al. 1993; Yuan et al. 1993). Specifically, the ced-3 gene product corresponds to mammalian caspase 1, also known as interleuken-1ß-converting enzyme. (Yuan et al. 1993; Hengartner and Horvits 1994). These molecules play critical roles in programmed cell death pathways.

Apoptosis in mammalian neurodegenerative diseases
In neurodegenerative diseases, death-receptor apoptotic pathways initiate when pro-death signals interact with one of several neuronal cell membrane receptors, thereby prompting a cascade of events that ultimately results in cell death (Yuan and Yanker 2000). Activation of neuronal cell membrane receptors may result in caspase activation, enhanced calcium levels and the generation of reactive oxygen species (ROS) (Lorenzo et al. 2000). Such events contribute significantly to programmed cell death: caspases are the molecules chiefly responsible for apoptosis; high calcium levels and ROS are known to contribute to the mitochondrial pathway (Lorenzo et al. 2000).

Mitochondrial apoptosis is initiated by a variety of signals, including Bcl-2 proteins, high intracellular calcium levels and reactive oxygen species (ROS) (Kruman et al. 1997; Li et al. 1997; Lorenzo et al. 2000). These signals accumulate at the mitochondria, resulting in the release of one of several pro-death molecules into the cytoplasm (Figure 1; Li et al. 1997). Mitochondria, in addition to their role in energy production, contribute to apoptosis by releasing pro-death molecules into the neuronal cytoplasm (Krohn et al. 1999). One pro-death molecule with particular implications in neurodegenerative diseases is cytochrome *c*, which exists normally in the electron transport chain on the mitochondrial membrane (Li et al. 1997). Upon entering the cytoplasm, cytocrome *c* forms an apoptosomal complex with a procaspase, ATP and Apaf-1, an apoptotic protease-activating factor (Figure 1; Hengartner 2000). This complex then works as a cell death signal by promoting caspase activation (Li 1997).

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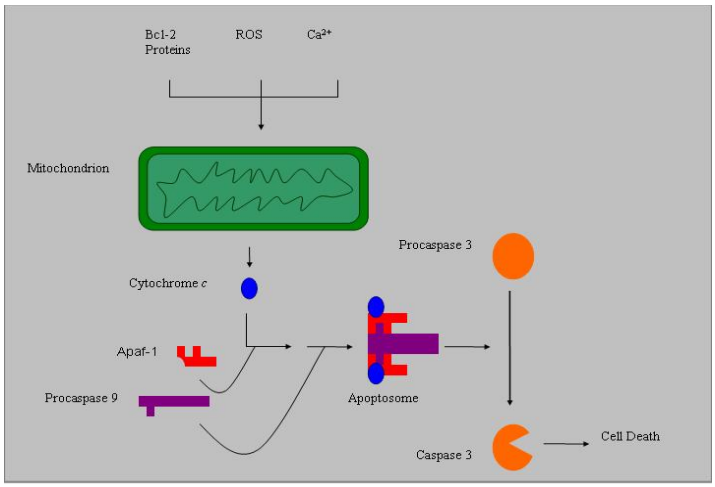

Figure 1. Generalized Mitochondrial Apoptotic Pathway. Various signals promote mitochrondrial release of proapoptotic molecules: Bcl-2 proteins, reactive oxygen species (ROS) and high Calcium levels. The mitochondria release, proapoptotic molecules, such as Cytochrome *c*. Cytochrome *c* binds Apaf-1 and procaspase 9 to form the apoptosome, thereby activating caspase 9. Caspase 9 activates caspase 3, ultimately leading to cell death. (Friedlander 2003).

