REVIEW

Inflammation, Autoimmunity, and Hypertension: The Essential Role of Tissue Transglutaminase

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Inflammatory cytokines cause hypertension when introduced into animals. Additional evidence indicates that cytokines induce the production of autoantibodies that activate the AT1 angiotensin receptor (AT1R). Extensive evidence shows that these autoantibodies, termed AT1-AA, contribute to hypertension. We review here recent studies showing that cytokine-induced hypertension and AT1-AA production require the ubiquitous enzyme, tissue transglutaminase (TG2). We consider 3 mechanisms by which TG2 may contribute to hypertension. (i) One involves the posttranslational modification (PTM) of AT1Rs at a glutamine residue that is present in the epitope sequence (AFHYESQ) recognized by AT1-AA. (ii) Another mechanism by which TG2 may contribute to hypertension is by PTM of AT1Rs at glutamine 315. Modification at this glutamine prevents ubiquitination-dependent proteasome degradation and allows AT1Rs to accumulate. Increased AT1R abundance is likely to account for increased sensitivity to Ang II activation and in this way contribute to hypertension. (iii) The increased TG2 produced as a result of elevated inflammatory cytokines is likely to contribute to vascular stiffness by modification of intracellular contractile proteins or by crosslinking vascular proteins in the extracellular matrix. This process, termed inward remodeling, results in reduced vascular lumen, vascular stiffness, and increased blood pressure. Based on the literature reviewed here, we hypothesize that TG2 is an essential participant in cytokine-induced hypertension. From this perspective, selective TG2 inhibitors have the potential to be pharmacologic weapons in the fight against hypertension.

Keywords: angiotensin II type I receptor; autoimmunity; blood pressure; GPCR; hypertension; inflammatory cytokines; rennin–angiotensin–aldosterone system; tissue transglutaminase; vascular stiffness.

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Hypertension is a "strong, continuous, graded, and etiologically significant" risk factor[1] for cardiovascular diseases affecting millions of people worldwide.[2,3] The pathogenesis of essential hypertension is multifactorial, with different mechanisms contributing to hypertension in different individuals. Because of this underlying heterogeneity, a broad spectrum of antihypertensive medications is needed to meet the personalized medical needs of different individuals. Classical areas of hypertension research include the rennin–angiotensin–aldosterone system, the sympathetic nervous system, the endothelin system, the vascular system, and renal hemodynamics.[4] However, mounting evidence suggests that hypertension is intrinsically associated with inflammation and autoimmunity.

INFLAMMATION CAUSES HYPERTENSION

Studies investigating the inflammatory response accompanying activation of the innate and adaptive arms of the immune system have determined a prominent role of proinflammatory cytokines in the development of hypertensive disorders.[5–10] The innate immune system is mainly composed of cells of the myeloid lineage, including monocytes, macrophages, granulocytes, and dendritic cells. These cells contain pattern recognition receptors that are rapidly activated by pathogen-associated molecular patterns and damage-associated molecular patterns. In the acute immune response produced by innate immunity, the effector cells produce potent cytokines that in turn activate the adaptive immune system for its follow-up immune response including antibody production. These cytokines are also produced by activated T cells of the adaptive arm of the immune system. A particularly important family of cytokines called IL-17 are produced by a subset of T cells referred to as T_H17 cells. The IL-17 family of cytokines have been implicated in autoimmune disease.[11] Research has shown that elevated levels of interleukin-1β,[12] tumor necrosis factor,[13] interleukin-6,[14] interleukin-17,[15] and C-reactive protein,[16–18] among others[10,19,20] are consistently associated with hypertension. The inflammatory conditions induced by these cytokines can cause posttranslational modifications (PTMs) of proteins that serve as neoantigens[21] that in some cases

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stimulate the production of autoantibodies contributing to hypertension.[22] Experimental support for a causative role of inflammation in hypertension comes from animal studies showing that the introduction of these inflammatory cytokines into pregnant or nonpregnant rodents results in hypertension.[23–28] Furthermore, research has shown that angiotensin II (Ang II) induces the synthesis of key proinflammatory cytokines in various cell types.[29–31] Reciprocally, Ang II-induced hypertension is attenuated in animals lacking these cytokines.[32–34] Overall, a critical role of inflammatory cytokines in hypertension has been well established, though the mechanisms by which these inflammatory cytokines cause hypertension is not well understood.

