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Review

Soluble epoxide hydrolase: Gene structure, expression and deletion

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ABSTRACT

Mammalian soluble epoxide hydrolase (sEH) converts epoxides to their corresponding diols through the addition of a water molecule. sEH readily hydrolyzes lipid signaling molecules, including the epoxyeicosatrienoic acids (EETs), epoxidized lipids produced from arachidonic acid by the action of cytochrome p450s. Through its metabolism of the EETs and other lipid mediators, sEH contributes to the regulation of vascular tone, nociception, angiogenesis and the inflammatory response. Because of its central physiological role in disease states such as cardiac hypertrophy, diabetes, hypertension, and pain sEH is being investigated as a therapeutic target. This review begins with a brief introduction to sEH protein structure and function. sEH evolution and gene structure are then discussed before human small nucleotide polymorphisms and mammalian gene expression are described in the context of several disease models. The review ends with an overview of studies that have employed the sEH knockout mouse model.

Contents

Abbreviations: 20-HETE, 20-hydroxyeicosatetraenoic acid; Ang-II, angiotensin II; AP-1, activator protein 1; ARIC, Atherosclerosis Risk in Communities; ATF-6, activating transcription factor-6; CAC, coronary artery calcification; CARDIA, Coronary Artery Risk Development in Young Adults; ChIP, chromatin immunoprecipitation; CPR, cardiopulmonary resuscitation; DHA, docosahexaenoic acid; DHETs, dihydroxyeicosatrienoic acids; EETs, epoxyeicosatrienoic acids; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; EpFAs, epoxy-fatty acids; FLAP, 5-lipoxygenase activation protein; GSIS, glucose-stimulated insulin secretion; Hcy, homocysteine; HUVECs, human umbilical vein endothelial cells; IBD, inflammatory bowel disease; IL-10, interleukin-10; LPS, lipopolysaccharide; NSAID, nonsteroidal anti-inflammatory drug; OVX, ovariectomized; PPARs, peroxisome-proliferator activated receptors; RAAS, renin–angiotensin aldosterone system; RBC, red blood cell; sEH, soluble epoxide hydrolase; SHR, spontaneously hypertensive rat; SNPs, single nucleotide polymorphisms; SP-1, specificity protein 1; STZ, streptozotocin; THF, tetrahydrofuran; UPREs, unfolded protein response elements; UTR, untranslated region; VSM, vascular smooth muscle; WKY, Wistar-Kyoto.

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1. Introduction

This review first summarizes the role of sEH in the hydrolysis of epoxy fatty acids (EpFAs), the proposed endogenous substrates of the enzyme. We then provide a comprehensive evaluation of sEH gene expression and regulation, including its localization in mammalian tissues. Finally, we discuss sEH genetic models that have associated sEH with diseases such as cardiovascular disease, cancer and diabetes as well as pain, and have contributed to the identification of the enzyme as a pharmaceutical target.

2. sEH protein structure and catalytic activities

Human sEH is a 62 kDa enzyme composed of two domains separated by a short proline-rich linker (see Fig. 1) (Newman et al., 2005). In mammals, sEH is a homodimer in the intracellular environment (Morisseau and Hammock, 2013). The N-terminal domain exhibits a phosphatase activity that hydrolyzes lipid phosphates, while the C-terminal domain exhibits an epoxide hydrolase activity that converts epoxides to their corresponding diols (see Fig. 2) (Morisseau and Hammock, 2013). sEH hydrolyzes EpFA, including one important class of lipid signaling molecules, the epoxyeicosatrienoic acids (EETs) (Spector and Norris, 2007). EETs have vasoactive, anti-inflammatory and analgesic properties (Imig, 2012). Through metabolism of these molecules and other EpFAs, sEH is implicated in several diseases, including hypertension, cardiac hypertrophy, arteriosclerosis, brain and heart ischemia/reperfusion injury, cancer and pain (Imig and Hammock, 2009; Morisseau and Hammock, 2013; Wagner et al., 2011). Because of its possible role in cardiovascular and other diseases, sEH is being pursued as a pharmacological target, and several potent small molecule inhibitors are available (Shen and Hammock, 2012).

