REVIEW

Urotensin II: an inflammatory cytokine

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Abstract

Urotensin II (UII) is a polypeptide molecule with neurohormone-like activity. It has been confirmed that UII is widely distributed in numerous organs of different animal species from fish to mammals, including humans. The UII receptor is orphan G-protein-coupled receptor 14, also known as UT. The tissue distribution of UII and UT is highly consistent, and their expression may be regulated by autocrine and paracrine mechanisms. In the body, UII has many physiological and pathophysiological activities, such as vasoconstrictor and vasodilatory actions, cell proliferation, pro-fibrosis, neuroendocrine activity, insulin resistance and carcinogenic and inflammatory effects, which have been recognized only in recent years. In fact, UII is involved in the process of inflammatory injury and plays a key role in the onset and development of inflammatory diseases. In this paper, we will review the roles UII plays in inflammatory diseases.

Introduction

UII is a polypeptide, the activity of which is similar to that of neurohormones. It was first isolated from the urophysis of teleost fish more than 40 years ago (Berlind 1972). UII is found not only in fish, but also in reptiles, rodents and primates, including apes and humans (Dun et al. 2001, Vaudry et al. 2010). Early studies have shown that UII has vasoconstrictor activity and is the most potent vasoconstrictive molecule. In the case of intact endothelial cells or endothelium, UII has been found to induce vasodilatation (Ishihata et al. 2005, Lacza & Busija 2006). UII is widely distributed in animal organs and tissues. Many organs, including the cardiovascular and central nervous systems, as well as the lung, kidney, spleen, hypophysis, adrenal gland, stomach, pancreas, ovary and liver, are found to express UII (Coulouarn et al. 1998, Nothacker et al. 1999, Ross et al. 2010). In humans, the effect of UII on peripheral vascular resistance and systemic hemodynamics is not obvious (Cheriyan et al. 2009).

In fact, UII is far from just a vasoactive molecule. It also has a variety of physiological activities (Vaudry et al. 2010) and plays a role in the onset of many diseases (Bousette & Giaid 2006, Liu et al. 2009, Wang et al. 2011, Langham & Kelly 2013, You et al. 2014, Garoufi et al. 2017, Li et al. 2017). In recent years, the relationship between UII and inflammation has been attracting greater attention. It has been confirmed that UII is involved in the process of inflammatory injury (Tomiyama et al. 2015, Yang et al. 2016, Ugan et al. 2018), and UII is a notable player in the development of inflammatory diseases.

UII and its biological activity

UII has variable sequence length of amino acids, predominantly residues 11–17, in different animal species. For example, there are 11 amino acid residues in human UII. At the C-terminus of the UII polypeptide, there is a covalent disulfide bridge formed by the

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CWFVKY hexapeptide cyclic conserved portion. The cyclic conserved portion is the main functional region of Ull (Castel et al. 2017). The human Ull gene, also known as UT2, contains five exons. Mature Ull is the result of alternative splicing of the precursor prepro-Ull, the UT2 gene expression product (Ames et al. 1999, Su et al. 2003). Ull can be secreted into extracellular fluid and can enter the circulation. Under physiological conditions, plasma Ull originates from the heart, liver and kidney, and its level is very low (picomolar range) (Carles et al. 2005). Ull-expressing cells include endothelial cells, endocardial endothelial cells, renal epithelial cells (Maguire et al. 2004), hepatobiliary epithelial cells and Kupffer cells (Leifeld et al. 2010).

The specific receptor for Ull is an orphan G-protein-coupled receptor, named GPR14 or UT. The biological activity of Ull must be transduced by UT signaling, so the two are commonly referred to as the Ull/UT system. In vitro, the tissue distribution of UT and Ull is highly consistent (Castel et al. 2017). In most cases, the Ull/UT-expressing cells are also highly consistent, showing an autocrine/paracrine regulatory mechanism (Balat et al. 2007, Wang et al. 2011). Ull binds and activates UT signaling to induce intracellular calcium mobilization and increases the levels of free Ca$^{2+}$ in cellular plasma (Sun et al. 2013). Increased intracellular free Ca$^{2+}$ induces spastic contraction of vascular smooth muscle cells (VSMCs) (Maguire et al. 2000) and VSMC proliferation and collagen synthesis by activating the EGFR and TGF-$\beta$/Smad2/3 signaling pathways (Rodriguez-Moyano et al. 2013, Zhao et al. 2013a,b). In addition, Ull also induces endothelial cell expression of eNOS and increases the release of vasodilating prostacyclin and PGE$_2$ into the blood, resulting in vasodilatation (Zhang et al. 2003, Ishihata et al. 2005). In the heart, Ull can enhance the cardiotoxic oxidative stress response (Rahimi et al. 2018) and increase PKA activity to induce the hypertrophy of neonatal cardiac myocytes (Xu et al. 2017). It also plays an important role in the development of adult hypertrophic cardiomyopathy (Jumaah et al. 2018) and rheumatic valvular disease (Elmadbouh et al. 2017). In fact, the biofunctions of Ull are not only confined to the cardiovascular system, but Ull also has extensive and profound effects on many tissues and cells in the body.