The role of caspases

Caspases, or cysteine-dependent, aspartate-specific proteases, are enzymes that cleave proteins after an aspartic acid residue (Hengartner 2000). They represent the chief components of the mammalian apoptotic mechanism (Friedlander 2003). At least 14 different caspases exist; 11 have been documented in humans (Yuan et al. 1993). These molecules, homologous to C.elegans ced-3 gene products, occur inactively as precursor procaspases and then launch the cell into apoptosis after activation (Yuan et al. 1993). Procaspases contain two subunits and an N-terminal activation region, and they exist as either upstream initiators or downstream executioners (Liu 1997). Upstream initiators contain long N-terminal regions and are regulated either by cell death signals or at the transcriptional level; downstream executioners contain short N-terminal regions and are activated by upstream initiators (Liu 1997). The apoptotic program includes destruction of essential cell elements; the process completes when active downstream executioners instigate DNA degradation (Liu et al. 1997). Caspases 9 and 3 are the initiator and executioner caspsases, respectively, that typically predominate neurodegenerative diseases (Friedlander, 2006). However, caspases 6, 7, 8, 12 and 14 are also involved in programmed cell death mechanisms (Chan et al. 2000; Friedlander, 2006).

Apoptosis in Alzheimer's disease

Disease background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by widespread cerebral atrophy beginning in the hippocampus and spreading to the temporal and frontal brain lobes (Kang et al. 1987; Mattson 2004). These brain regions are largely responsible for learning and memory capabilities, and their degeneration explains the short-term memory loss, slowed speech and cognitive dysfunction characteristic of AD (Mattson 2004). The disease exists in two forms: sporadic AD occurs in ~90% of cases, has no inheritance pattern and cannot be linked to a gene; familial AD (FAD) occurs in ~10% of cases, is inherited in an autosomal dominant pattern, and can be traced to the amyloid precursor protein (APP) gene, the presenilin-1 gene (PS1) or the presenilin-2 gene (PS2) (Nijhawan et al. 2000).

AD brains are distinguished primarily by the presence of two pathological protein inclusions: extracellular plaques composed of amyloid-ß (Aß) proteins, and intracellular neurofibrillary tangles composed of microtubule-binding tau proteins (Mattson 2004). The presence of these inclusions correlates with disease progression throughout the brain (Mattson 2004). In addition, Aß plaque presence in particular correlates with decreased neuronal synapses and increased neuritic damage, suggesting that this protein may have a neurotoxic role (Mattson 2004). Research in the last two decades has suggested that Aß plaques, as well as tau tangles, play a role in the degeneration and cognitive impairment that occurs in AD. Many of these studies have attempted to elucidate the way in which AD gene mutations may contribute to the disease's apoptotic mechanisms.

Amyloid precursor protein (APP) and its Aß cleavage product

Research on APP and its role in programmed neuronal death began to increase after the Aß protein had been sequenced, and its precursor's gene localized to chromosome 21 (Kang et al. 1987). Both the APP protein and its Aß cleavage product exist in normal individuals; however, AD patients with mutant APP genes produce a precursor that undergoes abnormal cleavage in neuronal cell membranes (Kang et al. 1987). The mutant precursor is cleaved twice to produce the Aß protein seen in AD plaques: the enzyme ß-secretase (BACE) performs an initial extracellular cleavage; the enzyme γ-secretase performs a second intramembrane cleavage (Mattson 2004). In addition to APP gene mutations being implicated in neuronal apoptosis, mutations in the presenilin genes encoding the APP-cleaving enzymes have also been linked to AD development (Levy-Lahad et al. 1995).

APP gene mutation: its role in neuronal apoptosis

The role of APP gene mutations and Aß plaques in the brains of AD patients is currently under heavy debate: researchers are unsure whether Aß plaques are toxic or protective protein depositions. Although this question remains to be answered, several observations have been made regarding Aß's potential role in the apoptotic machinery. Initial studies on this topic suggested that Aß plaques directly induce apoptosis *in vitro* (Yanker 1996). However, recent research shows that Aß is more likely to induce apoptosis indirectly, possibly by first promoting oxidative stress through the production of reactive oxidative species (ROS) (Behl et al.; Kruman 1997; Mattson 2006). ROS are known proapoptotic molecules within the mitochondrial cell death pathway (Kruman 1997; Mattson 2006). Aß may also instigate this pathway by upregulating the proapoptotic Bcl-2 bax protein (Paradis et al.1996), and inducing other apoptotic signal cascades (Mattson et al. 1998). Such research suggests that APP gene mutations and Aß plaques initiate apoptosis quite early within the mitochondrial cell death pathway. However, other research has found that some genes implicated further downstream in this pathway are upregulated in mutant APP mice, including those that encode caspases 6 and 8 (Reddy et al. 2004).

