Angiotensin II Upregulates Toll-Like Receptor 4 on Mesangial Cells

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Angiotensin II (AngII) mediates proinflammatory properties by activating NF-κB transcription factor nuclear translocation and inducing the expression of chemokines. For examination of whether AngII modulates the expression of Toll-like receptor 4 (TLR4), a key element of the innate immune system that senses LPS, mouse mesangial cells (MMC) were treated with AngII. AngII upregulated TLR4 mRNA and protein in MMC, and this effect was mediated through AngII type 1 receptors. Reporter gene experiments indicate that an activating protein-1 (AP-1) as well as an E-26 specific sequence (Ets) binding site in the TLR4 promoter are responsible for the AngII-stimulated transcriptional activity of the TLR4 gene. Preincubation of MMC with AngII enhanced LPS-induced NF-κB activation and chemokine expression. Immunohistochemical analyses revealed that double-transgenic rats that overexpressed human renin and angiotensinogen expressed higher levels of glomerular TLR4 compared with normal Sprague-Dawley rats. In vivo, infusion with AngII but not with norepinephrine into rats for 7 d also enhanced glomerular NF-κB activation after systemic application of LPS, suggesting that the effects are independent of concomitantly induced hypertension. Together, these observations suggest that AngII leads to an activation of the innate immune system by a novel mechanism involving the upregulation of TLR4. Our data contribute to a better understanding of how exogenous infections may trigger renal autoimmune processes, particularly in pathophysiologic situations with high renal AngII concentrations. Because TLR4 binds endogenous ligands (e.g., extracellular matrix components) in addition to microbial products, AngII-mediated upregulation of TLR4 also could be relevant for the development of inflammation in many noninfectious renal diseases.

been identified in the mouse and human genome. The first report involving a TLR in host response to a microbial product was published in 1998, when missense and null mutations of the mouse TLR4 gene were linked with the unresponsiveness phenotype to LPS, the major proinflammatory cell wall component of Gram-negative bacteria (5). Since then, TLR have been shown to recognize a broad range of microbial structures. Upon activation, most TLR induce a common intracellular signaling pathway that culminates in activation of the NF-κB, a key transcription factor involved in the induction of cytokines, chemokines, and cell-surface molecules such as adhesins, selectins, integrins, and co-stimulatory molecules (6–8). It is interesting that kidney mesangial as well as tubular cells express TLR4 (9,10).

There is accumulating evidence that angiotensin II (AngII) exerts proinflammatory effects in the kidney by locally stimulating chemokine expression by a NF-κB–dependent mechanism (11,12). Our study tested the whether AngII influences TLR4 expression in mesangial cells. Our in vitro and in vivo data indicate that AngII leads to an upregulation of TLR4 on mesangial cells that has functional consequences, such as an increase in the magnitude of LPS-induced NF-κB activation and chemokine expression.

Materials and Methods

Cell Culture

Mouse mesangial cells (MMC) are a cell line that originally was derived from SJL mice (13). These cells have been used by many investigators and have been characterized extensively (14). They express many features of mesangial cells, including expression of AngII type 1 (AT1) receptors (13). Cells were grown in DMEM (Life Technologies-BRL, Eggenstein, Germany) with 10% FCS in 5% CO₂ at 37°C. MMC were passaged every 4 to 5 d. Before stimulation with AngII or LPS, MMC were rested for 24 h in DMEM without FCS.

