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Transglutaminase 2 in neurodegenerative disorders

Qingmin Ruan, and Gail V. W. Johnson

Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, 1720 Seventh Avenue South, SC1061, Birmingham, AL 35294-0017, USA

TABLE OF CONTENTS

1. ABSTRACT

Type 2 transglutaminase (TG2) is a calcium-dependent acyltransferase which also undergoes a GTP-binding/GTPase cycle even though it lacks any obvious sequence similarity with canonical GTP-binding (G) proteins. As an enzyme which is responsible for the majority of transglutaminase (TG) activity in the brain, TG2 is likely to play a modulatory role in nervous system development and has regulatory effect on neuronal cell death as well. Most importantly, numerous studies have presented data demonstrating that dysregulation of TG2 may contribute to the pathogenesis of many neurodegenerative disorders, including Huntington's disease, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis as well as nervous system injuries. Although TG2's involvement in these disease conditions is strongly suggested by various findings, such as the increase of TG2 mRNA expression, protein level and TG activity in the pathological process of these neurodegenerative disorders, as well as the therapeutic effect of TG2 genetic deletion in animal models of Huntington's disease, the precise mechanism underlying TG2's role remain unclear. TG2 was originally proposed to contribute to the pathogenesis of these diseases by facilitating the formation of insoluble protein aggregates, however recent findings clearly indicate that this is likely not the case. Nonetheless, there is data to suggest that TG2 may play a role in neurodegenerative processes by stabilizing toxic oligomers of the disease-relevant proteins, although further studies are needed to validate these initial *in vitro* findings.

2. INTRODUCTION

Transglutaminases (TGs) are a family of enzymes that catalyze a calcium-dependent acyl transfer reaction between the gamma-carboxamide group of a polypeptide-bound glutamine (Gln) and a polyamine to form a (gamma-glutamyl)polyamine bond ('polyamination'). TGs also catalyze a reaction between a polypeptide-bound Gln and the epsilon-amino group of a polypeptide-bound lysine residue to form an epsilon-(gamma-glutamyl)lysine isopeptide bond ('crosslinking'). Further TGs also can catalyze the deamination of protein substrates under appropriate conditions (1). In addition, it has been reported that TGs can catalyze the incorporation of serotonin into small GTPases ("serotonylation") (2). In humans eight enzymatically active TGs have been identified and characterized, encoding biochemically and immunologically distinct TGs. In addition, the erythrocyte plasma membrane protein Band 4.2 is a non-catalytic TG homologue in the TG family (1).

Until recently, type 2 TG (TG2, also called tissue TG, liver TG or endothelial TG) was considered to be the only TG family member which also bound and hydrolyzed GTP in addition to being a transamidation enzyme (3). However recent findings have demonstrated that TG3 (4, 5) and TG5 (6) can also bind and hydrolyze GTP. Further GTP binding to TG2, TG3 or TG5 inhibits the transamidating activity of these enzymes, although in vitro the inhibition can be overcome by increasing the concentration of calcium in the reaction (3, 4, 6). However,

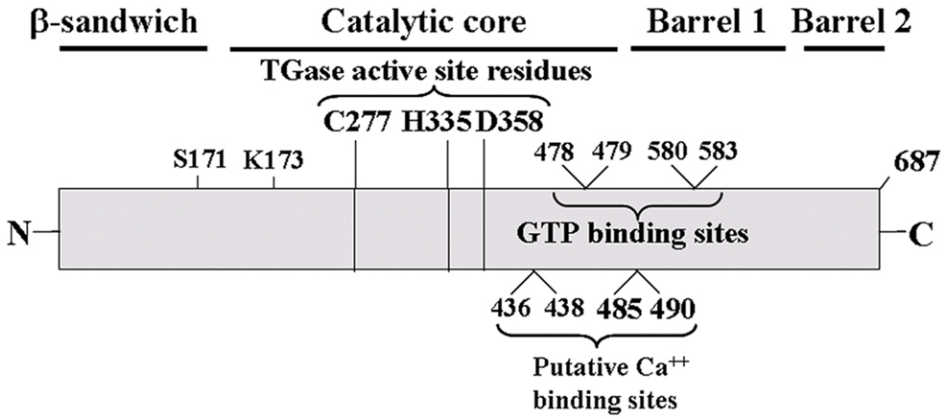

Figure 1. Functional domains and important amino acid residues of human TG2, representing a composite of the findings from numerous studies (see text for details) (10-14).

TG2 remains to be the only TG that has been reported to be involved in modulating signal transduction thus far (for a review, see (7)). In addition one research group has reported that TG2 may have unique intrinsic kinase activity (8, 9), however the mechanism and significance of this function remains unknown and further studies by other groups are required.