Ull functions in the following processes: (1) cell proliferation: Ull induces the proliferation of hepatic oval cells to promote liver regeneration (Yu et al. 2015) and of glomerular mesangial cells to lead to kidney diseases (Soni & Adebiyi 2017). (2) Pro-fibrotic activities: Ull promotes liver, kidney and lung fibrosis (Liu et al. 2009, Onat et al. 2012, Chen et al. 2017) through the TGF-$\beta$ signaling pathway. (3) Neurosecretory effects: Ull causes emotional imbalance by stimulating the cerebral cortex to release norepinephrine (Kawaguchi et al. 2009) and also induces the hypothalamus/pituitary axis to secrete growth hormone (Sun et al. 2013). (4) Insulin resistance: plasma levels of Ull increase in diabetic patients (Totsume et al. 2003) and high levels of Ull can induce insulin resistance (Li et al. 2016) and inhibit glucose uptake in skeletal muscles (Wang et al. 2013). (5) Carcinogenic effects: the expression of Ull/UT is correlated with tumor progression, metastasis and prognosis (Wu et al. 2010, Balakan et al. 2014, Yu et al. 2014). Ull mediates PKC- and ERK1/2-dependent pro-mitogenic signaling pathways (Wang et al. 2011) and induces cell transformation to malignant tumor phenotypes (Goldberg et al. 2016). (6) Pro-inflammatory effects: the Ull-mediated tissue inflammatory response has been a hot topic in recent years (Liang et al. 2013). As an inflammatory hormone-like molecule/inflammatory cytokine, Ull plays a crucial role in inflammation (Liu et al. 2015a,b).

**Roles of Ull in inflammatory diseases**

**Vascular injury diseases**

Inflammation of the vascular walls is critically involved in the pathogenesis of vascular injury diseases. For example, the development of atherosclerosis and essential hypertension is associated with vascular inflammation (Sun et al. 2017, Wang et al. 2018). High levels of Ull not only cause both contraction of vascular smooth muscle and an increase in vascular tone, but also participate, more importantly, in chronic inflammation and injury of vessel walls.

**Essential hypertension**

Essential hypertension is a chronic vascular inflammatory disease (Li et al. 2005, Small et al. 2018). Experimental studies have confirmed that a large number of lymphocytes and monocytes are gathered and activated in blood vessel walls of spontaneously hypertensive rats (Schmid-Schönbein et al. 1991). In hypertensive patients, monocyte preactivation, lymphocyte proliferation and pro-inflammatory cytokine production were observed in the peripheral blood (Dorfel et al. 1999, Ni et al. 2017). Therefore, essential hypertension is fundamentally a chronic inflammatory process characterized by the activation of lymphocytes and monocytes. In this process, high arterial pressure and oxidative stress can damage...
vascular endothelium and lead to an increase in vascular permeability. Under the action of adhesion molecules such as ICAM-1 and VCAM-1, monocytes can undergo chemotaxis and adhere to the vascular walls, causing inflammatory responses (Bermudez et al. 2002). In blood vessels, UII induces the expression and secretion of ICAM-1 and VCAM-1 (Cirillo et al. 2008), likely associated with inflammatory chemotaxis in hypertension. It is also found that high levels of UII can induce monocyte chemotaxis at sites of vascular injury through the RhoA/Rho kinase pathway (Segain et al. 2007), and the pro-inflammatory cytokine IL-1β can enhance the chemotactic activity of UII to inflammatory cells (Segain et al. 2007). It is proven that in patients with essential hypertension, plasma UII levels are significantly higher than those in their healthy counterparts, and the degree of elevation is positively correlated with the systolic/diastolic pressure (Cheung et al. 2004). A case-control comparison study showed that UII was associated with persistently increased blood pressure and was an independent risk factor for essential hypertension (Peng et al. 2013); indeed, the degree of elevation in plasma UII could be used as an indication of the severity of essential hypertension (Zhu et al. 2015). Previous studies also showed that UII can activate leukocytes and promote these cells to release active oxygen metabolites (Djordjevic et al. 2005), causing endothelial cell damage and exfoliation as well as increasing the permeability of blood vessels (Gendron et al. 2004), a pathogenic manifestation of hypertension. These results indicate that UII may be a significant element in the process of chronic vascular inflammatory injury in essential hypertension.

