HEPATOTOXICITY OF T-2 TOXIN, TRICHOTHECENE MYCOTOXIN

SHINOZUKA, J.1), MIWA, S.1), FUJIMURA, H.1), TORIUMI, W.1) and DOI, K.2)

1; TANABE SEIYAKU Co., Ltd., 2-50, Kawaguchi 2-chome, Toda, Saitama, Japan
2; The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, Japan

T-2 toxin is a trichothecene mycotoxin produced by various species of *Fusarium* spp. T-2 toxin has been found to contaminate food, animal food and agricultural products, and has been reported in many parts of the world. Oral, parenteral and cutaneous exposures of trichothecene mycotoxin produce damages in hematopoietic, lymphoid, cutaneous and gastrointestinal tissues and functional suppression of reproductive system in many animal species. Although it is well known that T-2 toxin also induces hepatotoxicity, there are only a small number of reports of T-2 toxin-induced hepatotoxicity examined from the multiple viewpoints. This study was carried out to clarify the characteristics and the mechanisms of T-2 toxin-induced hepatotoxicity in mice by blood biochemical and histopathological examinations and DNA microarray analysis.

Five-week-old female ICR:CD-1 mice were inoculated orally with 10 mg/kg b.w. of T-2 toxin. Hematological and blood biochemical examinations and histopathological examination of the liver were done up to 48 hours after treatment (HAT). In addition, the gene expression profile of the liver was examined at 0.5, 3 and 24 HAT by microarray analysis (Gene Chip, Mouse expression Set 430A 2.0).

In the T-2 toxin-treated group, the levels of AST and ALT increased while those of total cholesterol, total protein, fibrinogen and blood glucose decreased at and after 3 HAT. The coagulation test revealed the prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT). Histopathologically, dead hepatocytes were sporadically observed at and after 3 HAT, and the death of hepatocytes at the early stage was characterized by cellular swelling and that at the late stage by pyknosis with condensed eosinophilic cytoplasm, respectively. Microarray analysis on the liver showed the up-regulated expression of oxidative stress-, cell cycle- and apoptosis-related genes and the down-regulated expression of lipid metabolism-, glycogen metabolism- and drug metabolism- related genes. Especially, *c-fos* and *c-jun* mRNAs expression was significantly elevated immediately after T-2 toxin-treatment and kept high level until 24 HAT.

The present study clarified that T-2 toxin affected blood coagulation system and that morphological characteristics of hepatocyte death shifted from cellular swelling, i.e. necrosis, to pyknosis with condensed eosinophilic cytoplasm, i.e. apoptosis. From the results of microarray analysis, T-2 toxin was considered to damage hepatocytes mainly through oxidative stress and apoptosis.