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Plasma Exosomes and Drug Metabolic Cytochrome P450 Enzymes

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Abstract

The major drug metabolic enzymes, Cytochromes P450 (CYP), are abundantly present in hepatocytes, and to some extent in other extrahepatic cells such as monocytes. Since these enzymes metabolize the majority of xenobiotics leading to formation of Reactive Oxygen Species (ROS) and some toxic metabolites, hepatocytes and monocytes could produce extracellular vesicles such as exosomes. The exosomes produced by the liver and blood cells eventually secrete into the plasma, which may contain high levels of exosomes containing CYP enzymes. The level of plasma exosomal CYP enzymes may also be induced under certain conditions. Therefore, plasma exosomal CYP may be used as biological markers, as well as biocatalysts for various purposes in medicine, bioremediation, and industrial synthesis. This editorial briefly describes this novel and exciting area of research in the field of exosomes, and their potential as biomarkers and in therapy.

Description

Drug metabolic cytochrome P450 enzymes in the liver and extrahepatic cells

Cytochrome P450 (CYP) enzymes play a major role in the metabolic clearance of the majority of xenobiotics, including approximately 80% of the marketed drugs and drugs of abuse such as alcohol, tobacco, and methamphetamine [1,2]. Among them, CYP3A4 is the major therapeutic drug metabolic enzymes while CYP2E1, CYP2A6, and CYP1A1/1B1 are the major alcohol, nicotine, and Polyaromatic Hydrocarbons (PAH) metabolic enzymes, respectively. In addition, CYP3A4 is involved in the metabolism of several drugs of abuse such as methamphetamine and cocaine. These enzymes are highly abundant in the liver and function as the first pass metabolic enzymes to detoxify these drugs. In general 45-70% of drugs are metabolized in the liver through the first pass metabolism prior to entering the blood plasma [3]. Although metabolism of therapeutic drugs decreases their bioavailability, in turn leading to a decrease in their efficacy metabolism of these drugs also aids in decreasing toxicity [1,2]. The first pass metabolism of the drugs of abuse is critical for decreasing their concentrations in the plasma, which ultimately decreases the concentrations of these drugs in the brain. Thus, the liver safeguards xenobiotics from entering the blood and eventually entire body. However, CYP-mediated metabolism also produces Reactive Oxygen Species (ROS) and reactive metabolites, leading to increased oxidative stress and cellular toxicity. Therefore, high dose and/or increased frequency of the use of drugs as well as drugs of abuse cause the liver damage and liver-associated diseases [4,5]. Therefore, constant cellular toxicity of the liver cells is expected to produce extracellular vesicles, which may be released in the blood plasma. Extracellular vesicles are usually produced as a result of accumulation of toxic compounds in the cells so that they are secreted from the cells and eliminated from the system.

In recent years our group has shown that CYP enzymes (CYP3A4, CYP1A1, CYP1B1, CYP2A6, and CYP2E1) are also significantly present in blood monocytes and monocytes-derived macrophages, and to a lesser extent in lymphocytes [5-9]. Furthermore, we have shown that while monocytic CYP2E1 play important role in the metabolism of alcohol, monocytic CYP2A6 is important in metabolizing nicotine [5,6]. Furthermore, we have shown that alcohol and nicotine metabolism, mediated through the CYP enzymes, leads to increased production of ROS, which ultimately causes oxidative stress and cellular toxicity. Since 45-70% of the non-metabolized drugs enter into the plasma [3], monocytic and lymphocytic CYP enzymes may further help metabolize these drugs to avoid drug-mediated toxicity. A relatively high level of CYP3A4 and other drug-metabolizing CYP enzymes in the monocytes [5,6,8] also suggests an increased metabolism of therapeutic drugs as well as drugs of abuse such as methamphetamine and cocaine in monocytes. However, increased metabolism of therapeutic drugs and drugs of abuse in monocytes would further decrease their bioavailability to the target cells and increase ROS and drug metabolite-mediated cellular toxicity. For example, the targets of antiretroviral drugs are lymphocytes and monocytes, and the presence of CYP enzymes in these cells is expected to decrease the bioavailability of antiretroviral drugs. Since the metabolism of drugs in monocytes and lymphocytes causes oxidative stress and cellular toxicity, and thus these cells are also expected to produce extracellular vesicles that may be released into the blood plasma.

