論 文 要 旨

Effect of myeloperoxidase inhibition on gene expression profiles in HL-60 cells exposed to 1, 2, 4,-benzenetriol

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While it is known that benzene induces myeloid leukemia in humans, the mechanism has yet to be clarified. Previously, we suggested that myeloperoxidase (MPO) was the key enzyme because it promotes generation of powerful oxidant hypochlorous acid (HOCl) which, reacting with DNA, causes leukemogenesis. In this study, using a whole-human-genome oligonucleotide microarray to clarify the relationships between myelotoxicity of benzene and MPO, we analyzed the genome-wide expression profiles of HL-60 human promyelocytic cell lines exposed to 1,2,4-benzenetriol (BT) with or without MPO inhibition. The microarray analysis revealed that short (1 h) and longer (4 h) exposure to BT changed the expression in HL-60 cells of 1,213 or 1,214 genes associated with transcription, RNA metabolic processes, immune response, apoptosis, cell death, and biosynthetic processes (|Z-score|> 2.0), and that these changes were dramatically lessened by MPO-specific

inhibition. The presence of functionally important genes and, specifically, genes related to apoptosis, carcinogenesis, regulation of transcription, immune responses, oxidative stress, and cell-cycle regulation were further validated by real-time RT-PCR. Gene expression profiles along with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation analysis suggest that BT-induced DNA halogenation by MPO is a primary reaction in the leukemogenesis associated with benzene.