Atherosclerosis

The main pathomorphological feature of atherosclerosis is that atherosclerotic plaques are formed under the intima of the arteries. These plaques are a result of the constant deposition of lipid and a variety of inflammatory cells, including monocytes/macrophages, foam cells and leukocytes, in the arterial walls (Chistiakov et al. 2018, Koelwyn et al. 2018), producing immune inflammatory responses (Autier 2018, Miteva et al. 2018). As a disease of chronic vascular inflammation, atherosclerosis is also closely related to UII expression similar to essential hypertension (Zhao et al. 2013a,b). Studies have confirmed that UII is not significantly expressed in normal coronary arteries, but high levels of UII are found in plaques in patients with atherosclerosis (Maguire et al. 2004, Hassan et al. 2005, Loirand et al. 2008). In a study with atherosclerosis-related dementia, plasma UII and inflammatory markers IL-6 and high-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in patients than those in normal controls, and the increased degree of plasma UII was positively correlated with the thickness of the maximum carotid artery intima-media (Ban et al. 2009). Previous studies showed that in coronary atherosclerotic plaques, the UII-expressing cells are mainly endothelial cells and macrophages (Maguire et al. 2004, Loirand et al. 2008), and UII may play a role in the etiology of atherosclerosis (Hassan et al. 2005). Further classification of infiltrating white blood cells reveals that lymphocytes are also important sources of UII (Bousette et al. 2004). In addition, foam cells and smooth muscle cells can also express UII in areas of injury (Bousette et al. 2004, Maguire et al. 2004, Hassan et al. 2005, Ban et al. 2009). The specific receptor UT of UII is mainly expressed in monocytes and macrophages (Bousette et al. 2004), suggesting that monocytes or macrophages are the main effectors of UII in atherosclerotic plaque formation. Studies have confirmed that UII can, alone or in combination with IL-1β, induce monocytes to aggregate at vascular injury sites or atherosclerotic plaques (Segain et al. 2007) and promote monocyte transformation into macrophages at the site of inflammatory injury by upregulating acyl-coenzyme A cholesterol acyltransferase 1 (ACAT-1), thereby enhancing the ability of these cells to internalize lipids (Watanabe et al. 2005, 2009). UII can also reduce cholesterol efflux from macrophages thereby promoting their conversion into the foam cell phenotype (Wang et al. 2014). In addition, macrophages and lymphocytes secrete pro-inflammatory cytokines such as IL-6, IL-1β and IFN-γ in atherosclerotic plaques. These cytokines further upregulate the expression of UII and UT and accelerate the formation of atherosclerotic plaques (Birker-Robaczewska et al. 2003, Johns et al. 2004), with the autocrine/paracrine effects of macrophage UII significantly increasing macrophage-positive areas (Zhao et al. 2015) and destabilizing atherosclerotic plaques (Li et al. 2014, Albanese et al. 2016). Reports in recent years show that UII can induce the expression and secretion of various inflammatory cytokines, such as MCP-1 and TGF-β, causing arterial inflammatory injury (You et al. 2012, Zhao et al. 2014). UII can also induce apolipoprotein apoB expression and suppress apoA-1 expression, promoting the development of atherosclerosis (Khoshi et al. 2014). In addition, UII can promote the proliferation of VSMC to lead to vascular stenosis and remodeling, by activating the ERK/ROS signaling pathway in atherosclerotic lesions (Kim et al. 2017). UII receptor antagonist, urantide, has the ability to protect against atherosclerosis in the rat.
model (Zhao et al. 2013a, b). Therefore, UII has extensive and profound effects on the occurrence and development of atherosclerosis.