In an effort to understand the molecular mechanisms underlying cytokine-induced hypertension, a cytokine-induced model of experimental hypertension was developed based on the use of TNF superfamily member 14, LIGHT (*L*ymphotoxin, exhibits *I*nducible expression, and competes with HSV *G*lycoprotein D for *H*VEM, a receptor expressed by *T* lymphocytes).[28] LIGHT is also known as TNFSF14. Considerable evidence supports a role for LIGHT in inflammation initiation, autoimmune response, and cardiovascular disorders. Circulating LIGHT is mainly secreted by cells of the innate and adaptive immune system including granulocytes, monocytes, macrophages, dendritic cells, and T cells.[35,36] LIGHT activates 2 widely distributed receptors, the herpes virus entry mediator (HVEM)[37] and the lymphotoxin β[38,39] receptor, that activate the NFkB pathway.[40,41] Both receptors are present at elevated levels in trophoblasts, endothelial cells, and cardiomyocytes in human health complications related with hypertension.[28,42] LIGHT is significantly higher in the circulation of women with preeclampsia, a serious hypertensive condition of pregnancy, and is able to induce hypertension when introduced into pregnant or nonpregnant mice.[28,43]

AUTOIMMUNE HYPERTENSION

Recent years have witnessed increased evidence revealing the contribution of autoimmunity to hypertension.[5,6,9,44–46] Autoimmunity is a common medical condition affecting approximately 5% of the US population and known to be a major factor causing well-known health problems including type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and celiac disease. The autoimmune basis for these conditions was not initially recognized and only became evident after years of research. This history is now repeating itself for hypertension. Considerable evidence[22,47] suggests that many forms of hypertension result from the presence of agonistic autoantibodies that activate major G protein coupled receptors (GPCRs) associated with the regulation of blood pressure. Notable examples include: (i) cardiac β_1-adrenergic receptor agonistic autoantibodies in dilated cardiomyopathy,[48] (ii) α_1-adrenergic receptor agonistic autoantibodies in refractory hypertension,[49–51] (iii) angiotensin receptor type 1 (AT1) agonistic autoantibodies (AT1-AA) in preeclampsia,[52–55] malignant/refractory hypertension,[56–59] and primary aldosteronism,[60,61] and (iv) endothelin receptor type a agonistic autoantibodies in systemic sclerosis (SS)[62] and systemic lupus erythematosus[63] associated with pulmonary hypertension. Adoptive transfer experiments in laboratory animals provide convincing evidence that these receptor activating autoantibodies are active contributors to hypertension,[54] and blockade of these autoantibodies with stable D-amino acid epitope peptide prevents hypertension in rabbits.[64] The crucial role of agonistic autoantibodies in hypertension that has been extensively reviewed[22,47,65] is further supported by the findings that the induced blood pressure increase and vascular remodeling is attenuated in mice lacking mature B cells due to B-cell-activating factor receptor-deficiency or pharmacological depletion with anti-CD20 antibody.[66,67] We suggest the term "autoimmune hypertension" to describe these conditions.[22,47,65,68,69]

In order to understand the pathogenesis of autoimmune hypertension, it is necessary to have an experimental system in which antibody production can be induced. This has been achieved for animal models of cytokine-induced hypertension in pregnant and nonpregnant rodents.[23–28] A series of reports[70–73] show that cytokine-induced hypertension is associated with production of AT1-AA. Initial efforts focused on preeclampsia, a condition known to be associated with elevated inflammatory cytokines including TNF-α, IL-6, IL-17, and LIGHT/TNFSF14.[70–73] Blockade of the inflammatory cytokine receptors ameliorates hypertensive features in preeclamptic rodents.[74,75] A rat model of PE based on placental ischemia (the RUPP model) is characterized by elevated TNFα and the presence of AT1-AA.[76] TNFα blockade with etanercept (also called Enbrel, a soluble form of the TNFα receptor) blocks AT1-AA production and prevents hypertension.[74,75] Similar results were obtained with rituximab (anti-CD20, inhibits B-lymphocytes) showing a significant reduction in the number of B cells and in AT1-AA titer.[67] Both Enbrel[77] and rituximab[78] are used to treat autoimmune diseases. Subsequent experiments showed that IL-6 is required for LIGHT/TNFSF14-induced hypertension and AT1-AA production in nonpregnant mice.[43] These inflammatory cytokines establish a causal link between inflammation and autoimmunity in the pathogenesis of hypertensive disorders and provide a convenient experimental animal model to determine the mechanism of cytokine-induced autoantibody production and the contribution of these autoantibodies to hypertension.

