Transglutaminase 2 in inflammation

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1. ABSTRACT

Many reports have shown that the expression of transglutaminase 2 (TG 2) is increased in inflammatory diseases. Although during the last several decades multiple physiological roles for TG 2 have been demonstrated in various cell types, its role in the inflammatory process is not yet clear. TG 2 is a crosslinking enzyme that is widely used in many biological systems for tissue stabilization purposes and immediate defense against injury or infection. Aberrant activation of TG 2 activity in tissues contributes to a variety of diseases including neurodegenerative diseases, autoimmune diseases, and cancers. In most cases, TG 2 appears to form an inappropriate protein aggregate that may be cytotoxic enough to trigger inflammation and/or apoptosis. In some cases, such as celiac disease and rheumatoid arthritis, TG 2 is also associated with the pathogenic progression, as well as in the generation of autoantibodies. Recently, we discovered that increased TG 2 activity triggers NF-κB activation without I-κBα kinase signaling. TG 2 induces the polymerization of I-κBα rather than stimulating I-κBα kinase. This polymerization of I-κB results in the direct activation of NF-κB in various cell lines. We also found that TG inhibition reverses NF-κB activation. Interestingly, this coincides with the reversal of inflammation in conjunctivitis models by treatment with TG 2 inhibitors. Here, I introduce a new role for TG 2 as a signal modulator, which may suggest a new paradigm for the inflammatory process.

2. INTRODUCTION

Transglutaminase 2 (TG 2; EC 2.3.2.13) catalyzes the formation of isopeptide linkages between the carboxamide group of protein-bound glutamine residues and the ε-amino group of protein-bound lysine residues (Figure 1)(1). TG 2 has been considered to be a key factor in the prevention of and protection against injury and the promotion of repair(2). Aberrant induction of TG 2 activity contributes to various disease pathologies, including neurodegenerative diseases, atherosclerosis, inflammatory diseases, autoimmune diseases, and fibrosis (3). Although TG 2 is closely associated with the formation of insoluble deposits in diseases, it remains unclear whether the crosslinked protein inclusion itself is pathogenic. In some disease cases, TG 2 induction does not accompany protein deposit formation. Increased TG 2 activity is commonly detected both in diseased tissues with inflammation and in cells with inflammatory stress. We have found that increases in TG 2 activity induce or exacerbate inflammation via NF-κB activation without I-κBα kinase signaling (4). The mechanism of activation of NF-κB by TG 2 is unique as compared to the normal pathway of NF-κB activation. An increase in TG activity reduces free I-κBα in the cytosol via I-κBα polymerization, which leads to the translocation of free NF-κB into the nucleus (Figs. 2, 3). Interestingly, TG 2 also can be induced directly by NF-κB activation since the TG 2 promoter contains a NF-κB binding motif (5). Therefore, if TG 2 activity is aberrantly
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**Figure 1.** TG 2 reaction. Protein A is a protein/peptide substrate with a glutamyl (Gln) residue (acyl donor, amine acceptor). Protein B is a protein/peptide substrate with a lysyl (Lys) residue (acyl acceptor, amine donor). TG 2 catalysis with calcium results in a very strong covalent crosslinkage of the proteins/peptides by the isopeptide bond, \( \text{N}^{\text{ε-(γ-glutamyl)}}\text{-L-lysine} \).

**Figure 2.** Proposed model for treating celiac disease (CD) via TG 2 inhibition. Gliadin is the major dietary component of wheat and rye. The intake of wheat or rye initiates an inflammatory reaction in CD patients with type HLA-DQ2+. TG 2 in the activated T cells is secreted into the matrix of lamina propria where the gliadin can be modified by TG 2 to increase its antigenicity. Increased TG 2 activity in the jejunum of CD patients appears to be responsible for the inflammatory chain reaction. TG 2 inhibition may prevent and/or reverse the consequences of T-cell activation. MMPs, matrix metalloproteinases; TGRF, TG 2 regulatory factor (hypothetical); TGF-β, transforming growth factor-β; auto-Ab, autoantibody against TG 2. Black bars represent inhibition of TG 2 activity.

Activated, NF-κB continues to activate inflammation. Thus, regulating TG 2 activity would enable us to stop this vicious inflammatory loop (Figure 2). Recently, we demonstrated the possibility that TG inhibitors could reverse the inflammatory process in brain injury (4), conjunctivitis (6), uveitis (7), and lung fibrosis models (8).