Heart failure

Heart failure is a chronic inflammatory injury disease of the myocardium. Immune inflammation greatly contributes to the pathogenesis of heart failure (Zhang et al. 2017, Yu & Feng 2018). During this process, many cytokines and inflammatory molecules are expressed and released, such as TNF-α, IL-1β and IL-6, adhesion molecules and CRP (Torre-Amione et al. 2000, Alonso-Martínez et al. 2002, Deten et al. 2003). UII can promote the expression and secretion of IL-6 from cardiac myocytes (Johns et al. 2004). IL-6 is a cytokine with significant pro-inflammatory effects (Lichtman et al. 1998) and is increased more than fourfold in H9c2 myocardial cells after 6h of UII stimulation (10nM). This induction is equivalent to the expression levels of IL-6 protein produced by stimulation with 10ng/mL LPS in cardiac myocytes (Johns et al. 2004). Indeed, it has been found that plasma UII levels are significantly elevated in patients with acute and chronic heart failure (Jani et al. 2013). In addition, high levels of UII and its receptor UT are observed in myocardial tissues in patients with heart failure (Douglas et al. 2002). UII receptor antagonists can significantly reduce UII-induced fibrosis and cell hypertrophy in cardiomyocytes, as well as heart dysfunction in experimental heart failure (Park et al. 2016, Oh et al. 2017). In a rat model of heart failure, the expression levels of UII, UT, IL-1β and IL-6 are prominently increased in ventricular myocytes in parallel to the duration and degree of myocardial injury (Johns et al. 2004). At the same time, UII, through IL-6, acts on its receptor gp130 to activate Jak/STAT signaling, resulting in myocardioctye hypertrophy and ventricular remodeling (Yamauichi-Takahara & Kishimoto 2000). At the same time, UII inhibits the proliferation of endogenous cardiac side population stem cells through the JNK pathway (Chen et al. 2014), thus aggravating heart failure and making it difficult to reverse.

Chronic renal disease

Most chronic kidney diseases (CKD), including glomerulonephritis, renal tubular diseases and renal fibrosis, are inflammation-related diseases (Rodriguez-Moyano et al. 2013, Sun et al. 2013). Innate immune inflammatory responses are considered to be the main pathophysiological mechanism of kidney diseases and kidney injury (Wang & Zhang 2017). Macrophages are involved in the occurrence and development of various CKD (Guiteras et al. 2016). During the disease process, TLR4 signaling is activated, and many pro-inflammatory cytokines such as TNF-α, IL-6 and IL-17A are released (Cortvriendt et al. 2017, Garibotto et al. 2017, Su et al. 2017). Immunohistochemistry and mRNA assays show that the kidney expresses UII and its receptor UT (Song et al. 2006). In a normal human kidney, UII is mainly expressed in the renal tubular epithelial cells, while the glomerular endothelial cells exhibit only focal expression (Shenouda et al. 2002), and circulating UII is low and difficult to detect (<50pg/mL) (Matsushita et al. 2001). In patients with chronic glomerulonephritis, abundant UII can be seen in the glomerular basement membrane, mesangial membrane and glomerular capsule (Balat et al. 2007). The glomerular crescent, which is composed of glomerular capsule epithelial cells and infiltrating macrophages, is also found to have high UII expression in CKD patients (Balat et al. 2007, Balat 2010). It is worth noting that crescentic formation is a sign of severe glomerular injury and rapid progression of disease (Li & Chen 2013). In addition, plasma UII levels increased significantly in patients with CKD (Ashton 2006), and higher levels of UII were found in CKD patients with metabolic acidosis (Garoufi et al. 2017). In patients with chronic kidney failure, urinary UII is also notably increased (Ashton 2006), with the concentration of urinary UII 1650 times higher than that of blood (Song et al. 2006). These data suggest the importance of UII in the pathogenesis of kidney diseases. Studies have shown that UII can induce the release of inflammatory mediators via paracrine or autocrine modes during the deposition of antigen–antibody complexes, triggering and amplifying the inflammatory responses to aggravate renal damage (Balat et al. 2007). In CKD, an increase in UII secretion is an early event, followed by an elevation in oxidative stress parameters (Tabur et al. 2015) and the expression of the cytokine TGF-β in renal tubular epithelial cells (Cernaro et al. 2017). UII-induced oxidative stress, cytokine release and inflammation are like a ‘devil’s triangle’ (Balat & Büyükelik 2012), which promotes and aggravates the inflammatory damage of CKD.