TRANSGLUTAMINASE AND AUTOIMMUNITY

A well-recognized cause for an autoimmune response is PTM of proteins, a process that sometimes creates autoantigens recognized as foreign by the immune system.[79–84] One of the best studied examples is celiac disease, an autoimmune complication affecting approximately 1% of people in developed countries.[85] Celiac disease is a chronic autoimmune disorder of the small intestine caused by an abnormal immune response to a post-translationally modified dietary protein called gliadin, a component of wheat. The enzyme causing the pathogenic PTM of the glutamine-rich gliadin in celiac disease is tissue transglutaminase (TG2),[86–88] the most ubiquitous and prominent member of a family of crosslinking enzymes that catalyze the PTM of glutamine residues on proteins (Figure 1a).[89] In addition to the modified gliadin peptides, celiac autoantibodies also recognize TG2.[90]

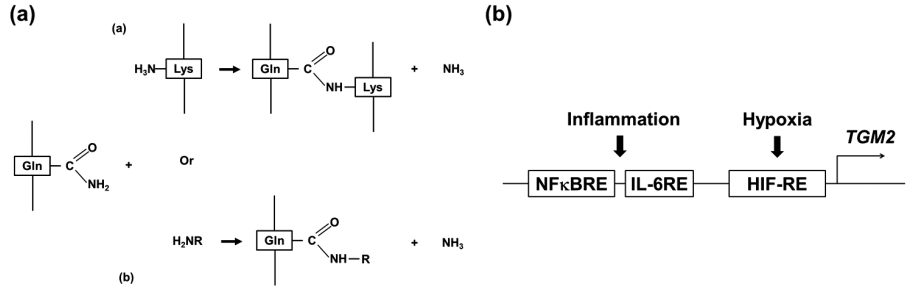

Figure 1. Illustration of the crosslinking function (**a**) and gene regulation (**b**) of tissue transglutaminase in cardiovascular disorders. (a) In cardiovascular diseases tissue transglutaminase is known to crosslink the glutamine residue in a peptide to either a peptide-bound lysine residue (a) or a primary amine such as serotonin (b). R in panel b could be an alkyl or aryl group. (b) The expression of tissue transglutaminase is usually induced in cardiovascular diseases due to the presence of major inflammation and hypoxia response elements in the promoter region of the gene encoding tissue transglutaminase (*TGM2*).

Recent evidence indicates that TG2 modifies and stabilizes AT1 receptors in placentas of women with preeclampsia.[91] More importantly, the epitope sequence of AT1-AA on the second extracellular loop of the receptor (AFHYESQ) can be crosslinked to TG2 *via* glutamine residue, Q187.[73] The potential importance of TG2 in cytokine-induced autoantibody production in preeclampsia is enhanced by the recognition that the *TGM2* gene is transcriptionally activated by hypoxia and inflammatory cytokines (Figure 1b),[92–94] conditions associated with preeclampsia. Taken together, the autoimmune and inflammatory threads in the pathogenesis of hypertension converge at tissue transglutaminase.

Transglutaminases are a group of structurally related enzymes that modify glutamine residues on proteins. The PTM results in the covalent isopeptide bond formation in a calcium-dependent manner between the γ-carboxamide group of a peptide-bound glutamine residue and a free amine or a peptide-bound lysine[89] (Figure 1a). As the first discovered transglutaminase,[95] TG2 is especially enriched in endothelial and smooth muscle cells[96] and is the most ubiquitous member of the 8 enzyme family whose conserved catalytic core sequence (GQCWVFA) shares a common feature of hydrophobicity.[97] Consistent with this, a general preference for the substrate glutamine residue surrounded by hydrophobic residues was identified by a combination of phage display and bioinformatics approaches.[98,99] However, unlike other transglutaminases, TG2 is inhibited under normal physiological conditions where cells maintain an environment of low free calcium and high GTP and ATP that inhibits its transamidation function.[100,101] In hypoxic and/or inflammatory conditions usually associated with cardiovascular disorders, TG2 is activated to perform PTMs of protein substrates due to GTP and ATP depletion and calcium influx.[100,101] TG2 is involved in numerous cardiovascular disorders including preeclampsia,[91] hypertension,[43] cardiac hypertrophy,[102,103] and atherosclerosis,[104–107] although its precise role in disease pathogenesis is unclear.