3. CONTROVERSY SURROUNDING THE ROLE OF TG 2 IN APOPTOSIS

One group of scientists observed a significant increase in TG 2 activity during the involution of lead nitrate-induced hyperplasia of rat liver, which coincided with apoptosis of hepatocytes (9). Later, another group reported that U937 cells (promonocytic cells) transfected with antisense TG 2 showed a significant decrease in apoptosis (10). Although TG 2 itself was not sufficient for triggering apoptosis, an increase in TG 2 expression sensitized cells to apoptotic stimuli (11). However, the role of TG 2 in apoptosis remains controversial, since other groups have reported that TG 2 expression is linked to cell survival (12). It is known that retinoic acid (RA) and its various synthetic analogs affect mammalian cell growth, differentiation, and apoptosis. Treatment with RA or its analogs also induces TG 2 (12). Interestingly, TG inhibition eliminated RA-induced protection against cell death and, in fact, caused RA to become an inducer of apoptosis. This implies that the anti-apoptotic effect of RA on N-(4-hydroxyphenyl)-retinamide-induced apoptosis is linked to the induction of TG 2 expression (13). Although the anti-
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Apoptotic mechanisms of TG 2 are poorly understood, several possible pathways have been suggested, including protection against the degradation of tumor suppressor protein p110 Rb in N-(4-hydroxyphenyl)-retinamide-induced apoptosis (14) and inhibition of caspase 3 in thapsigargin-induced apoptosis (15). Recently, evidence that TG 2 expression is associated with anti-apoptosis has been found in drug-resistant and metastatic breast cancer cells with up-regulated TG 2 expression (16). Furthermore, TG 2 inhibition in chemo-resistant breast cancer cells promotes sensitivity to chemotherapy (17). TG inhibition has been clearly demonstrated to efficiently regress glioblastomas (18). These reports support the activation of NF-κB by TG (see 4.4.), which results in a milieu of inductions of survival factors.

Taken together, there is no doubt that increased TG 2 expression balances the promotion of apoptosis in response to apoptotic stress and resistance to chemical stress to promote survival.

4. TG 2 IN INFLAMMATION

It is well-known that TG 2 promotes wound healing (19). Throughout the healing process, TG 2 is induced in endothelial cells, macrophages, and skeletal muscle cells. Increases in TG expression occur in association with TGF-β, TNF-α, IL-6, and VEGF production in wounds (19). TG 2 is also involved in the control of dynamic adhesion formation during cell spreading and migration via regulation of phospholipase C activity (20). Therefore, TG 2 is directly involved in wound healing and extracellular matrix formation.

TG 2 is immediately induced and/or activated by injury or infection to help in recovery from the damage, as well as to defend against infection. This immediate response is reminiscent of the innate immune system. The host defense system is divided into two major categories, immune and non-immune. Immunity is characterized by an antigen-specific response to a foreign antigen or pathogen. A key feature of immunity is memory of the antigen such that subsequent exposure leads to a more rapid and often a more vigorous response. Non-immune host defense is not antigen-specific and is an immediate response that does not require previous exposure to the eliciting stimulus. This process is called innate immunity. Neutrophils, eosinophils, basophils, NK cells, monocytes, and macrophages are the mediators of this immediate response system. Does TG 2 have an important role in this non-immune host defense system? To understand the role of TG 2 in the inflammatory reaction, we might examine TG in a living fossil such as the horseshoe crab, which belongs to the subclass Xiphosura that spans more than 500 million years of evolution (21). All invertebrates, including the hemolymphs of horseshoe crabs, lobsters, sand crabs, and sponges contain TG activity (22).

