

MINI-REVIEW: CYTOCHROME P-450; DISCOVERY TILL IMPORTANCE

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Abstract

The purpose of this review is to provide the importance of cytochrome P-450 regarding information from their discovery and till how much work is done on them in different era. Their functional importance and properties are also very important to study.

Keywords: Cytochrome P-450, Heme molecule, Metabolic enzyme, Catalytic role, CYP4A

WHAT IS CYTOCHROME P-450?

Cytochrome P-450 is a group or family of enzymes which contain a heme molecule that is bond with a polypeptide chain covalently. The main role of the heme is to carry one atom of iron that has ability to bind oxygen in active site of CYP as a necessary part of catalytic cycle.

HISTORY OF CYTOCHROME P-450

Cytochrome P-450, a cellular chromophore, when bound and reduced with carbon monoxide give spectral peak at 450 nm and was first named in 1958 by Martin Klingenberg. This spectral peak at 450nm is different from other heme proteins and this is consider as special characteristics of P450 Proteins (Klingenberg, 1958). The scientists think in early 1960s that P-450 was the one enzyme and in mid 1960s it is discovered that it was also involved in drugs and steroids metabolism. In late 1970s, six P-450 enzymes were discovered and number of proteins which were involved could not be counted because of less experimental techniques. In 1980s, the advancement in different purification techniques, Gonzalez and colleagues discovered the first cDNA encoding a complete protein of cytochrome P-450 (Gonzalez et al., 1984) and till 2002 there are more than 270 CYP gene families with 18 in mammals recorded (Daniel W. Nebert & Russell, 2002).

NOMENCLATURE OF CYTOCHROME P-450

CYPs are classified and named with CYP starting followed by number(1-9) denoting the family, then a alphabetic letter (A-Z) denoting the subfamily, and in last another number(1-9) denoting the CYP form (Hilal-Dandan & Brunton, 2014).

Like, CYP3A4 now starts with CYP, then 3 family, A subfamily and 4 CYP form.

PROPERTIES OF CYTOCHROME P-450

The main role of CYP families are involved in hormone synthesis and bile acid, metabolism of retinoic acid and fatty acids and limited number of CYPs (1-3 families) are primarily involved in xenobiotic metabolism. These enzymes can metabolize structurally diverse chemicals found in diet, environment and administered as drugs (Hilal-Dandan & Brunton, 2014).

DW Nebert, TP Dalton demonstrates the role of CYPs in endogenous signaling pathways and carcinogenesis (Daniel W Nebert & Dalton, 2006). Ketter and his colleagues studies the main role of Cytochrome P-450_{3A} in Psychopharmacology because of their involvement in metabolism of

steroids and medication including antidepressants, benzodiazepines and calcium channel blockers (Ketter et al., 1995). M Chiba and his colleagues demonstrates the role of human CYP3A4 on the metabolism of a potent human immunodeficiency virus protease inhibitor (Chiba et al., 1996).

M Kizaki and his colleagues demonstrates the role Cytochrome P-450 inhibitor and P-glycoprotein antagonist on cell growth and differentiation in retinoid resistance leukemic cells (Kizaki et al., 1996). B.kevin and his colleagues studies the main role of cytochrome P-450 enzymes in human drug toxicity which may be hepatic and extrahepatic and suggest that toxicity may be avoided at the time of discovering new chemical entities that are metabolized by wide range of enzymes and also focus on the point that there must be minimum or they do not undergo bio-activation through these enzyme systems (Park et al., 1995).

Graeme.I.Murray studies the main role of cytochrome P-450 in tumor growth, progression and its use in tumor treatment. Many carcinogens are substrate of P-450 and on other hand anti-cancer drugs are also substrates of P-450s thus they have very important role in tumor diagnosis and therapeutic strategies (Murray, 2000).

Assaad A.Eid and his colleagues investigate the basic role CYP4A family, NADPH oxidases in diabetic mice and concluded that inhibition of selected type of cytochrome P-450 isoforms reduced proteinuria and prevented podocyte apoptosis in diabetic mice model (Eid et al., 2009). Andres A. Caro and his colleagues review the role of cytochrome P-450 as central role in the phospholipase A₂- and arachidonic acid mediated cytotoxicity in different types of human diseases and suggest that novel treatment strategies by inhibition of phospholipase A₂ and specifically cytochrome P-450 (Caro & Cederbaum, 2006).

David Sacerdoti and his colleagues studies the role of cytochrome P-450 dependent arachidonic acid metabolites in normal liver and its pathophysiology. Liver contain highest number of CYPs content as compared to other organs involved in metabolism of fatty acids. CYP-AA metabolites are group of compounds that are involved in the normal liver metabolic process and hemodynamics. They are of great importance because they are deeply involved in liver diseases, specifically Cirrhosis and play a key role in portal hypertension and renal failure (Sacerdoti et al., 2003)

Stephen C. Bondy and his fellow study the involvement and role of cytochrome P-450 to the generation of reactive oxygen species in hepatic microsomes (Bondy & Naderi, 1994).

CYTOCHROME P-450 ENZYMES: FUNCTIONAL IMPORTANCE

Most of the drugs are lipophilic and biotransformation is required for their excretion from the body. In the absence of metabolic process (phase 1 and phase 2) drugs would be cleared more slowly and can accumulate in the body for long time and cause toxicity. The Cytochrome p-450 has a leading role in the biotransformation of drugs to polar compounds before their excretion from the body. Hepatic CYPs has unusual property of oxidizing a wide range of exogenous and endogenous substrates (Hasler et al., 1999).

Hodgson and Rose (2007) reported that Cytochrome P-450 2B6 is found in different amount in liver and other organs involved in the metabolism of environmental chemicals. It was already well known that it was inducible and has a range of xenobiotic substrates. They used the term environmental chemicals, to include industrial and indoor domestic environments as well as natural ecosystem. They may serve as inhibitors, inducers and substrates of CYP2B6 and discussed metabolism based interactions between clinical drugs and chemicals.

Cytochrome P-450 3A4, in humans it is the main drug metabolizing enzyme of phase 1 present in liver and small intestine. In small intestine the MDR1 gene products P-glycoprotein are also present than CYP3A4 and have greater substrate specificity than CYP3A4. There was a great impact of CYP3A4 on the bioavailability of orally administered dosage form. Now it was reported that drug extrusion by MDR1 can decrease drug absorption and change the effects of inhibitors and inducers on CYP3A4 mediated metabolism. So there must be role of P-glycoprotein and CYP3A4 in limiting oral absorption of peptides and peptidomimetics for example, HIV-protease inhibitor saquinavir and a newly discovered cysteine protease inhibitor Ko2 (Morpholine-Urea-Phe-Hphe-Vinyl sulfone; Axys Pharmaceuticals) establish the impact of Cytochrome P-450 on oral absorption (Wacher et al., 1998).

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