The general functional domains of human TG2 are shown in Figure 1, based on the findings from numerous studies (10-14). The cysteine, histidine and aspartic acid residues of the TG catalytic triad are conserved in all enzymatically active TGs (15-18), with the active site cysteine (Cys-277 in human TG2 (12)) being essential for the formation of the thioester bond with a substrate-bound glutamine. Also, it was shown that Trp-241 in TG2 was essential for catalysis by making an important contribution to stabilization of the transition-state intermediates (19, 20). At the same time, many studies have been carried out to define the amino acid residues important for GTP binding and cell signaling. In 2002 an x-ray crystallographic model of human TG2 was published identifying several amino acid residues including Arg-580 which were likely essential for the stability of TG2's GTP/GDP binding site (14), Recent study has confirmed that Arg-580 is important for GTP/GDP binding of TG2 (21). Interesting, several amino acid residues from the N-terminal of TG2, such as Ser-171 and Lys-173 were also found to be critical in this function since mutagenesis of both residues significantly impaired both GTP binding and GTPase activity of TG2 (22). Data from the crystallographic structure suggested that these amino acid residues might stabilize the hydrophobic pocket surrounding the guanine nucleotide binding site of TG2 (14).

Calcium is required for the transamidation activity of TG2, both *in vitro* (3) and *in situ* (23) and the putative calcium-binding site on TG2 is located near the end of the loop that connects the catalytic transamidation domain to the first β-barrel domain (14). Calcium binding likely results in an alteration in the position of the hydrogen bonds that stabilize the nucleotide-binding site resulting in a decrease in nucleotide binding affinity and a subsequent increase in transamidation activity (14). It is suggested that the transamidation activity of TG2 in normal cells is mostly inhibited due to the relatively high concentration of nucleotide and low intracellular calcium levels while in an apoptotic cell, falling nucleotide levels and increasing calcium levels could result in the activation of TG2 (23, 24). Although early studies have shown that the concentrations of calcium necessary to activate the transamidating activity of TG2 *in vitro* are supraphysiological (25, 26), the intracellular regulation of TG2 activity is a likely a complex process, and is not solely dependent on the levels of calcium and guanine nucleotides. While it is clear that TG2 requires calcium to adopt a conformation that is catalytically active, some evidence also indicates that the concentration of calcium necessary to activate this enzyme may be modulated by various intracellular factors. For example, research showed that sphingosylphosphocholine, a phospholipid, selectively and significantly enhances the affinity of TG2 for calcium and allows the enzyme to be activated at lower calcium concentrations (27). In addition it has been demonstrated that the transamidation activity of TG2 can be significantly increased *in situ* in response to physiological stimuli such as muscarinic receptor activation (23). Therefore, TG2 is likely playing important roles in a broad range of physiological and pathological processes.

3. TG2 IN NERVOUS SYSTEM DEVELOPMENT

In contrast with most TGs, which show limited tissue distribution, TG2 is ubiquitously expressed and found at substantial levels in the brain (1). Further, there is evidence suggesting that TG2 plays a role in the development of the nervous system. TG2 is widely expressed in various types of cells in the nervous system (28, 29), but seems to be enriched in neurons (30). TG activity is present in many different neural tissues including brain, spinal cord, peripheral nerve and superior cervical ganglia (for a review see (31)). Moreover, TG activity analyses have clearly demonstrated that TG2 is responsible for the majority (at least two-thirds) of TG activity within the mouse forebrain (32). Specifically, compared with TG2 wild-type forebrain, TG activity was reduced by 41% in TG2 heterozygous knock-out mouse forebrain and by 67%

in TG2 homozygous knock-out mouse forebrain. These findings also suggest that in the TG2 homozygous knock-out there maybe a compensatory upregulation of another TG.

During the development of the central nervous system (CNS), TG2 mRNA level, protein expression and TG activity change significantly. For example, in the hippocampus, TG2 expression is highest during embryonic development and falls off dramatically after 1 week of life (33). Recent study shows that in contrast with TG2 mRNA content, which was increased in mouse forebrain at postnatal ages compared with prenatal ages, TG2 protein content was decreased at each time point from E12 to P56. Interestingly, TG activity increased significantly at the beginning of the brain growth spurt, suggesting that TG2 is involved in forebrain maturation (34). These findings suggest that TG2's expression and activity in the developing nervous system are tightly regulated in a regional and post-transcriptional manner.

The most extensively characterized possible role for TG2 in CNS development is facilitation of neurite outgrowth. Neurite outgrowth has been associated with TG induction in various studies. In mouse neuroblastoma cells, serum withdrawal induces neurite outgrowth concomitant with a robust increase in TG specific activity and the extent of increase is much higher than that in non-dividing neuroblastoma cells lacking neurites. TG activity does not reach maximal levels until extensive neurite formation has occurred (35). Treatment of human neuroblastoma SH-SY5Y cells with retinoic acid (RA) results in neurites extending and significant increase in TG2 expression in the same time frame (23). Furthermore, another study demonstrated that TG2 is not only necessary but also sufficient for neurite outgrowth. SH-SY5Y neuroblastoma cells overexpressing wild-type TG2 spontaneously differentiated into a neuronal phenotype. In contrast, cells overexpressing enzymatically inactive TG2 or antisense TG2 which suppressed the expression of endogenous TG2 failed to develop neurite outgrowth even with the presence of RA, an inducer for neurite outgrowth which has been proved effective in many neuronal cell model (36). These studies, together with the finding that treatment of TG inhibitor, monodansylcadaverine, inhibited RA-induced differentiation in SH-SY5Y cells, demonstrated that TG2 was essential for neurite outgrowth (37). However TG2's role in the formation of neurites in primary neurons has not been investigated thoroughly, although there was some data suggesting that TG facilitated the stabilization of neurites in cerebellar granule neurons (38).

