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INVITED REVIEW

Transglutaminase 2 and neuroinflammation

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Abstract Neuroinflammatory processes seem to play a pivotal role in various chronic neurodegenerative diseases, characterized also by the pathogenetic accumulation of specific protein aggregates. Several of these proteins have been shown to be substrates of transglutaminases, calcium-dependent enzymes that catalyze protein crosslinking reactions. However, it has recently been demonstrated that transglutaminase 2 (TG2) may also be involved in molecular mechanisms underlying inflammation. In the central nervous system, astrocytes and microglia are the cell types mainly involved in the inflammatory process. This review is focused on the increases of TG2 protein expression and enzyme activity that occur in astroglial, microglial and monocyte cell models in response to inflammatory stimuli. The transcription factor NF-κB is considered the main regulator of inflammation, being activated by a variety of stimuli including calcium influx, oxidative stress and inflammatory cytokines. Under these conditions, the over-expression of TG2 results in the sustained activation of NF-κB. Several findings emphasize the possible role of the TG2/NF-κB activation pathway in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis. Although further studies are needed to characterize the TG2/NF-κB cross-talk in monocytes/macrophages/microglia within the central nervous system, some results show that TG2 and NF-κB are co-localized in cell compartments. Together, evidence suggests that TG2 plays a role in neuroinflammation and contributes to the production of compounds that are potentially deleterious to neuronal cells.

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Abbreviations

Aβ	Amyloid β
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
CSF	Cerebrospinal fluid
DA	Dopaminergic
HD	Huntington disease
Hsps	Heat shock proteins
Htt	Huntingtin
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IL-8	Interleukin-8
LPS	Lipopolysaccharide
MS	Multiple sclerosis
NF-κB	Nuclear factor-kappa B
NO	Nitric oxide
PD	Parkinson's disease
PLA2	Phospholipase A2
SOD1	Superoxide dismutase 1
TG2	Tissue transglutaminase
TG2-S	TG2 short form
TGM2	Transglutaminase 2 gene
TGs	Transglutaminases
TNF-α	Tumor necrosis factor-α

Introduction

Transglutaminases (TGs) are a family of calcium-dependent enzymes able to catalyze post-translational modifications of many protein substrates through the formation of ε-(γ-glutamyl)lysine bonds. Tissue transglutaminase (tTG,

TG2) is the most ubiquitously expressed member of mammalian TGs (Lorand and Graham 2003).

Most of available studies focused on the involvement of Ca^{2+}-dependent transamidating activity of TG2 that leads to protein cross-linking with formation of protein aggregates (Lorand and Graham 2003). More recently, several observations suggest a multifunctional role for this enzyme which, in the absence of Ca^{2+}, acts as either a GTPase, a protein disulfide isomerase, a protein kinase or a scaffold protein (Nurminskaya and Belkin 2012; Eckert et al. 2014). Additionally, it has been suggested that TG2 may be first externalized and then retained at the cell surface where is involved in cross-linking of matrix proteins (Wang et al. 2012).

The involvement of TG2 in different pathological conditions is dependent on stimulus- and cell type-specific responses. A large body of literature has suggested that TG2 is involved in neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and progressive supranuclear palsy. In these diseases, transglutaminase (TG) enzyme activity is upregulated in selectively vulnerable brain regions, and TG2 co-localizes with inclusion bodies that are pathognomic signs of the diseases. Moreover, prominent proteins in the inclusion bodies, i.e. tau protein, alpha-synuclein, and huntingtin, are substrates for TG activity both in vitro and in cultured cells (Muma 2007). The increasing evidence for an association between TG2-dependent production of insoluble protein aggregates and neurotoxic events highlights the importance of developing approaches aimed at inhibiting the transglutaminase reaction as potential neuroprotective strategies (Jeitner et al. 2009; Caccamo et al. 2010). However, whether cross-linked protein inclusions themselves are responsible for pathological conditions or not is an issue to be further addressed. Notably, previous results demonstrated that TG2, when expressed at high levels, undergoes alternative splicing that generates a TG2 short form (TG2-S) with increased activity leading to dysregulated cross-linking (Citron et al. 2002). However, this feature has been reported in AD and progressive supranuclear palsy, while no evidence has been provided for HD and other neurodegenerative disorders (Zainelli et al. 2005).

Many studies have attempted to demonstrate that increases in TG2 enzyme activity and protein expression could be involved in inflammatory response. Indeed, increased TG activity is commonly detected both in diseased tissues with inflammation and cells with inflammatory stress (Kim 2006).

