Consequently, exposure of cultured human cells to heavy metals dramatically altered the gene expression of oxidative-responsive genes. However, in human tissues of the GSE7967 study, the p53 signaling pathway differed from that of heavy metals in the GDS2780 study. Overall, the gene expression signals were weaker than those examined in the GDS2780 study. The GSE7967 study examined cord blood collected at birth from infants whose mothers were exposed or unexposed to arsenic (0.1–68.63 mg/g), showing activation of inflammation and NFκB signaling in infants born to mothers exposed to arsenic at high concentration. Therefore, after downloading the datasets, we selected four subjects according to blood concentrations of 0.1, 1.76, 9.66, and 68.63 mg/g; then gene expression of the arsenic (As) exposure-induced responses were visualized in the p53 signaling pathway map. The highest concentration subject showed Gadd45, p53-inducible ribonucleotide reductase small subunit 2 (p53R2), spermatogenic leucine zipper 1 (TSP1), cyclinB, Cdc2, Fas, Noxa and ATR that were higher than those of the subject with the low concentration. However, p53 was opposite: high in the low-exposure subject and low in the high-exposure subject, suggesting that the down-regulation of p53 facilitates apoptosis and promotes cell proliferation.

Previous works described in our study showed that GSS (glutathione synthetase) and PRDX2 (peroxiredoxin 2) regulated TRADD (TNFRSF1A-associated via death domain), NUDT1 （nucleoside diphosphate linked moiety X-type motif 1）, SOD1 (superoxide dismutase 1, soluble), and INSIG1 （Insulin induced gene 1） in the low-exposure group (mean blood concentration 0.142 μg/g), and that NUDT1 regulated TRADD, TXNRD2 (thioredoxin reductase 2), and PRDX2 in the high-exposure group

(21.41 μg/g) using the theoretical algorithm for identifying optimal gene expression networks (TAO-Gen), which is a Bayesian network algorithm used to describe gene interaction networks [18, 132-134] (Figure. 13.3). In fact, NUDT1 is a DNA repair and recombination protein. The H_2O_2 treatment significantly increased this gene and other oxidative-stress genes involved in cell cycle arrest [135]. Results of our analyses suggest that anti-oxidative stress-related genes play key roles in protection against cellular damage in the low-exposure group, but a DNA damage-related gene was dominant in the high-exposure group, in which cell damage would progress. Datasets used in this chapter are fundamental exposure to environmental stressors in normal tissues and cell lines, Therefore, this discrepancy indicates that gene expression signatures in human clinical tissues or epidemiological studies apparently reflect more inflammation than those of experimental materials, which show acute toxicity in animals after short exposure to oxidants in cell cultures.

13.3 CONCLUSION

In this chapter, we have reviewed gene expression signatures of oxidative stress-mediated signaling pathways by environmental stressors and proposed categorical pathways and canonical pathways of oxidative stress in ras and human systems. Analyses of gene expression signatures in environmental related disease such as neuronal disorders, cancer and diabetes is an important approach in etiology and risk assessment for human health to elucidate the underlying mechanisms of induced health effects. It will take

many more genetic and reverse genetic analyses, combined with functional analysis studies. Furthermore, we have shown that oxidative stress have been associated with many signaling pathways and different environmental stressors impact different molecules, but they connects with the others to the same goals like apoptosis or cell cycle. From a therapeutic point of view, researchers must consider that the best biomarker and/or therapy for oxidative stress-related disease may relies on a combination of several different agents, each targeting specifically one aspect of the oxidative stress machinery.

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