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REVIEW

New Findings in Studies of Cytochromes P450

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Abstract—Cytochromes P450 represent a numerous family of heme-containing enzymes belonging to the group of monooxygenases. In prokaryotes, cytochromes P450 usually perform a plastic function, whereas in eukaryotes their functions are very diverse. Mammalian cytochromes P450 are components of membranes and are involved in biosynthesis and metabolism of many physiologically active substances; moreover, these cytochromes are unique in their ability to catalyze biotransformation of xenobiotics, i.e. metabolize substances of foreign origin (drugs, toxins, environmental pollutants). The latter promotes elimination of xenobiotics, but sometimes intermediates of their metabolism are even more toxic and dangerous than the original xenobiotics *per se*. Some catalytic features of cytochromes P450 still need unambiguous explanation, i.e. broad substrate specificity, diversity of catalytic reactions, and unusual kinetics. Under some conditions cytochromes P450 can produce reactive oxygen species, and this is another problem attracting increasing attention. In this respect, a recent finding in mitochondria of analogs of microsomal cytochromes P450 seems especially intriguing; it was postulated that P450 can be responsible for mitochondrial dysfunction, cell apoptosis, and pathogenesis of some diseases. In this paper the present state of the art concerning these problems is considered.

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Cytochromes P450 comprise a family of autooxidizable heme proteins named after the specific absorption band at 450 nm of their reduced complex with carbon monoxide. These cytochromes were first identified and described in 1958 as pigments of the liver cell microsomal fraction concurrently by Klingenberg [1] and Garfinkel [2] and later characterized by Omura and Sato [3-5]. Members of this family are found in all organisms in the evolutionary spectrum (from bacteria to humans). In eukaryotes, cytochromes P450 (CYPs)[1] are usually incorporated in membranes. In mammals, CYPs are found in all organs and tissues except skeletal muscles and mature erythrocytes. Successful interpretation of the human genome during recent years revealed 57 genes of different CYPs. The metabolic function of about a quarter of these is unclear [7, 8].

Catalysis in monooxygenase reactions occurs with NADPH and NADH as donors of reducing elements in eukaryotes and bacteria, respectively:

$$NAD(P)H + H^+ + O_2 + RH \rightarrow NAD(P) + H_2O + ROH,$$

i.e. upon breaking of the O–O bond one oxygen atom is included in a substrate (R) and the other into a water molecule [7, 8].

Attention was first given to non-membranous bacterial CYPs due to their solubility and availability. A camphor-oxidizing cytochrome $P450_{cam}$ from *Pseudomonas putida* (or CYP101A1 according to the modern nomenclature) was taken as a model for studies of CYP structure and properties [8, 9].

Interest has been mainly focused on two groups of mammalian CYPs because of their metabolic function: CYPs from adrenal cortex mitochondria and those from liver cell endoplasmic reticulum. The first are involved in

Abbreviations: BSO) buthionine sulfoximine; CYP) cytochrome P450; ROS) reactive oxygen species.

[1] CYP (cytochrome P450) is the name adopted in the modern nomenclature for isoforms of this heme protein with addition of an alphanumeric code for each form according to a classification of cytochromes P450 [6]. The classification is based on the amino acid sequence: number–letter–number–family–subfamily–individual number of the form.

steroid hormone biosynthesis, and the liver cell CYPs are unique in their ability to catalyze biotransformation of xenobiotics, i.e. organic molecules foreign to the body (drugs, toxins, various environmental pollutants, etc. [7, 8]).

Hydroxylation of such compounds is associated with their hydrophilization, which facilitates their elimination from the body; therefore, CYPs of the liver cell endoplasmic reticulum were long considered as components of the major detoxification system of mammals. But sometimes oxidation products are more toxic and dangerous for the body than the original xenobiotics compounds. Thus, hydroxylation results in activation of potential carcinogens: polycyclic aromatic carbohydrates (including benz(a)pyrene, which is poorly oxidized chemically); heterocyclic amines, which are present in smoked meat; aromatic amines, which are components of pesticides, tobacco smoke, some drugs, etc. [8].

Different CYPs of hepatocytes are characterized by specific substrate preferences; test substrates of individual heme proteins are used for determination of their catalytic activities and as *in vivo* inducers. Nevertheless, broad catalytic activity of cytochromes P450 is surprising. In addition to hydroxylation, these cytochromes can catalyze reactions of N-, S-, and O-dealkylation, epoxidation, heteroatom oxygenation, oxidative cleavage of ester and amide bonds, peroxidation, isomerization, desaturation, etc. [7, 8]. Reactions catalyzed by CYPs do not follow Michaelis–Menten kinetics. These catalytic peculiarities of CYPs remain ambiguous and are the main object of recent studies.

