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MINIREVIEW ARTICLE

Monitoring of transglutaminase2 under different oxidative stress conditions

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Abstract Transglutaminase 2 (TG2) is a multifunctional calcium-dependent enzyme which catalyzes the post-translational protein crosslinking with formation of intra- or intermolecular epsilon(gamma-glutamyl)lysine bonds or polyamine incorporation. The up-regulation and activation of TG2 have been reported in a variety of physiological events, including cell differentiation, signal transduction, apoptosis, and wound healing, as well as in cell response to stress evoked by different internal and external stimuli. Here we review TG2 role in cell response to redox state imbalance both under physiological and pathological conditions, such as neurodegenerative disorders, inflammation, autoimmune diseases and cataractogenesis, in which oxidative stress plays a pathogenetic role and also accelerates disease progression. The increase in TG activity together with mitochondrial impairment and collapse of antioxidant enzymatic cell defences have been reported to be the prominent biochemical alterations becoming evident prior to neurodegeneration. Moreover, oxidative stress-induced TG2 pathway is involved in autophagy inhibition and aggresome formation, and TG2 has been suggested to function as a link between oxidative stress and inflammation by driving the decision as to whether a protein should undergo SUMO-mediated regulation or proteasomal degradation. Literature data suggest a strong association between oxidative stress and TG2 up-regulation, which in turn may result in cell survival or apoptosis, depending on cell type, kind of stressor, duration of insult, as well as TG2 intracellular localization and activity state. In particular, it may be suggested that TG2 plays a pro-survival role when the alteration of cell redox state homeostasis is not associated with intracellular calcium increase triggering TG2 transamidation activity.

Keywords Transglutaminase 2 · Oxidative stress · Neurodegeneration · Autoimmune diseases

Abbreviation

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
CF	Cystic fibrosis
CFTR	Transmembrane conductance regulator gene
chlTGZ	Chloroplast transglutaminase
Hcy	Homocysteine
HD	Huntington's disease
4-HPR	*N*-(4-hydroxyphenyl)retinamide
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
NF-κB	Nuclear factor-κB
3-NP	3-Nitropropionic acid
PBMC	Peripheral blood mononuclear cells
PD	Parkinson's disease
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
SUMO	Small ubiquitin-like modifier
TG	Transglutaminase
TG2	Tissue transglutaminase
TGF-beta	Transforming growth factor-beta

Introduction

Tissue transglutaminase (TG2) is the most ubiquitous member of the mammalian transglutaminase (TG) family.