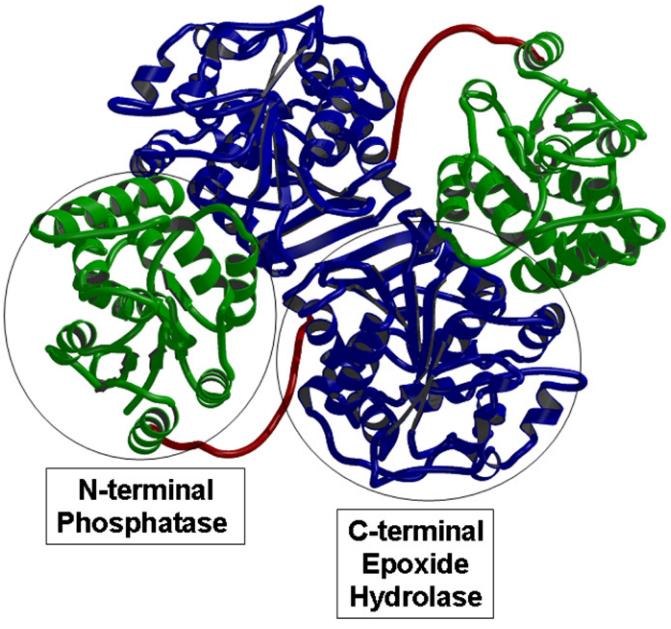

Fig. 1. Crystal structure of the sEH dimer (PDB accession code 1S80 (Gomez et al., 2004).) The sEH monomer is composed of two globular regions displaying alpha/beta fold tertiary structure connected by a short proline-rich linker. The sEH dimer is anti-parallel, so that the N-terminal region of one monomer is in contact with the C-terminal region of the other. The catalytic site for the epoxide hydrolase activity is located within the C-terminal region, while the phosphatase activity is located within the N-terminal region.

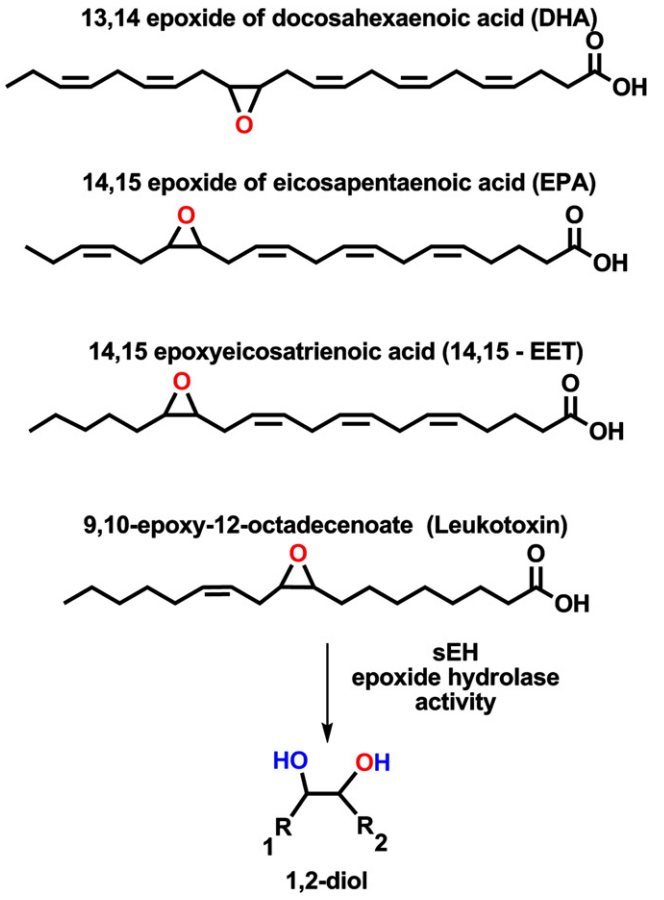

Fig. 2. Substrates and products of sEH epoxide hydrolase activity. Through the addition of water, sEH converts lipid epoxides to diols (the oxygen of the epoxide moiety is in red). Potential substrates for sEH include the omega-three lipid epoxides formed from DHA and EPA, the omega-six lipid epoxides formed from arachidonic acid (ARA), linoleic acid, and stearic acid. The regioisomers preferred by the human sEH are displayed (Morisseau et al., 2010).