Cytochrome P450 Enzymes

Cytochrome P450 (CYP450) enzymes are a large **superfamily of heme-containing monooxygenases** that play a central role in **phase I metabolism**, catalyzing the **oxidation** of lipophilic compounds into more **hydrophilic derivatives** for easier excretion via the kidneys.

? **Primary Function**: Detoxification of **xenobiotics** (drugs, toxins, pollutants) and metabolism of **endogenous compounds** (steroids, fatty acids, bile acids, and hormones).
? Located mainly in the **smooth endoplasmic reticulum** of **hepatocytes**, but also found in intestines, lungs, kidneys, and brain.

II. Reactions Catalyzed

CYP450 enzymes catalyze various **oxidation-reduction** reactions, notably:

- **Hydroxylation**
- **Epoxidation**
- **N-dealkylation**
- **O-dealkylation**
- **S-oxidation**
- **Deamination**
- **Desulfuration**

These reactions introduce or expose polar functional groups to enhance solubility.

III. Classification and Nomenclature

CYP enzymes are named based on their **gene family**, **subfamily**, and **individual gene**:

- **CYP** = Cytochrome P450
- **Number** = Gene family (e.g., **CYP3**)
- **Letter** = Subfamily (e.g., **CYP3A**)
- **Second number** = Specific isoenzyme (e.g., **CYP3A4**)

? Over **57 functional CYP genes** have been identified in humans.

IV. Clinically Relevant CYP450 Isoenzymes

Enzyme	Function	Common Substrates	Clinical Significance
CYP3A4	Most abundant (~30-50%)	Statins, benzodiazepines, calcium channel blockers	Affected by grapefruit juice (inhibitor)
CYP2D6	Polymorphic	Antidepressants, beta-blockers, opioids (e.g.,	Gene duplication leads to ultra-rapid

Enzyme	Function	Common Substrates	Clinical Significance
		codeine)	metabolism
CYP2C9	Important in warfarin metabolism	Warfarin, NSAIDs, sulfonylureas	Genetic variants require dose adjustment
CYP2C19	Metabolizes PPIs and clopidogrel	Omeprazole, clopidogrel	Poor metabolizers have reduced drug efficacy
CYP1A2	Inducible by smoking	Theophylline, caffeine	Influenced by lifestyle factors

V. Pharmacogenomics (PGx) and Clinical Application

CYP450 polymorphisms affect:

- **Drug efficacy**
- **Adverse drug reactions (ADRs)**
- **Drug dosing**

? **Pharmacogenetic testing** is increasingly used to personalize medicine.

Metabolizer Phenotypes

Phenotype	Description
Poor metabolizer (PM)	Little/no functional enzyme activity
Intermediate (IM)	Reduced enzyme activity
Extensive (EM)	Normal enzymatic activity
Ultra-rapid (UM)	Increased activity due to gene duplication

VI. Inducers and Inhibitors (High-Yield NCLEX/USMLE Table)

CYP450 Inducers (? Enzyme activity)	**CYP450 Inhibitors** (? Enzyme activity)
Rifampin	**Ketoconazole**
Phenytoin	**Cimetidine**
Carbamazepine	**Macrolides (e.g., erythromycin)**
St. John’s Wort	**Grapefruit juice**
Phenobarbital	**Ritonavir**

?? *Inducers* can **lower drug levels**, while *inhibitors* can **increase toxicity**.

VII. Clinical and Toxicological Implications

- **Drug Interactions**: Multiple drugs metabolized by the same CYP can lead to **competition**,

altering expected effects.
- **Toxicity Risk**: Impaired metabolism can lead to **accumulation** of active/toxic compounds.
- **Cancer Susceptibility**: Some CYP variants are involved in **bioactivation** of environmental **procarcinogens**.
- **Example**: **CYP1A1 polymorphisms** linked to **lung cancer risk** in smokers.

VIII. Summary (High-Yield Key Points)

- ? **CYP450** enzymes metabolize **>50% of all drugs**.
- ? Found primarily in the **liver**; involved in **phase I** reactions.
- ?? Subject to **genetic polymorphism**—especially **CYP2D6, CYP2C9, and CYP2C19**.
- ? Modulated by **age, genetics, diet, smoking, and concurrent drugs**.
- ? Pharmacogenetic profiling is essential for **personalized therapy**.
- ?? **Drug-drug interactions** are common—always check **CYP450 pathway** when prescribing.

Mnemonic to Remember CYP Inhibitors: "SICKFACES.COM"

Sodium valproate
Isoniazid
Cimetidine
Ketoconazole
Fluconazole
Amiodarone
Chloramphenicol
Erythromycin
Sulfonamides
.Ciprofloxacin
Omeprazole
Metronidazole