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**ROLE OF METABOLISM BY FLAVIN-CONTAINING  
MONOOXYGENASE IN THIOACETAMIDE-INDUCED  
IMMUNOSUPPRESSION**Woo S. Koh<sup>1</sup>, Jeong W. Lee<sup>1</sup>, Tae C. Jeong<sup>2</sup><sup>1</sup>Korea Institute of Toxicology, Daejeon<sup>2</sup>College of Pharmacy, Yeungnam University, Kyungsan

Thioacetamide has been known to cause immune suppression. The object of the present study is to investigate the role of metabolic activation by flavin-containing monooxygenases (FMO) in thioacetamide-induced immune response. To determine whether the metabolites of thioacetamide produced by FMO causes the immunosuppression, methimazole (MMI), an FMO inhibitor, was used to block the FMO pathway. Antibody-forming cell (AFC) response measured in BALB/c mice sensitized with sheep red blood cells (SRBCs) was compared between the groups treated with thioacetamide in the presence or absence of MMI pretreatment. The pretreatment abolished the decrease in AFC number observed in the mice treated with thioacetamide alone. In addition, when spleen cells isolated from untreated mice were exposed to thioacetamide with a drug-metabolizing system, liver microsome and NADPH, for 4 hrs in vitro prior to the stimulation with mitogens, such as lipopolysaccharide (LPS) or concanavalin A (Con A), spleen cell proliferation was also decreased. The inhibitory effect of thioacetamide on cell growth was not detectable without the liver microsome. Moreover, the thioacetamide-suppressed proliferation of spleen cells in the presence of the metabolic activation system was prevented when coincubated with either SKF-525A, a cytochrome P450 (P450) inhibitor, or MMI. We also found that the level of interleukin-2 (IL-2) in the culture supernatant was decreased by thioacetamide treatment and that the decrease of IL-2 level can be prevented by either SKF-525A or MMI coincubation. Since IL-2 is one of the responsible factors that determine the proliferation level of lymphocytes, the change of IL-2 production was consistent with that of lymphoproliferation. In conclusion, thioacetamide-induced immunosuppression was, at least in part, due to the metabolites produced by FMO as well as by P450.

keyword : thioacetamide; cytochrome P450 (P450); flavin-containing monooxygenases (FMO); immunosuppression; metabolic activation