Plasma exosomes

Exosomes are small cell-derived extracellular vesicles (30-100 nm), which are secreted from a variety of cells into biological fluids including blood and cell culture media [10-12]. In recent years, exosomes are gaining importance for clinical applications such as prognosis, therapy, and use as biomarkers for a variety of health and disease conditions [13,14]. Exosomes that are present in the plasma can be derived from many healthy cells such as liver, spleen, and blood as well as cancer cells [12] (Figure 1). Importantly, by virtue of their roles in metabolizing and transporting/distributing xenobiotics, respectively, liver and blood cells appear to play important roles in secreting exosomes in the plasma [15]. Although there are many cell types in the liver, hepatocytes constitute the major cell in the liver and

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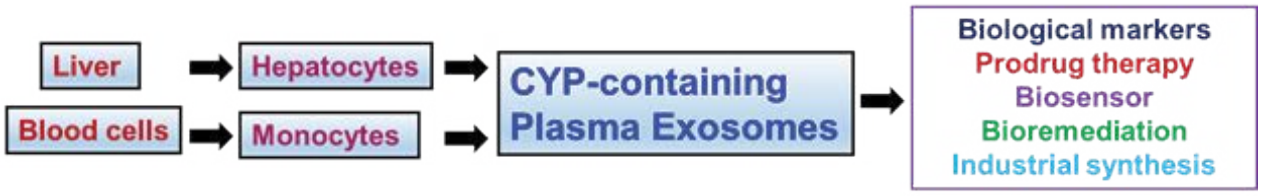

Figure 1: Potential applications of plasma exosomes containing CYP enzymes. The major liver cells (hepatocytes) and important blood cells (monocytes) are likely to produce exosomes under stress conditions that contain specific CYP enzymes. These CYP-containing exosomes may be secreted in the plasma, which can be utilized as specific biomarkers and in therapy.

are responsible for metabolizing the majority of xenobiotics via the CYP systems. Thus, hepatocytes may produce exosomes as a result of xenobiotic metabolism induced toxicity and secret into the blood [15]. Similarly, among many blood cells, monocytes may produce exosomes as a result of xenobiotic metabolism induced toxicity and secret into the plasma (Figure 1). Thus, plasma exosomes produced by hepatocytes and monocytes are likely to be a by-product of CYP-mediated drug metabolism and its associated oxidative stress and toxicity. Therefore, it is possible that plasma exosomes contain high levels of CYP enzymes, which may eventually be degraded. It is also possible that plasma exosomal CYP enzymes have important functions, which are yet to be discovered. For example, plasma exosomal CYP enzymes may play a role in drug metabolism, which is generally not accounted for in drug design and development. It is also possible that plasma exosomal CYP enzymes are modulated under specific conditions, such as in different disease states, combination therapy, and use of illicit substances. If this is so, then plasma exosomal specific CYP enzyme may act as a biological marker for these specific conditions. There is absolutely nothing known about the occurrence and role of drug metabolic enzymes in plasma exosomes.

Plasma exosomal cytochrome P450 enzymes

In our laboratory, for the first time, we have shown the presence of several CYP enzymes in plasma exosomes (unpublished observations). Although it is difficul to compare, but the relative levels of these enzymes appear to be even higher than other known exosomal protein markers such as CD63. These observations are very important because these CYP enzymes could play a unique and critical role in the metabolism of drugs and drugs of abuse in plasma exosomes. Since these enzymes are known to be induced by their respective substrates in both hepatocytes and monocytes, it is likely that their plasma exosomal levels are also increased in the influence of their substrates. In our other observation, we have shown altered levels of specific CYP enzymes when plasma exosomes were isolated from HIV-infected subjects, alcohol users, and smokers compared with uninfected nonsmokers (unpublished observations). We are now in the process of characterizing the plasma exosomal CYP enzymes and their possible role under physiological conditions. Studies are also underway to examine the underlying mechanism of secretion of CYP enzymes in plasma exosomes. Finally, we plan to utilize the specific CYP enzymes as biological markers, as well as, their role in various applications as described below.