This review will address how TG2 is directly involved in neuroinflammation associated with chronic neurodegenerative disorders. Moreover, the underlying molecular mechanisms of TG2-mediated neuro-immunomodulatory processes in astrocytes, microglia and cell models in general will be described.

Neuroinflammation

The central nervous system (CNS) and the peripheral immune system actively cross-talk to control immune responses both centrally and peripherally. Indeed, recent studies explain how peripheral immune system-mediated events can influence CNS processes. These features suggest that inflammation may have important long-term implications for the brain. Different events, including cell injury or exposure to infections, trigger inflammatory response in the immune system cells, leading to a gradual activation of processes that promote morphological changes and secretion of pro-inflammatory elements such as cytokines, cytotoxic elements and radical oxygen species (ROS) production (Colton and Wilcock 2010; Ha et al. 2012).

At present, the term "neuroinflammation" is employed to describe the inflammatory response generated in the nervous system after injury. Typically, such a response consists in the activation of brain resident microglial and astroglial cells, producing pro-inflammatory mediators and acting as their targets, respectively. This neuroinflammatory response also promotes the accumulation of glial cells at the site of damage, an event often referred to as gliosis (O'Callaghan and Sriram 2005). Thus, astrocytes and microglia play a critical role in the regulation of the CNS immune responses. Activated astrocytes, for example, are important in the detoxification of excess excitatory amino acids, in response to neuronal dysfunction or injury, and also produce several factors that may modulate inflammatory responses. Similarly, microglial activation is an important factor in the glial response to tissue injury or dysfunction. However, resting or activated microglia and astrocytes are also responsible for the production and secretion of trophic factors promoting development, plasticity and repair in the CNS (Bauer et al. 2007).

Neuroinflammatory features suggest that numerous CNS diseases are frequently associated with peripheral immune cell infiltrates. These observations emphasize the involvement of CNS peculiar events versus invading immune cells in the inflammatory response.

In several pathological conditions including AD, PD and multiple sclerosis (MS) both astroglial and microglial responses appear to be involved in important mechanisms leading to neuronal dysfunction (Block and Hong 2005).

Although many studies demonstrate that brain and immune system regulate each other, the innate immune system directly influences the CNS through cytokines and chemokines, or release of CNS-derived cytokines (Saeed et al. 2005; Zimring et al. 2005). In fact, it has been shown

that the CNS responds to systemic bacterial infection by innate immune reaction even if the pathogen does not have direct access to the brain (Rivest 2003).

The underlying mechanisms leading to microglial activation have been characterized by numerous in vitro experiments. Several approaches often considered different changes in glial cell cultures after exposure to lipopolysaccharide (LPS) or pro-inflammatory cytokines to evaluate glia activation and/or to evaluate anti-inflammatory effects of several compounds (Sheng et al. 2011).

Transglutaminase in astroglial and microglial cells

TG2 expression is constitutive in many different cell lines, but it may be also actively regulated in a cell type-dependent manner. Interestingly, together with those for several transcriptional activators recognition motifs for cytokines are located within the TG2 gene (TGM2) promoter sequence (Ikura et al. 1994; Kuncio et al. 1998).

TG2 up-regulation has been shown to be involved in astroglial cell alterations in response to glutamate and pro-inflammatory cytokines (Ientile et al. 2003; Campisi et al. 2004; van Strien et al. 2011a). TG2 may also differentially modulate ischemic cell death in astrocytes and neurons (Colak and Johnson 2012). Moreover, increases in TG2 levels within astroglial cells are involved in astrogliosis as a component of the biochemical response to neuro-inflammatory stimuli (Hostenbach et al. 2014).

During focal cerebral ischemia, granulocytes and, later, T cells as well as macrophages gradually infiltrate ischemic and borderline brain areas, leading to a marked inflammatory response. Indeed, the expression of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), increases within hours of an ischemic brain lesion (Block et al. 2005). Interestingly, we demonstrated an increase in TG2 mRNA and protein expression that is delayed following ischemic injury (Ientile et al. 2004).

The pro- or anti-inflammatory cell signaling is mediated by different cytokines and the overall effects of a molecular pathway elicited by cytokine production may differ, depending on the location within the CNS and the context of disease.

Several studies emphasized the prominent role of nuclear factor-kappa B (NF-κB) which is considered a master regulator of inflammation (Luedde and Schwabe 2011; Viatour et al. 2005). Additionally, proteins of NF-κB complex also induce c-jun N-terminal kinase (JNK) pathways, which activate various other transcription factors that modulate apoptosis and inflammation (Hohmann et al. 1990). Certainly, the NF-κB family of transcription factors is of interest in inflammatory processes because it regulates the expression of numerous genes including cytokines as well as enzymes, such as nitric oxide (NO)-synthase 2 and cyclooxygenase 2 (Hoesel and Schmid 2013).