The mechanism by which TG2 may contribute to neuronal differentiation has been extensively explored. An early study suggested that *in vitro* TG stimulates both the rate and extent of microtubule assembly (35), however these findings have not been subsequently extended. TG2 might promote neurite outgrowth by stabilizing neurites during the initial outgrowth period, potentially via covalent dimerization of the neurotrophic protein midkine (39). A previous study showed that the microtubule-associated protein tau is polyaminated by TG2 *in situ* and this modification makes tau more resistant to degradation by calpain, which might help maintain higher levels of tau in the cell (40). Given the significant role that tau plays in facilitating axonal outgrowth (for a review, see (41)), TG2 might affect CNS development by polyaminating the tau protein (40). In addition, RhoA and mitogen-activated protein (MAP) kinases, which are known to have a significant role in neuronal differentiation (42, 43), may be involved in the TG2-facilitated neurite outgrowth as the inhibition of RhoA or MAP kinase effectively blocked RA-induced neuronal differentiation in SH-SY5Y cells (37). While transamidated MAP kinases might differentially regulate RA-induced neurite outgrowth, RhoA, when activated by TG2, may induce expression of genes required for neuronal differentiation (37).

TG2 has been found to modulate the activation of the cyclic AMP-response element (CRE)-binding protein (CREB) (44), an event that likely plays a central role in cell differentiation (45, 46). In SH-SY5Y cells, TG2 overexpression prolonged CREB activation induced by forskolin treatment, an adenylyl cyclase activator. The essential contribution of active TG2 to this process is evident as forskolin failed to elicit CREB activation in the same type of cells overexpressing enzymatically inactive or anitsense TG2. The TG2-mediated enhancement of CREB activation probably is due to its effect on potentiating cAMP production by modulating the conformation state of adenylyl cyclase although the exact mechanism is not clear (44). However, given the central role of CREB in neuronal development, its effect on CREB could certainly be an essential mechanism by which TG2 modulates neurite outgrowth.

4. TG2 IN NEURONAL CELL DEATH

Numerous studies have provided evidence that TG2 can facilitate the process of apoptosis (for a review, see (47)). Early studies showed that in neural crest-derived neuroblastoma SK-N-BE cells, induction of apoptosis by RA correlated with an increase in TG2 expression (48). Overexpression of TG2 in the Balb-C 3T3 fibroblasts (49) and SK-N-BE (50) resulted in an increase in spontaneous apoptosis and rendered these cells highly susceptible to death by apoptosis. In support of a pro-apoptotic role for TG2, transfection of neuroblastoma cells with human antisense TG2 cDNA resulted in a pronounced decrease of both spontaneous and RA-induced apoptosis (51). Moreover, one study showed that TG2 knock-out mice have defects in the clearance and stability of apoptotic cells (52). The mechanism by which TG2 facilitates cell death is unclear although it has been proposed to depend on its effect on mitochondria. One study found that changes of morphological and functional features in mitochondria, as well as increased susceptibility to stressors, were associated with TG2 overexpression. Importantly, TG2 overexpression lead to a rapid loss of mitochondrial membrane potential in response to staurosporine treatment, a general inducer for apoptosis, suggesting that TG2 might act as a 'sensitizer' towards apoptotic stimuli specifically by modulating mitochondrial function (53), either directly or indirectly. There is also data to suggest that TG2 may enhance the production of reactive oxygen species by the mitochondria, which could be one mechanism by which

TG2 enhances cell death (53). In another study it was shown that certain domains of TG2 have some homology with the of Bcl-2 family BH3 domain and TG2 peptides of the homologous domain, as well as full length TG2 interacted with Bax, but not with Bcl-2 or Bcl-X_L (54). It is important to note that although TG2 may modulate mitochondrial function, a recent finding clearly showed that TG2 is not located in mitochondria and most of the mitochondrial/mitoplast TG activity in highly purified mouse brain/liver mitochondria is not due to TG2 (55). Nonetheless, TG2 does not have to be inside the mitochondria to modulate mitochondrial function.

