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# Development of Biomarkers for Cadmium Toxicity
# 카드뮴 독성의 생체지표 (유전자 지표)

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The heavy metal cadmium is a xenobiotic toxicant of environmental and occupational concern and it has been classified as a human carcinogen. Inhalation of cadmiumhas been implicated in the development of emphysema and pulmonary fibrosis, but, the detailed mechanism by which cadmium induces adverse biological effects is not yet known. Therefore, we undertook the investigation of genes that are induced after cadmiumexposure to illustrate the mechanism of cadmium toxicity. For this purpose, we employed the polymerase chain reaction-based suppression subtractive hybridization technique. We identified 29 different cadmium-inducible genes in human peripheral mononuclear cells, such as macrophage migration inhibitory factor, lysophosphatidic acid acyltransferaseα, enolase-1α, VEGF, Bax, neuron-derived orphan receptor-1, and Nur77, which are known to be associated with inflammation, cell survival, and apoptosis. Inductionof these genes by cadmium treatment was further confirmed by semi-quantitative reverse-transcription polymerase chain reaction. Further, we found that these genes were also induced after cadmium exposure in normal human lung fibroblast cell line, WI-38, suggesting potential use of this induction profile to monitor cadmium toxicity in the lung. Next, Nur77, one of cadmium-inducible genes, was further studied since the products of Nur77 are known to be involved in the apoptotic process of lung cells. Following cadmium treatment, Nur77 gene expression was increased at protein-levelin A549 cells. Consistently, the reporter containing Nur77 binding sequence was activated by 2.5-fold after exposure to cadmium in reporter gene analysis by transient transfection experiments. When the

plasmid encoding dominant negative Nur77 that represses the transcriptional function of wild-type Nur77 was transfected into A549 cells, the expression of Bax was significantly reduced, suggesting that induction of Nur77 was an important process in cadmium-induced apoptosis in the cells. Cadmium induced the expression of Nur77 *in vivo*, confirming the relevance of the data obtained *in vitro*. Together our results suggest that Nur77 gene expression in exposure to cadmiumleads apoptosis of lung cells which may cause pathological changes in lung.