Acute hepatic failure

Acute liver failure (ALF) is an immune inflammatory injury disease. Cascading release of inflammatory cytokines is the main pathophysiological mechanism of the development of ALF (Yoshimura et al. 2007, Liu et al. 2009). Mononuclear phagocytes, especially hepatic...
Kupffer cells, are thought to be the main cell source for the production of inflammatory cytokines, including IFN-γ, IL-6 and TNF-α (Ramadori & Armbrust 2001, Zhang et al. 2003). It has been demonstrated that in patients with ALF, there are not only a large number of inflammatory cytokines in the circulation, but also high levels of UII and its receptor UT in the liver, and the increased plasma levels of UII are closely correlated with the elevated levels of the inflammatory cytokines IFN-γ and IL-6 (Leifeld et al. 2010). In lipopolysaccharide (LPS)/D-galactosamine (D-GalN)-induced ALF, the expression and activity of hepatic UII and UT were significantly upregulated (Liang et al. 2013). The UII receptor antagonist urantide inhibited LPS/D-GalN-induced UII/UT liver expression in ALF rats, and at the same time, it protected experimental rats from death and hepatic inflammatory injury caused by LPS/D-GalN attack by blocking UII signal transduction (Liang et al. 2013). It has further been confirmed that in ALF, UII mediates hepatic immune inflammatory injury mainly by activating the TLR4 signaling pathway and the release of its downstream pro-inflammatory cytokines, including TNF-α and IL-1β (Liang et al. 2013). It is known that hepatic parenchymal cells do not express UII and UT, with the UII/UT-expressing cells mainly comprising innate immune cells, such as Kupffer cells, vascular endothelial cells and bile duct epithelial cells in the liver in ALF (Leifeld et al. 2010, Liang et al. 2013). In primary Kupffer cells, LPS stimulation markedly induces the production of UII/UT, TNF-α and IL-1β; after urantide pretreatment, the expression and secretion of TNF-α and IL-1β were significantly downregulated, as was the release of UII (Liu et al. 2015a,b). These data suggest that autocrine/paracrine regulatory mechanisms of Kupffer cell UII can establish a positive feedback loop, which may induce cascading release of pro-inflammatory cytokines and gradually enhance intrahepatic inflammatory reactions. In a study of the time-dependent secretion of plasma UII, high levels of plasma UII are demonstrated to be an earlier event than TNF-α and IL-1β production in ALF (Liu et al. 2015a,b). This result further suggests that UII may be the trigger for the inflammatory reaction in the liver and may be crucial to the pathogenesis of ALF by initiating early production and release of inflammatory cytokines.

Other inflammatory diseases

In addition to the diseases mentioned above, UII has a prominent effect on the development of many other inflammatory diseases. Studies have confirmed that UII and its signaling system mediate carrageenan-induced inflammatory responses, and pretreatment with the UII receptor antagonist reduces tissue inflammation and decreases TNF-α and IL-6 expression (Cadirci et al. 2016). UII also mediates vascular inflammation and vascular remodeling, both of which are inhibited by UII receptor antagonists through their blockade of ERK1/2 and NF-κB signaling pathways in experimental pulmonary hypertension (Lee et al. 2016). In vivo and in vitro studies of colitis have also confirmed that the UII/UT system mediates tissue inflammatory responses through NF-κB signaling (Yang et al. 2016). In addition, UII expression increases in patients with cancer (Liu et al. 2016a,b), diabetes (He et al. 2015) and metabolic syndrome (Barrette & Schwertani 2012). In a sense, these diseases are also the result of chronic local or systemic inflammation. The increased expression and secretion of UII in these patients may have a key impact on the inflammatory damage induced in these diseases.

Pro-inflammatory mechanisms of UII

Inflammatory responses involve innate immune cells such as macrophages, endothelial cells and others. Exogenous (Borlak et al. 2016) and endogenous (Wheeler 2003) stimuli can induce the activation of these cells, resulting in the release of pro-inflammatory cytokines that cause tissue inflammation and injury (Tsutsui & Nishiguchi 2014). In this process, injurious stimuli, including pathogons and toxins (i.e., LPS), activate the pattern recognition receptor TLR4 on the cell surface. Through adaptor proteins, TLR4 activates two important cellular signaling pathways – the MyD88-dependent and TRIF-dependent (or MyD88-independent) pathways (Liu et al. 2015a,b). After activation, the MyD88-dependent pathway induces the expression and release of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 through the p38 MAPK and NF-κB signaling pathways (Liu et al. 2015a,b). TRIF signaling induces the production of type 1 interferons such as IFN-β through the activation of interferon regulatory factor 3 (IRF3) to promote an innate immune response (Tsutsui & Nishiguchi 2014).