Although these findings indicate that TG2 is a facilitator of cell death, this is not always the case. Induction of TG2 expression either by RA treatment (23, 36) or stable transfection with TG2 cDNA (36) did not produce any changes in the rate of spontaneous apoptosis in human neuroblastoma SH-SY5Y cells. In addition, some studies showed that in TG2 knock-out mice, there is no apparent deficit in the major apoptotic pathways and the mice were phenotypically normal (56). Furthermore, TG2 can actually attenuate neuronal cell death in response to specific stimuli. The expression of active TG2 induced by RA in fibroblast NIH3T3 cells strongly protects cells against N-(4-hydroxyphenyl) retinamide (HPR) induced apoptosis (57, 58). While the mechanism by which TG2 attenuates cell death is still not clear, the interaction of TG2 with one of its substrate, retinoblastoma (Rb) protein, which is widely implicated in cell survival functions, has been examined. Experiments performed with fibroblasts from Rb(-/-) mice demonstrated that the presence of Rb was required for TG2 to exhibit its anti-apoptotic activity (57). In HEK293 cells transiently transfected with TG2 cDNA, TG2 complexes with Rb *in situ* both in the cytosol and nucleus and this dynamic interaction in the nucleus occurs only when TG2 lacks it transamidation activity, which may be significant for TG2's effects on attenuating apoptosis (59). Taken together, these data suggest that TG2, by interacting with Rb protein, may play an important role in attenuating cell death processes.

Very interestingly, studies indicate that the effect of TG2 on the cell death process is highly dependent on how its transamidating activity is affected in response to these stimuli, as well as its intracellular localization. In SH-SY5Y cells, overexpression of TG2 facilitated apoptosis in response to stressors that resulted in an increase in the transamidating activity of this enzyme. However, when the stressors did not result in the activation of TG2, TG2 could ameliorate the apoptotic response (60). Importantly, it also has been found that intracellular localization of TG2 is an important determinant of its effect on apoptosis. TG2 is primarily a cytosolic protein, however, it is also found associated with membranes (61-63), in the extracellular space (64, 65) and in the nucleus (66, 67). It seems that cytosolic TG2 was pro-apoptotic while nuclear or membrane-targeted of TG2 had no significant effect on cell death. At the same time, transamidating inactive TG2 residing in the nucleus ameliorated apoptosis in response to certain stress (59). Overall these findings clearly demonstrate that TG2 plays an important role in modulating neuronal cell death, depending on its activity status and intracellular localization in response to specific stimuli. Further work is required to delineate its exact contribution to this process.

5. TG2 IN NEURODEGENERATIVE DISEASES

Numerous studies suggest that TG2 may contribute to the pathogenesis of many neurodegenerative disorders, including but not limited to Huntington's disease (HD) (30, 68, 69), Alzheimer's disease (AD) (70, 71), Parkinson's disease (PD) (72, 73) and amyotrophic lateral sclerosis (ALS) (74, 75). Studies showed that TG2 mRNA and protein level, as well as TG enzymatic activity were elevated in many of these disease conditions (76, 77). The administration of an TG inhibitor cystamine, as well as genetic deletion of TG2 has been found protective in several mouse models of HD (68, 69, 78-81), which further proved the important role that TG2 played in the pathogenesis of these diseases.

TG2 was originally proposed to contribute to these disease conditions by facilitating protein aggregation (72, 82, 83), which is a common characteristic for these neurodegenerative disorders (84). Although some *in vitro* studies support this hypothesis (82), accumulating evidence strongly suggests that TG2 does not contribute directly to the formation of aggregates. For example, neither mutant (containing an expanded polyglutamine domain) nor wild-type huntingtin (htt) was a TG2 substrate *in situ* (85), and TG2 was totally excluded from the polyglutamine aggregates in human neuroblastoma SH-SY5Y cells (86). HD mouse models that were TG2 knockouts showed a significant increase in aggregate number compared with HD mice that were wild-type with respect to TG2 (68, 87). Recent *in vitro* studies actually showed that TG2 actually inhibited the formation of insoluble protein aggregates (88, 89). Meanwhile, given the growing body of data suggesting that protein oligomers, instead of protein aggregates may be the toxic species (90), and TG2 has been found to facilitate the formation of soluble complexes of disease-related proteins (88, 89, 91), it can be speculated that TG2 contributes to the pathogenesis of these neurodegenerative disorders by facilitating the stabilization of these toxic oligomeric species. It is also interesting to note that in many of these diseases, including AD, HD and other neurodegenerative disorders, there is likely a dysregulation of calcium homeostasis (92). In addition to triggering the release of pro-apoptotic factors from mitochondria into the cytoplasm and stimulating a variety of calcium-sensitive enzymes that engage other apoptotic mechanisms (93), calcium dysfunction would also result in the overactivation of TG2 (23) and consequently cause more pathological protein modifications to occur.

5.1. TG2 in HD

The possible role of TG2 in the pathogenesis of HD has been examined quite extensively. HD is a dominantly inherited disorder that is characterized by progressive motor dysfunction and psychiatric disturbances with gradual dementia. HD is one of nine identified neurodegenerative diseases that are caused by a

polyglutamine expansion mutation in otherwise unrelated proteins (94). The mutation causing HD is a CAG repeat expansion in the gene encoding htt (95). In the normal population the number of CAG repeats varies from 6 to 35, whereas lengths of 40 and over invariably cause HD (96) and the length of CAG repeat significantly correlate with the severity of clinical symptoms in HD patients (97). Though htt is expressed ubiquitously in human tissues (98, 99), neuronal degeneration appears to be confined mostly to the striatum and cortex (100, 101). The precise mechanism of this selective neuronal death is still unknown.

