BioMetals **17:** 569–570, 2004.

Extended Abstract

The application of metallothionein (MT) gene expression in peripheral blood lymphocytes (PBLs) as a biomarker of cadmium exposure

Jian Lu[1,2], Taiyi Jin[1,2], Gunnar F. Nordberg[2] & Monica Nordberg[3]
[1]*Department of Occupational Health, Fudan University, Shanghai, 200032, China;* [2]*Environmental Medicine; Department of Public Health and Clinical Medicine, Umeå University, S-90187 Umeå, Sweden;* [3]*Institute of Environmental Medicine, Karolinska Institutet, S-171 77, Stockholm, Sweden*

Advances in –omics technologies, including genomics, proteomics and metabolomics have increased understanding of individual adaptive and toxicological responses after toxicant exposure. These technologies can analyze the expression of all genes transcribed in a specific cell or tissue and provide information on genetic variability and its impact on susceptibility. Information on posttranscriptional and posttranslational events are simultaneously provided by proteomics technologies. These -omics technologies can be applied to the practice of risk assessment of toxicant exposure including cadmium.

Metallothioneins (MTs) are a family of Cd- binding proteins with low molecular weight, high cysteine content and high affinity to divalent metal e.g. zinc and cadmium. Presently four major forms, MT I-IV have been identified and also a number of isoforms of MT-I. MT-I and MT-II genes are expressed in many tissues, but mostly found in liver, kidney, while MT-III is found in brain and MT-IV is expressed in keratinocytes. Among the various physiological functions of MT, the role of MT in the detoxification of toxic metals is most well established (Nordberg *et al.* 1992, Nordberg & Nordberg 2000, 2002). Since MT plays an important role in the metabolism of toxic metals especially cadmium, the possibility of using MT expression levels in tissues as a biomarker of metal exposure has been suggested. For example, MT protein in urine was found to increase in cadmium-exposed populations, suggesting MT protein in urine as an indicator of both cadmium exposure and cadmium-caused kidney dysfunction (Nordberg 1992).

In order to study the validity of metallothionein (MT) gene expression in peripheral blood lymphocytes (PBLs) as a biomarker of cadmium exposure and related susceptibility to renal dysfunction, MT mRNA levels were measured using RT-PCR in PBLs of Cd-workers (Ganguly *et al.* 1996, Lu *et al.* 2001) and from residents living in a cadmium-contaminated area (recent study, to be reported in detail elsewhere). MT mRNA level was found to increase with the increase of blood cadmium (BCd) and urinary cadmium (UCd) levels. Basal MT mRNA levels were significantly correlated with the logarithm of BCd levels and logarithm of UCd levels. A dose-effect relationship between internal dose of cadmium and MT mRNA level confirmed the validity of MT expression in PBLs as a biomarker of cadmium exposure. Both the study in Cd workers and the study in environmentally Cd exposed persons have tried to measure the *in vitro* induced MT mRNA level in PBLs as an indicator reflecting the ability of the body to synthesis MT upon cadmium exposure. Similar to the findings in the previous study (Lu et al. 2001) in occupationally exposed persons, the data from the environmentally exposed population in the present study also revealed an negative correlation between urinary N-acetyl β-D-glucosaminidase (UNAG), a renal effect indicator and the *in vitro* induced MT mRNA level in the subjects with high UCd level (over 10 μg/g creatinine). The lower proportion of individuals expected to have exceeded their individual critical concentration in the renal cortex at UCd levels below 10 μg/g creatinine explains why we did not observe a statistically significant correlation between *in vitro* induced MT mRNA level and UNAG in 2–10 μg/g creatinine UCd groups. UNAG is considered to be a sensitive renal effect indicator of cadmium exposure. As Jin *et al.*

(1999) have shown, UNAG increased already in 2–5 μg/g creatinine UCd group compared to the control (<2 μg/g creatinine). There is an increase in this range also in the present study. The previously advanced idea that the *in vitro* induced MT mRNA level could serve as a marker of susceptibility to cadmium was supported by the data presented both in the study on environmentally exposed persons (present study to be reported) and in Cd-workers (Lu *et al.* 2001). Rapidly improving technology for quantitative assessment of the various isoforms of MT mRNA will allow future studies of defined groups with different MT gene expression level and more convincing evidence will be provided concerning that MT gene expression levels really influence the response of the subject to cadmium exposure. Low expression of MTmRNA in individuals exposed to Cd would give rise to an increased risk of developing adverse health effects upon Cd exposure.

A reverse relationship between *in vitro* induced MT-mRNA level in PBLs and urinary N-acetyl-β-D-glucosaminidase (UNAG) indicates that MT gene expression in PBLs can be used as a biomarker inversely related to the susceptibility to renal toxicity of cadmium. It is suggested to apply MT gene expression in PBLs to the practice of risk assessment of cadmium exposure.

References

Ganguly S, Taioli E, Baranski B, Cohen B, Toniolo P, Garte SJ. 1996 Human metallothionein gene expression determined by quantitative reverse transcription-polymerase chain reaction as a biomarker of cadmium exposure. *Cancer Epidemiol Biomarkers Prev.* **5**, 297–301.

Jin T, Nordberg G, Wu X, Ye T, Kong Q, Wang Z *et al.* 1999 Urinary N-Acetyl-β-D-glucosaminidase isoenzymes as biomarker of renal dysfunction caused by cadmium in a general population. *Environ Res* **81**, 167–173.

Jin T, Nordberg M, Frech W, Dumont X, Bernard A, Ye T *et al.* 2002 Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad). *BioMetals* 15, 397–410.

Lu J, Jin T, Nordberg G and Nordberg M. 2001 Metallothionein gene expression in peripheral lymphocytes from cadmium exposed workers. *Cell Stress Chaperones* **6**, 97–104.

Nordberg GF. 1992 Application of the 'critical effect' and 'critical concentration' concept to human risk assessment for cadmium. In Nordberg GF, Herber RFM, Alessio L eds., *Cadmium in the Human Environment: Toxicity and Carcinogenicity.* IARC Scientific Publications; Vol. 118, 3–14.

Nordberg M, Jin T and Nordberg GF. 1992 Cadmium metallothionein and renal tubular toxicity In Nordberg GF, Herber RFM, Alessio L eds. *Cadmium in the Human Environment: Toxicity and Carcinogenicity*. France, Lyon: IARC Scientific Publications, Vol. 118, 293–297.

Nordberg M, Nordberg GF. 2000 Toxicological Aspects of Metallothionein. *Cellular Molecular Biology* **46**, 451–463.

Nordberg M, Nordberg GF. 2002 Cadmium. In Sarkar B ed., *Handbook of Heavy Metals in the Environment*. New York: Marcel Dekker Inc.; 231–269.