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Human cytochrome P450 epoxygenases: Variability in expression and role in inflammation-related disorders

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ABSTRACT

Beyond their contribution to the metabolism of xenobiotics, cytochrome P450 (CYP) epoxygenases are actively involved in the metabolism of endogenous substances, like arachidonic acid (AA). The main human CYP epoxygenases, i.e. CYP2C8, CYP2C9, CYP2C19 and CYP2J2, convert AA to four regioisomer epoxyeicosatrienoic acids (EETs). EETs possess a wide range of established protective effects on the human cardiovascular system of which anti-inflammatory actions have gained great recent interest. The expression of CYP epoxygenases is regulated through an extremely complex network of nuclear receptors, microRNAs and genetic/epigenetic factors. Accordingly, a large number of biological variables as well as xenobiotics and environmental factors can influence the expression of CYP epoxygenases, resulting in a significant intra- and inter-individual variability in the expression and activity of these enzymes and subsequently in EET biosynthesis. Moreover, human CYP epoxygenases are mainly expressed in the liver; however, these enzymes are also expressed, at various extents, in most extrahepatic tissues, resulting in a marked inter-tissue variability in the expression of CYP epoxygenases. The inter-tissue, inter- and intra-individual variability in the expression of epoxygenases may lead to differences in the relative abundance of EETs among tissues, among individuals of a population and/or different ethnicities and in a given individual under various conditions. The variation in the abundance of EETs may explain, at least in part, the inter-tissue and inter-individual differences observed in the prevalence of inflammation-related disorders including cardiovascular disease, and why in a given individual, various conditions can contribute to the development of diseases with an important inflammatory component.

Contents

Abbreviations: AA, arachidonic acid; AhR, aryl hydrocarbon receptor; AP-1, activator protein-1; bZIP, basic leucine zipper; CAR, constitutive androstane receptor; CCRP, cytoplasmic CAR retention protein; CNV, copy number variation; COUPTF, chicken ovalbumin upstream promoter transcription factor; DHA, docosahexaenoic acids; DMet, DNA methylation; EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factors; EDP, epoxydocosapentaenoic acid; EEQ, epoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic; FXR, farnesoid X receptor; GR, glucocorticoid receptor; GTF, general transcription factor; HDAC, histone deacetylases; HETE, hydroxyeicosatetraenoic acid; HNF4α, hepatocyte nuclear factor 4α; HSP90, heat shock protein 90; LETF, liver-enriched transcription factor; LPS, lipopolysaccharide; LXR, liver X receptor; miRNA, microRNA; mRNA, messenger RNA; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear transcription factor kappa B; NR, nuclear receptor; POR, CYP oxidoreductase; PP-2A, phosphatase 2A; PUFA, polyunsaturated fatty acids; PXR, pregnane X receptor; RE, receptor element; ROR, retinoid acid-related orphan receptor; sEH, soluble epoxyhydrolase; SHP, small heterodimer partner; SRC-1, steroid receptor activator-1; TIF-2, transcriptional intermediary factor 2; TF, transcriptionl factor; TGF, transforming growth factor; VDR, vitamin D receptor.

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1 . Introduction

Inflammation is a complex and highly orchestrated process that has a domino-like effect on the initiation and development of a wide range of systemic illnesses including cardiovascular disease (CVD) (Gabay & Kushner, 1999). Our knowledge about the contribution of inflammation to the development of CVDs has progressed to the point that, currently, coronary artery disease (CAD) and arterial hypertension (HTN) are believed to be diseases of inflammation characterized by interaction among platelets, leukocytes and endothelial cells (ECs) (Harrison et al., 2011; Libby, 2002; May et al., 2007).

A growing body of evidence suggests that, beyond their well-established contribution to the metabolism of xenobiotics, cytochrome P450 (CYP) epoxygenase enzymes play an indispensable role in the regulation of inflammation through the biosynthesis of endogenous bioactive lipid mediators that modulate inflammation, such as the arachidonic acid (AA) derivatives, epoxyeicosatrienoic acids (EETs) (Deng et al., 2010; Fleming, 2011).

Even though human CYP epoxygenases are predominantly expressed in the liver, they are also expressed, on a smaller scale and in a heterogeneous pattern, in extrahepatic tissues (Zanger & Schwab, 2010), resulting in inter-tissue variability in CYP epoxygenase expression in a given individual. In addition, a large number of factors have been demonstrated to affect the expression pattern of CYP genes, leading to significant inter- and intra-individual differences in the expression levels of CYP epoxygenases. These heterogeneities could potentially give rise to a marked inter-tissue, inter- and intra-individual variability in the production and relative abundance of EETs and, subsequently, in the EET-mediated inflammation-reduction. Given the importance of inflammation in the pathophysiology of a wide range of CVDs, variability in the anti-inflammatory effects of EETs may have clinical consequences.

In this review, we first provide an overview of the structure, activity and regulation of expression of human CYPs as well as the mechanism of synthesis and action of CYP-dependent AA metabolites, i.e. EETs. The review then presents in some detail, the factors affecting the expression of CYP epoxygenase genes and resulting in an inter- and intra-individual heterogeneity in the epoxygenase-mediated EET formation. Next, we discuss the potential influence of variation in the relative expression of CYP epoxygenase genes in various human organs on the local/systemic abundance and biological functions of EETs in a given individual. Lastly, the possible clinical implication of the inter-tissue, intra-individual and inter-individual variability in the epoxygenase expression and the EET production will be discussed.

