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.

Key Words

- ▶ urotensin II
- ▶ biological activity
- ▶ cytokine
- ▶ inflammatory injury
- ▶ cardiovascular
- ▶ liver
- ▶ kidney

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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 vasoconstrictor found so far, with a vasoconstrictive effect 100 times stronger than that of endothelin-1 (Ames *et al.* 1999, Maguire *et al.* 2000). However, 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 (Cherian *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 (Tomiya *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

CFWKYC hexapeptide cyclic conserved portion. The cyclic conserved portion is the main functional region of UII (Castel *et al.* 2017). The human *Uii* gene, also known as *UTS2*, contains five exons. Mature UII is the result of alternative splicing of the precursor prepro-UII, the *UTS2* gene expression product (Ames *et al.* 1999, Su *et al.* 2003). UII can be secreted into extracellular fluid and can enter the circulation. Under physiological conditions, plasma UII originates from the heart, liver and kidney, and its level is very low (picomolar range) (Carles *et al.* 2005). UII-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 UII is an orphan G-protein-coupled receptor, named GPR14 or UT. The biological activity of UII must be transduced by UT signaling, so the two are commonly referred to as the UII/UT system. *In vivo*, the tissue distribution of UT and UII is highly consistent (Castel *et al.* 2017). In most cases, the UII/UT-expressing cells are also highly consistent, showing an autocrine/paracrine regulatory mechanism (Balat *et al.* 2007, Wang *et al.* 2011). UII 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- β /Smad2/3 signaling pathways (Rodriguez-Moyano *et al.* 2013, Zhao *et al.* 2013a,b). In addition, UII 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, UII 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 UII are not only confined to the cardiovascular system, but UII also has extensive and profound effects on many tissues and cells in the body.

UII functions in the following processes: (1) cell proliferation: UII 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: UII promotes liver, kidney and lung fibrosis (Liu *et al.* 2009,

Onat *et al.* 2012, Chen *et al.* 2017) through the TGF- β signaling pathway. (3) Neurosecretory effects: UII 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 UII increase in diabetic patients (Totsune *et al.* 2003) and high levels of UII 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 UII/UT is correlated with tumor progression, metastasis and prognosis (Wu *et al.* 2010, Balakan *et al.* 2014, Yu *et al.* 2014). UII 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 UII-mediated tissue inflammatory response has been a hot topic in recent years (Liang *et al.* 2013). As an inflammatory hormone-like molecule/inflammatory cytokine, UII plays a crucial role in inflammation (Liu *et al.* 2015a,b).

Roles of UII 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 UII 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 (Dorffel *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-1 β 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 (Autieri 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-1 β , 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-1 β 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-1 β 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 6 h of UII stimulation (10 nM). This induction is equivalent to the expression levels of IL-6 protein produced by stimulation with 10 ng/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-1 β 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 myocardiocyte hypertrophy and ventricular remodeling (Yamauchi-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 (Rodríguez-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 (Cortvrindt *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 (<50 pg/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 & Büyükçelik 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-1 β (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-1 β ; after urantide pretreatment, the expression and secretion of TNF- α and IL-1 β 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-1 β 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- κ B 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- κ B 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 pathogens 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-1 β and IL-6 through the p38 MAPK and NF- κ B 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-1 β , 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- κ B 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-1 β (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-1 β protein (a post-transcriptional regulation) and promotes inflammatory reactions by upregulating IFN- β without affecting p38 MAPK and NF- κ B 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-1 β 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- κ B 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- κ B 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-1 β 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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