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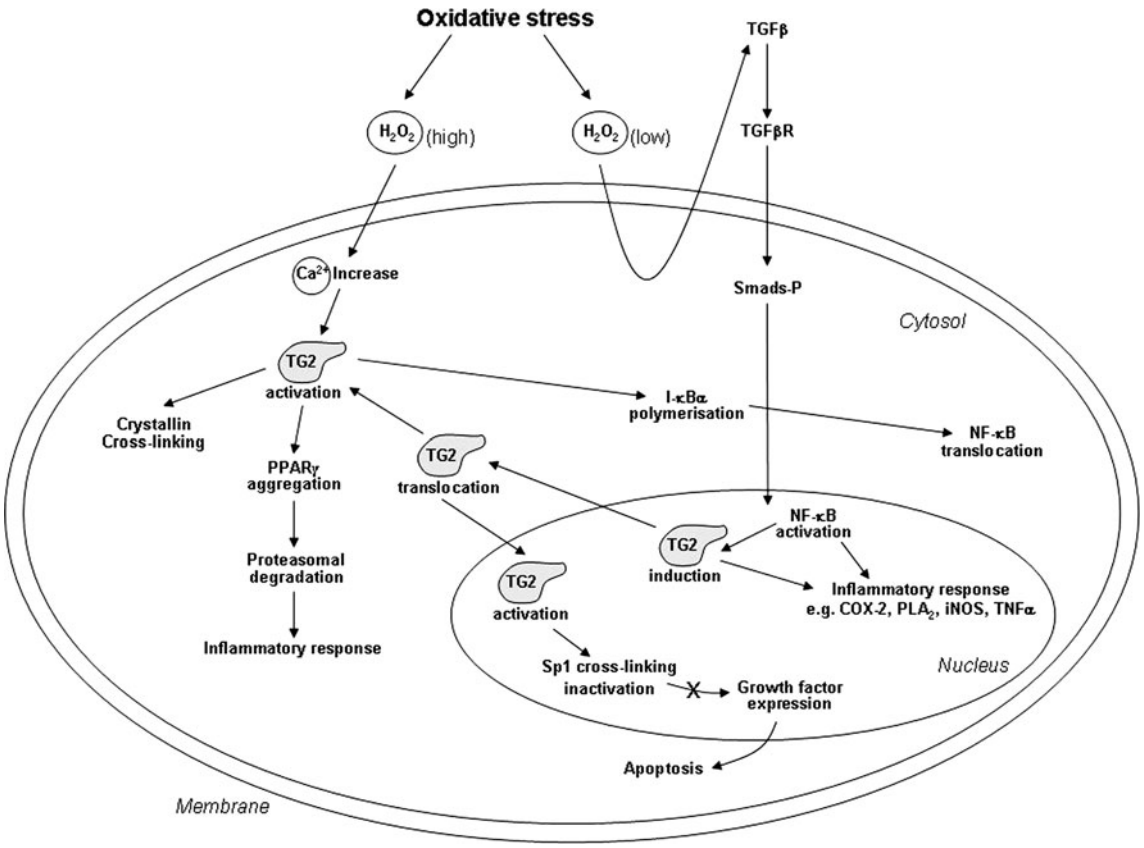

Fig. 1 Signaling pathways involving TG2 activation in cell response to oxidative stress (modified from Iismaa et al. 2009)

This multifunctional calcium-dependent enzyme catalyzes the post-translational protein modification of proteins leading to the formation of intra- or inter-molecular epsilon(gamma-glutamyl)lysine bonds (cross-links), or polyamine incorporation into proteins (Griffin et al. 2002).

In addition, TG2 can bind and hydrolyze GTP, and display protein disulfide isomerase activity as well as protein kinase activity (Park et al. 2010). Given the pleiotropic functions of this protein, TG2 has been implicated in a variety of events including the suppression of cell proliferation, cell differentiation, signal transduction, apoptosis, and wound healing (Fesus and Piacentini 2002; Telci and Griffin 2006). Moreover, it has been reported that TG2 up-regulation and subsequent activation play a functional role in the cell response to stress evoked by many different stimuli, both internal and external, including cell insult (Ientile et al. 2007; Iismaa et al. 2009).

This review will focus on the role played by TG2 in the cell response to redox state imbalance both under physiological and pathological conditions, such as neurodegenerative disorders, inflammation, and autoimmune diseases, in which oxidative stress plays a pathogenetic role and also accelerates the progression of the disease.

The most relevant signaling pathways involving TG2 activation in cell response to oxidative stress-inducing agents are shown in Fig. 1.

The interplay between TG2 and oxidative stress

Oxidative stress occurs when cell defences against the production of reactive oxygen species (ROS) fail (Azzi 2007).

Experimental in vitro observations on TG2 behavior in oxidative stress conditions were first made using beta H-crystallin exposed to hydroxyl radicals in the presence of TG2. By the use of radioactive methylamine, as a probe for labeling beta H-crystallin amine-acceptor sites, and biotinylated hexapeptide to label amine-donor sites, TG-mediated primary amine as well as hexapeptide incorporation were shown to be dramatically increased after oxidative attack on the crystallin (Groenen et al. 1993).