4.1. A lesson from living fossils

One of the major defense systems of horseshoe crabs is carried by circulating hemocytes called granulocytes (23). The granular hemocyte contains large and small dense granules. Horseshoe crab hemocytes are very sensitive to lipopolysaccharides (LPS). This implies that hemocytes may have evolved into circulating blood and immune cells in higher eukaryotes. Interestingly, all of them have very high TG 2 expression and immediate activation of TG 2 in response to LPS (24-26). When hemocytes are exposed to LPS, they respond by degranulating (27). The large granules contain many proteins, the majority of which are clotting and degradation factors, including TG substrates and proteases (28). This degranulation response involves the engulfing and killing of invading microbes, as well as the prevention of hemolymph leakage. Briefly, this defense reaction consists of two major steps: the immobilization of invaders by coagulation factors including TG and the degradation of the coagulated protein mass by proteases. Interestingly, TGs and matrix metalloproteases (MMPs) are often associated in the lesions of inflammatory diseases such as rheumatoid arthritis (29) and celiac disease (30). There is no doubt that TG plays a key role in the immediate defense system of the horseshoe crab that mimics innate immunity in higher vertebrates. There is significant amino-acid sequence similarity (32.3%) between the horseshoe crab TG and the guinea pig liver TG (31). In innate immunity, adequately designed biosensors are required for the recognition of various epitopes on a variety of pathogens, in order to distinguish ‘self’ and ‘non-self’. If ancient TG participates in removing intruders by coagulation, theoretically the TG-substrate domains of intruders could be serving as inflammatory sensors.

4.2. TG 2 in macrophages

TG activity was first reported in human peripheral lymphocytes almost three decades ago and was found to increase up to 15-fold within 30 min after concanavalin A treatment of the lymphocytes (32). Later, due to its immediate induction, TG 2 was identified as a new marker for macrophages of a certain differentiation or activation state (33). A 150-fold increase in synthesis of the enzyme occurs within 90 min of exposure of macrophages to a heat-labile constituent of serum or plasma (34). The induction of both gene transcription and protein synthesis is responsible for the increased levels of TG 2 observed in cultured human monocytes (35). Interestingly, freshly prepared monocytes contain only the A subunit of cellular factor XIII, consisting of blood-clotting factor XIIIa and TG 2 (36). The phagocytotic capacity of monocytes is about 25% of that of macrophages (36). In continuous cultures, the monocytes mature into macrophages. During this differentiation, factor XIIIa disappears and TG 2 increases. Incubation with a TG inhibitor inhibits phagocytosis in macrophages by approximately 60% (36). This result suggests that factor XIIIa is gradually replaced by TG 2 during maturation of monocytes into macrophages, and that this replacement is associated with TG-dependent phagocytosis. Although TG 2 and factor XIIIa both are expressed on the surface of monocytes, only surface-bound TG 2 is associated with multiple integrins of the β1 and β3 subfamilies (37). The amount of integrin-bound TG 2 is sharply increased concomitantly with increased surface levels of TG 2 during the conversion of monocytes into macrophages (37). The cell-surface-bound
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TG 2 serves as an integrin-associated adhesion receptor that may be responsible for the extravasation and migration of monocytes into tissues containing fibronectin matrices during inflammation. In addition to its role in adhesion, we will suggest a new role for TG 2 as a regulator of the inflammatory process in activated macrophages (see Section 4.4).

4.3. TG 2 in inflammatory diseases

4.3.1. TG 2 in ischemia

Focal cerebral ischemia elicits a strong inflammatory response involving early recruitment of granulocytes and delayed infiltration of ischemic areas and the boundary zones by T cells and macrophages (see review 38). In the infarct region, microglia are activated within hours and transform into phagocytes within days. Local microglia and infiltrating macrophages demarcate infarcts and rapidly remove debris. Remote from the lesion, astroglia and microglia are activated but no cellular infiltration occurs. In focal ischemia neurons die immediately from necrosis and in a delayed fashion via programmed cell death or apoptosis (38). Pro-inflammatory cytokines such as TNF-α and IL-1β are up-regulated within hours in ischemic brain lesions (38). Inflammatory cytokines may contribute to infarct progression in the post-ischemic period, either directly or via induction of neurotoxic mediators such as nitric oxide in microglia (38). In global ischemia, inflammatory responses are limited, although the inflammatory response strongly activates microglia and astroglia. TG 2 increases progressively after ischemia, with greater expression in the cortex than in the hippocampus (39). Interestingly, these results demonstrate that increased TG 2 mRNA and protein expression are delayed following ischemic injury (39, 40). Cerebral ischemia causes increased calcium influx with membrane depolarization (41), which triggers activation of TG 2 (42) and proteases (43). TG 2 induction in response to cerebral ischemia is similar to that following traumatic brain injury (44). In a model of spinal cord ischemia, TG activity is transiently increased but declines to control levels after 1 week (45). The increase in TG 2 expression also has been observed after spinal cord injury (46) and vagus-nerve-crushing injury (47). This suggests that TG 2 may be not only a good predictor for the pathophysiology accompanying traumatic and ischemic brain injury, but also a key molecule in the response to the inflammatory stress.