An early study found that TG activity was higher in lymphocytes from HD patients than that in healthy individuals (102) although opposite result was showed in another study (103). Since brain is the tissue that is most effected in HD, further studies have focused on whether TG2 protein levels or activity were altered in the CNS and whether the changes are of significance to the pathogenesis of HD. Levels of N(epsilon)-(gamma-L-glutamyl)-L-lysine (GGEL), a 'marker' isodipeptide produced by the TG reaction, were elevated in the cerebrospinal fluid (CSF) of HD patients compared to that of controls, supporting the hypothesis that TG activity is increased in HD brain *in vivo* (104). Two independent studies found that the TG enzymatic activity was greater in the brain of HD patients compared to control cases and the increase was especially notable in the nuclear fraction (30, 103). One of these studies went further to show that total TG activity was increased in HD striatum in a grade and region specific manner compared to control (30). In R6/2 mice, a well-characterized transgenic mice model for HD, TG activity was elevated in whole lysate (79) with notable increases in the nuclear fraction of the brain (103). The strongest proof of TG2's contribution to the pathogenesis of HD comes from studies using animal models in which TG2 was knocked out of HD transgenic mice. In both R6/1 (68) and R6/2 (87) HD transgenic mouse, TG2 ablation lead to a significant increase in life span and improved motor dysfunction. These two independent studies strongly suggest that TG2 contributes to the pathogenesis of HD.

The therapeutic effect of cystamine in HD has often been attributed to its inhibitory effect on TG activity. Although the administration of cystamine delayed the onset of pathogenesis in the R6/2 HD mouse (79, 105) as well as the YAC128 mouse model of HD (106), these results should be regarded with caution because cystamine also acts as an inhibitor of caspases (107) and leads to increased glutathione production as well (108, 109), both of which could provide beneficial effects in HD. Further, a recent study showed that the protective effects of cystamine in the R6/2 HD mouse involved mechanisms other than the inhibition of TG2 since administration of cystamine delayed motor dysfunction and extended life span to a similar extent in R6/2 mice that had a normal genetic complement of TG2 compared with R6/2 mice that did not express TG2 (69). Furthermore, the absence of cystamine and its metabolic product cysteamine in the brains of YAC128 mice treated daily with cystamine suggested that cystamine was not directly involved in mitigating the progression of HD (110). Additionally, cystamine's effect on aggregate formation also provided evidence suggesting that its therapeutic effect in the HD mouse models was independent of TG2 inhibition. While TG2 ablation in HD transgenic mice increased aggregate formation (68, 87), one group found that cystamine treatment did not influence the appearance or frequency of neuronal nuclear inclusions (105), while another study revealed that the formation of cellular inclusions was reversed in a dose dependent manner in the cystamine treated HD transgenic mice (78). Therefore, cystamine's therapeutic effect in HD is unlikely due to its inhibitory effect on TG2.

While TG2's role in the etiology of HD is not clear, it was initially postulated that TG2 could contribute to the HD disease process by facilitating the formation of htt protein aggregates (111), which are pathological hallmarks in HD patients (112) as well as HD transgenic mice (113-115). The basis for this postulate is the fact that HD is a polyglutamine disease and proteins containing polyglutamine stretches are good substrates for TG2 at least *in vitro* (82). However, there is now convincing evidence suggesting that TG2 does not contribute to the formation of the insoluble aggregates in HD brain, and in fact likely inhibits their formation. HD R6/2 mice that were TG2 knockouts showed a significant increase in aggregate number within the striatum compared with HD R6/2 mice that were wild-type with respect to TG2, and yet knocking out TG2 ameliorated disease progression (87). In another study done in HD R6/1 mice, the formation of neuronal intranuclear inclusions was potentiated in the absence of the TG2 (68).

Interestingly, there is now evidence suggesting that TG2's inhibition of aggregate formation and facilitation of the formation of high molecular weight soluble protein complexes might be a contributing factor in the pathogenesis of HD. Based on a growing body of evidence, it has been proposed that a soluble form of mutant htt protein, but not the insoluble aggregates, contributes to the pathogenesis of HD (90). For example, inhibition of the formation of nuclear aggregates in a cellular model of HD potentiated cell death (116). Also one study showed that the formation of inclusion bodies of the mutant polyglutamine containing protein correlated with an increase in survival time in neurons (117). Importantly TG2 has been found to facilitate the formation of soluble complexes of disease-related proteins, at least *in vitro*. Studies using an *in vitro* solubility assay found that TG2 cross-linked mutant polyglutamine monomers into high molecular weight soluble complexes and this calcium-dependent reaction to form soluble complexes was inhibited by primary amine substrates, which antagonize TG reaction (88). Another study indicated that the aggregation and precipitation of some unfolded proteins were inhibited by TG2-catalyzed reaction, in contrast to the previous hypothesis that TG2 enhances these processes (91). The study also showed that TG2-catalyzed cross-linking yielded high molecular weight soluble polymers but inhibited the growth of insoluble aggregates, which might be the underlying mechanism for TG2's contribution to the pathogenesis of HD.