Plasma exosomal cytochrome P450 enzymes: novel biomarkers, novel therapy, and other applications

Since they are known to contain many molecules, including proteins, siRNA, and miRNA, exosomes are being considered for utilization in novel therapies for various diseases including cancer [16]. Similarly, specific exosomes and/or exosomal proteins have potential to be used as biological markers under many conditions including cancer [17,18]. Plasma exosomes enriched with CYP enzymes have potential to be used as biological markers under specific conditions such as liver disease, lung cancers, HIV infection, alcohol use, smoking, and use of other illicit drugs (Figure 1). It is widely known that certain CYP enzymes are highly induced under specific conditions. For example, CYP2E1 is induced in chronic alcohol users [5] and CYP1A1, CYP1B1 are induced in smokers [6], and CYP3A4 is induced by several therapeutic drugs such as phenobarbitals, rifampin, ritonavir, and St. John's Wort [1-2,19]. Finding novel CYP biomarkers from plasma exosomes would further contribute to fast and cost-effective diagnosis for different health and disease conditions

Plasma exosomes containing CYP enzymes can be used as biocatalysts for various purposes in medicine, bioremediation, and industrial synthesis [1,2] (Figure 1). In medicine, these exosomes can be used to prepare CYP biosensors to monitor the plasma levels of drugs. Monitoring drug level in the plasma is critical because plasma drug concentration varies in combination therapy, patients with liver disease, as well as, in specific populations who have CYP single nucleotide polymorphism [1,2,19]. Thus, the use of exosomal CYP biosensors may help avoid drug-drug interactions and adverse drug reactions. Plasma exosomes containing CYP enzymes can also be used as a drug delivery carrier to activate particular prodrugs at the site of action, e.g. activation of cyclophosphamide by CYP2B6 in the case of cancer treatment [1,2]. CYP2B6 is known to activate cyclophosphamide prodrug in the liver; however, it also leads to decreased efficac to the cancer cells. In addition, CYP2B6-mediated metabolism of cyclophosphamide produces a neurotoxic metabolite. Thus, cyclophosphamide metabolites distribution to the healthy cells concurrent with neurotoxic metabolites together causes adverse drug reactions in cancer patients. In bioremediation, CYP-containing plasma exosomes can be immobilized on a matrix/column to detoxify industrial contaminants such as polyaromatic hydrocarbons, petroleum products, herbicides, and pesticides. This would help expedite the conventional bioremediation process, which utilizes immobilized enzyme or cells to a column/matrix for bioremediation. Immobilization of enzymes, cells, or exosomes on a matrix helps increase the stability and activity of those biocatalysts and decreases the burden of down-stream processing in separating the detoxified chemicals from the original toxic chemicals. With regard to industrial synthesis of pharmaceuticals, agrochemicals, and other fine chemicals, these exosomes can be used to synthesize specific drug metabolites that are otherwise impossible to achieve by chemical synthesis. CYP enzymes are known to metabolize substrates with strict regio- and stereo-selectivity, which is difficul to achieve using chemical methods. Several CYP enzymes have already been utilized to achieve synthesis of novel drugs and drug metabolites. In the past few years, several CYP enzymes have been engineered to synthesize specific drugs and drug

metabolites for pharmaceutical purposes. For details on the application of CYP enzymes as biocatalysts, you may refer to the recent review in Expert Opinion in Drug Metabolism and Toxicology [1] and a book chapter in Industrial Bio catalysis [2].

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