

Figure 1 Regulatory network of cytochrome P450 under hypoxia. Four main mechanisms are involved: ① Hypoxia reduces the expression of nuclear receptors such as PXR, CAR, AHR, PPAR, and HNF, and further regulates the activity and expression of CYP. ② Hypoxia induces epigenetic changes, miRNA and lncRNA expression are suppressed under hypoxia, while hypoxia induces DNA methylation and histone modification, which together regulate CYP expression. ③ High-altitude hypoxia activates inflammatory factors and transcription factors, the NF-kB signaling pathway is activated under the influence of inflammation; the same inflammatory factors regulate the expression of CYP; and HIF-1 binds to hypoxia-responsive elements of downstream genes to regulate the expression of CYP and nuclear receptors. ④ High-altitude hypoxia alters the structure and diversity of the gut microbiota, mediating changes in CYP protein and mRNA expression through the release of extracellular vesicles.

PXR: Pregnane X receptor; CAR: Constitutive androstane receptor; AHR: Aryl hydrocarbon receptor; ARNT: Aryl hydrocarbon receptor nuclear translocator; PPAR: Peroxisome proliferator-activated receptor; HNF: Hepatocyte nuclear factor; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; NF-κB: Nuclear factor-κB; HIF-1: Hypoxia inducible factor-1

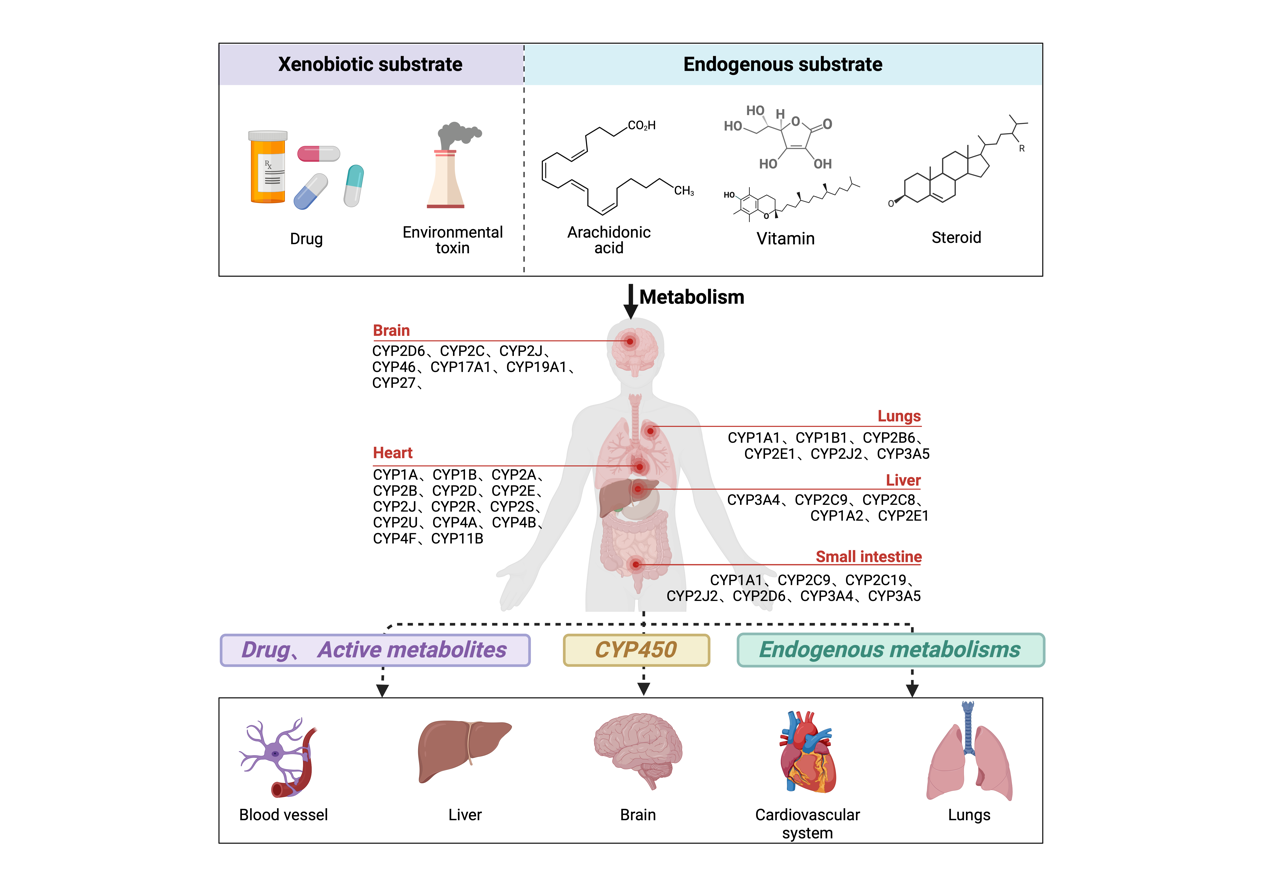
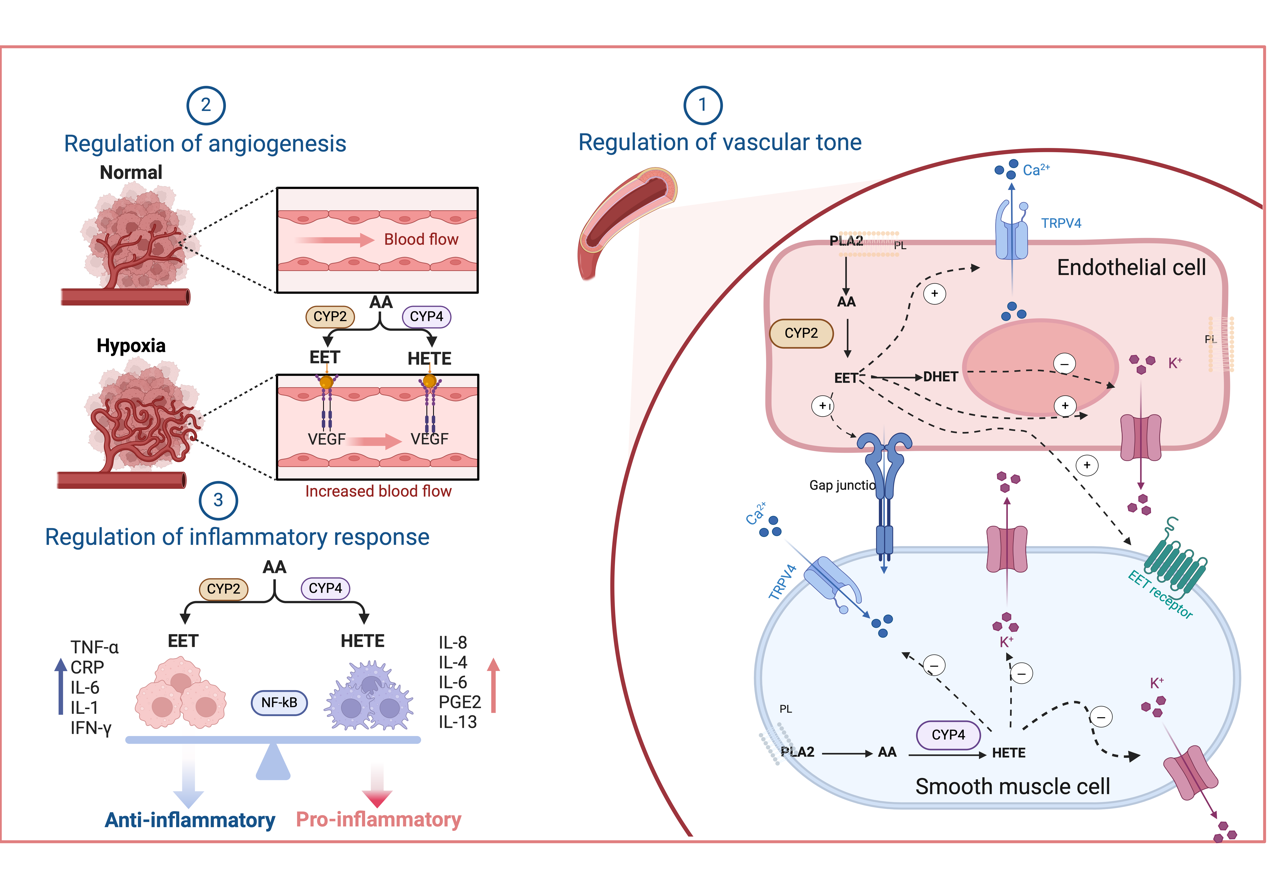


