Participation of Intracellular Anti-oxidant in Cell Death Induced by Arsenic and Cadmium

Masanobu UCHIYAMA[1], Shiro JIMI[2], Aya TAKAKI[3],
Junji SUZUMIYA[4], Keita YAMAUCHI[1], Shuuji HARA[1],
Nobufumi ONO[1] and Kazuo TAMURA[4]

[1] *Medicinal Informatics and Research Units, Faculty of Pharmaceutical Sciences, Fukuoka University*
[2] *Central Laboratory for Pathology and Morphology, School of Medicine, Fukuoka University*
[3] *Department of Pathology, School of Medicine, Fukuoka University*
[4] *First Department of Internal Medicine, School of Medicine, Fukuoka University*

Abstract：Arsenic (As) and cadmium (Cd) are toxic metals found in humans. Recently, As trioxide has been used as a mitochondria-targeting drug in relapsed or drug-resistant acute promyelocytic leukemia (APL). In the present study, we examined the intracellular action of these metals using rat kidney tubular cells. The cells were cultured with DMEM + 5 % FBS, containing As_2O_3 (1-2.5 μM) or $CdCl_2$ (1-10 μM). Tolerant cells, called As2.5-R and Cd10-R, were thus obtained only for the cells which survived a toxic concentration of each metal. Both of these tolerant cells grew at a similar rate as that of control cells. As and Cd induced cell toxicity was accompanied by both fragmented DNA and a decreased mitochondria membrane potential. Intracellular metallothionein was strongly expressed after the addition of Cd, but not after the addition of As. Intracellular lipid peroxidation product was found to be accumulated in both of the cultures. Intracellular glutathione (GSH) increased in line with increases in the As and Cd concentrations. In As2.5-R and Cd10-R, GSH increased more than twice the level seen in the normal cells for both metals. When the metal tolerant cultures were exposed to different metals, the protective property of metal toxicity was still maintained. However, when DL-buthionine-(*S*, *R*)-sulfoximine (BSO) was added to the cultures that were tolerant for each metal, apoptosis was restored. We therefore conclude that As and Cd induced apoptosis is mediated by GSH-reactive intracellular oxidization.

Key words：**Arsenic, Cadmium, Apoptosis, Glutathione, Oxidation**