TRANSGLUTAMINASE IS A CRITICAL LINK AMONG INFLAMMATION, AUTOIMMUNITY, AND HYPERTENSION

Circulating transglutaminase levels show a strong positive correlation with blood pressure, proteinuria, and AT1-AA titers in women with preeclampsia.[73] These findings suggest a possible role for TG2 in the production of AT1-AA in hypertensive disorders like preeclampsia. This possibility is further supported by the presence of a Q residue in the epitope sequence (AFHYESQ) on the second extracellular loop of the AT1R, a sequence recognized by TG2 and crosslinked to the enzyme *in vitro*.[73]

In an effort to understand the role of TG2 in hypertension, renal impairment and AT1-AA production experimental models of hypertension were developed based the infusion of the inflammatory cytokine LIGHT/TNFSF14 into pregnant and nonpregnant mice. In addition to the increased blood pressure and renal impairment, elevated levels of plasma transglutaminase activity were observed in both pregnant[73] and nonpregnant[43] mice injected with LIGHT/TNFSF14. Cytokine injected mice also produced AT1-AA. To test the role of TG2 in cytokine-induced hypertension, renal impairment and AT1-AA production, pregnant, and nonpregnant mice were injected with LIGHT/TNFSF14 in the presence or absence of the transglutaminase inhibitor cystamine.[73] The results show that cytokine-induced hypertension, renal impairment, and AT1-AA production were prevented by the presence of cystamine. Additional experiments showed that IL-6 and endothelial HIF-1α are required for LIGHT-induced hypertension, renal impairment, AT1-AA production, and increased transglutaminase.[43] The requirement for endothelial HIF-1α suggests that endothelial TG2 is critical for LIGHT-induced hypertension, renal impairment, and AT1-AA production. These findings are consistent with earlier reports showing that transcription of the TG2 gene is activated by inflammatory cytokines and HIF (Figure 1). Thus, although the requirement for TG2 in cytokine-induced hypertension has only been shown for LIGHT/TNFSF14,[43,73] this is likely to be the case for other cytokines that induce hypertension (e.g., TNF, IL-6, and IL-17). A related study showed that TG2 is required for AT1-AA induced hypertension in a mouse model of preeclampsia.[91] Because AT1-AA active the AT1R, an in this way mimick AngII, the latter results suggest that Ang II-induced hypertension may require TG2. This possibility is supported by the fact that Ang II induces the production of inflammatory cytokines[29–31] and requires these cytokines to induce hypertension.

MODIFICATION OF AT1RS BY TRANSGLUTAMINASES

The first evidence of AT1R modification by transglutaminases was presented by AbdAlla *et al.* who showed that AT1Rs are covalently crosslinked into homodimers by FXIIIa transglutaminase in monocytes resulting in enhanced receptor signaling.[108] These receptor homodimers in monocytes show increased sensitivity to Ang II activation. As a member of the transglutaminase family, FXIIIa transglutaminase is predominantly expressed in macrophages, monocytes, and platelets,[109] and is also the major plasma transglutaminase crucial in the blood clotting cascade.[110,111] However, due to the limited expression pattern of FXIIIa transglutaminase, the overall molecular nature and functional consequences of AT1 receptor modification in most tissues and organs were not addressed in these early studies. Recent studies have examined AT1R modification in preeclampsia, a condition characterized by hypoxia and elevated inflammatory cytokines, conditions expected to stimulate production and activation of TG2 (Figure 1). The results show that AT1Rs[112,113] and TG2[114,115] are co-localized[91] in the syncytiotrophoblasts at the maternal–fetal interface of the human placenta. Due to highly elevated inflammatory cytokines[116] and hypoxia[117] associated with preeclampsia, a significantly increased level of TG2 and isopeptide protein modification were found in the syncytiotrophoblast layer of preeclamptic placentas.[91] AT1Rs were among the TG2 modified proteins and TG2-mediated AT1 receptor modification was associated with increased AT1 receptor abundance.[91] Unlike the AT1 receptor dimerization observed in hypertensive monocytes[108] where the FXIIIa transglutaminase is predominantly expressed, the AT1 receptor modified by TG2 in placentas shows no significant change in molecular weight. Thus, the molecular nature of TG2-mediated AT1 receptor modification in preeclamptic placentas is either intramolecular[118] or a posttranslational incorporation of a small primary amine (e.g., serotonin, histamine, norepinephrine, and dopamine) as originally observed in other examples of TG2 PTM.[95,119,120]