Aß plaques, in addition to their role in mitochondrial apoptosis, may also be involved in the death-receptor pathway. Aß interacts with microglia and a variety of neuronal cell membrane receptors to promote this apoptotic pathway (Figure 2; Yuan and Yanker 2000). These receptors include: the tumor necrosis factor-α (TNF-α) receptor, the p75 receptor, receptors for glycation advanced endproducts (RAGE), and others (Figure 2; Lorenzo et al. 2000; Yan et al. 1996; Yarr et al. 1997). Aß interaction with microglia induces the secretion of TNF- α, a protein known to promote neuronal apoptosis (Giulian et al. 1996, Tan et al., 1999). Aß activation of neuronal cell membrane receptors results in ROS generation, increased calcium levels and other events that also contribute to mitochondrial apoptosis (Figure 2; Lorenzo et al. 2000). Particularly interesting is the fact high calcium levels may activate, in addition to the mitochondrial pathway, molecules known as calpain proteases (Figure 2; Yuan and Yanker 2000). Calpain proteases prompt the kinase Cdk5 to phosphorylate tau, thus activating the protein (Figure 2; Patrick et al. 1999). Activated tau protein binds itself, creating the neurofibrillary tangles characteristic of AD (Figure 2; Mattson 2004). These tangles are also considered to be possible contributors to neuronal apoptosis, perhaps through their ability to increase ROS levels and thus promote apoptotic pathways (Mattson 2004; Yan et al. 1994).

Presenilin mutations and their role in neuronal apoptosis

In addition to the role of APP mutations in promoting apoptosis, mutations in the presenilin genes, particularly presenilin 1, have been associated with apoptotic pathways in AD. For example, neurons from presenilin 1 mutant mice are more susceptible to apoptotic events than their non-mutant counterparts (Chan et al. 2000). This increased susceptibility could be the result of several causes; however, research points toward the possibility that presenilin-1 gene mutations may increase intracellular calcium levels by altering the endoplasmic reticulum's calcium balance (Guo et al. 1997). Cell cultures taken from presenilin 1 mutant mice showed elevated calcium levels, a factor known to contribute to mitochondrial apoptotis (Friedlander 2006; Guo et al. 1997). In addition, presenilin gene mutations increase Aß plaque production and may thus contribute to apoptosis through this molecule (Schuener et al. 1996).

Evaluating AD Apoptosis and Devising Target-Based Treatments

Although many studies suggest that programmed cell death plays a critical role in AD neurodegeneration, researchers remain largely unable to quantify the amount of cell loss that can be attributed to apoptosis. Although many degenerating neurons display the cytoplasmic and nuclear condensation and chromatin aggregation characteristic of apoptosis, not all declining AD brain cells present these signs (Liu, 1997; Su et al. 1994). In addition, pinpointing the direct cause of apoptosis in AD will also require additional research. Many studies suggest that the disorder's pathological inclusions play a role in programmed cell death pathways; however, additional research is necessary to evaluate the full function of these protein aggregates.

Despite the fact that many questions regarding apoptosis in the AD brain remain unanswered, current research on this topic has enabled scientists to develop potential therapeutic strategies for AD treatment. For example, Aß's ability to promote apoptosis through interaction with neuronal cell membrane receptors suggests that blocking these receptors may prevent the apoptotic pathway in AD (Yuan and Yanker 2000). In addition, inhibiting the caspases that ultimately drive apoptosis may also be a potential treatment for the disorder: caspase inhibition in AD mouse models has resulted in decreased evidence of neuronal death by apoptosis (Nakagawa et al. 2000).

