Fumiyo Saito, Adv Genet Eng 2013, 2:3
http://dx.doi.org/10.4172/2169-0111.S1.002

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International Conference on
Genetic Engineering & Genetically Modified Organisms
August 12-13, 2013 DoubleTree by Hilton, Raleigh, NC, USA

CARCINOscreen®: Novel short-term prediction system for carcinogenicity of chemicals by hepatic transcriptome analysis in a 28-day repeated dose toxicity study

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Carcinogenicity is one of the most important endpoint of chemical safety for not only pharmaceutical compound but industrial chemicals. However, rodent tests for carcinogenicity such as a traditional 2-year study, requires large number of animals and large amount of compounds. In this study, we have been trying to develop a highly accurate and wide applicable prediction method of carcinogenicity with short-term toxicity test up to 28 days. Gene expression profiles of the livers of Fischer 344 rats administered with 46 carcinogenic and 22 non-carcinogenic compounds as test data set were analyzed using a custom microarray and Affymetrix GeneChip®. Functions and networks analyses of up- or down-regulated genes were conducted using the Ingenuity Pathways Analysis (IPA) software. A prediction formula was developed by most plausible method using gene expression profiles of test data set with SVM approach. The established formula showed a concordance of 94.4% with test data set, this system was named CARCINOscreen®, and the formula was validated by application of 18 compounds as the training data with a concordance of 83.3%. Furthermore, gene expression data obtained from Sprague-Dawley or Wistar-Hannover rats treated with known carcinogens were applied to the prediction formula, and all hepatic carcinogens were accurately predicted. In addition, key genes used in the prediction formula showed a common gene network contained tumor suppressor gene, p53 concerned with cell cycle, DNA repair, and apoptosis. Thus, we developed a promising short term prediction system for carcinogenicity of chemicals using transcriptome in livers of rats before neoplastic changes.

Biography

Fumiyo Saito is Assistant chief of Chemicals Assessment and Research Center, CERI and studies development of the prediction system of carcinogenicity by gene expression analysis and mechanism elucidation of reproductive toxicity, hepatotoxicity, and nephrotoxicity. She has completed her Ph.D. in Biotechnology from Tokyo University of Agriculture and Technology. She has published more than 10 papers in reputed journals and serving as a leader of genomics team of the project named ARCH-Tox to carry out five years from 2011 funding from Ministry of Economy, Trade and Industry (METI), Japan.

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