Northern Blots

MMC were stimulated with various concentrations of AngII (10⁻¹⁰ to 10⁻⁶ M; Sigma) for 24 h. After washing in ice-cold PBS, cells were lysed on ice in 150 μl of a buffer that contained 2% SDS and 60 mmol/L Tris-Cl (pH 6.8) supplemented with a cocktail of protease inhibitors (Complete; Boehringer Mannheim, Mannheim, Germany; contains antipain-HCl, chymostatin, leupeptin, bestatin, pepstatin, phosphoramidon, aprotinin, and EDTA). In addition, for selected experiments, glomeruli that were isolated from rats that received an infusion of PBS, AngII, or LPS (see below) were lysed directly in this buffer or into the buffer. The protein content was measured by a modification of the Lowry method. Proteins (70 μg in 5% glyceral/0.03% bromophenol blue/10 mmol/L dithiothreitol [DTT]) were boiled for 5 min. They then were separated under denaturing conditions on a 7% NuPAGE precast gel (Invitrogen) and subsequently electroblotted onto a nitrocellulose membrane (Hybond-N; Amersham, Braunschweig, Germany) in transfer buffer (50 mmol/L Tris-HCl [pH 7.0], 380 mmol/L glycine, 0.1% SDS, and 20% methanol). The blots were blocked in 5% nonfat dry milk in PBS with 0.1% Tween 20 for 1 h at 22°C. For the detection of TLR4, a 1:100 dilution of a goat polyclonal IgG antibody that was generated against an epitope that mapped within an extracellular domain of mouse TLR4 was used (Santa Cruz Biotechnology, Santa Cruz, CA). Washes, incubation with horseradish peroxidase–conjugated anti-goat secondary antibodies (Santa Cruz Biotechnology), and detection using the ECL reagent (Amersham) were performed according to the manufacturers’ recommendations (16). For controlling for variations in protein loading and transfer, membranes were washed for 30 min in PBS with 0.1% Tween 20 and incubated with a mouse mAb against β-actin (1:2000 dilution; Sigma). TLR4 signals were normalized to β-actin signals and expressed relative to the ratio, set at 1.0, that was obtained from the control cells (no AngII). Western blots were repeated independently four times for cell culture experiments and three times for animal experiments. Exposed films were analyzed by densitometry as described above.

Gel Shift Assay

MMC were preincubated for 24 h with 10⁻⁷ M AngII and subsequently received 10 ng/ml LPS for 30 min or were stimulated directly with LPS. After incubation, cells were washed twice with ice-cold PBS, collected, centrifuged, and resuspended in buffer A, which was composed of 20 mmol/L HEPES, 0.1 mmol/L EDTA, 0.1 mmol/L EGTA, 1 mmol/L DTT, 1 mmol/L PMSF, 1 μg/ml leupeptin, and 1 μg/ml aprotinin. Cells were lysed by the addition of Nonidet-P40 for 10 s, lysates were centrifuged for 30 s at 13,000 rpm, and pellets were resuspended in buffer B (30 mmol/L HEPES, 0.5 mol/L NaCl, 0.1 mmol/L EDTA, 0.1 mmol/L EGTA, 1 mmol/L PMSF, 1 μg/ml leupeptin, and 1 μg/ml aprotinin). Supernatants that contained nuclear proteins were aliquoted, frozen, and stored in liquid nitrogen. A total of 3.50 pmol of a consensus NF-κB DNA binding site double-strand oligonucleotide (5'-AGTTGAGGGACTTTCGGC-3') was end labeled with [γ-³²P]ATP (3000 Ci/mmol; Amersham) using T4 polynucleotide kinase (12). Binding reactions were performed in gel shift binding buffer (10 mmol/L Tris-HCl [pH 7.5], 4% glycerol, 1 mmol/L MgCl₂, 0.5 mmol/L EDTA, 0.5 mmol/L DTT, 50 mmol/L NaCl, 50 μg/ml poly [dl-dC] poly [dl-dC]) with and without cold competitor oligonucleotides at room temperature for 30 min. OCTI double-strand consensus oligonucleotides (5'-TGTCGAATGCACACTTGA-3') were used as nonspecific competitors. Reactions were stopped by ad-
tion of loading buffer, and samples were run on a nondepurinating 6% polyacrylamide gel. Gels were exposed to x-ray films. Specific bands were quantified by densitometry as described above, and binding of nuclear proteins from cells without AngII was assigned a value of 1.0. Gel shift analysis was performed independently four times with qualitatively similar results.