Apoptosis in Huntington's disease

Disease background

Hungtington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by motor dysfunction, cognitive impairment and psychosis (Sharp et al. 1995). The disease is caused by an *IT15* gene mutation on chromosome 4 (Sharp et al. 1995). This mutation produces a CAG/polyglutamate repeat expansion in the gene's protein product, huntingtin (htt) (Sharp et al. 1995). The DNA sequence CAG encodes the protein glutamate, an amino acid known primarily for its roles in metabolism and as a neurotransmitter (Cotman and Monaghan 1986; Kandel 2001). Normal huntingtin protein contains 9-35 CAG repeats; however, its mutant form may contain up to 250 of these repeats (Cattaneo et al. 2002). Both forms of the protein are known to undergo caspase cleavage to generate smaller, truncated fragments; however, the mutant protein's fragments are distinct in their correlation with neurodegeneration (Wellington et al., 2002).

Researchers are unsure why the mutant protein's CAG repeats cause HD; however, two theories exist to explain disease onset. One theory, the loss of function hypothesis, suggests that the CAG expansion disables huntingtin from carrying out its normal function (Catteneo et al. 2002). A second theory, the gain of function hypothesis, suggests that the *IT15* mutation produces a toxic huntingtin protein with a distinct conformation that enables it to stick to both itself and normal huntingtin (Catteneo et al. 2002). This conformation allows mutant huntingtin fragments to clump in aggregates and simultaneously inhibit the normal protein's proper function (Catteneo et al. 2002).

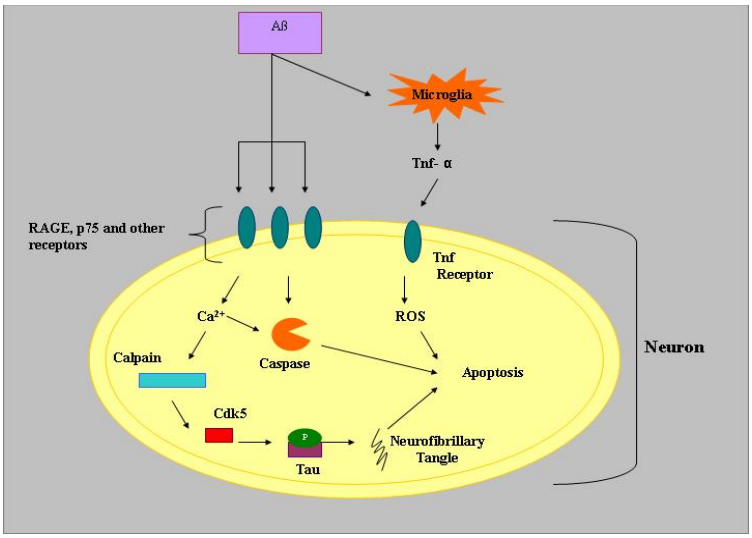

Figure 2. Death-Receptor Apoptotic Pathway in Alzheimer's Disease. Aß plaques activate neuronal cell membrane receptors and microglia, resulting in signal cascades that activate caspases, produce ROS and increase intracellular Ca^{2+}. Caspase activation leads directly to apoptosis. ROS generation and increased Ca^{2+} contribute to the mitochondrial apoptotic pathway, eventually resulting in apoptosis. High Ca^{2+} levels may also activate calpain proteases, resulting Cdk5 phosphorylation of tau and the creation of neurofibrillary tau tangles that may also lead to neuronal apoptosis. (Yuan and Yanker 2000).

