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Xenobiotic metabolizing enzymes as biomarkers for levels of environmental pollution

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Living organisms have several mechanisms of detoxification of xenobiotics for their selfprotection. The general pathways of biotransformation follow the conversion of lipophillc xenobiotics into more hydrophilic metabolites. The pathway of xenobiotic biotransformaation can be divided into phase I and phase II pathways. The reactions of phase I metabolism include oxidation, reduction and hydrolysis of xenobiotics. In the most of organisms, cytochrome P450 (P450) is the major phase I enzyme. Following the initial oxidative metabolism by phase I enzymes, the xenobiotics are subject to conjugating reactions catalyzed by phase II enzymes. Glutathione Stransferase (GST), UDP-glucuronosyl transferase (UDPGT) and sulfotransferase are the important enzymes catalyzing the phase II metabolism of xenobiotics.

The reactions of xenobiotic metabolism are influenced by numerous endogenous and exogenous factors, which include age, gender, stress, genetic polymorphism, diets, hormone, and exposure to the inducers and inhibitors of xenobiotic metabolizing enzymes. Especially, a number of environmental pollutants are known as inducers of phase I and II enzymes. Therefore, I thought that this induction phenomenon of phase I and II enzymes in organisms by xenobiotics may be useful as a biomarker for monitoring the levels of environmental pollution.

The biomarkers can be defined at biochemical levels as ; a toxicant-induced change in gene expression leading to alteration in protein content and enzyme activity that is linked to the amount of environmental contaminants. To use the phase I and II enzymes as biomarkers, it is needed to understand the alteration of activities of xenobiotic metabolism in animals, at the levels of individual enzyme species. Some endogenous and exogenous factors are known to alter the activities of xenobiotic metabolizing enzyme activites.

In the first section of this study, I concern the alteration of xenobiotic metabolizing enzyme activities due in animals to the stressful situations. Following the liver injury, e.g., surgical partial hepatectomy, hepatitis, hepatic infections and carcinoma, the liver is capable of total regeneration. In the first chapter, I demonstrated that the alterations of the levels of 7 hepatic P450 during liver regeneration after liver injury were isozymes selective. The objectives of second chapter were to determine the effects of xenobiotics on activities of phase I and II enzymes. The pesticides affected the activitieis of many xenobiotic-metabolizing enzymes in rat liver. Furthermore, it was suggested that the induction mechanisms of phase I enzymes by the pesticide may be different from those of phase II enzymes. From the studies of the first section,

it became apparent that the activities of xenobiotic metabolizing enzymes can be affected in the stressful situation such as the hepatic injury and the exposure to the environmental pollutants. Furthermore, it was found that the patterns of alteration of the enzyme activities due to these stresses are isozyme specific. Therefore, I judged that the alteration of these enzyme activities can be used as a marker of environmental stress imposed on the animals inhabiting in that environment, and when we use them as biomarkers, we must measure activities of several isozymes to grasp the whole picture of the environmental stress on the animals of interest.

In the second section, I examined in the field study the suitability of xenoiotic metabolizing enzymes as the biokarkers for the risk assessment for environmental pollutants, in particular planar compounds including polycyclic aromatic hydrocarbons (PAHs), polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs). The present study used a freshwater crab (Eriocheir Japonicus), which commonly inhabits rivers and estuaties in Japan and is at the top of food chain in the aquatic environment. The degree of accumulation of environmental pollutants in the hepatopancreas of crabs obtained from several sites was determined. Identification of a number of PCDD and PCDF congeners in crabs provided evidence that one of the major sources of PCDDs and PCDFs was the waste incineration. The present study demonstrated that the crab may be useful "absorbefacient" of lipophillic environmental pollutants. To monitor and asssess the toxicological risks of environmental pollution, I used the toxic equivalency (TEQ) approach and discussed the suitability of P450 and GST activities as biomarkers. TEQ is a sum of the concentration of dioxin-like chemicals, corrected for their biological potency and has beed proposed to be a useful tool for the risk management of halogenated aromatic hydrocarbons. The crabs with the highest TEQ levels showed the highest P450 and GST dependent activities in hepatopancreas. Furthermore, to examine the response of xenobiotic metabolozing enzyme system in this species to inducing agents, I also investigated the alterations of P450 contents and the related activities in hepatopancreas microsomes after injecting PAHs to the crab. P450 contents were significantly higher in hepatopancreas from 3MC treated crabs.

The present results lead me to suggest that P450 and GST dependent enzyme activities are likely to be useful biomakers for the contamination of environment by planar aromatic hydrocarbons such as PAHs, PCDDs, PCDFs and coplanar PCBs. Although a more detailed analysis for each enzyme activity and TEQ level may be required before I can come to this conclusion, the fact that animal with the highest TEQ levels showed the highest enzyme activity is highly supportive of the possibility.

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