Although TG2's role in the aggregate formation is not yet well established, it is clear that TG2 could contribute to the pathogenesis in HD through mechanisms other than aggregate formation. The interplay between TG2 and mitochondrial function could be one of the mechanisms for the pathogenesis of HD, although supporting evidence for this hypothesis is still lacking. Impaired mitochondrial function, which has been one pathological mechanism for HD, resulted in a significant increase of TG activity in situ (24). At the same time, studies showed that TG2 might act as a 'sensitizer' towards apoptotic stimuli by modulating mitochondrial function (53). Since HD is characterized by impaired mitochondrial function together with increased TG2, there is likely an important interplay between TG2 and mitochondrial function which could contribute to the pathogenesis of HD.

5.2. TG2 in AD

AD is the most common age-related neurodegenerative disorder, with pronounced neurodegeneration and pathology in the cortex, hippocampus, and amygdala (118). AD involves loss of memory and other cognitive functions, a decline in the ability to perform activities of daily living, changes in personality and behavior, and eventual death (for a review, see (119)). Two major defining hallmarks of AD pathology are the extracellular neuritic senile plaques and the intraneuronal neurofibrillary tangles (120). Purification and analysis have demonstrated that senile plaques contain amyloid fibrils composed of the amyloid β-protein (Aβ) (121). Neurofibrillary tangles (NFTs) are predominantly comprised of the hyperphosphorylated form of the microtubule associated tau protein (122).

There is some evidence showing that TG2 may play a role in the pathology of AD. Significant increases in TG activity were observed in AD prefrontal cortex (71) where the pathology of AD is prevalent. In contrast, in the cerebellum, which is mostly spared in AD, there was no significant difference in TG activity between controls and AD subjects (71). A highly significant increase in TG2 protein level in the CSF was also observed in the AD groups compared with controls (123). The frequency of GGEL cross-links, a TG product, is significantly higher in AD cortex than that in age-matched controls (124). In hippocampus and cortex of AD brain, TG2 mRNA analysis indicated an absolute increase in TG2 synthesized (70). Interestingly, this study also identified the presence of another shorter transcript of TG2 mRNA in all AD brains in addition to a full-length isoform and this special form of TG2 was referred as the short (S) isoform of TG2. However the physiological or pathological relevance of this short TG2 isoform is not yet clear.

Although these results show that TG2 is altered in AD, its role in the pathogenic processes has not been established. It was originally thought that TG2 contribute to the formation of the insoluble senile plaques and/or NFTs. Supporting evidence for this hypothesis include the facts that both Aβ and tau are in vitro substrates of TG2 (125, 126), and tau can be polyaminated by TG2 in vivo (40). However, there has been no direct, biochemical demonstration that tau or Aβ are crosslinked by TG2 in vivo. Several studies have used antibodies that recognize the GGEL crosslinks formed by TGs to suggest that TGs contribute to NFT formation in AD brain (127), but unfortunately these antibodies do not specifically recognize GGEL crosslinks (128), therefore these data are difficult to interpret. Furthermore, neither tau nor Aβ were found to contain TG catalyzed crosslinks in control or AD brains in a study that used analytical techniques to identify crosslinked proteins (124). Therefore further investigations are needed to identify the mechanisms by which TG2 may contribute to the pathogenesis of AD.

5.3. TG2 in PD

PD is a neurodegenerative disorder which is characterized by the loss of dopaminergic neurons in the substantia nigra, resulting in extrapyramidal motor dysfunction, including tremor, rigidity, and bradykinesia (129). One of the characteristics of PD is the presence of intraneuronal inclusions called Lewy bodies which contain alpha-synuclein (130). However, neither the mechanism of Lewy body formation nor its role in the pathogenesis of PD has been fully elucidated.

The role of TG2 in PD has not been studied as extensively as in HD and AD, however there are some studies suggesting that TG2 might be involved in the pathogenesis of PD. Upregulation of TG2 mRNA expression was noted in PD brains compared to age matched controls. In PD, higher TG2 expression was found in both membrane and cytosol extracts from the substantia nigra, as compared to controls (73). Other studies found that TG2 protein levels were increased in PD nigral dopamine neurons (72, 131). Significant elevations in TG2 concentration were found in the CSF of patients with PD compared with that in control subjects (132).