In this context, it has been demonstrated that TG2 expression is increased by LPS treatment in BV-2 microglia, and NO release is dramatically reduced by TG inhibitors (Park et al. 2004). Additionally, it has also been reported that TG2 inhibitor cystamine is able to reduce cyclooxygenase 2 in mouse microglia (Oono et al. 2014).

Notably, LPS also induces a TG2-mediated activation of NF-κB via polymerization of NF-κB inhibitory subunit IκB-α. This is an alternative way to IκB-α kinase-mediated activation leading to IκB-α phosphorylation and degradation. The IκB-α polymerization results in the dissociation and translocation of p65 and p50 subunits to the nucleus, where they are capable of up-regulating the transcription of inflammatory genes (Lee et al. 2004). These data suggest that TG2 may regulate transcriptional processes both directly, acting at nuclear level and indirectly acting at cytosolic level.

The biochemical mechanisms thought to participate in the constitutive activation of NF-κB have been evaluated. In different experimental models (Verma and Mehta 2007). Although the relationships between TG2 and NF-κB in the activated microglia are not well understood, it is evident that these key proteins usually co-localize. The effects of alterations in TG2/NF-κB signaling loop in immune cell response may be relevant as potential targets of therapeutic strategies against neuroinflammation and neurodegenerative diseases.

Interestingly, nuclear staining for NF-κB, localized predominantly in peri-vascular microglia and macrophages present in the basal ganglia and deep white matter, has been related to the severity of the AIDS-dementia complex (Rostasy et al. 2000).

Alzheimer's disease

Various pathological conditions, such as ischemia, brain inflammation and neuronal cell stress, have been regarded as risk factors for AD (Butterfield et al. 2002; Candore et al. 2006; Sastre et al. 2006). Increases in TG2 expression and transamidating activity, triggered by various stressors, i.e. calcium influx, oxidative stress, inflammatory cytokines and UV exposure, have been reported as co-occurring conditions (Kim 2006; Ientile et al. 2007). There are indications that activated TG2 is redistributed to the plasma membrane, where it may play an active role in neuronal cell death following calcium cell homeostasis disruption. This may be a component of acute excitotoxic injury leading to CNS neurodegeneration (Caccamo et al. 2004; Tucholski et al. 2006).

The contribution of inflammatory events to AD pathology, sustained by a chronic activation of microglial and

astrocytic cells, is strongly supported by multiple epidemiological studies concerning anti-inflammatory drugs which were associated with a reduced probability of AD development.

In order to explore underlying mechanisms at both the cellular and molecular levels many studies were carried out using THP-1 cells as model for microglia, the so-called inflammatory brain resident cells. Previously, we suggested that TG2 might be required for the functional activation of monocytes by amyloid β_{1-42} ($A\beta_{1-42}$). Indeed, the expression of cell surface markers and adhesion molecules as well as pro-inflammatory mediators was found to be dependent on $A\beta_{1-42}$-induced TG2 up-regulation. Furthermore, we demonstrated that TG2 silencing was able to reduce the $A\beta_{1-42}$-induced TNF-α up-regulation in THP-1 monocytes, indicating a role for TG2 in the regulation of $A\beta_{1-42}$-dependent inflammatory response (Currò et al. 2010). Interestingly, it has also been reported that inhibition of TG activity by antinflammins may have anti-inflammatory effects (Moreno 2006). Therefore, TG2 inhibition most likely result in a decrease of inflammatory cell infiltrate.

On the basis of results indicating various substrate proteins and interaction partners for TGs, we also hypothesized the existence of a cross-talk between TG2 and phospholipase A2 (PLA2). Interestingly, it has been suggested that PLA2 polyamination may contribute to the inflammation associated with neurodegeneration (Jeitner et al. 2009). Indeed, in THP-1 cells we also demonstrated that, after incubation with LPS, PLA2 activation may be dependent on the high levels of TG2 activity. Given that PLA2 plays a role in the first rate-limiting step leading to eicosanoid production, these findings may reveal a functional interaction between these enzymes leading to a mechanism involved in inflammatory response amplification (Currò et al. 2014).