Figure 2 Possible effects of cytochrome P450 on high-altitude diseases. Some CYPs have drug-metabolizing ability, they can convert exogenous drugs into active substances to exert therapeutic effects or convert them into hydrophilic substances to promote their excretion from the body; some CYPs have endogenous substance-metabolizing ability; they are involved in the biosynthesis and oxidative metabolism of arachidonic acid, vitamins, and steroids in the body, and these metabolites are involved in the regulation of physiological functions of blood vessels, heart, brain, lungs, and other tissues.

Figure 3 Possible mechanisms for the involvement of CYP-derived endogenous metabolites in the pathophysiological processes of high-altitude disease. The involvement of CYP-derived endogenous metabolites in the development of plateau diseases is mainly related to the following three mechanisms: ①CYP metabolism produces metabolites such as EET and HETE, which are the main regulators of vascular tone. Changes in CYP expression under hypoxia lead to changes in metabolites, which in turn regulate vascular tone and regulate blood flow to promote hypoxic adaptation. ②Endogenous metabolites produced by CYP metabolism promote endothelial cell tubularity by affecting the expression of VEGF, which then promotes angiogenesis under hypoxia. ③Metabolites produced by CYP metabolism regulate the inflammatory response under hypoxia, which is involved in the development and progression of many hypoxic diseases. Metabolites produced by CYP metabolism regulate the inflammatory response under hypoxia; some metabolites, such as EET, have anti-inflammatory effects, and some metabolites, such as HETE, have pro-inflammatory effects, stimulating the production of inflammatory cytokines and chemokines in endothelial cells through activation of NF-κB pathways and maintaining the body's homeostasis.

AA: Arachidonic acid; EET: Epoxyeicosatrienoic acid; DHET: Dihydroxyeicosatrienoic acid; sEH: Soluble epoxide hydrolase; HETE: Hydroxyeicosatetraenoic acid; K+Ca: Calcium-dependent K+ channels; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α; IL: Interleukin; NF-κB: Nuclear factor-κB; IFN-γ: Interferon-gamma; PGE2: Prostaglandin E2