Transient Transfection Experiments

The pNF-xB-Luc reporter plasmid contains four tandem copies of the κ-enhancer that is fused to the herpes simplex virus thymidine kinase promoter that is linked to the reporter gene luciferase (12). The mouse TLR4 promoter was cloned in the pGL3-basic vector (Promega, Madison, WI). Wild-type, deleted, and mutant constructs have been described in detail previously (17,18). The activating protein-1 (AP-1) consensus DNA binding sequence (GTCAGATGAC) in −518 TLR4 promoter construct was disrupted by site-directed mutagenesis (to GTCAGAACCAC, construct −518AP-1mut). Because Ets (E-26 specific sequence) transcription factor was described recently to play a role in AngII-mediated inflammation and induction of MCP-1 (19), we also used a construct in which an Ets site was mutated (construct −518Ets−mut). Cells were transfected with 10 μg of pNF-xB-Luc or mouse TLR4 promoter luciferase reporter vectors together with the same amount of pSV-β-galactosidase vector using Lipofectin (Invitrogen). After transfection, the medium was changed (serum-free DMEM) and incubation was prolonged for 24 h with or without 10−7 M AngII. Transfected cells then were challenged with 10 ng/ml LPS for 60 min. At the end of the experiments, cells were washed three times in PBS, and cell layers were lysed. Luciferase and β-galactosidase activities were measured using standard techniques (12). The ratio between luciferase and β-galactosidase activities was calculated, and data from unstimulated control cells were assigned an arbitrary value of 1.0. Results are representative of at least three independent experiments performed in triplicate.

Animal Experiments

For analysis of the role of AngII on TLR4 expression in vivo, male Wistar rats (body weight 200 g) received intraperitoneal infusion for 7 d with either AngII or norepinephrine (Sigma) using osmotic minipumps (Alzet 2002, Sulzfeld, Germany; infusion rate 0.5 μl/h, 250 ng AngII/min, norepinephrine 600 ng/min [20,21]). Control animals received infusion of PBS. Systolic BP was measured on awake, slightly restrained animals on day 6 using tail plethysmography. Rats then received 2 mg LPS/kg body wt intraperitoneally for 4 h. At the end of the experiment, animals were slightly anesthetized with ether, and the kidneys were perfused in situ via the aorta with 20 ml of ice-cold PBS. Glomeruli were isolated by differential sieving as described previously (22). The final preparation had a purity >90% as judged by light microscopy. Isolated glomeruli were used for gel shift experiments. The whole experiment was repeated three times with three to six rats in each individual group.

For studying whether TLR4 expression is stimulated in vivo under prolonged conditions of high AngII, double-transgenic rats (dTGR; obtained from the Max-Delbrück Center, Berlin, Germany) that harbored human renin and angiotensinogen genes were used (23). dTGR have high circulating and local renal AngII levels and develop a renal inflammatory state with infiltration of monocytes/macrophages and T cells (24). Immunohistochemical staining was performed on paraffin sections with microwave treatment using a polyclonal anti-TLR4 antibody generated against C-terminal sequence of the mouse receptor, which cross-reacts with rat TLR4 (Santa Cruz Biotechnology). An antigoat peroxidase-labeled antibody was used as secondary reagent, and development of the color reaction was performed as described (25).

Statistical Analyses

All data are presented as means ± SEM. Statistical significance of various different groups first was tested with the nonparametric Kruskal-Wallis test. Individual groups subsequently were tested using the Wilcoxon-Mann-Whitney test. P < 0.05 was considered significant.

Results

AngII (10−8 to 10−6 M) for 24 h stimulated a significant increase of TLR4 mRNA expression (Figure 1) and TLR4 protein (Figure 2) dose-dependently in MMC. Densitometric analysis of Northern and Western blots demonstrated that these changes were statistically significant (Figures 1 and 2). The AT1 receptor antagonist losartan but not the AT2 receptor antagonist PD123177 blocked AngII-mediated increase of TLR4 mRNA expression,

Figure 1. Northern blot analysis of Toll-like receptor 4 (TLR4) expression by mouse mesangial cells (MMC). Stimulation of cells with 10−8 to 10−6 M angiotensin II (AngII) for 24 h induced a significant increase in TLR4 mRNA expression. *P < 0.05 versus unstimulated controls; n = 5.
indicating that the AT1 receptor transduced the AngII effect (Figure 3).