Parkinson's disease

PD is a chronic and progressive movement disorder, involving neuronal dysfunction and death leading to a massive and preferential loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (Fahn 2000). Although there is little evidence for the role of inflammatory factors in PD, some results have shown a remarkable microglial activation associated with the release of pro-inflammatory cytokines and the production of cytotoxic substances, such as NO and ROS (Hirsch and Hunot 2009). These events may not be specific consequences of neuronal death, even if damaged DA neurons may be involved in activating microglia and sustaining neuroinflammation. In this context, the activated Toll-like receptors (TLRs) have been considered the more relevant components in glial cells, promoting the release of cytokines that are ultimately responsible for the death of DA neurons in the *substantia nigra pars compacta* (Laflamme and Rivest 2001).

Heat shock proteins (Hsps), a group of highly conserved proteins that are constitutively expressed in most cells under physiological conditions, may be effective activators of TLR-dependent pathway in microglia cells. Interestingly, Hsp60 interacts with receptors at the cellular membrane and may be involved in neuron-glia cross-talk. Although a deleterious role of Hsp60 on DA neurons in different PD models has been reported, a direct effect of Hsp60 on DA neurons should be further clarified in this scenario (Noelker et al. 2014).

Under cell stress conditions leading to endoplasmic reticulum stress and intracellular calcium increase, Hsps undergo cell translocation and play a role in protein conformational changes in response to stress. Recently, we demonstrated that TG2 is able to interact with Hsps. In particular, we found that the interaction between TG2 and both Hsp20 and Hsp27 play a protective role against NMDA-evoked excitotoxic insult in neuronal-like differentiated SH-SY5Y cells (Caccamo et al. 2013).

Huntington's disease

Nuclear TG2 was first suggested to play a relevant role in the formation of protein aggregates of huntingtin (Htt) with expanded polyglutamine (Karpuj et al. 1999). In HD brain tissues postmortem analysis demonstrated the 99 % co-localization of TG2-catalyzed ε-(γ-glutamyl)lysine cross-links with Htt nuclear aggregates (Zainelli et al. 2003). Moreover, TG2 inhibition partly reduced the formation of aggregates of mutant Htt in a cell model of HD (Lazarev et al. 2013). These observations suggest that nuclear TG2 is involved in the mechanisms of aggregate formation contributing to neurodegeneration in HD.

Lines of evidence observed that neuroinflammation, particularly microglial activation, is involved in the pathogenesis of HD. Indeed, other than being primarily localized in neurons the expression of mutant Htt also occurs in microglia (Björkqvist et al. 2008). Remarkably, some in vivo investigations by PET study give evidence for a close relationship between microglia activation and severity of the pathology in HD patients; moreover, the cerebrospinal fluid (CSF) and striatum of HD patients exhibit immune activation associated with high levels of interleukin-6 (IL-6), interleukin-8 (IL-8) and TNF-α (Pavese et al. 2006; Silvestroni et al. 2009). The most recent observations show that the neuroinflammatory process within the brain of HD patients is paralleled by inflammatory changes detected in peripheral plasma, as suggested by the significant increase of IL-6, matrix metalloprotease-9, vascular endothelial growth factor and transforming growth factor beta-1 plasma levels (Chang et al. 2014).

The reason for specific effects of mutant Htt on microglia gene expression and inflammatory response has not yet been clarified. Given the reported involvement of TG2 in microglial activation, as discussed above, it is possible to hypothesize that TG2 may also contribute to Htt-induced microglial activation. However, further investigations are needed to address this issue.

Multiple sclerosis

MS is a neurodegenerative disorder characterized by the irreversible damage of myelin, causing a wide range of symptoms including vision loss, ataxia and interference in the communication between brain, spinal cord and rest of the body (Dalakas 2013). MS is associated with chronic neuroinflammation through the release of inflammatory cytokines within the CNS (Dalakas 2013). Under these conditions, the cytokine IL-1β stimulates the activation of a reactive astrocytic phenotype resulting in the adhesion of astrocytes to fibronectin or laminin (John et al. 2004). Notably, the molecular changes, such as cytoskeletal reorganization and focal adhesion dissolution stimulate TG2 interaction with fibronectin to facilitate cell adhesion, suggesting that TG2 may be involved in numerous other adhesion-dependent phenomena (Wang et al. 2012).

TG2 may also be present on the surface of astrocytes, and this localization is enhanced by cytokine exposure. In particular, TG2 contributes to dense astrogliosis in MS. Indeed, TG2 interacts with fibronectin at the cell surface and contributes to astrocyte adhesion and migration. The inhibition of TG2 activity by KCC009 reduces astrocyte proliferation independently of cytokine treatment. Thus, this suggests that TG2 is not responsible for the observed cytokine-specific effects on migration (van Strien et al. 2011b; Hostenbach et al. 2014).