TG2 has been proposed to contribute to the PD disease process by facilitating the formation of Lewy body, which is comprised mostly of alpha-synuclein. In vitro, purified TG2 catalyzed alpha-synuclein cross-linking, leading to the formation of high molecular weight aggregates. TG2 protein co-precipitated with alpha-synuclein in extracts of PD substantia nigra but not in control brain (131). It has been suggested that TG2 cross-links alpha-synuclein in a cell culture model and facilitates aggregate formation (72), although there is also data suggesting that this may not be the case (133). Although immunohistochemical studies on postmortem PD brain tissue demonstrated the presence of GGEL crosslinks in the Lewy bodies (72), the GGEL antibody used in this study, as noted above, does not specifically recognize the isopeptide bonds formed by TG (128). Further studies are required to elucidate TG2's role in the pathogenesis of PD. However, it is interesting to note that in AD brain, alpha-synuclein was found to be crosslinked using an analytical, biochemical approach (124).

5.4 TG2 in ALS

ALS is one of the most common adult-onset neurodegenerative diseases, which is characterized by selective death of upper motor neurons in the motor cortex and lower motor neurons in the brainstem and spinal cord, leading to progressive skeletal muscle atrophy and death (134). About 10% of cases are familial, with a fifth of these familial cases associated with mutations in the gene encoding the free radical scavenging enzyme copper-zinc superoxide dismutase (SOD1) (135). A common feature, shared by both mutant SOD1 transgenic mouse models (136, 137) and in tissue samples from ALS patients (138, 139), is the appearance of intracellular inclusions containing detergent-insoluble protein aggregates that contain CuZnSOD, neurofilament and ubiquitin (140).

There are only a few studies that suggest TG2 may be involved in the pathogenesis of ALS, and detailed mechanistic studies are still lacking. TG activity increased in the serum and CSF obtained from patients with sporadic ALS at early stages of the disease, but was found to decrease at the terminal stages when most of the spinal motor neuronal perikarya have been destroyed (74). Another study using human spinal cord obtained at autopsy showed that TG activity in thoracic and lumbar cords was markedly lower in ALS than that in non-ALS patients (141). Some research regarding the involvement of TG2 in the pathogenesis of ALS was carried out using motor neuron degeneration (Mnd) mice model. Mnd mice is an autosomal dominant mutant substrain of mice, characterized by a progressive deterioration of motor function, concomitant with dramatic degeneration of lower motor neurons in the spinal cord as well as upper motor neurons in the cerebral cortex, exhibiting significant similarities to human ALS (142, 143). Studies found that TG activity in the Mnd spinal cord was increased during early development, and then decreased at later stages (75, 144). Another study using Mnd mice showed that TG activity in the CNS was significantly greater than that of healthy animals at similar age (145). Overall, at this point there is no compelling evidence supporting that TG2 is involved in the pathogenesis of ALS, clearly indicating the need for further investigations.

6. TG2 IN NERVOUS SYSTEM INJURIES

Increases in TG2 mRNA and/or protein levels in response to various types of neuronal injury have been well documented. In rats following transient middle cerebral artery occlusion, TG2 mRNA and TG2 protein expression progressively increased reaching a peak on day 5 after injury (81). TG activity also increased in the vagus nerve after crush injury (146). In the adult rat spinal cord after unilateral occlusion of a branch of the dorsal spinal artery, the affected half of the spinal cord showed a significant rise in endogenous TG activity compared to the contralateral side without ischemic damage (141). In the superior cervical ganglion, TG activity was increased within 1 hour of axotomy and returned to baseline after 24 h (147, 148). In a model of spinal cord ischemia, TG activity underwent a transient increase that declined to control levels after 1 week (141). Another interesting observation in nervous system injuries is the appearance of a short isoform (S) of TG2, an isoform which was suggested to play a role in the pathogenesis of AD (70). In a rat model of neurotrauma, appearance of the short isoform (S) transcript, in addition to the normal long (L) isoform has been reported (80, 149). Although these results indicate a possible role that TG2 plays in neurotrauma, the relatively delayed response of TG2 to brain injury suggests that it is not a major contributor to the more acute pathophysiological events, but may be involved in the delayed apoptotic death that occurs following injury (150).

The role of TG2 induction in the neural response to injuries is not well understood although it is possible that TG2 contribute to nervous system recovery by promoting axonal regeneration. TG activity is elevated during axonal regeneration (151). Exogenous application of TG to injured optic nerve promoted axonal regeneration and recovery of visual-evoked responses in fish (152). The failure of axons of the CNS to regenerate spontaneously after injury is attributed in part to inhibitory molecules produced by oligodendrocytes, and TG has been shown to dimerize interleukin-2, resulting in cytotoxicity in cultured oligodendrocytes (153), which might provide a mechanism to permit nerve growth (153). Finally, TG2 stimulated neuronal differentiation and neurite outgrowth in SH-SY5Y neuroblastoma cells (36). Overall, further studies are needed to elucidate TG2's involvement in the disease conditions of nervous system injuries.