Purified CYPs isolated from native membranes are hydrophobic oligomeric heme proteins incapable of producing three-dimensional crystals, and their high hydrophobicity makes difficult to study their features. Different CYPs from hepatocytes are shown by electron microscopy to have a similar hexameric structure [10-12]. Monomers can be prepared only upon substantial modification of the polypeptide chain. Thus, deletion of the hydrophobic N-terminal domain (~20 amino acids), which serves a membrane anchor, was insufficient to abolish the ability of microsomal CYP 2C5 to oligomerize. For this, it was also necessary to replace some amino acid residues in the middle region of the chain and introduce an additional polyhistidine sequence in the C-terminus [13]. Such "hydrophilized" heme protein was crystallized from aqueous solution [14]. Membranous crystallizable CYPs modified in such manner can be obtained using recombinant techniques, site-specific mutagenesis, and vector heterological expression.

The region encoding just the catalytic domain usually remains unaffected on constructing the gene of such CYPs. These forms can be crystallized, and now some analogs of different membranous human and animal cytochromes P450 (2C5, 2B4, 2C9, 2C8, 3A4, 2A6, 2D6) have been obtained as trimeric crystals [14-21].

X-Ray crystallographic analysis of such crystals has revealed similarity between the studied CYP forms and soluble $P450_{cam}$ of *P. putida* (CYP101A1), which was prepared as crystals already in 1985 [22, 23]. X-Ray crystallograms of free CYP101A1 crystals and of the heme protein in complexes with the substrate or other ligands have shown the so-called closed conformation having the entrance to the pocket near the heme closed by a helix turn [9]. But these studies gave no information about how the substrate reaches the active site and could not explain the unusual kinetics.

Interpretation of the human genome made the moderately hydrophobic cytochrome P450 3A4 (CYP3A4) from endoplasmic reticulum of human liver cells the most suitable object for studies of crystals of CYP complexes with substrate and inhibitors. Sufficient amounts of this cytochrome can be isolated in a modified form from *Escherichia coli* lysate. This CYP can metabolize no less than 50% of medicinal drugs now on the market [24, 25] and, thus, provides for a broad choice of substrates with different molecular weights for such studies. Crystals of this cytochrome P450 in a complex with a rather large substrate (erythromycin, 754 daltons) and inhibitor (the fungicidal drug ketoconazole, 531 daltons) have been prepared [24]. Based on the atypical kinetics of CYP reactions, it was supposed earlier that two and more substrate molecules could be simultaneously bound in the active site (examples are presented in [26, 27]), but this was the first direct demonstration of such a simultaneous binding of two ketoconazole molecules in the hydrophobic pocket near the CYP3A4 heme, whereas erythromycin molecules could be differently bound in the active site. Pronounced conformational changes occurred in both models compared with the free heme protein structure [22, 23], and these changes were different in the case of the two ligands. The changes were accompanied by increase in the active site volume (up to 80% additional volume). Considering these data, the variability of conformational changes in the heme pocket region partially explaining the broad substrate specificity of CYPs is discussed.

The simultaneous presence of two or more ligand molecules in the active site of CYP suggests putative homotrophic or heterotrophic (in the case of different molecules) cooperative effects. In this connection, it should be noted that the known phenomenon of an activating effect of some nonionic detergents upon reactions of P450 has the following characteristics [28, 29]: i) the detergents activate hydroxylation only if their concentrations are lower than the critical concentration of micelle formation, when the solution contains only separate molecules; ii) detergent is bound in the region of the CYP active site and, similarly to substrates, leads to certain changes in the heme protein absorption spectrum and does not prevent substrate binding within some limits; the associated concurrent enlargement of the pocket close to

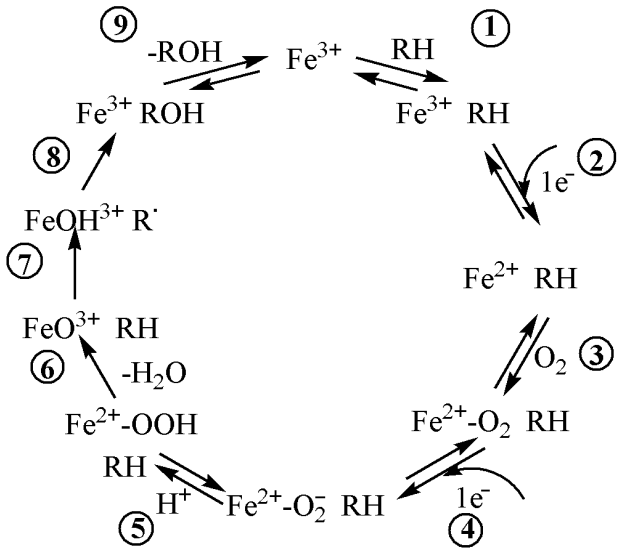
the heme seems to underlie the activating effect of a detergent.

