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Title of research project	Toxicological characterization of chemical-induced liver hypertrophy: studies based on the analyses of nuclear receptor activation and enzyme induction
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【Abstract】

Liver hypertrophy and hepatocyte hypertrophy are often observed upon exposure to chemical compounds. But mechanism and toxicological relevance of such effects are yet unknown, and whether they are adverse effects or not remain a matter of debate. The aim of this study was to identify the toxicological characteristics of liver hypertrophy and hepatocyte hypertrophy. Especially, we sought to clarify the association between liver/hepatocyte hypertrophy and the induction of drug-metabolizing enzymes to investigate whether development of liver/hepatocyte hypertrophy is an adaptive response to the xenobiotic-induced expression of drug metabolizing enzymes. To this end, we mainly took two approaches: 1) in silico data analysis of in vivo toxicity tests results and 2) in vitro evaluation of the effects of xenobiotics on the nuclear receptors associated with enzyme induction.

The association between hepatocyte/liver hypertrophy and other toxicological findings was analyzed using the results of rat 28/90-day repeated dose toxicity tests obtained from HESS database as well as the results of rat 90-day and 2-year repeated dose toxicity tests collected from pesticide evaluation reports available from the website of Food Safety Commission of Japan. The statistically significant association was found between the thyroid hypertrophy, which is an indicator of the enzyme induction in the liver, and centrilobular but not diffuse hepatocyte hypertrophy. This suggests that centrilobular but not diffuse hepatocyte hypertrophy is associated with the induction of hepatic drug metabolizing enzymes. Moreover, there is a significant differences between toxicological findings associated with centrilobular hepatocyte hypertrophy and those with diffuse hepatocyte hypertrophy. These suggest that the mechanisms of centrilobular and of diffuse hepatocyte hypertrophy are different. In addition, it is suggested that hepatocyte/liver hypertrophy is not an early event of liver tumors.

Second, we performed reporter assays of rat nuclear receptors (AHR, CAR, PXR, PPARα) that are involved in enzyme induction, in order to determine the potential of the chemicals to induce centrilobular hepatocyte hypertrophy using HESS database and the pesticides database that provides rat toxicity data. The compounds that caused centrilobular hepatocyte hypertrophy in rats in vivo showed a tendency to activate these nuclear receptors more than hepatocyte hypertrophy-negative compounds or compounds that caused diffuse hepatocyte hypertrophy in rats in vivo. These data are in agreement with the results obtained by data analysis mentioned above and support the interpretation that centrilobular but not diffuse hepatocyte hypertrophy is associated with the induction of hepatic drug metabolizing enzymes and that the mechanisms of centrilobular and diffuse hepatocyte hypertrophy are not identical.

Finally, using perfluorooctanoic acid (PFOA) which is an environmental and food contaminant that causes liver/hepatocyte hypertrophy in rodents, we investigated a role of CAR in the PFOA-induced liver hypertrophy. Our results with in vivo and in vitro experiments suggest that PFOA is an indirect activator of CAR and that CAR, as well as PPARα, is an important transcription factor in the PFOA-induced liver hypertrophy.

In conclusion, the present results suggest that hepatocyte/liver hypertrophy is not an early event of liver tumors, that centrilobular hepatocyte hypertrophy is closely associated with the induction of hepatic drug-metabolizing enzymes, and that centrilobular and diffuse hepatocyte hypertrophy have different toxicological characteristics. In addition, we identified several compounds that induce liver/hepatocyte hypertrophy in rats in vivo but do not show enzyme induction, and constructed a database of the results of rat repeated dose toxicity tests. These will be useful in future studies to investigate the mechanism of hepatocyte hypertrophy that are not associated with enzyme induction and the detailed toxicological evaluation of liver/hepatocyte hypertrophy.