7. SUMMARY AND PERSPECTIVE

As the enzyme responsible for the majority of TG activity in the brain, TG2 plays an important role in nervous system development and neuronal cell death. While numerous studies suggest that the deregulation of TG2 contributes significantly to the pathogenesis of many neurodegenerative disorders, it is still not clear how TG2 is involved in these disease conditions. The diagram in Figure 2 summarizes some of the suggested roles of TG2 in pathological events. Although TG2 was originally proposed to contribute to the pathogenesis of these diseases by facilitating protein aggregate formation, recent finding showed that it might not be TG2's real role in these disease conditions. Instead, it is possible that TG2's inhibition of aggregate formation and facilitation of the high molecular weight soluble protein complexes formation accelerates disease progress. The real effect of TG2 on soluble protein complex formation still needs more support from *in vivo* and *in situ* studies. The interplay between TG2 and mitochondrial function may also contribute to the pathogenesis of various disease conditions and is therefore another area that requires further studies. Overall, given the wide range of diseases in which TG2's involvements have been clearly demonstrated, the elucidation of the role that TG2 plays and how its activities are modulated in these

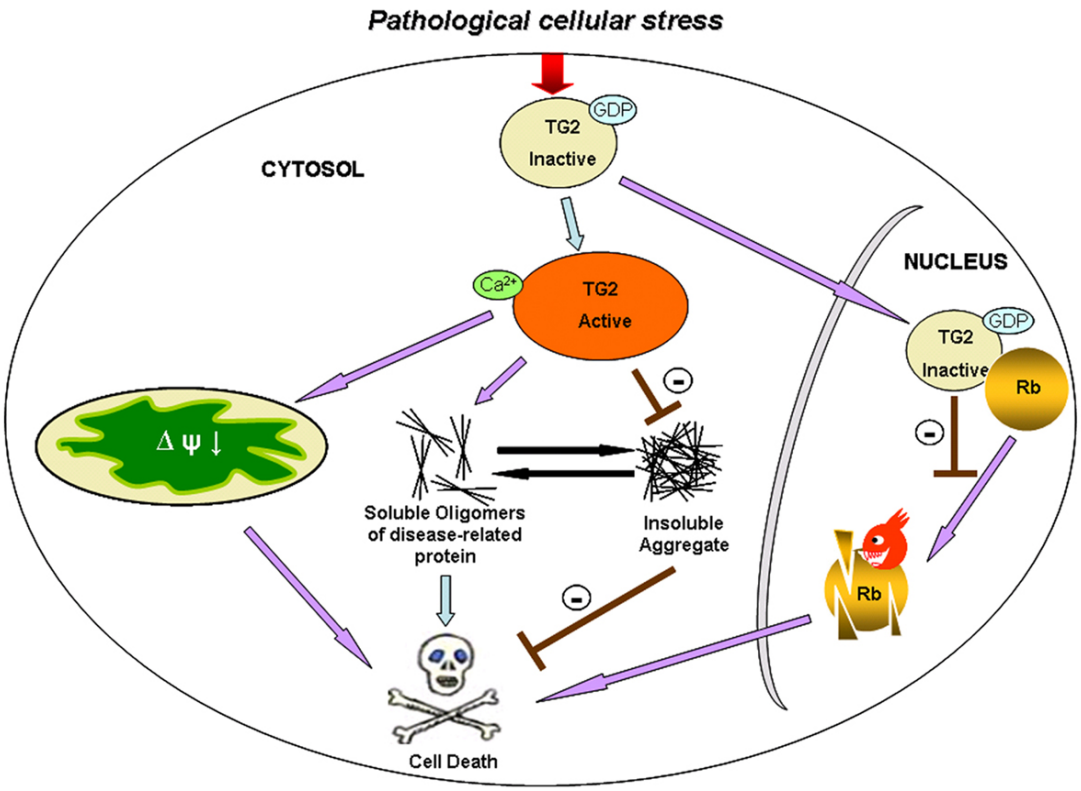

Figure 2. Schematic diagram of TG2's pro-apoptotic and anti-apoptotic functions within neurons. The effect of TG2 on the cell death process is highly dependent on how its transamidating activity and intracellular localization are affected in response to specific stimuli. In models of polyglutamine disease, TG2 protein content and activity is increased. Cytosolic TG2 may mediate cellular pathology by inhibiting the formation of insoluble protein aggregates and increasing the levels of high molecular weight soluble oligomers of the disease-related protein, which are likely to be the more toxic species (88, 91). In addition, TG2 might also contribute to the disease conditions by alteration of the mitochondrial membrane potential (53). However, when the stressors do not induce an increase in the transamidating activity of TG2, TG2 can ameliorate cell death (60). In response to certain stimuli, transamidating inactive TG2 translocates from the cytosol to the nucleus, interacting with Rb protein (59). The resulting interaction of Rb protein with TG2 may maintain Rb's anti-apoptotic transcriptional activity perhaps by preventing its degradation, therefore ameliorating cell death (57).

disease conditions is of significance not only to our understanding of the pathogenesis of these diseases but also the development of effective therapy for these neurodegenerative disorders.

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Send correspondence to: Dr. Gail V.W. Johnson, Dept. of Psychiatry, 1720 7th Ave., South, SC1061, University of Alabama at Birmingham, Birmingham, AL 35294-0017, Tel: 205-934-2465, Fax: 205-934-2500, E-mail: gvwj@uab.edu