For further exploration of potential mechanisms by which AngII increased TLR4 mRNA expression, MMC were transiently transfected with mouse TLR4 promoter luciferase reporter vectors (17,18). As shown in Table 1, AngII significantly increased $518$ promoter activity. Because the $518$ gene region of the mouse TLR4 gene contains a putative AP-1 binding site (18) that could mediate the AngII effect, this site was mutated in $518$ construct ($518$AP-1mut) and the activity of the mutant promoter was compared with that of the wild-type promoter in MMC. AngII failed to stimulate the activity of $518$AP-1mut, indicating a pivotal role of the AP-1 site in AngII-mediated increased transcriptional activity of TLR4 (Table 1). It Ets also was described recently as an important transcription factor for AngII-mediated inflammatory effects, at least in vasculature (19). Therefore, we also studied a different reporter gene construct in which an Ets consensus binding site in the $518$ gene region is mutated. Compared with the wild-type $518$, construct basal transcription was already significantly reduced in the $518$Ets$^d$mut construct, indicating that ETS transcription factors are important for TLR4 expression in MMC (Table 1). AngII ($10^{-7}$ M) completely failed to stimulate reporter gene activity in the $518$Ets$^d$mut construct (Table 1). To test whether AngII-mediated stimulation of TLR4 expression leads to enhanced NF-κB activation, we performed gel shift assays. As shown in Figure 4, incubation of MMC with 10 ng/ml LPS for 30 min or $10^{-7}$ M AngII for 24 h increased NF-κB nuclear translocation. However, the LPS-mediated increase was higher in cells that were pretreated with AngII for 24 h (Figure 4). Densitometric analysis revealed that these changes were statistically significant (Figure 4). For confirmation that NF-κB nuclear translocation increased gene transcription, MMC were

![Figure 2. Western blot analysis of TLR4 by MMC.](image1)

![Figure 3. Northern blot analysis of TLR4 expression by MMC.](image2)

![Table 1. Reporter gene studies](table1)
versus controls; 

5, preincubation of MMC for 24 h with 10^-7 M AngII enhanced LPS-mediated increase in chemokine transcripts compared with LPS challenge of cells that were grown without AngII. Representative of three independent experiments with qualitatively similar results.

For investigation of whether similar mechanisms are operative in vivo, AngII or norepinephrine was infused by osmotic minipumps in rats for 7 d. Systolic BP increased significantly compared with controls, but systolic BP was not significantly different between the AngII and norepinephrine infusion groups (AngII infusion 198 ± 11*; norepinephrine 164 ± 7*; controls 112 ± 3 mmHg; n = 6 to 10, *P < 0.01 versus controls, NS between AngII and norepinephrine). Kidneys were removed 4 h after intraperitoneal injection of LPS, and nuclear proteins were prepared from isolated glomeruli. Compared with PBS infusion, AngII infusion increased LPS-induced NF-κB activation in isolated glomeruli (controls 1.0; AngII 1.1 ± 0.1, LPS 8.4 ± 1.2*; LPS + AngII 15.9 ± 1.8* relative increase in NF-κB activation; *P < 0.01 versus controls; †P < 0.05 versus LPS only; n = 3; see Figure 6A). However, infusion with norepinephrine to increase the systolic BP failed to enhance LPS-induced NF-κB activation (Figure 6B). In fact, norepinephrine infusion reduced LPS-induced NF-κB activation by 30% compared with AngII (two independent experiments; Figure 6B). In addition, isolated glomeruli were lysed from control and AngII-infused rats, and Western blots were performed for detection of TLR4 protein expression. As shown in Figure 7, AngII infusion for 7 d but not LPS injection for 4 h significantly increased glomerular TLR4 protein expression.

Four-week-old dTGR that harbored human renin and angiotensinogen genes with high intrarenal AngII concentrations revealed a glomerular upregulation of TLR4 protein compared with age-matched Sprague-Dawley rats (controls 0.88 ± 0.11; dTGR 1.38 ± 0.20 staining score; P < 0.01; Figure 8, A through C). In addition, tubular TLR4 expression was increased in dTGR (controls 1.25 ± 0.09; dTGR 1.93 ± 0.11 staining score; P < 0.001; Figure 8, D and E).

Discussion

Many clinical observations have suggested that infections may trigger the onset and/or worsening of glomerulonephritis and renal vasculitis. For example, in a Japanese study, 68% of

transiently transfected with an NF-κB reporter plasmid. Although LPS as well as AngII increased NF-κB–mediated transcriptional activity in MMC, MMC preincubation of cells with AngII before addition of LPS enhanced this response (Table 2).

Because NF-κB is an important regulator of the expression of chemokines, we used MCP-1 and RANTES mRNA expression as a readout to investigate whether AngII enhanced LPS-stimulated expression of these chemokines. As shown in Figure 5, preincubation of MMC for 24 h with 10^-7 M AngII significantly increased LPS-induced MCP-1 and RANTES mRNA as compared with cells that were not pretreated with AngII.