To investigate whether the TG2-mediated isopeptide modification is responsible for the increased AT1 receptor abundance observed in preeclamptic placentas an experimental model of preeclampsia in pregnant mice was used based on injection of autoantibodies from women with preeclampsia. The results showed that placental TG2 was elevated in this model and that this was accompanied with elevated AT1Rs that were modified by TG2. To determine the role of TG2 in this experimental model of preeclampsia the autoantibody-injected pregnant mice were treated with cystamine, a well-established transglutaminase inhibitor[121] or nanoparticle-embedded *TG2* siRNA. These treatments prevented placental AT1 receptor accumulation and the transglutaminase modification together with the increase in blood pressure and urinary protein in this preeclampsia model.[91] These results indicate that TG2-mediated AT1 receptor modification results in increased AT1R abundance in preeclampsia.

These were the first results to show modification of a GPCR by TG2 with the functional consequence of increased receptor abundance. The increased abundance of AT1Rs on the membrane likely contributes to the hypersensitivity to Ang II that is associated with preeclampsia[122] and other hypertensive disorders. Increased abundance of TG2-modified AT1Rs may also serve as neoantigens that promote AT1-AA production. Thus, increased AT1R abundance could contribute to hypertension in multiple ways. Given the ubiquitous expression pattern of TG2[89] and its known association with a wide range of GPCRs,[69,78–82] a previously unrecognized and general role for TG2 is the PTM of GPCRs to enhance and amplify GPCR signaling by increasing receptor abundance under stress or pathogenic conditions associated with hypoxia and inflammation.[91]

TISSUE TRANSGLUTAMINASE STABILIZES PLACENTAL AT1RS BY PREVENTING UBIQUITIN-DEPENDENT PROTEOSOMAL DEGRADATION

To elucidate the molecular mechanism by which TG2 modification results in an increase in AT1R abundance initial efforts focused on a glutamine residue (Q315) in the cytoplasmic tail of AT1 receptors that was shown previously to be the site for FXIIIa transglutaminase-mediated receptor crosslinking.[108] Indeed, Q315 is embedded in a hydrophobic motif ($FLQ_{315}LL$) evolutionarily conserved among all vertebrates higher than fishes (Figure 2) and therefore is an ideal modification site for TG2. To evaluate the importance of TG2-mediated modification on Q315 in the AT1R the glutamine was replaced with an alanine. When co-expressed with human TG2 in a stable Chinese hamster ovary cell line, the Q315A mutant AT1 receptor was no longer modified by TG2 and showed a lower cellular abundance compared with the wild-type receptor.[91] These results indicate that the cellular accumulation is a direct functional consequence of TG2-mediated AT1 receptor modification at Q315. Additional experiments showed that TG2-mediated modification on Q315 of AT1 receptor prevents ubiquitin-dependent degradation[123] allowing for increased receptor abundance.[91] Functionally, the increased concentration of AT1Rs on the plasma membrane is likely to contribute to the heightened Ang II sensitivity characteristic of preeclampsia.[122,124] These studies are the first to reveal a role for TG2-mediated PTM

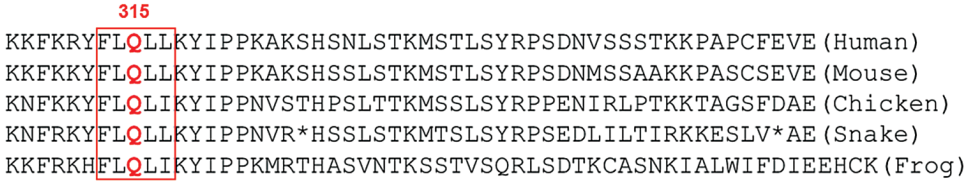

Figure 2. The hydrophobic motif (in box) with the glutamine residue (in bold) for transglutaminase modification at the cytoplasmic tail of AT1 receptor is evolutionarily conserved among all the representative vertebrates higher than fish.

in regulating AT1R's ubiquitin-dependent degradation with consequences on receptor abundance and signaling. These findings regarding TG2 modification of AT1Rs will likely apply to other GPCRs.