Despite these opposing hypotheses regarding the exact role of CAG expansion, one idea is accepted across the board: mutant huntingtin forms inclusions in cell nuclei depending on the length of its CAG repeat, and longer repeats correlate with an increased presence of huntingtin inclusions (Senut et al. 2000). Moreover, these nuclear inclusions are associated with premature neuronal cell death, especially in the striatum and globus pallidus (Hickey and Chesselet 2003). Theories on the potential role of these HD inclusions in apoptosis have circulated for years, and studies on this topic increased markedly after the development of a mouse model for the disease in 1996 (Mangiarini et al. 1996). Since that time, the HD transgenic mouse model has been used to elucidate the disease's cell death machinery.

Mutant huntingtin inclusions: facilitators of HD apoptosis?

Although the exact mechanism of apoptosis in HD remains to be uncovered, several insights into the disease's apoptotic mechanisms have been made. Originally, huntingtin inclusions were believed to directly cause apoptosis in HD (Wellington et al. 1998). This possibility was reinforced by the fact that antiapoptotic factors inhibited aggregate establishment in HD mice (Wellington et al. 1998). Despite this finding, newer research suggests that aggregate formation does not initiate cell death, but may instead be the cell's attempt to sequester mutant huntingtin fragments and thereby inhibit their toxic effects (Saudou et al. 1998). This latter possibility suggests that the mechanisms of inclusion formation, rather than the inclusions themselves, may be influential within HD cell death machinery (Hickey and Chesselet 2003).

Inclusions inhibit vital protein transcription, thereby promoting apoptosis

These inclusions develop when mutant huntingtin undergoes cleavage by caspase 1 or 3 in the cytoplasm, thus generating truncated fragments of the mutant protein that can both deplete normal huntingtin function and enter the nucleus prior to aggregation (Saudou et al. 1998; Wellington et al. 1998). Shorter fragments are more likely than longer fragments to form such mutant inclusions (Wheeler et al. 2000). Once accumulated in the nucleus, aggregates may alter transcription processes by interacting with a myriad of intranuclear proteins (Cha 2000).

The transcriptional effects of mutant huntingtin aggregates have been studied heavily in terms of the role these effects play in apoptotic pathways. Over the course of the last decade, researchers have found that these aggregates interact with several nuclear proteins and are likely implicated in the programmed cell death machinery of HD neurons (Hickey and Chesselet 2003; Steffan et al. 2000*)*. Many such research attempts have focused on the mutant protein's effect on the transcriptional ability of three particular molecules: p53, GAPDH and Sp1 (Hickey and Chesselet 2003). Each of these will be described in greater detail throughout the following paragraphs.

Mutant huntingtin interacts with p53 and cAMP responsive binding element (CREB) binding protein (CBP) (Steffan et al. 2000). p53 is a tumor-supressing transcription factor that transcribes proapoptotic proteins and regulates cell repair; CBP simply co-activates p53 (Hickey and Chesselet 2003). Mutant huntingtin decreases the transcriptional activity of these proteins (Steffan et al. 2000), thereby reducing repair pathway function and promoting negative symptoms in HD mouse models (de Boer et al. 2002). In fact, HD mice deficient cell repair proteins experienced severe wasting and died prematurely (De Boer et al. 2002). In addition to mutant huntingtin's ability to interact with p53 and CBP, it also binds glyceraldehyde 3-phosphate dehydrogenase (GAPDH), an enzyme known primarily for its role in glucose catabolism during glycolysis, but also involved in apoptotic pathways (Burke et al. 1996; Sheline and Choi 1998). Despite GAPDH's known association with apoptosis, the exact mechanism by which it activates programmed cell death has yet to be determined (Sheline and Choi 1998). Finally, recent research

suggets that mutant huntingtin also interacts with the Sp1 transcription factor: the mutant protein inhibits Sp1 transcriptional activity, as well as Sp1's ability to promote such activity in other proteins (Dunah et al. 2002). Intranuclear mutant huntingtin fragments were found to bind Sp1 and prevent the transcription factor from interacting normally with DNA; such research suggests that mutant huntingtin plays a role in preventing the production of necessary survival proteins, and may thus mark these deficient cells as targets for apoptosis.