All CYPs, and especially CYP3A4, can metabolize virtually all drugs; therefore, heterotrophic cooperativity can be clinically important as a cause of unpredictable events at the concurrent use of different drugs.

Variability of conformational changes upon ligand binding was confirmed by data on CYP2B4 from rabbit liver obtained by X-ray crystallographic analysis of modified CYP2B4, isothermal calorimetry, and spectroscopic approaches. Imidazole derivatives with different structure (CYP inhibitors) were shown to induce different conformational rearrangements in the active site region [30-33].

But it is unclear how a substrate can enter the active site region of CYP in the initially closed conformation, as occurs in the case of CYP101A1 [9]. The authors of reference [9] also postulated the presence of another site for camphor binding outside the heme pocket at a distance of 15-16 Å from the heme iron, and this suggests a subsequent movement of the molecule by this distance. A two-step mechanism of substrate binding (including the initial binding of the substrate in the peripheral site and the subsequent translocation into the active site) was supposed earlier for CYP3A4 [34].

The catalytic cycle of cytochromes P450 (Scheme) includes some intermediate states of the heme iron complex with atmospheric oxygen. The cyclic process starts by substrate entrance into the pocket near to the heme in the Fe^{3+} state and low-spin electron configuration. Changes in the sixth ligand region (the sixth coordination state in CYP is occupied by a water molecule) allow the system to preferentially acquire a high-spin configuration, although in many cases substrates induce only a partial spin shift. Then an electron is transferred from a partner providing reducing equivalents, and iron is reduced to Fe^{2+}, which can bind molecular oxygen. In mammalian endoplasmic reticulum, the role of such a partner is played NADPH-cytochrome P450 reductase (FAD- and FMN-containing flavoprotein).



Catalytic cycle of cytochrome P450 [8]. R – substrate. Electrons for the cycle are provided by NADPH-cytochrome P450 reductase

The catalytic cycle of cytochrome P450 in mitochondria differs from the cycle in the endoplasmic reticulum only by the electron-donating partner. Instead of NADPH-cytochrome P450 reductase, the cycle is supplied by an NADPH-dependent system consisting of two mitochondrial matrix proteins: [2Fe–2S]-protein adrenodoxin and adrenodoxin reductase (FAD-flavoprotein). The system is similar to the bacterial system, which includes the adrenodoxin analog ferredoxin, but, unlike the mammalian systems, the bacterial system obtains reducing equivalents from NADH [35].

The structure of intermediate complexes (Scheme) suggests that uncoupling of oxygenation reactions in the catalytic cycle in both endoplasmic reticulum and mitochondria can give rise to products of one- and two-electron reduction of molecular oxygen, i.e. superoxide anion and hydrogen peroxide. However, monooxygenases located in the inner mitochondrial membrane are close to the respiratory chain components, the initial and middle regions of which also can produce superoxide anion and, under the influence of reactive oxygen species (ROS), the ATP/ADP antiporter protein forms a nonspecific channel permeable for any low molecular weight substance. This leads to osmotic disbalance between the intermembrane mitochondrial space and matrix [36].

Mitochondrial cytochromes P450 include adrenal cortex cytochromes 11A ($P450_{scc}$ by the previous nomenclature), 11B1, and 11B2 involved in biosynthesis of steroid hormones and also some CYP forms in liver and kidney tissues that catalyze biosynthesis of bile acids from cholesterol and activation of provitamin D_3 [35]. The specific content of cytochromes P450 in steroid-producing tissues is markedly higher than in the liver, and they have been repeatedly shown to produce ROS. In particular, CYP11A catalyzing synthesis of pregnenolone from cholesterol was shown to take an electron from a redox partner with production of O_2^-. Cholesterol as a substrate sharply decreases this possibility [37, 38]. Adrenals are known to have a high concentration of ascorbic acid, which as an antioxidant can play a protective role in the case of ROS superproduction by monooxygenase systems.

Findings of microsomal type cytochromes P450 capable of metabolizing some drugs in mitochondria in cells of the liver, lung, brain, and other tissues have been reported from the 1980s. At first, some of these data were explained as being a small admixture of microsomes in the mitochondrial fraction. But further studies of drug biotransformation in mitochondria have shown that they

contain microsomal type cytochromes P450. The data now indicate that mitochondria isolated from liver and lung tissues contain cytochromes P450 1A, 2A, 2B, 2C, 2E, and 3A, which correspond immunologically to cytochromes of the endoplasmic reticulum, and their expression is increased in response to the *in vivo* injection of the same inducers of biosynthesis [35, 39, 40]. The most important recent works were performed on a highly purified mitochondrial fraction free of microsomes [41, 42]. On investigating by immunoblotting the mitochondrial fraction components, the authors assessed the fraction purity using marker proteins inherent in only one type of these membranes. Some membranous CYPs have been isolated and characterized. Two variants have been shown: i) a ~40-kD CYP shortened as a result of the loss of a large (~100 amino acid residues) N-terminal fragment of microsomal forms which included a signaling-anchoring sequence of heme proteins [42-45]; ii) a ~52-kD CYP with a complete polypeptide chain but with the N-terminal region modified by phosphorylation of a serine residue [41, 46, 47]. Note that unlike microsomal CYPs, both these forms can use the adrenodoxin–adrenodoxin reductase system as a redox partner.