4.3.2. TG 2 in CNS inflammation

Multiple sclerosis and AIDS dementia complex (also called HIV-associated dementia) are two examples of CNS diseases with a strong inflammatory component (48). In particular, macrophage/microglia activation in the deep white matter is a key feature of both diseases (48). Cerebrospinal fluid from multiple sclerosis patients contains autoantibodies against myelin basic protein and myelin-associated glycoprotein (49). It is not clear why and how autoantibodies are generated in multiple sclerosis. Interestingly, it has been demonstrated that glial filaments and myelin basic protein can serve as TG 2 substrates in vitro (50). Recently, we found that TG 2 activation plays a key role in at least a part of microglial NF-κB activation (4). These findings suggest that uncontrollable activation of TG 2 in activated microglia may contribute to the development of inflammation in multiple sclerosis, either by continuous inflammatory signaling through NF-κB activation or by autoantibody generation through modification of myelin basic proteins. The latter is supported by evidence that TG 2-mediated modification of gliadin creates a new epitope in celiac disease lesions (51).

HIV infection in humans, accompanied by CNS infection and dysfunction, has the same pathological characteristics as experimental infection with simian immunodeficiency virus (SIV) in rhesus macaques. Cognitive and motor dysfunction, neurophysiological abnormalities, and neuropathological changes in HIV encephalitis (HIVE) are also found in SIV-infected monkeys (48). SIVE arises sporadically in infected rhesus macaques, similar to HIVE in humans. Macrophages and microglia produce molecules that are potentially harmful to neurons, including nitric oxide and TNF-α. Although such products are common candidates in proposed pathogenic mechanisms mediating HIV/SIV-initiated damage to the CNS, identification of the molecules responsible for neuropathogenesis is helpful for understanding the molecular pathogenesis. Using human GeneChips, researchers identified the gene transcripts found in infiltrating and activated macrophages (52). The many identified genes included TG 2, α1-antichymotrypsin, cyclin D3, and STAT1, in addition to CD163, Glut5, and ISG15. In particular, TG 2 was significantly up-regulated in the frontal lobe of brains with SIVE, where inflammation was highly advanced, compared to brains from uninfected animals (52). Interestingly and coincidently, nuclear staining for NF-κB also localized predominantly to perivascular microglia and macrophages in the basal ganglia and deep white matter, and correlated with the severity of the AIDS-dementia complex (53). Although the association between TG 2 and NF-κB activations in the activated microglia remains to be elucidated, it is obvious that expressions of these key factors are co-localized.

4.3.3. TG 2 in inflammatory skin diseases

Activated macrophages are an integral component of inflammatory skin diseases and many reports have demonstrated that TG 2 activation is closely associated with macrophage activation (32-34). Most studies on TG and inflammatory skin diseases have focused on TGs 1 and 3 rather than TG 2. However, because expression of TGs 1 and 3 is often detected in tissues other than the epidermis (54), I believe that TGs 1 and 3 have more important roles in skin differentiation than in maintaining structural integrity. For example, dermatitis herpetiformis is a gluten-sensitive inflammatory disease with symmetrically distributed blistering of the skin and is characterized by granular IgA deposits in the papillary dermis (55). Its association with celiac disease is recognized because of the high levels of IgA autoantibodies to endomysium in patients with dermatitis herpetiformis. After TG 2 was identified as the endomysial autoantigen in celiac disease (56), IgA antibodies to TG 2 were identified in patients with dermatitis herpetiformis (57). In addition, the sera from dermatitis herpetiformis patients react both with TG 2 and TG 3 (57, 58). IgA autoantibodies in
Continuous activation of TG 2 may exacerbate the inflammatory process by continuous activation of the inflammatory pathway in the pathogenic lesion (Figure 3). A proposed mechanism will be introduced in Section 4.4. Although further investigation of TG 2 expression in atopic and psoriatic pathogenesis is needed, I suggest that TG inhibition may be beneficial for reducing dermatitis herpetiformis as well as atopic and psoriatic symptoms.