Intracellular ROS elevation has also been shown to promote TG2 in situ activation, evaluated as TG-mediated incorporation of 5-(biotinoamido)-pentylamine, in response to lysophosphatidic acid (LPA) and transforming growth factor-beta (TGF-beta) in Swiss 3T3 fibroblasts. TG activity was strongly inhibited by cystamine and ROS scavengers.

ROS involvement in the LPA- and TGF-beta-induced TG activation was confirmed by TG2 in situ activation by exogenous H_2O_2 (Lee et al. 2003).

Increases in ROS production have also been shown to mediate the activation of TG2 and stress fibers formation in a dose- and time-dependent manner when induced by arachidonic acid in NIH3T3 fibroblasts. The effects of arachidonic acid were suppressed by the ROS scavenging action of *N*-(2-mercaptopropionyl)glycine and catalase (Yi et al. 2004).

The intracellular ROS accumulation has a number of direct and indirect consequences on cell signaling pathways, ultimately leading to apoptosis or necrosis. In the last decade, numerous studies investigating the involvement of TG2 in oxidative stress-induced cell death, have reported conflicting data showing that TG2 exhibits a different behavior in cell response to injury/stress, acting either as a facilitator or attenuator of the apoptotic process (Fésüs and Szondy 2005).

Ex vivo studies have shown that the plasma level of the stable product of TG activity, epsilon(gamma-glutamyl)lysine isodipeptide, is a marker of total body apoptotic rate in fresh human peripheral blood mononuclear cells (PBMC) exposed to 2-deoxy-D-ribose, an agent which interferes with the cell redox status and mitochondrial membrane potential (Monti et al. 2000). Similarly, the increase in TG activity has also been associated with human PBMC apoptotic cell death induced in a time- and concentration-dependent manner by the ROS generating enzyme xanthine oxidoreductase (Battelli et al. 2001). On the other hand, the inhibition of TG activity led to enhanced apoptosis in leukemia cells exposed to the synthetic retinoid *N*-(4-hydroxyphenyl)retinamide (4-HPR), which induces ROS overproduction triggering the intrinsic (mitochondrial) apoptotic pathway. Cell sensitivity to 4-HPR could be reduced by increasing intracellular glutathione content using *all-trans* retinoic acid, at the same time inducing TG2 up-regulation (Morales et al. 2005).

Recent investigations on cardiac myocyte apoptosis under oxidative stress, a condition that can be observed in ischemic conditions, show that the increase in the expression of apoptotic markers, such as caspase-3, caspase-8, cytochrome c, and Bax, was positively correlated with TG2 up-regulation in H_2O_2-treated cardiomyocytes. Moreover, TG2 increases were involved in the down-regulation of phospholipase C-δ1 and phospho-protein kinase C that was rescued by TG2 silencing (Song et al. 2011).

These data suggest a strong association between oxidative stress and TG2 up-regulation. This latter in turn may result in cell survival or apoptosis, depending on the cell type, the kind of stressor and the duration of insult. In particular, TG2 appears to be protective against cell death when the stressors that are used do not result in an increase in transamidation activity (Antonyak et al. 2001, 2003; Tucholski and Johnson 2002).

TG2 role in oxidative stress-related neuronal death

A strong TG2 up-regulation and increase in enzyme activity has been reported in most acute and chronic neuropathological conditions, such as ischemia, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), in which oxidative stress is suggested as a significant causative factor for pathogenesis of neuronal degeneration (Caccamo et al. 2004, 2010; Ruan and Johnson 2007).

The increase in TG activity together with the decline of cytochrome *c* oxidase as well as superoxide dismutase activities have been reported to be the prominent biochemical alterations becoming evident prior to the appearance of clinical motor neuron dysfunction in animal model of ALS (Fujita et al. 1998).

