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COMMENTARY

TLR4 as a possible key regulator of pathological vascular remodeling by Ang II receptor activation

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Activation of the renin-angiotensin system has important roles in the development of hypertension and cardiovascular and kidney injury, mainly via pathological stimulation of downstream signaling networks of type 1 angiotensin II (Ang II) receptor (AT1R) in tissues. Specifically, the renin-angiotensin system is a major determinant of both physiological and pathological vascular function. Vascular hypertrophy is a hallmark feature of the end-organ damage from hypertension that actively contributes to clinical morbidity and mortality.[1] Ang II is the most potent component of the renin-angiotensin system and induces vasoconstriction in a variety of tissues, mainly through binding to the AT1R in vascular smooth muscle cells (VSMCs). Long-term stimulation of vascular AT1R leads to cell proliferation, inflammation, hypertrophy and fibrosis in the vascular wall.[2,3] These adverse effects of pathological activation by tissue AT1R signaling are accompanied by sustained increases in oxidative stress and chronic low-grade inflammatory responses.[4–7]

Toll-like receptors (TLRs) are a family of receptors that have key roles in the innate immune system by activating pro-inflammatory signaling pathways in response to pathogen-associated molecular patterns.[8] Of the TLRs, TLR4 recognizes and responds to LPS, the main component of cell walls of Gram-negative bacteria as well as other non-infectious compounds, such as products from tissue death and/or damage (DAMP), heat shock proteins (Hsp), high-mobility group box 1 (HMGB1) protein, fibronectin, heparan sulfate and fibrinogen.[9] In addition to being expressed on immune cells, TLR4 is ubiquitously expressed on various cells of the cardiovascular and renal systems, including vascular wall component cells such as endothelial vascular cells and VSMCs. TLR4 signaling has been proposed to contribute to vascular inflammatory pathologies such as atherosclerosis, diabetes and metabolic syndrome.[10–15]

Both Ang II and TLR4 reportedly activate NADPH oxidase to enhance the production of reactive oxygen species (ROS). Activation of AT1R and TLR4 signaling pathways contribute to inflammatory cardiovascular diseases, following the activation of pro-inflammatory responses.[16] However, little is known about the causal role of TLR4 in Ang II-mediated pathological vascular remodeling. In this issue, Nakashima *et al.*[17] used TLR4 knockout mice with a BALB/c genetic background and showed that TLR4 has an important role in the promotion of Ang II-mediated vascular remodeling via ROS production. The authors used a presser dose of Ang II for chronic infusion experiments, thereby making it difficult to directly dissect the consequences of AT1R activation from the effects of BP elevation.[17] Therefore, to eliminate the effect of blood pressure elevation on the Ang II-mediated responses, the authors used norepinephrine as another model of hypertension and demonstrated that blood pressure elevation would not cause vascular remodeling. In a dose that clearly caused an equivalent degree of hypertension as Ang II, norepinephrine had no effect on vascular remodeling *in vivo*. A similar approach has been previously used.[18,19] Because the results in that study were exclusively derived from an *in vivo* analysis, the weakness of their results is a lack of *in vitro* experiments. A recent *in vitro* study demonstrated that by using VSMCs derived from spontaneously hypertensive rats, Ang II increased TLR4 mRNA levels, and an AT1R blocker reduced the increase in TLR4 mRNA. A TLR4 inhibitor also diminished the Ang II-induced increases in NADPH oxidase activity, ROS production, migration and proliferation in VSMCs.[9]

A recent study in mice showed that a chronic Ang II infusion increased aortic TLR4 mRNA expression and demonstrated that an anti-TLR4 antibody treatment in Ang II-infused mice inhibited an Ang II-mediated elevation of blood pressure with concomitant suppression of proinflammatory responses and pathological vascular consequences.[20] The results also revealed that MyD88-dependent activation and JNK/NF-κB signaling pathways were involved in Ang II-induced hypertension and vascular remodeling in these mice.[20] Interestingly, the results by Nakashima *et al.*[17] in this issue showed that a chronic Ang II infusion also increased the vascular expression of the extracellular antioxidant enzyme superoxide dismutase (ecSOD). The Ang II infusion-induced increase in ecSOD expression and activity was enhanced in the TLR4 knockout mice compared with wild-type mice, whereas the increase in ROS levels and NADPH oxidase activity in response to Ang II infusion was markedly blunted in the TLR4 knockout mice.[17] In addition, similar effects were observed in WT mice treated with a sub-depressor dose of an AT1R antagonist.

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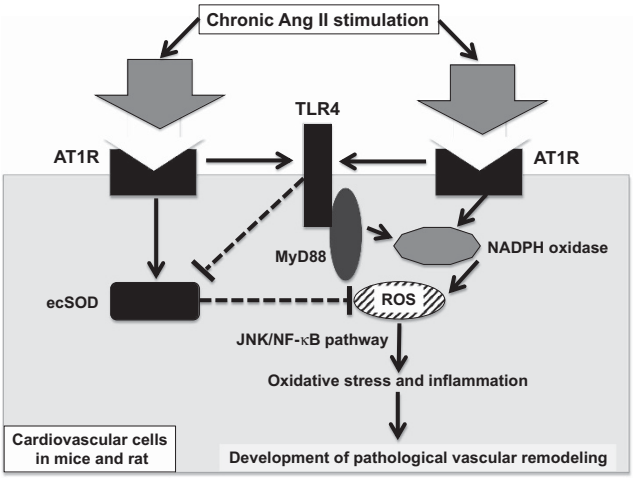

Figure 1 The schematic representation of the possible mechanism for the AT1R-mediated effects of chronic Ang II infusion on pathological vascular remodeling in mice and rats.

This treatment had no effect on TLR4 knockout mice.[17]

Collectively, these accumulated data by Nakashima *et al.* and other groups clearly indicate that TLR4 pathways have a pivotal role in regulating Ang II-induced vascular ROS levels by inhibiting the expression and activity of the antioxidant enzyme ecSOD as well as by activating NADPH oxidase, which enhances inflammation to facilitate the progression of pathological vascular remodeling. Therefore, TLR4 signaling may be a possible target of interest for the efficient treatment of pathological vascular remodeling (Figure 1). Further experimental and clinical evidence is expected to determine the utility of targeting TLR4 signaling.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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