Table 2. NF-κB transactivation in MMC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative Luciferase Activity Normalized to β-Galactosidase</th>
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<tbody>
<tr>
<td>Control</td>
<td>1.00 ± 0.064</td>
</tr>
<tr>
<td>LPS</td>
<td>1.16 ± 0.055b</td>
</tr>
<tr>
<td>AngII</td>
<td>1.12 ± 0.054b</td>
</tr>
<tr>
<td>AngII + LPS</td>
<td>1.51 ± 0.057c</td>
</tr>
</tbody>
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aData: MMC, mouse mesangial cells. 
bP < 0.05 versus control. 
cP < 0.01 versus control; P < 0.05 versus LPS alone.

Figure 4. NF-κB nuclear translocation in MMC. Nuclear extracts from MMC that were incubated with AngII (10^-7 M for 24 h) and then with or without LPS (10 ng/ml for 30 min) were analyzed by electrophoretic mobility shift assay (EMSA) using a consensus NF-κB site oligonucleotide. Intensity of the NF-κB bands was quantified by densitometry. Although LPS induced NF-κB activation, preincubation with AngII led to a significant increase in NF-κB binding to consensus nucleotides. *P < 0.05 versus controls; †P < 0.05 versus LPS alone; n = 4.

Figure 5. Northern blot analysis of monocyte chemoattractant protein-1 (MCP-1) and RANTES mRNA expression in MMC. Preincubation with 10^-7 M AngII enhanced LPS-mediated increase in chemokine transcripts compared with LPS challenge of cells that were grown without AngII. Representative of three independent experiments with qualitatively similar results.
renal biopsy specimens from patients with IgA nephropathy, an envelope antigen of *Staphylococcus aureus*, was co-localized with an IgA antibody in glomeruli (27). In Wegener’s granulomatosis, respiratory tract infections frequently precede or accompany initial symptoms of upper airway involvement (3). Treatment with co-trimoxazole reduces the incidence of relapses in patients with Wegener’s granulomatosis in remission (28). However, whether Gram-negative bacteria as a major source of LPS are involved in triggering human glomerulonephritis and vasculitis is unknown.

We previously reported that experimentally induced glomerulonephritis has a much more severe course in rats with Goldblatt (two kidneys, one clip) hypertension, a condition with high local AngII concentrations (29). There also is experimental evidence that AngII itself exerts proinflammatory effects, mainly by inducing chemokines such as MCP-1 and RANTES and by upregulating the expression of endothelial adhesion molecules that initiate the transfer of circulating leukocytes into the renal tissue (22,30).

Our study shows that AngII upregulates TLR4 mRNA and protein expression by mesangial cells both in vitro and in vivo. This upregulation had functional consequences as revealed by the fact that LPS-mediated NF-κB activation and LPS-induced chemokine gene transcription were enhanced in MMC that were preincubated with AngII. Ruiz-Ortega et al. (30) described that AngII alone for 3 to 6 h but not for 24 h induced MCP-1 mRNA. Our results that AngII alone for 24 h in the preincubation group failed to stimulate MCP-1 is in excellent agreement with these findings. Reporter gene experiments indicated that AngII increased TLR4 promoter activity, an effect that was dependent on the presence of a functional AP-1 as well as on Ets sites. The protein products of *c-fos* and *c-jun* form a heterodimer that binds to AP-1 sites. Because we and others previously demonstrated that AngII stimulates the expression of *c-fos* and *c-jun* (30,31), it is likely that AngII promotes TLR4 expression by increasing AP-1–dependent TLR4 gene transcription in MMC. Zhan et al. (19) recently reported that Ets is a critical regulator of AngII-mediated vascular inflammation and remodeling. In this study, MCP-1 expression was reduced in Ets1−/− mice compared with control mice in response to AngII (19). We observed a marked reduction already in basal transcriptional activity with the Ets mutant construct. AngII was ineffective in stimulating transcriptional activity of this construct, suggesting a major role of the Ets site in TLR4 gene transcription. These data are in agreement with observations in macrophages demonstrating a pivotal role of the Ets sites in mouse TLR4 transcription under basal conditions (18). In addition, our reporter gene experiments may shed light on a new angle of the results of Zhan et al. Because the TLR4 promoter contains several Ets sites (18) and the Ets family of transcription factors comprises >35 members, further experiments will have to address the exact role of the individual sites on overall TLR4 mRNA expression.