Using neuroblastoma SH-SY5Y cells stably over-expressing human TG2 or mutated inactive TG2, it has been shown that the irreversible inhibition of succinate dehydrogenase by 3-nitropropionic acid (3-NP), leading to impairment of mitochondrial function and fall in GTP and ATP levels, caused a significant increase in TG activity in situ (Lesort et al. 2000). TG2 expression was suppressed by exposure to 3-NP in combination with antioxidants, demonstrating that oxidative stress significantly increases TG activity in situ, a relevant finding to the etiology of HD and other diseases in which mitochondrial impairment plays a major role. Other studies had previously demonstrated in TG2 over-expressing 3T3 fibroblasts that TG activity could only be observed after a drastic ATP depletion occurring when the cells was entering necrosis (Verderio et al. 1998).

In this context, cystamine, a competitive inhibitor of TG activity, has been shown to significantly protect against 3-NP-induced PC12 cell death as well as striatal injury in HD transgenic mice (Fox et al. 2004). Cystamine's neuroprotective effects have been suggested to rely on a pleiotropic action that includes TG inhibition and antioxidant activity through the enhancement of L-cysteine synthesis (Fox et al. 2004). Recently, however, the long held assumption that cystamine protects through TG2 inhibition has been challenged. In fact, it has been shown that cystamine-mediated neuroprotection from 3NP toxicity in cell cultures and brain tissues is strongly dependent on the activation of NF-E2 related factor 2-mediated signaling through the antioxidant response element (Calkins et al. 2010).

The close relationship between TG2 and preservation of mitochondrial function has also been demonstrated in neuronal cell line SK-N-BE, in which TG2 over-expression

was associated with constitutive mitochondrial hyperpolarization and increases in ROS production. Moreover, TG2 over-expressing cells exhibited an increased apoptotic rate after stimulation with staurosporine, specifically targeting mitochondria, suggesting that TG2 may facilitate cell death induced by mitochondrial impairment (Piacentini et al. 2002).

However, it has also been reported that TG2 knockout results in a defective function of mitochondrial respiratory complex I, facilitating the oxidative damage of nigro-striatal neurons in response to exogenous toxins as experimental models of extra-pyramidal disorders (Battaglia et al. 2007).

These controversial data may be explained by reports showing that over-expressed TG2 sensitize cells to apoptosis only when its transamidation activity is switched on, while it is protective when its transamidation activity is dormant (Tucholski and Johnson 2002; Fésüs and Szondy 2005). In this regard, experimental approaches using different TG2 mutants have shown that TG2 intracellular localization affects the cell death process and that the transamidation activity, which is mostly quiescent except in extreme stress conditions, is necessary for its pro-death role (Milakovic et al. 2004; Gundemir and Johnson 2009).

However, the recent observations also suggest that the role of TG2 in apoptosis depends on the level of calcium influx triggered by oxidative stress. Monitoring TG2 expression, activity and calcium concentration in cells treated with A23187 revealed that the initial rise of calcium activates TG2, but subsequent calcium-overload induces the degradation of TG2 via calcium-mediated poly-ubiquitination (Jeong et al. 2009), as a kind of negative feedback keeping transamidation activity levels beyond the threshold of toxicity for cells. Thus, TG2 increases in response to low levels of oxidative stress, whereas it diminishes under high stress conditions.

In this context, accordingly to the well-described interdependence of excitotoxicity and oxidative stress (Bondy and Le Bel 1993), we recently investigated the involvement of TG2 in redox state alterations induced by exposure to excitatory aminoacids, i.e. homocysteine (Hcy), in nervous cells. Hcy dose-dependently increased ROS production, and produced the appearance of apoptotic features in undifferentiated neuroblastoma cell line Neuro2a (Ferlazzo et al. 2008). Antioxidants, such as *N*-acetylcysteine and IRFI 016, a synthetic alpha-tocopherol analog, were able to significantly reduce ROS increases and recover cell viability (Ferlazzo et al. 2008). Moreover, Hcy-evoked oxidative stress involved both TG2 up-regulation and in situ TG activity, which were associated with nuclear factor-κB (NF-κB) activation (Currò et al. 2009). Given that a neuroprotective role for NF-κB in brain oxidative stress upon different stimuli has been largely demonstrated (Blondeau et al. 2001), it is likely that TG2 up-regulation may be involved in activating cell survival pathways in this model of cell damage.