The role of caspase cleavage in the HD apoptotic mechanism

As mentioned earlier, mutant huntingtin's ability to affect DNA transcription depends largely on the assumption that the protein underwent earlier caspase cleavage (Saudou et al. 1998; Wellington et al. 1998). The apoptotic program in HD may therefore initiate during the disease's early stages: upregulation of caspase 1 gene transcription has been documented in HD mice prior to the onset of symptoms (Ona et al. 1999) and probably occurs when mutant huntingtin fragments translocate from the cytosplasm to the (Li et al. 2000). This trend is also evident in the activity of the proapoptotic protein, caspase 3 (Chen et al. 2000). The signals prompting caspase activation and mutant huntingtin cleavage remain to be discovered; however some insights have been made into this question. One possibility involves self-activation on the part of the caspases themselves; another suggests that the presence of CAG repeats, which are rarely accepted by cells, could result in the activation of proapoptotic proteins by mutant huntingtin (Hickey and Chesselet 2003).

Proapoptotic protein activity in human patients and HD mouse models

For example, cytochrome c release and caspase-9 activation have been documented in mice exhibiting severe symptoms, indicating that the apoptosis mechanism is also active during late stages of HD (Kiechle et al. 2002). Significantly, similar results have also been documented in human cases: HD cells studied *in vitro* have demonstrated depolarization of the mitochondria, release of cytochrome *c*, and heightened activity of caspase-3, -8 and -9 (Ciammola et al. 2006; Kiechle et al. 2002; Ona et al. 1999). As mentioned earlier, mitochondria play an important role in programmed cell death through their interactions with proapoptotic proteins (Krohn et al. 1999). Depolarization of the mitochondrial membrane has been associated with mitochondrial release of such proteins, including cytochrome *c* (DuBmann et al. 2003; Krohn et al. 1999). After cytochrome *c* release, apoptotic pathways are well underway: caspase activation, DNA degradation and cell death follow thereafter (Li 1997).

Evaluating HD Apoptosis and Devising Target-Based Treatments

Although many studies suggest that programmed cell death plays an important role in HD progression, researchers are still unable to quantify the amount of neuronal loss that can be attributed to apoptosis. Although many degenerating HD neurons display morphological features characteristic of apoptosis, not all declining cells present these signs (Liu et al. 1997; Su et al. 1994). Moreover, determining the direct cause of apoptosis in HD will also require additional research. Many studies suggest that the disorder's mutant huntingtin aggregates play a role in programmed cell death pathways; however, additional research is necessary to evaluate the full function of these inclusions.

Despite the fact that many questions regarding the role of apoptosis in HD remain to be answered, research on this topic has enabled scientists to devise potential therapeutic strategies HD treatment. Mutant huntingtin's post-cleavage ability to induce apoptosis by altering DNA transcription suggests that preventing such cleavage events may inhibit apoptotic pathways (Wellington et al. 1998). In addition, inhibiting the caspases that ultimately drive apoptosis may be a potential treatment for the disorder. Treatment of HD with minocycline, a neuroprotective tetracycline antibiotic, is also a possible therapeutic method: minocycline prevents mitochondrial release of cytochrome *c* and thus inhibits the molecule's ability to promote further apoptotic events (Friedlander 2003; Zhu et al. 2002). This effect of minocycline has also been seen in other neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease (Friedlander 2003).

Conclusion

Over the course of the past two decades, scientific understanding of neurodegenerative processes has seen remarkable advances. Insight into the mechanisms of apoptosis within neurodegenerative disease now suggests these pathways may play a critical role in neuronal cell death through the activity of molecules, including Bcl-2 proteins, calcium and ROS, known to set off proapoptotic signal cascades via caspase activation. These developments have elucidated the molecules that can be targeted for neurodegenerative disease treatment.

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