TISSUE TRANSGLUTAMINASE AND VASCULAR STIFFNESS

As a ubiquitous protein, TG2 is widely distributed in the vasculature, including endothelial cells, smooth muscle cells, and fibroblasts.[89,96,125,126] Within arterial vascular smooth muscle cells TG2 modifies proteins that function in contraction by the addition of serotonin and norepinephrine.[119,127] Excess TG2 modification of these contractile proteins could have adverse effects on vascular properties. TG2 is also found abundantly in the extracellular matrix (ECM).[128–131] In the ECM, the enzyme's transamidation function is activated by high extracellular concentrations of calcium,[100,132] resulting in the crosslinking and stabilization of ECM proteins[133] such as fibrinogen,[134] fibronectin,[135] and collagen.[136] TG2-mediated vascular ECM protein crosslinking leads to thickening of the vascular wall, reduced vascular lumen, increased vasoconstriction, and vascular calcification/stiffening,[137,138] all of which contribute to the development of vascular remodeling, a well-known feature of essential hypertension.[139,140] Therefore, one of possible explanations for the beneficial effects of transglutaminase inhibitor cystamine on blood pressure[141] is by preventing the effect of extracellular TG2 on vascular remodeling and stiffness.[137,142,143] In addition to calcium concentration, the activity of TG2 in the vascular ECM is also known to be controlled by several other factors including nitrosylation,[143,144] redox state,[145] and mechanical force.[125] Moreover, inflammation is also considered as one of the key causative factors of vascular remodeling in hypertension.[140,146] Recent studies[43] suggest the elevated proinflammatory cytokines in hypertension may also contribute to the detrimental vascular remodeling process by up-regulating the transcription of *TGM2* in the vasculature. The results show that LIGHT/TNFSF14-induced hypertension and transglutaminase elevation are prevented in mice with an endothelial specific deletion of HIF-1α, a key transcriptional regulator of *Tgm2* gene expression,[92,147,148] suggesting that inflammation-induced endothelial TG2 may contribute to hypertension, in part, by triggering inward remodeling and stiffening of small arteries.

CONCLUSIONS AND FUTURE DIRECTIONS

Inflammatory cytokines (TNF, IL-6, IL-17, LIGHT) cause hypertension when introduced into experimental animals.[23–28] However, the mechanism by which they cause hypertension is not understood. Here, we reviewed recent literature that has begun to bridge this gap in our understanding and to reveal mechanisms by which cytokines cause hypertension. Specifically, recent publications[43,73] have shown that cytokine-induced hypertension requires the widely distributed enzyme TG2. The TG2 gene (*Tgm2*) is transcriptionally activated by cytokines and hypoxia due to the presence of the relevant gene regulatory elements in the promoter region of the gene. Three potential mechanisms by which elevated TG2 may contribute to cytokine-induced hypertension are considered below (Figure 3).

(i) One mechanism involves the PTM of the AT1R at glutamine 187[73] that is present at the end of the epitope sequence (AFHYESQ) recognized by AT1-AA.[52] It has been clearly established that these autoantibodies contribute to hypertension by activation of AT1Rs based on interaction with this epitope sequence.[53–55] Thus, a very likely mechanism by which TG2 contributes to hypertension is by PTM of Q187 on AT1Rs resulting in the creation of a neo-epitope that stimulates AT1-AA production by the adaptive immune system. This process requires autoimmune activation of the adaptive immune system, and for this reason is expected to require sufficient time for autoantibody production to become significant.

(ii) Another, potentially more rapid, mechanism by which TG2 may contribute to hypertension is by PTM of AT1R at glutamine 315.[91] Modification at this glutamine by TG2 prevents ubiquitin-dependent proteosomal degradation and allows AT1Rs to accumulate in various cells. Increased AT1R abundance is likely to account for increased sensitivity to Ang II activation and in this way contribute to hypertension. Reduced AT1R turnover, and increased receptor abundance, caused by PTM of Q315 occurs more quickly than the time required to activate the adaptive immune system and produce AT1-AA. Chronic receptor accumulation in inflammatory and hypoxic conditions will finally result in increased sensitivity to Ang II-induced hypertension. Additionally, increased abundance of TG2-modified receptor may also serve as a neoantigen and promote AT1-AA production.