Interestingly, recent investigations suggest that Hcy toxic effects may be modulated by TG2 levels within the cells. Indeed, using undifferentiated and retinoic acid-differentiated human neuroblastoma SH-SY5Y cells towards neuronal cells, we observed that high Hcy concentrations dramatically decreased viable cell number only in undifferentiated cells having very low TG2 levels, while it did not significantly affect cell viability in differentiated cells over-expressing TG2 (unpublished data). Given that the intracellular calcium rise upon Hcy stimulation does not match the 1 mM threshold required for TG transamidation activity in the presence of intracellular GTP and these observations confirm that TG2 over-expression plays a protective role when the protein remains catalytically inactive within the cytosol.

The activation of glia has been observed in neurodegenerative diseases, such as PD, AD, multiple sclerosis and brain ischemia. Several experimental studies have demonstrated an age-related sensitivity of astroglial cells to oxidative stress, which makes neurons more susceptible to injury (Wang et al. 2006; Jou 2008). The exposure of primarily cultured astrocytes to excitotoxic glutamate concentrations resulted in TG2 up-regulation associated with oxidative stress, consistently with a glutamate uptake-induced impairment of cystine/glutamate antiporter leading to GSH depletion and intracellular ROS elevation (Campisi et al. 2004). The pre-incubation with antioxidants, such as GSH ethyl ester, cysteamine-HCl, genistein and IRFI-016 was able to recover redox basal conditions and decrease TG2 levels (Campisi et al. 2004; Caccamo et al. 2005a). This latter effect was achieved by the reduction of glutamate-induced NF-κB activation given that experiments with specific NF-κB inhibition demonstrated the NF-κB involvement in TG2 up-regulation, as well as competition experiments, showed a preferential binding of the oligonucleotide probe containing the NF-κB consensus sequence present in the TG2 promoter in the nuclear extracts of glutamate-treated astrocytes when compared with untreated ones (Caccamo et al. 2005b, c).

Further evidence of the involvement of NF-κB activation in TG2 up-regulation associated with oxidative stress has been provided by experiments in cultured rat hippocampal astrocytes activated by lipopolysaccharide (LPS), which is generally used for a stimulant of iNOS induction (Takano et al. 2010). Both TG2 and iNOS up-regulation induced by LPS stimulation were suppressed by ammonium pyrrolidine-1-carbodithioate, an inhibitor for NF-κB activation, and an antioxidant, ethyl pyruvate, in a dose-dependent manner (Takano et al. 2010).

Oxidative stress-related TG2 up-regulation in autoimmune diseases and cataractogenesis

In cell models of cystic fibrosis (CF), it has been reported that the generation of an oxidative stress induced by the transmembrane conductance regulator gene (CFTR)-defective function led to TG2 SUMOylation, that is the covalent attachment to TG2 of the small ubiquitin-like modifier (SUMO)-1. SUMOylation was mediated by protein inhibitor of activated STAT (PIAS) and resulted in sustained TG2 activation, which in turn led to NF-κB activation, peroxisome proliferator-activated receptor (PPAR)gamma ubiquitination, and an uncontrolled inflammatory response. Cell homeostasis could be restored by PIASy gene silencing, which induced TG2 ubiquitination and proteasome degradation, preventing IkBalpha cross-linking and degradation, thus switching off inflammation (Luciani et al. 2009). Manganese superoxide dismutase overexpression, as well as the treatment with the synthetic superoxide dismutase mimetic EUK-134 control PIASy-TG2 interaction and TG2 SUMOylation (Luciani et al. 2009). Thus, TG2 may function as a link between oxidative stress and inflammation by driving the decision as to whether a protein should undergo SUMO-mediated regulation or degradation.