Like all CYPs, mitochondrial CYPs are encoded by nuclear DNA, and therefore these heme proteins have to move from the cytoplasm into the inner mitochondrial membrane. In the case of well-studied CYPs of mitochondria from steroid-producing tissues, the precursor protein is transferred into the mitochondrial matrix from the cytoplasm across both membranes. Under the influence of a specific protease, the protein loses the "excess" fragment and is incorporated into the inner membrane with the catalytic domain facing the matrix [35].

It is still unclear how microsomal cytochromes P450 are distributed in membranes of two different types. To explain the import into mitochondria of a newly synthesized protein, two molecular mechanisms have been proposed: first, proteolysis of the heme protein part in the cytoplasm associated with removal of the of N-terminal domain and converting the adjacent latent sequence to the addressing-anchoring one [35, 43-45]; second, phosphorylation of the newly synthesized protein in the cytoplasm under the influence of cAMP-dependent protein kinase A resulting in modification of the addressing-anchoring N-terminal region of the polypeptide chain of microsomal CYPs and thus forming another address sequence [35, 46, 47].

Both 40- and 52-kD forms are catalytically active and can generate ROS, and their specific contents in mitochondria can be considerably increased upon the *in vivo* injection of inducers of the corresponding microsomal forms of P450 into animals [35, 39-42].

These statements are the best illustrated by results of studies on cytochrome P450 2E1 (CYP2E1). CYP2E1 can metabolize small molecules of both endogenous and exogenous origin: ethanol, acetone, carbon tetrachloride, nitrosamines, halothane, etc. Expression of mRNA and CYP2E1 protein in liver cells increases under some physiological and pathological conditions: starvation, diabetes, lipid-rich diet, obesity, and alcohol intoxication [41].

The CYP2E1 content in liver mitochondria of laboratory animals is ~30% of its content in microsomes, and this fraction increases under some conditions, e.g. up to 40% on injecting rats with pyrazole [46]. Repeated injections of streptozotocin (a model of diabetes) increased contents of microsomal and mitochondrial CYP2E1 2-3- and 5-6-fold, respectively [48]. Long-term repeated injection of alcohol, which is a known inducer of microsomal CYP2E1 depending on the dose and duration of injections, increased by 1.5-3-fold the expression of mitochondrial CYP in mice and rats [41, 42] and 2-fold in hepatocyte culture [41]. CYP2E1 generates considerable amount of ROS and, therefore, is suggested to play an important role in pathogenesis of both alcohol-related and non-alcohol-related liver diseases.

An increase in the CYP2E1 content in mitochondria is associated with a considerable decrease in the level of the major mitochondrial antioxidant glutathione [41, 42]. In mitochondria, CYP2E1 exists as a 52-kD phosphorylated form and also as a 40-kD form. Cell populations capable of hyperproducing mitochondrial 40-kD CYP were obtained in HepG2 culture by genetic approaches [42]. These cells displayed much lower viability than the control cells when the glutathione content was decreased by addition of a glutamate-cysteine ligase inhibitor, buthionine sulfoximine (BSO). Using fluorescent spectroscopy with an oxidant-sensitive dichloro-derivative of fluorescein acetate, these cells were shown to have an increased level of intracellular ROS. This was also indicated by a decreased activity of mitochondrial aconitase, which is a marker for the presence of superoxide anion, H_2O_2, and other oxidants, which inactivate the enzyme by destroying its [4Fe–4S]-cluster. A decrease in membrane potential (observed by intensity of the rhodamine 123 fluorescence) was also recorded in mitochondria. Antioxidants and cyclosporin A enhanced cell viability by decreasing the effect of BSO. Thus, accumulation of CYP2E1 in mitochondria of liver cells was shown to induce cell death as a result of an increased production of ROS and dysfunction of mitochondria, and, consequently, to play an important role in development of liver diseases associated with induction of CYP2E1.

CYPs have been also found in mitochondria of other tissues, including brain, and some findings suggest that ROS can contribute to dysfunction of mitochondria and development of some neurodegenerative diseases [49]. Thus, CYPs are involved in pathogenesis of such diseases as Parkinson's disease.

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