In order to provide evidence for the involvement of TG in MS, the possible association of MS with other autoimmune processes has also been investigated. Interestingly, an increased prevalence of serological markers of celiac disease has been observed in patients with relapsing-remitting form of MS (Rodrigo et al. 2011).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the predominant loss of motor neurons in primary motor cortex, brainstem and spinal cord. Although many observations provided a great deal of information about histopathological and clinical features of ALS, little is known about the biochemical mechanisms occurring in this disease, especially in the spinal cord. Preliminary results suggested that TG activity, leaking out of the spinal cord tissue into the CSF during the progression of ALS, may be used as biomarker at the terminal stages of the disease when most of the spinal motor neurons have been destroyed (Fujita et al. 1998). More recent evidence suggests a possible involvement of TG protein expression and enzyme activity in neurotrauma. In this regard, important modulators of TG2 expression are the inflammatory cytokines, IL-1β, IL-6 and TNF-α (Kuncio et al. 1998). In particular, TNF-α can induce the transcription of TG2 specific isoforms regulating the alternative TG2 mRNA splicing. Therefore, changes in cytokines and immune response probably induce the GTP-independent TG2-S isoform, triggering apoptosis cascade (Festoff et al. 2002).

It has been shown that neurotoxicity, caused by glutamate exposure or oxidative stress, is associated with the increase of TG2 transamidating activity. In this regard, it is noteworthy that oligomerization of misfolded superoxide dismutase 1 (SOD1) by TG2 occurred in both BV-2 microglia cultured cells and mouse model (Oono et al. 2014). Therefore, SOD1 aggregates, occurring in ALS, may be functionally associated with increases in TG2 and cytokine production in microglia cells. Furthermore, inhibition of spinal TG2 by cystamine significantly delayed the progression of disease reducing SOD1 oligomers and microglial activation (Oono et al. 2014).

Neuro-AIDS

The AIDS-related dementia is a type of dementia that occurs in advanced stages of AIDS. The neurodegenerative process is characterized by encephalitis with a varying degree of perivascular inflammation occurring in approximately one-third of patients infected with HIV (Lawrence and Major 2002).

Several studies suggest that, in HIV-induced CNS disease, the products of activated macrophages and astrocytes lead to CNS dysfunction by directly damaging neurons, as well as by induction of altered gene and protein expression profiles in neurons themselves which are deleterious to their function. Moreover, monocyte migration is also promoted by TG2, which was found to be prominently expressed on endothelial cells as well as on macrophages/microglia (Roberts et al. 2003).

Monocytes and glial cells occurring in the gray and white matter, perivascular lymphocytes and brown-pigmented macrophages further contribute to inflammatory changes associated with pathogenetic mechanisms. Biomarkers for apoptotic cascade in syncytia both in vitro and in lymphoid tissues of HIV-1-infected patients have been investigated (Castedo et al. 2001). Interestingly, in the brains of HIV-associated encephalitis (HAE)-affected patients TG2 up-regulation has been shown to be associated with increase of pro-apoptotic transcription factor p53.

TG2 itself was able to interact with the pro-apoptotic Bcl-2 family member Bax which was active at the mitochondrial level triggering apoptotic cascade (Nardacci et al. 2005).

Conclusions

Some studies have shown that specific proteins such as glial filaments and myelin basic protein can serve as TG2 substrates in vitro (Pittier et al. 2005).

Undoubtedly, TG2 protein and enzyme activity play a key role in microglial NF-κB activation. Thus, TG2 may contribute to the development of inflammation in multiple sclerosis by regulation of NF-κB signaling as well as autoantibody generation through modification of myelin basic proteins.

Although the mechanisms regulating the functional relationship between TG2 and NF-κB in the activated microglia remain to be fully elucidated, it seems clear that these key factors co-localize. These findings are relevant given that microglia as well as macrophages produce compounds that are potentially deleterious for neurons, including nitric oxide and TNF-α.

Clear evidence suggests that high levels of TG2 may be dependent on different stimuli in the brain, such as increased production of Aβ due to trauma and ischemia in sporadic AD or overproduction of Aβ in familial AD. These stimuli increase cellular stress conditions in the brain and further upregulate TG2, leading to a prolonged inflammatory response. The Aβ aggregates also promote chronic increases of TG2 expression and activity and exacerbate the pathogenic process. The possibility that TG2 expression is susceptible to molecules involved in the inflammatory response suggests that common mechanistic pathways are activated. However, the balance of pro-inflammatory and anti-inflammatory enzymes on the onset of stress conditions may be an appropriate target to prevent conversion to the pathological state.

Conflict of interest There is no conflict of interest with regard to this work.

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