4.3.4. The benefit of TG 2 inhibition in conjunctivitis

Our recent studies have proposed that inhibition of TG 2 may be a profitable new approach to the treatment of inflammatory diseases (4, 6-8). Although phospholipase A2 (PLA2, EC 3.1.1.4) plays a key role in arachidonic acid-mediated inflammation, it is difficult to find therapeutic inhibitors of PLA2. Interestingly, treatment of purified PLA2 with TG 2 strikingly increased PLA2 activity in vitro (64). Therefore we hypothesized that inhibition of both TG 2 and PLA2 activities might reverse PLA2-mediated inflammation. We showed that recombinant peptides from lipocortin-1 and pro-elafin (cementoin) abolished the TG 2-catalyzed activation of PLA2 in vitro and had a remarkable anti-inflammatory effect on allergic conjunctivitis in vivo (6). Nona peptides (antiflammins) corresponding to uteroglobin residues 39-47 and lipocortin-1 residues 246-254 have been identified as PLA2 inhibitors (65). In addition to the recombinant peptides, we found that the proelafin sequence itself was a TG inhibitor and had dramatic anti-inflammatory effects (6). A recent study from another group revealed that the anti-inflammatory effect of antiflammins was due to TG 2 inhibition rather than PLA2 inhibition (66). This strongly supports the proposal that TG 2 participates in the inflammatory process. Recently, we found that TG 2 activates the transcriptional activator NF-κB, which up-regulates the expression of inflammatory genes such as inducible nitric oxide synthase and TNF-α (4). Therefore TG 2-mediated NF-κB activation may provide a new possibility for understanding the pathological progression of inflammation (Figure 3; see Section 4.4.), since NF-κB is a key inducer of inflammation in immune cells.

4.4. TG 2: a kinase-independent pathway for NF-κB activation

The NF-κB family of transcription factors is critical in inflammatory processes because it regulates the expression of genes including IL-1, TNF-α, iNOS, and GM-CSF. NF-κB appears to be involved in the pathogenesis of inflammatory diseases and cancers (67, 68). Therefore NF-κB has been targeted for the development of therapeutic inhibitors of those diseases. However, due to the complexity of its subunits and its various regulating signaling pathways, it has not been easy to develop specific inhibitors of NF-κB activation. Here, I introduce a new paradigm for inflammation, suggesting that TG 2 may be the key for therapeutic developments.

It has been shown that an increase in TG 2 activity is associated with NF-κB activation via an IKK-independent pathway in microglia (24) and SH-SY5Y cells (4). Western blotting using a tetracycline-inducible TG 2
expression system in an EcR293 cell line shows that the I-κBα level decreases as TG 2 expression increases in a time-dependent manner (Figure 4). However phosphorylated I-κBα is not detected because TG 2 induces the polymerization of I-κBα rather than stimulating I-κBα kinase. This polymerization of I-κBα results in the direct activation of NF-κB in various cell lines (4, 24). In the LPS-induced brain injury model, we found that increased TG 2 expression is restricted to the subfornical organ and choroid plexus (4) concomitantly with the increase in TG 2 in a time-dependent manner, implying that TG 2 activates NF-κB directly. Phosphorylated I-κBα could not be detected (data not shown).

Figure 4. Induction of TG 2 causes disappearance of monomeric I-κBα. A tetracycline-induced expression system was used with the EcR293 cell line (Flp-In T-Rex-293). After the introduction of full-length human TG 2 cDNA into EcR293 cells, using pcDNA5/FRT, and selection with hygromycin, TG 2 was induced with a 1-mg/ml tetracycline treatment for 0–24 h. I-κBα disappeared concomitantly with the increase in TG 2 in a time-dependent manner, implying that TG 2 activates NF-κB directly. Phosphorylated I-κBα could not be detected (data not shown).

TG 2 can be induced by various stresses including LPS (24–26), oxidative stress (70), UV (71,72), calcium ionophores (73,74), retinoic acid (75), inflammatory cytokines (61, 76), and viral infection (52). Intermediates of oxidative stress and reactive oxygen have been shown to increase TG 2 expression (69). The increase in I-κBα mRNA parallels both I-κBα protein degradation and NF-κB activation because transcription of I-κBα is regulated by NF-κB. Therefore, the TG 2 expression pattern shows an early-phase activation in the inflammatory process (4). The fate of the polymerized I-κBα in vivo remains to be elucidated.

