Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects

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Abstract

Long-term arsenic exposure is associated with an increased risk of vascular diseases including ischemic heart disease, cerebrovascular disease, and carotid atherosclerosis. The pathogenic mechanisms of arsenic atherogenicity are not completely clear. A fundamental role for inflammation in atherosclerosis and its complications has become appreciated recently. To investigate molecular targets of inflammatory pathway possibly involved in arsenic-associated atherosclerosis, we conducted an exploratory study using cDNA microarray and enzyme-linked immunosorbent assay to identify genes with differential expression in arsenic-exposed yet apparently healthy individuals. As an initial experiment, array hybridization was performed with mRNA isolated from activated lymphocytes of 24 study subjects with low (0-4.32 microg/L), intermediate (4.64-9.00 microg/L), and high (9.60-46.5 microg/L) levels of blood arsenic, with each group comprising eight age-, sex-, and smoking frequency-matched individuals. A total of 708 transcripts of known human genes were analyzed, and 62 transcripts (8.8%) showed significant differences in the intermediate or high-arsenic groups compared with the low-level arsenic group. Among the significantly altered genes, several cytokines and growth factors involving inflammation, including interleukin-1 beta, interleukin-6, chemokine C-C motif ligand 2/monocyte chemotactic protein-1 (CCL2/MCP1), chemokine C-X-C motif ligand 1/growth-related oncogene alpha, chemokine C-X-C motif ligand 2/growth-related oncogene beta, CD14 antigen, and matrix metalloproteinase 1 (interstitial collagenase) were upregulated in persons with increased arsenic exposure. Multivariate analyses on 64 study subjects of varying arsenic exposure levels showed that the association of CCL2/MCP1 plasma protein level with blood arsenic remained significant after adjustment for other risk factors of cardiovascular diseases. The results of this gene expression study indicate that the expression of inflammatory molecules may be increased in human subjects after prolonged exposure to arsenic, which might be a contributory factor to the high risk of atherosclerosis in arseniasis-endemic areas in Taiwan. Further multidisciplinary

studies, including molecular epidemiologic investigations, are needed to elucidate the role of arsenic-associated inflammation in the development of atherosclerosis and subsequent cardiovascular disease.