2. Cytochrome P450, human epoxygenases

2.1. Cytochrome P450 enzyme; general considerations

CYP enzymes belong to the ubiquitous superfamily of thousands of closely related hemoproteins found throughout the phylogenetic spectrum, from animals, plants and fungi to bacteria. Of more than 11,000 genes and 1000 CYP families which have been found in nature in total, approximately 115 CYP genes, including 57 putatively active genes and 58 pseudogenes have been identified in human, and are grouped into 18 and 44 families and subfamilies, respectively (http://drnelson.uthsc.edu/human.P450.table.html).

CYP enzymes share a common structure but also share a conformational flexibility. In addition to the structural similarities, CYP enzymes essentially function in the same way. The structure and catalytic activities of CYP enzymes have been described in detailed, previously (Coleman, 2010; Denisov et al., 2005; Hart & Zhong, 2008).

2.2. Human cytochrome P450 epoxygenases; epoxyeicosatrienoic acid formation

CYP enzymes, particularly those in the CYP1, CYP2 and CYP3 genes families, catalyze the biotransformation of 75% of xenobiotics and pharmaceuticals in human (Sim & Ingelman-Sundberg, 2010; Zanger et al., 2010). In addition, human CYPs play central roles in the overall metabolism and disposition of a wide range of endogenous chemicals including steroid hormones (estrogen and testosterone), vitamin D, bilirubin, cholesterol and fatty acids (Fleming, 2011).

AA is a 20-carbon, omega-6 polyunsaturated fatty acid (PUFA) that resides in the cell membrane phospholipids in the stereospecific numbering (*sn*)-2 position and is released upon stimulation by the cytosolic enzyme phospholipase A_2 (Sudhahar et al., 2010). The free intracellular AA is converted to a series of biological active metabolites referred to as "eicosanoids" (Imig, 2012). Cyclooxygenases catalyze the biosynthesis of prostaglandins/thromboxanes and lipoxygenases mediate the production of leukotrienes (Kuehl & Egan, 1980; Zordoky & El-Kadi, 2010). Referred to as the "third eicosanoid enzymatic pathway", AA is also metabolized to EETs and hydroxyeicosatetraenoic acids (HETEs) by CYP epoxygenases and CYP hydroxylases, respectively (Oliw, 1994; Zeldin, 2001).

CYP epoxygenase enzymes belong to a complex superfamily of genes with a common evolutionary origin, a conserved peptide that provides them with a cysteine heme ligand, and the capacity to take an active form of atomic oxygen to ground state carbons (Imig, 2012). Indeed, CYP epoxygenases catalyze the epoxidation of four olefin bonds of the intracellular AA that gives rise to four corresponding regioisomers: 5,6-EET, 8,9-EET, 11,12-EET and 14,15-EET (Spector & Norris, 2007) (Fig. 1). Several CYP subfamilies including CYP1A, CYP2B, CYP2C, CYP2E and CYP2J have been classified as CYP epoxygenases (Imig, 2000; Zeldin, 2001), and potentially contribute to the conversion of AA to EETs; however, human epoxygenases are predominantly members of CYP2C and CYP2J classes (Imig, 2000; Zeldin, 2001; Capdevila & Falck, 2002Imig, 2000; Elbekai & El-Kadi, 2006; Zordoky, et al., 2010). In particular, CYP2C8, CYP2C9, CYP2C19 and CYP2J2 isoforms have been identified as the main CYPs involved in the biotransformation of AA to EETs in human (Enayetallah et al., 2004; Campbell & Fleming, 2010; Pfister et al., 2010). Each epoxygenase is, supposedly, capable to convert AA to all four EETs; however, 11,12- and 14,15-EETs are the main products in many cases (Capdevila et al., 2000; Zeldin, 2001). Furthermore, there is mounting evidence that human CYP epoxygenases are relatively regioselective for EET formation. For instance CYP2C8 catalyzes the biosynthesis of 14,15-EET and 11,12-EET in a ratio of 1.3:1.0 whereas its capability for the formation of 8,9-EET and 5,6-EET is negligible. Similarly, CYP2C9 also generates 14,15-EET and 11,12-EET in a ratio of 2.3:1.0; this epoxygenase, however, does not form significant amounts of 8,9-EET (Daikh et al., 1994; Zeldin et al., 1995).

2.3. Physiological roles of epoxyeicosatrienoic acids in vascular biology

There is a large volume of evidence that EETs possess a wide range of potent cardiovascular protective effects including regulation of vascular tone (Harder et al., 1995; Campbell et al., 1996; Fisslthaler et al., 1999; Campbell et al., 2010), and homeostasis (Enayetallah et al., 2004; Spector et al., 2007; Campbell et al., 2010; Sudhahar et al., 2010; Imig, 2012). Fig. 2 is a schematic illustration of the protective effects and the postulated mechanism of action of EETs on the myocardium and vasculature. It long has been known that EETs act as endothelium-derived hyperpolarizing factors (EDHFs) and exhibit vasodilatory effects in various arterial territories including coronary, renal, mesenteric and cerebral vasculatures (Campbell et al., 2010; Pfister et al., 2010; Sudhahar et al., 2010; Imig, 2012). In addition, EETs stimulate EC proliferation and angiogenesis, protect ECs from apoptosis (Medhora et al., 2003; Sudhahar et al., 2010), have anti-migratory effects on smooth muscle cells (SMCs) (Spector et al., 2007; Sun et al., 2002; Sudhahar

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