Do Endothelial Cells Eat Tryptophan to Die?

Charity Duran, Alejandra San Martín

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. Vascular NADPH oxidases (Nox) are predominant contributors to Ang II–induced ROS. In particular, Nox2 and p47phox proteins are recognized to be involved in Ang II–induced hypertension and endothelial dysfunction, which is in agreement with in vitro data showing that the activity of the Nox2-based NADPH oxidase activity from EC, although constitutive, is augmented by Ang II via a mechanism that absolutely requires p47phox phosphorylation and translocation to the plasma membrane. 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.

In this issue of Circulation Research, additional pieces of the Ang II signaling pathways are connected as Wang et al examine a novel mechanism for Ang II–mediated ROS production and vascular dysfunction in vivo involving the crosstalk between interferon-γ (INF-γ) and the kynurenine pathway (Figure 1). The kynurenine pathway is a major catabolic route of tryptophan, an essential amino acid, infrequently found in proteins. This pathway begins with the oxidation for tryptophan, which in most cell types is catalyzed primarily by the enzyme indoleamine 2,3-dioxygenase (IDO). , a protein known to be upregulated in the early 1980s, experimental evidence has linked the catabolism of tryptophan to the modulation of immunotolerance. The known fact that INF-γ–producing cells are recruited and participate in vascular inflammation 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. 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.

Recent studies demonstrate that the kynurenine pathway metabolites are associated with increased oxidative stress, inflammation, and cardiovascular disease prevalence and atherosclerosis in end-stage renal patients. In addition, kynurenine has been identified as an endogenous ligand for the aryl hydrocarbon receptor. Interestingly, a recent report showed that EC-specific aryl hydrocarbon receptor knockout mice exhibit hypotension and an attenuated response to Ang II.

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 apoptosis and in gliomas the induction in QPRT expression positively correlates with tumor malignancy. 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 al reported that the inhibition of kynurenine monoxygenase (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 target for the prevention of cardiovascular disease.

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Kynurenine 3-monooxygenase (KMO) and Kynurenine 3-monoxygenase (KMO).

Figure 1. Principal metabolic outcomes of the kynurenine pathway.

Figure 2. Proposed model. Circulating angiotensin II stimulates immune cells to secrete interferon (INF)-γ, which induces key enzymes of tryptophan (Trp) catabolism. The formation of 3-hydroxykynurenine (3-OHky), a product of the Trp degradation pathway, induces the modification and subsequent translocation of phox cytosolic subunits to the membrane activating NADPH oxidase activity. NADPH oxidase–derived reactive oxygen species reach the mitochondria where they are able to induce release of cytochrome C and apoptosis. IDO indicates indoleamine 2,3-dioxygenase; KMO, kynurenine monoxygenase; and Kyn, kynurenine.
References


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