**Figure 6.** EMSA for NF-κB binding using nuclear proteins from isolated glomeruli. (A) LPS injection into rats that received infusion for 7 d with AngII exhibited in isolated glomeruli significantly more nuclear proteins binding to NF-κB sequences compared with control animals the received infusion with PBS only (quantification; see Results). (B) For testing whether these effects were mediated by AngII-induced hypertension, rats received infusion with norepinephrine for 7 d. However, norepinephrine infusion failed to increase LPS-mediated NF-κB activation. This experimental series was performed three times (A) and twice (B) with pooled kidneys (three to six rats).

**Figure 7.** Western blot analysis of TLR4 protein expression in isolated glomeruli from rats that received PBS (controls), AngII (250 ng AngII/min) infusions for 7 d by osmotic minipumps, or 2 mg LPS/kg body wt intraperitoneally for 4 h (LPS). Densitometric analysis was normalized to β-actin. AngII infusion for 7 d but not LPS injection for 4 h caused a significant upregulation of TLR4 protein expression in isolated glomeruli. *P < 0.05; n = 4.*
Other TLR, such as TLR9, which detects microbe-specific unmethylated cytosine-guanosine rich DNA, have been implicated in systemic immune disorders (32,33). It therefore remains to be explored whether AngII modulates the expression of other TLR besides TLR4, especially TLR9. A link between the Tamm-Horsfall glycoprotein (THP), which is expressed abundantly at the luminal surface of tubular cells and excreted into the urine and is known for its critical role in antibacterial host defenses, and activation of TLR4 was described recently (34). THP activates myeloid dendritic cells via TLR4 to acquire a fully mature phenotype. Therefore, THP links innate immune cell activation with adaptive immunity. We have not tested whether AngII may induce the upregulation of TLR4 on dendritic cells, but it is tempting to speculate that this mechanism might function by enhancing adaptive immunity. Although we focused on mesangial cells in this study, we observed tubular upregulation of TLR4 in transgenic rats that express high local AngII concentrations. Semiquantitative analysis of immunohistochemical stainings demonstrated that tubular TLR4 expression was even stronger than glomerular staining in dTGR. This interesting issue and a potential relationship to THP will be investigated further in future studies.

Although TLR4 recognizes primarily LPS, it seems to recognize endogenous ligands as well. For example, the immune-stimulatory activity of heat-shock protein 60 is mediated by TLR4 (4). It is interesting that extracellular matrix components such as fibronectin, hyaluronic acid, and fragments of heparan sulfate have been reported to activate TLR4 (4,35). Recently, Schaefer et al. (36) found that the matrix component biglycan is proinflammatory and signals through TLR2 and TLR4. Possibly in conditions such as rapid progressive glomerulonephritis, a destruction of the glomerular ultrafiltration barrier with the potential release of extracellular matrix components and mesangial deposition of fibrin may lead to activation of locally upregulated TLR4, thereby enhancing glomerular inflammation. Indeed, a striking concurrence of biglycan overexpression and enhanced numbers of infiltrating cells has been described in the kidney, albeit in a model of tubulointerstitial inflammation (37).

It is interesting that a recent study suggested that Asp299Gly TLR4 polymorphism in renal transplant recipients is associated with a lower risk for acute rejection (38). This mutation affects the extracellular domain of TLR4 and impairs its function (38). Because activation of AT1 receptors has been linked to refractory rejection, part of this effect may be mediated through the upregulation of TLR4 (39). In addition, exogenous or endogenous ligands (e.g., fibronectin) for TLR4 may trigger further acute and chronic rejections, particularly subsequent to ischemia-perfusion injury (40).

Other pathophysiologic situations in which our results may be of relevance are acute renal failure and sepsis (41). AngII concentrations are very high in sepsis and septic shock (42). Consequently, induction of TLR4 by AngII would trigger further inflammation in the kidney, thereby contributing to the development of acute renal failure in sepsis.

**Conclusion**

AngII stimulates transcription of TLR4 mRNA through activation of AP-1 and Ets-dependent TLR4 promoter activity in mesangial cells. This results in an upregulation of TLR4 protein with enhanced NF-κB signaling and induction of chemokines. Our findings provide new insight into the process by which AngII contributes to inflammation: By modifying innate immunity.
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