In the same CF cell models as well as human nasal biopsies, it has been reported that the ROS-TG2 pathway activated by CFTR defective function is involved in autophagy inhibition and aggresome formation, and that the addition of cystamine or antioxidants is able to restore autophagy (Luciani et al. 2010a).

These data were confirmed by experiments in Caco-2 epithelial cell lines and cultured coeliac disease biopsies showing that the epithelial uptake and lysosomal accumulation of gliadin fraction p31-43 induced an intracellular pro-oxidative environment favouring the increase of TG2 protein levels and activation through inhibition of TG2 ubiquitination. This ROS-TG2 axis induced cross-linking, ubiquitination and proteasome degradation of PPAR-gamma, driving innate immune response and inflammation (Luciani et al. 2010b). The treatment with the antioxidant EUK-134 as well as TG2 gene silencing restored PPAR-gamma levels and reversed all features of innate activation, as indicated by the dramatic reduction of tyrosine and p42/p44 phosphorylation (Luciani et al. 2010b).

Oxidative stress or UV irradiation has been reported to induce an aberrant in situ TG activation in human lens epithelial cells and dermal fibroblasts (Gross et al. 2003; Shin et al. 2004). UVA irradiation resulted in the increased TG-mediated cross-linking of both intracellular and extracellular proteins (Gross et al. 2003). Moreover, ROS-activated TG2 catalyzed the in vitro formation of water-insoluble dimers or polymers of alphaB-crystallin, betaB(2)-crystallin, and vimentin in HLE-B3 cells, providing evidence that TG2 may play a role in cataractogenesis (Shin et al. 2004). These data support the proposal that oxidative stress and TG activity may be jointly involved in the changes found in lens crystallins with age and in the development of cataract.

More recently, using lens tissues from TG2-deficient as well as wild-type mice, it has been shown that low levels of oxidative stress triggered the release of TGF-beta, which subsequently activated TG2 through the nuclear translocation of Smad3. TG2-mediated protein modification resulted in decreased protein solubility and collapse of the intermediate filament network, which led to protein aggregation (Shin et al. 2008). This suggests that the TG-mediated assembly of oxidatively damaged proteins may be an active cellular response to oxidative stress.

Conclusions

Recent studies have demonstrated that the continuous overexpression of maize plastidial TG (chlTGZ) in transplastomic tobacco leaves is associated with oxidative stress, as shown by the drop in reduced glutathione, increase in H_2O_2 and lipid peroxidation, as well as decrease in catalase activity (Ortigosa et al. 2010). Given that maize chlTGZ shares with TG2 both catalytic triad (Cys, His, Asp) and conserved ATP/GTP binding domain as well as calcium-dependent cross-linking activity (Villalobos et al. 2004), these data suggest that from an evolutionary point of view TG2 as well as TG2-like proteins are intrinsically related to the generation of oxidative stress, so that an interplay even occurs between the increase in TG2 intracellular levels and redox state imbalance.

However, in the cells under normal conditions with relatively low levels of Ca^{2+} (100–200 nM) and relatively high levels of GTP (50–300 μM), the transamidation activity of TG2 is very low, even when it is overexpressed because of inhibitory effects of GTP binding (Smethurst and Griffin 1996; Tucholski et al. 2001). When certain stimuli increase cytosolic Ca^{2+} concentration above a certain threshold the transamidation activity of TG2 is no longer inhibited by GTP and facilitates cell death processes. Indeed, a TG2 mutant (C277S) that is able to bind and hydrolyze GTP but is catalytically inactive as a transamidating enzyme does not facilitate apoptosis and in some cases is actually protective (Antonyak et al. 2001; Milakovic et al. 2004; Tucholski and Johnson 2002).

In the light of these observations, it may be suggested that TG2 plays a pro-survival role in alterations of cell redox state homeostasis when cell stress is not associated with intracellular calcium increase triggering TG2 transamidation activity.

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