UII and its receptor signaling system mediate the production of pro-inflammatory mediators including TNF-α, IL-1β, IFN-γ, IL-8 and leukotriene C4 and have a positive effect on the TLR4 downstream MyD88-dependent signaling pathway (Liang et al. 2013, Dong et al. 2013, Lee et al. 2014). It has been demonstrated that this signaling system upregulates the levels of phosphorylated nuclear p38 MAPK protein (Liu et al. 2015a,b). p38 is a MAPK
family member and is activated by phosphorylation in the nucleus, thereby inducing the transcription and expression of pro-inflammatory cytokines (Lee et al. 1994). The UII/UT system also activates the NF-κB inflammatory pathway by promoting nuclear translocation and DNA-binding activity of the p65 subunit (Liu et al. 2015a,b), which induces the transcription and expression of various inflammation-related genes, that is, the pro-inflammatory cytokines TNF-α and IL-1β (Baldwin 1996). In addition, the UII/UT system can activate the MyD88-independent signal IRF3 by inducing IRF3 gene transcription and nuclear translocation of the protein (Liu et al. 2016a,b). Previous reports have shown that the IRF3 molecule increases the levels of TNF-α and IL-1β protein (a post-transcriptional regulation) and promotes inflammatory reactions by upregulating IFN-β without affecting p38 MAPK and NF-κB activity (Liu et al. 2016a,b) (Fig. 1). Therefore, UII may be the unifying factor underlying the molecular basis of the innate immune and inflammatory responses.

**Last but not least**

Inflammatory injury is closely related to immune responses in the body. Indeed, innate immune cells and recruited inflammatory cells, like neutrophils and lymphocytes, are involved in the development of tissue inflammatory injury. Insight into the inflammatory injury and immune role of the small polypeptide UII has shown remarkable progress in recent years. In fact, most tissue inflammation in the body involves UII and its signaling system, and UII is a common molecular basis for these tissues to produce inflammatory reactions.

In the process of inflammation, injury factors stimulate the expression and secretion of UII from innate immune cells (including vascular endothelial cells and macrophages) in local tissues. The release of UII, through autocrine/paracrine effects, stimulates the further upregulation of UII expression and induces cascading release of pro-inflammatory cytokines, including TNF-α, IL-1β and so on. At the same time, UII serves as an inflammatory chemotactic molecule to recruit circulating UT-expressing inflammatory cells, such as monocytes and macrophages, to local lesions, thereby aggravating inflammatory damage to tissues (Segain et al. 2007). In addition, UII can be secreted into the blood from the inflamed organs, which may produce inflammatory hormone-like effects on distant organs and even induce systemic inflammatory responses.

However, the mechanism of the UII-mediated inflammatory injury response is still not fully understood. As a key molecule in inflammatory responses, UII has gained more and more attention from many scholars. By measuring UII/UT levels, investigators can monitor inflammation in the injured area, including the

**Figure 1**

UII pro-inflammatory mechanisms: LPS binding to TLR4 initiates MyD88-dependent and -independent (or TRIF) signaling pathways to induce the production of pro-inflammatory cytokines by activating NF-κB and p38 MAPK and IRF3, respectively. Association of the UII polypeptide with its receptor UT upregulates the levels of nuclear p38 MAPK phosphorylated protein and promotes nuclear transfer and DNA-binding activity of the NF-κB p65 subunit, leading to gene expression of pro-inflammatory cytokines. In parallel, the UII/UT system activates IRF3-IFN-β signaling to increase TNF-α and IL-1β protein levels. A full color version of this figure is available at https://doi.org/10.1530/JOE-18-0505.
inflammatory microenvironment of tumors (Zhou et al. 2012) and sepsis-induced damage (Cadirci et al. 2018); these levels may even serve as a way to judge the degree of inflammation. In recent years, UII and its signaling system have been used as targets for drug therapy for various inflammatory diseases. In animal experiments, UII receptor antagonists are used to block signal transduction of the UII/UT system, achieving satisfactory anti-inflammatory results. However, the research and development of drugs has not yet started in the area of human disease treatment. In view of the wide range of diseases related to inflammation, breakthroughs in inflammatory therapy research will bring revolutionary progress in clinical disease treatment in the future. For example, by inhibiting the inflammatory responses induced by UII, it may be possible to treat heart failure, liver failure, chronic nephritis and diabetic complications. It may even be possible to treat metabolic syndrome caused by obesity as well as to prevent and treat cancer.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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