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Cytochrome P450 enzymes: Central players in cardiovascular health and disease

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Abstract

Cardiovascular disease (CVD) is a human health crisis that remains the leading cause of death worldwide. The cytochrome P450 (CYP) class of enzymes are key metabolizers of both xenobiotics and endobiotics. Many CYP enzyme families have been identified in the heart, endothelium and smooth muscle of blood vessels. Furthermore, mounting evidence points to the role of endogenous CYP metabolites, such as epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs), prostacyclin (PGI_2), aldosterone, and sex hormones, in the maintenance of cardiovascular health. Emerging science and the development of genetic screening have provided us with information on the differences in CYP expression among populations and groups of individuals. With this information, a link between CYP expression and activity and CVD, such as hypertension, coronary artery disease (CAD), myocardial infarction, heart failure, stroke, and cardiomyopathy and arrhythmias, has been established. In fact many currently used therapeutic modalities in CVD owe their therapeutic efficacy to their effect on CYP metabolites. Thus, the evidence for the involvement of CYP in CVD is numerous. Concentrating on treatment modalities that target the CYP pathway makes ethical sense for the affected individuals and decreases the socioeconomic burden of this disease. However, more research is needed to allow the integration of this information into a clinical setting.

Keywords: Cytochrome P450; Cardiovascular disease; Arachidonic acid; Aldosterone; Sex hormones; Prostacyclin; Thromboxane

Abbreviations: 17-ODYA, 17-octadecynoic acid; AA, arachidonic acid; ACE, angiotensin converting enzyme; B[*a*]P, benzo[*a*]pyrene; βNF, β-naphthoflavone; CAD, coronary artery disease; CBF, cerebral blood flow; CO, carbon monoxide; COX, cyclooxygenase; CSF, cerebral spinal fluid; CVD, cardiovascular disease; CYP, cytochrome P450; DiHETE, dihydroxyeicosatetraenoic acid; DMBA, 7,12-dimethylbenz[*a*]anthracene; EDHF, endothelium-derived hyperpolarizing factor; EET, epoxyeicosatrienoic acid; EROD, 7-ethoxyresorufin *O*-deethylase; GRA, glucocorticoid-remediable aldosteronism; HETE, hydroxyeicosatetraenoic acid; HIF-1, hypoxia inducible factor-1; HPETE, hydroperoxyeicosatetraenoic acid; ICa, L-type calcium current; IHD, ischemic heart disease; IPC, ischemic preconditioning; LDL, low-density lipoproteins; LVH, left ventricular hypertrophy; MCA, middle cerebral artery; MI, myocardial infarction; NF-κB, nuclear factor-κB; NO, nitric oxide; PGG_2, prostaglandin G_2; PGI_2, prostacyclin; PGIS, prostacyclin synthase; PMN, polymorphonuclear leukocytes; SHRSP, stroke-prone spontaneously hypertensive rats; SAH, subarachnoid hemorrhage; SHR, spontaneously hypertensive rats; SMC, smooth muscle cells; TIA, transient ischemic attack; Trp-P-1, 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole; TS-011, *N*-(3-chloro-4-morpholin-4-yl) phenyl-*N*′-hydroxyimido formamide; TXA_2, thromboxane A_2; VCAM-1, vascular cell adhesion molecule-1; VSMC, vascular smooth muscle cells.

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1. Introduction

Translating advances in molecular and genetic medicine to patient care is a considerable challenge. Meeting that challenge requires bench-work knowledge to be bridged into clinical practice. Molecular and genetic approaches to diseases and an epidemiologic perspective on how these approaches affect health are of vital importance to improving the health of individual patients.

Cardiovascular disease (CVD) is a prime example. While the rate of deaths from CVD has been on the decline over the past few decades, it remains as one of the leading causes of death worldwide. It constitutes one of the major human health problems of modern times. Heart disease and stroke account for nearly 40% of all the causes of mortality in the US (CDC, 2005). Close to 1 million Americans die of CVD each year, amounting to 1 death every 34 sec. In addition, it is the leading cause of disability in the US workforce. Thus, its economic burden is huge. These figures alone point to the importance of research in addressing the yet to be solved puzzle of the pathogenesis of CVD.

In an attempt to configure the individual susceptibility to CVD, increasing evidence is shedding the light on the role of the cytochrome P450 (CYP) superfamily of enzymes in the onset, progression, and prognosis of CVD. The CYP are a superfamily of cysteinato-heme enzymes that are key mediators of the oxidative transformation of exogenous molecules (Guengerich, 2001). They are classified into families, subfamilies, and individual isoenzymes based on similarities in their amino acid sequence. Of these enzymes, 3 families have been identified as the major contributors to phase I metabolism: CYP1, CYP2, and CYP3.

The CYP enzyme system also metabolizes endogenous compounds in various biosynthetic pathways and expression of CYP has been reported in both hepatic and extra-hepatic tissues. Thus tissue specific metabolism of endogenous substrates may be of vital importance for physiological function. The recognition that CYP expression is altered in disease (Elbekai et al., 2004; Gharavi & El-Kadi, 2004; Korashy et al., 2004; Liu et al., 2004) and that genetic differences contribute to inter-individual differences in enzyme activity seen within a patient population have resulted in an explosion of research on the role of these enzymes in diseases.

CYP reaction products, or metabolites, have been detected in cardiovascular tissue (Roman, 2002; Gottlieb, 2003; Spiecker & Liao, 2005) and recently, specific isoforms of the enzyme superfamily have been detected (Thum & Borlak, 2000b; Thum & Borlak, 2002). Emerging studies have documented the role of these endogenous CYP metabolites in the maintenance of cardiovascular health (Roman, 2002), thus it comes at no surprise that dysregulation of their production may be associated with the onset and progression of the various cardiopathies.

This review will highlight the expression of CYP in the cardiovascular system, the role of the endogenous metabolites in the maintenance of cardiovascular health, and a summary of the expression and role of certain CYP enzymes in CVD.

2. Cytochrome P450 expression in cardiovascular tissue

Despite much work on the production of CYP metabolites in cardiovascular tissue, little information is available about the expression and regulation of the CYP enzymes in the heart and blood vessels. Nonetheless, evidence published by various groups has given us some information on the expression of various CYP families, including CYP1, CYP2, CYP3, CYP4, CYP8, CYP11, and CYP19 (Table 1). The following will discuss the evidence available on the expression of these CYP families in cardiovascular tissue.

2.1. CYP1 family

There is a large sum of evidence on the expression of the CYP1 family in both humans and animals. Autoradiograms of