(iii) The increased TG2 produced as a result of elevated inflammatory cytokines is likely to contribute to vascular stiffness[137,138] by crosslinking vascular proteins[134–136]

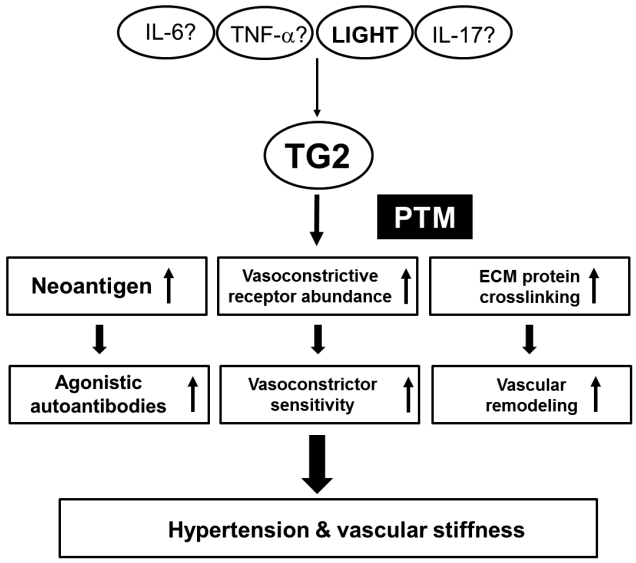

Figure 3. A proposed role of tissue transglutaminase (TG2) in the inflammatory cytokine-induced hypertension. The induction of TG2 in hypertension by other inflammatory cytokines than LIGHT/TNFSF14 needs to be confirmed. For more details see text (Conclusions and Future Directions).

in the ECM. This process, termed inward remodeling, results in reduced vascular lumen, vascular stiffness, and increased blood pressure. Vascular remodeling as a result of increased TG2 in the ECM will commence quickly as a result of inflammation/hypoxia-mediated induction of TG2 gene expression and enzyme activation. Elevated TG2 secreted from endothelial and other cell types in the ECM will cause inward remodeling, vascular stiffness, and reduced vascular lumen by crosslinking important ECM proteins. Excess TG2 modification of contractile proteins within vascular smooth muscle cells could also have adverse effects on vascular properties.[119,127] Although these vascular remodeling processes are expected to commence soon after cytokine-mediated activation of the TG2 gene and enzyme, the kinetics of the process is yet to be investigated.

The relative contributions of each of these processes to cytokine-induced hypertension can be readily examined in an experimental model of hypertension in mice. For example, the temporal relationship between the onset of hypertension and AT1-AA production can be determined. Furthermore, the role of AT1-AA in cytokine-induced hypertension can also be determined in a number of ways, most directly by stable epitope peptides that neutralize these pathogenic autoantibodies and prevent their ability to activate AT1Rs.[64] Additionally, cytokine infusions could be performed in mice treated with rituximab, a monoclonal antibody that targets the B-cell antigen CD20, and prevents antibody production. The roles of AT1R receptor stabilization or vascular remodeling in cytokine-induced hypertension can be examined in the absence of autoantibody production using rituximab treated or immune-deficient mice that cannot make antibodies.[66,67] Time course experiments could determine how quickly AT1R levels increase relative to how quickly hypertension occurs. Cytokine-treated animals could also be examined for increased pressor sensitivity to Ang II infusion.

Based on the literature reviewed here, we hypothesize that TG2 is an essential contributor to cytokine-induced hypertension. From this perspective, selective TG2 inhibitors are promising candidates as pharmacologic weapons to be used in the fight against hypertension. A variety of additional TG2 inhibitors are being produced and evaluated.[149] With regard to drug safety, it is reassuring that TG2-deficient mice are viable with no overt pathological phenotype resulting from their enzyme deficiency. Thus, TG2-specific inhibitors may be well tolerated for the treatment of hypertension.

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DISCLOSURE

The authors declared no conflict of interest.

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