To Move or Not To Move?
Cytochrome P450 Products and Cell Migration

Ingrid Fleming

Over the last 5 to 8 years, researchers have begun to appreciate the prominent role played by cytochrome P450 (CYP) enzymes in the regulation of vascular tone, homeostasis, and blood pressure. For example, interfering with CYP genes markedly affects blood pressure in mice, and numerous reports have demonstrated that CYP expression is altered in genetic and experimental models of hypertension (for a recent review, see Moreno et al.).

Vascular CYP enzymes can be divided into two classes, the epoxygenases, which metabolize arachidonic acid to a series of regiospecific and stereospecific epoxides (5,6-, 8,9-, 11,12- and 14,15-epoxyeicosatrienoic acids or EETs), which are potent vasodilators, and the ω-hydroxylases, which generate the vasoconstrictor eicosanoid, 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE is thought to mediate the myogenic response as well as the contraction induced by a number of contractile agonists and is generally assumed to augment basal blood pressure. EETs, on the other hand, are potent vasodilators and play a central role in the nitric oxide– and prostacyclin-independent relaxation of coronary, renal, and cerebral arteries. Although identified as potential endothelium-derived hyperpolarizing factors (EDHFs), it is now appreciated that EETs regulate much more than vascular tone and are in fact intracellular signal transduction molecules that have a central function in the regulation of vascular homeostasis.

The effects of EETs can be attributed to their ability to activate a number of signal transduction pathways (in addition to those responsible for the activation of Ca2+-dependent K+ channels and hyperpolarization) in endothelial as well as vascular smooth muscle cells (Figure). A number of intracellular EET effectors have been identified and include tyrosine kinases and phosphatases, mitogen-activated protein kinases (ERK1/2, p38 MAPK, and the c-Jun N-terminal kinase), the protein kinase B/Akt, ADP ribosyl transferases, the IκB kinase, and adenylyl cyclase (for review, see Roman). EETs, in particular 11,12-EET, also seem to possess antiinflammatory properties, because the exogenous application of EETs to TNFα-stimulated mice or endothelial cells promotes the activation of NF-κB and the expression of vascular cell adhesion molecule-1 (VCAM-1).

As EETs are generated within endothelial and smooth muscle cells, it is tempting to suggest that enhancing the vascular production of these antiinflammatory eicosanoids may protect against vascular disease. There is in fact strong circumstantial evidence supporting this hypothesis. Interventions that prevent the further metabolism of EETs to the respective dihydroxyeicosatrienoic acids by the soluble epoxide hydrolase inhibit PDGF-induced smooth muscle cell proliferation and have been associated with beneficial changes in blood pressure in spontaneously hypertensive rats as well as in animals treated with angiotensin II. Enhancing CYP expression and EET generation, on the other hand, are reported to protect against apoptosis as well as the injury induced by hypoxia and reoxygenation.

In this issue of Circulation Research, Sun et al report that EETs affect cellular processes involved in smooth muscle cell migration and show that 11,12-EET can inhibit the PDGF-induced migration of rat aortic smooth muscle cells. The effector pathway involved in this response, like the EET-mediated vasodilatation of afferent arterioles, induction of tissue-type plasminogen activator gene transcription, and increase in interendothelial gap junctional communication, requires the activation of adenylyl cyclase, accumulation of cAMP, and activation of protein kinase A. However, in contrast to the effects of most autacoids on cyclic nucleotide production, the activation of adenylyl cyclase by 11,12-EET was prolonged, and intracellular levels of cAMP remained elevated for at least 4 hours. Despite the pronounced effects on cAMP levels, Sun et al were unable to detect any effect of 11,12-EET on smooth muscle cell proliferation, a finding that contrasts with a recent report that EETs as well as an inhibitor of the soluble epoxide hydrolase effectively prevented the PDGF-stimulated proliferation and expression of cyclin D1 in human fibroblasts and coronary artery smooth muscle cells.

The antimigratory effects observed by Sun et al in response to the application of exogenously applied EET were much more marked than those detected in cells overexpressing the EET-generating epoxygenase CYP 2J2. The latter observation could be explained by the fact that the CYP 2J2 enzyme does not generate only 11,12-EET but rather a spectrum of EETs. Indeed, Sun et al report that the antimigratory effects of 5,6- and 14,15-EET were markedly less potent than those of 11,12-EET. However, because EET production in the CYP 2J2–overexpressing cells used was not assessed, it is impossible to exclude the possibility that other CYP metabolites and/or EET metabolites contribute to or interfere with the effects of 11,12-EET.
Although the data presented certainly provide support for the concept that EETs help to maintain the vascular wall in an antiatherogenic state, it should be stressed that the effects of EETs on proliferation and migration vary markedly with the cell type under investigation. In human endothelial cells and kidney epithelial cells, for example, EETs and CYP overexpression enhance cell proliferation via a mechanism involving the activation of the EGF receptor\(^\text{17}\) and an increase in cyclin D1 expression.\(^\text{18}\) EETs also promote cell migration and angiogenesis in cerebral artery endothelial cells.\(^\text{19}\)

Not only is the cellular response to EETs determined by the cell type investigated, but the substrate available to the CYP enzymes as well as the co-products generated during the oxidation of the CYP substrate can also have a pronounced effect on the vasculature. Indeed, it should be borne in mind that although CYP enzymes metabolize arachidonic acid, these enzymes also oxidize other endogenous lipids such as retinoic and linoleic acid to generate products that also elicit physiological as well as pathophysiological responses. For example, the CYP 2J2 and CYP 2C epoxygenases, which are both expressed in the coronary vascular wall,\(^\text{20}\) can generate EETs from arachidonic acid, epoxycosasatrienoic acids from eicosapentanoic acid, and linoleic acid epoxides (leukotoxins) from linoleic acid.\(^\text{21}\) All of these metabolites can elicit biological effects, some antiinflammatory and therefore vasculoprotective, and others, especially those mediated by the leukotoxins, proinflammatory and cytotoxic.\(^\text{22}\) In fact, the generation of leukotoxins by CYP epoxygenases has been implicated in the development of adult respiratory distress syndrome\(^\text{23}\) and possibly also coronary artery disease.\(^\text{24}\) One additional point that is highly relevant to the regulation of vascular function is that some CYP enzymes generate substantial amounts of oxygen-derived free radicals. For example, the CYP 2C enzyme identified as the EDHF synthase in porcine coronary artery endothelial cells generates enough superoxide anions to suppress the antiinflammatory effects of the EETs.\(^\text{7}\) The CYP 2J2 enzyme, however, on which Sun et al focused, seems to generate little or no free radicals and may even possess antioxidant properties.\(^\text{12}\)

In summary, the data presented by Sun et al\(^\text{13}\) provide further evidence for a central role for CYP epoxygenase products in the regulation of vascular homeostasis. However, the substrates oxidized by the vascular CYP enzymes and the conditions in which these enzymes are actually active (CYP enzymes are inhibited by nitric oxide\(^\text{25}\)) still remain to be determined, particularly in intact vascular segments under different physiological as well as pathophysiological conditions.

### References


**KEY WORDS:** epoxyeicosatrienoic acid, migration, proliferation
To Move or Not To Move?: Cytochrome P450 Products and Cell Migration
Ingrid Fleming

Circ Res. 2002;90:936-938
doi: 10.1161/01.RES.0000019742.48706.F0
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/90/9/936

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/