TG 2 can induce NF-κB activation via two pathways – an IKK-independent and an IKK-dependent pathway (Figure 3). Here we propose a model for the therapeutic use of TG 2 inhibition during inflammation (Figure 2). TG 2-mediated NF-κB activation may be an important defense against infection or, conversely, a disease-associated mechanism in the inflammation process. We have demonstrated that TG inhibition is effective as a therapeutic approach in brain injury (4), conjunctivitis (6), uveitis (7), and lung fibrosis models (8). This suggests that TG inhibition may be beneficial in diseases associated with inflammation.

5. REVISITING AUTOIMMUNE DISEASES

Since TG 2 has been identified as a major target of autoantibodies in celiac disease (CD) (56), it has been proposed that TG 2 plays a key role in autoimmune diseases via the generation of new epitopes by crosslinking. Thus, TG 2 may be related to the loss of tolerance and initiation of autoimmune disease. In addition, the increase in TG 2 activity in the lesion may exacerbate inflammatory pathogenesis. Based on a series of in vitro experiments, TG 2 is thought to be responsible for generating neoepitopes of gliadin through deamidation of glutamine residues (51) or by crosslinking itself to gliadin (83). This is a plausible hypothesis because the serum anti-TG antibody titer falls dramatically when wheat products are removed from the diet. The increase in TG 2 expression by pro-inflammatory cytokines may be a novel mechanism because TG 2 expression in jejunal biopsies of CD patients is elevated (84). The inflammatory infiltrates of the jejunal tissues of CD patients are rich in T cells, which increase inflammatory cytokines including INF-γ (85). It has been shown that INF-γ can induce expression of TG 2 in rat IEC-6 small intestinal cells, whereas TGF-β suppresses TG 2 expression (62). Another possibility is that the source of TG 2 is macrophages and T cells. Activated T cells and macrophages increase TG 2 expression (34, 86, 87). Immunohistostaining of TG 2 in CD biopsies supports this, since there is strong staining of the subepithelial membrane that is rich in macrophages and T cells (60). The fact that the severe inflammation of CD is not triggered until gliadin is delivered, even though autoimmun e antibodies against TG 2 are abundant in the subepithelial region, supports this theory. Taken together, these observations suggest that TG 2 is involved in the pathogenesis of CD in the jejunum. It is not clear whether the role of TG 2 is direct or indirect. Regardless of a TG 2 role in modification of gliadin to increase antigenicity at the lamina propria or in NF-κB activation of T cells, TG 2 inhibition may be a useful treatment for CD (Figure 2).

Idiopathic inflammatory myopathies are the most common progressive muscle disorders that affect older
individuals. Using immunocytochemistry and quantitative RT-PCR, the level of TG 2 expression was found to be significantly increased in idiopathic inflammatory myopathies (IMs), including dermatomyositis (DM), polymyositis (PM), and sporadic inclusion body myositis (s-IBM) (88). DM and PM do not present any deposition of inclusion bodies containing highly crosslinked amyloid or other proteins. Therefore, a plausible role for TG 2 may be to contribute to the inflammatory process in these myopathies. Autoantibodies against TG 2 are found in the blood of patients with dermatitis herpetiformis (89), type 1 diabetes (90), and systemic lupus erythematosus (SLE) (91), and in the synovial fluid in rheumatoid arthritis (92). At the present time, we do not have a clear mechanism to explain these phenomena. TG 2 involvement in the pathogeneses of common autoimmune diseases requires further investigation.

6. CONCLUSIONS AND PERSPECTIVES

We suggest that TG 2 is strongly associated with the pathogenesis of many inflammatory diseases. Others have also come to this conclusion, as evidenced by the large number of publications devoted to TG 2 inhibitors as potential therapeutic agents. Therefore, it seems reasonable that some effort should be devoted to the development of safer and more specific inhibitors. Furthermore, screening TG 2 inhibitors from natural sources is important because many safe TG 2-inhibiting substances may exist in nature. This is likely because our immune defense systems have co-evolved with the rest of the natural world for over 500 million years.

7. ACKNOWLEDGMENTS

I wish to express my thanks to my postdoctoral fellows and assistants who diligently carried out the experiments discussed in this review. The work in my laboratory has been supported by funds provided by a research grant (No. 0510270-1) from the National Cancer Center in Korea.

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Key Words: Inflammation, Inflammatory Disease, Transglutaminase 2, NF-kB, I-kBα, Review

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