The endothelium is a vital homeostatic organ fundamental for the regulation of vascular tone and structure. As such, endothelial dysfunction is intimately linked to the development and progression of cardiovascular disease. The ability of the vasoactive peptide angiotensin II (Ang II) to induce vascular contractility, endothelial cell (EC) apoptosis, and dysfunction via the induction of reactive oxygen species (ROS) is well appreciated.1–3 Vascular NADPH oxidases (Nox) are predominant contributors to Ang II–induced ROS.4 In particular, Nox2 and p47phox proteins are recognized to be involved in Ang II–induced hypertension and endothelial dysfunction,4,5 which is in agreement with in vitro data showing that the activity of the Nox2-based NADPH oxidase activity from EC, although constitutive,9 is augmented by Ang II10 via a mechanism that absolutely requires p47phox phosphorylation and translocation to the plasma membrane.11 Recently, it has also been established that, along with its role in ROS production, Ang II signaling modulates innate and adaptive immunity that critically contributes to the genesis and maintenance of hypertension and vascular dysfunction.12–14

An IDO1-dependent manner. In fact, the deletion of IDO1 alleviates Ang II–induced EC apoptosis and dysfunction by inhibiting superoxide production in vivo (Figure 2).

In agreement with its positive regulation by INF-γ described in the early 1980s,18 experimental evidence has linked the catabolism of tryptophan to the modulation of immunotolerance.19 The known fact that INF-γ–producing cells are recruited and participate in vascular inflammation20 raises the interesting possibility that tryptophan and its metabolites participate in the cross talk among different cell types during Ang II–induced hypertension. The mechanism presented could promote a positive feedback loop that maintains and amplifies the effect of Ang II in the EC, or it may serve the opposite purpose, where activation of tryptophan metabolism within the EC may help to resolve inflammation by reducing tryptophan in immune cells.19 This idea is supported by the fact that the cellular stress imposed by local depletion of tryptophan has been shown to induce T-cell anergy.21

Recent studies demonstrate that the kynurenine pathway metabolites are associated with increased oxidative stress, inflammation, and cardiovascular disease prevalence and ath erosclerosis in end-stage renal patients.22 In addition, kynurenine has been identified as an endogenous ligand for the aryl hydrocarbon receptor.23 Interestingly, a recent report showed that EC-specific aryl hydrocarbon receptor knockout mice exhibit hypotension and an attenuated response to Ang II.24 Downstream kynurenine pathway metabolites seem to have differential effects. Ang II induces the production of both kynurenine and its metabolite, 3-OHkyn; however, only 3-OHkyn, and not kynurenine, induces ROS production and apoptosis in ECs. In other cell types, the expression of quinolinic acid phosphoribosyltransferase (QPRT), which metabolizes quinolinic acid to nicotinamide adenine dinucleotide (Figure 1), suppresses caspase-3, inhibiting apoptosis25 and in gliomas the induction in QPRT expression positively correlates with tumor malignancy.26 It could be that the effect of this pathway on the cell cycle is cell type specific, or that in other cell types 3-OHkyn has similar effects as in EC and the increased activity of downstream enzymes actually reduces the intracellular concentration of 3-OHkyn.

In addition, Wang et al15 reported that the inhibition of kynurenine monooxygenase (KMO) prevents NADPH oxidase–induced ROS generation and INF-γ–induced apoptosis. In particular, the role of (KMO) warrants further study. Because it is the enzyme responsible for the metabolism of kynurenine to 3-OHkyn, KMO is a potential target for alleviating Ang II–induced oxidative stress. Interestingly, nonstimulated ECs have no KMO basal activity because kynurenine is unable to induce apoptosis and thus, most likely is not metabolized to 3-OHkyn in cells that have not been exposed to INF-γ. Therefore, KMO activity does not seem to be required for EC normal function, making it an attractive
pharmacological target. Indeed, KMO is already being investigated as a potential neuroprotective target because of its involvement in pathologies of the central nervous system such as neurodegenerative disorders, pain syndromes, and autoimmune diseases. Although the role of kynurenine metabolites in oxidative stress and cardiovascular disease has not been examined closely, kynurenine induction of oxidative stress has been more extensively studied within the context of neurodegenerative disorders such as Huntington disease. Both 3-HK and quinolinic acid exhibit neurotoxicity and can induce oxidative stress and apoptosis in neurons. Another kynurenine pathway metabolite, kynurenic acid, exhibits neuroprotective effects in part because of its ability to scavenge free radicals. It has yet to be determined whether kynurenic acid can exert similar protective effects in the context of Ang II–induced inflammation.

Because 3-OHKyn–mediated ROS production is attenuated by treatment with either a superoxide dismutase mimetic or apocynin, the authors conclude that the major source of Ang II–induced ROS is NADPH oxidase. Furthermore, 3-OHKyn treatment increases translocation of both p47phox and p67phox to the membrane fraction and increases the fraction of these proteins that are modified by 3-OHKyn–keyhole limpet hemocyanin adducts, suggesting that 3-OHKyn regulates Nox activity by promoting modification and the subsequent translocation of these subunits to the complex. As it has been discussed extensively in the field, the interpretation of data obtained using apocynin in vascular cells has to be done cautiously, and more work is necessary to determine whether the translocation of the subunits to the plasma membrane is in fact a consequence of the direct modification of the phox proteins by 3-OHKyn.

Taken together, the study presented by Wang et al reveals a novel role for the kynurenine pathway in mediating Ang II–induced ROS production and EC dysfunction. Even if the contribution of Ang II–induced EC apoptosis to vascular pathology is relatively minor, the involvement of the kynurenine pathway in Ang II–induced ROS production could modulate a variety of Ang II effects in the vasculature. This, alongside the recent discovery that increased circulating 3-OHK is associated with cardiovascular disease, opens intriguing new avenues of research.

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References


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