Organ Specific Gene Expression by Low Dose Radiation

Woo-Jung Lee, Chang-Mo Kang, Dea-Hoon Lee, Snagwoo Bae, and Yun-Sil Lee
Laboratory of Radiation Effect, Korea Institute of Radiological and Medical Sciences

1. Introduction

Whole gene expression profiling has become one of the most widely used approaches identify genes and their functions in the context of specific biological questions. There is growing acknowledgement of the usefulness of determining expression patterns to identify and categorize genes, be it to use as disease markers, to discover drug targets, to map specific pathways, or to find markers of drug toxicity in early drug testing (1-3). Cellular and tissue sensitivity against ionizing radiation depends on many endogenous gene expression patterns. It is well known that various stimuli such as ionizing radiation produce genetic alteration and an important factor seems to be whether the cell dies, repair all the damage, undergoes defective repair or responds in a way which leads to transformation. The decision whether the damage is dealt with apoptosis, rescue or repair is critical. Death of the individual cell removes the problem from the tissue, however, if the cell does not die, it may acquire genomic instability and lead to a population of cells with abnormally high susceptibility to chromosomal instability mutation and other delayed effects. Studies using inbred strains of rodents have clearly shown genotype-dependent differences in response to radiation exposure, including susceptibility to radiation-induced cellular transformation and tumor formation, as well as differences in susceptibility to radiation-induced chromosomal instability. In this study, we analyzed the genes which have previously been reported to be overexpressed in human peripheral blood lymphocytes (4), in brain, heart, spleen, intestine, and lung which have been shown to have different intrinsic radiosensitivity, especially after low dose radiation exposure (0.2Gy), and examined the correlation between gene expression patterns and organ sensitivity and attempted to identify genes which are possibly responsible for radiation sensitivity.

2. Materials and Methods

Animals

Female C57BL/6 mice, 6-7 weeks old, were purchased from Charles River Japan Inc. and were kept in clean conventional environment.

Reverse Transcriptase PCR (RT-PCR)

Total RNA from each mouse was isolated with TRITM reagent according to the manufacturer's instructions. The reaction mixture contained 1xRT buffer, 1 mM each of dNTPs, 2.5U RNAsin, 0.5mg of oligo (dT)-15 primer, 1 mg of total RNA, and 15U of AMV reverse transcriptase in a final volume of 20 ml. The mixture was incubated at 42C for 20 min. The transcription reaction was terminated by heating the mixture at 95C for 10min and then chilling it on ice.

3. Results

In our recent microarray study, we identified 44 genes that were overexpressed in human PBL (4), and we selected 24 genes for application for the present mice system and designed primer sequences. When expression patterns of these genes in brain and heart (radioresistant), lung (moderately radioresistant), and spleen and intestine (radiosensitive) of female mice were examined, expressions of neogenine, APO-1, nuclease sensitive element binding protein-1, syntaxin, cyclin G1, hNOP56, paraoxonase, and glutathione peroxidase were observed in all 5 organs, including brain, heart, lung, spleen and intestine, after 0.2 Gy radiation. Even though induction times were different depending on the individual gene and were not correlated with radiation sensitivity of organs, these genes can be used as the detection markers for radiation exposure, especially for low dose radiation

exposure. If intestine was excluded, more genes such as PCNA, HSP70, and transducin beta like protein 1, can also be added as detection markers in radiation exposure. Sialyltransferase was expressed only in intestine and spleen which showed the highest radiosensitivity, therefore, this gene can be a radiosensitive marker. Protein tyrosine kinase and platelet membrane glycoproteinlib in lung and spleen responded to radiation, and these genes in intestine were rapidly degraded by the 3rdday after the radiation, suggesting to be a potential candidate for radiosensitive markers. Since aB crystalline and Cu/Zn SOD were expressed only in spleen by radiation, these genes might be used as the markers for radiation exposure to spleen.

4. Conclusion

Our previous data which showed intrinsic gene expression patterns of brain, lung and spleen did not correlate with our present results. However, there is controversy of which factor is more important between the intrinsic genetic background of each organ or expression patterns after stimuli: Furtherfunctional studies are needed to elucidate which genes were responsible for organ sensitivity or which factors among intrinsic expression or post exposure expression patterns were important in radiation sensitivity, especially low dose radiation exposure.

Acknowledgements

This study was supported by Korea Institute of Science &Technology Evaluation and Planning and Ministry of Science & Technology (MOST), Korean government, through its National Nuclear Technology Program

References

1. Brent R. Genomic biology. *Cell* 2000;1: 169-183.
2. Lockhart DJ, Winzeler EA. Genomics, gene expression and DNA arrays. *Nature* 2000;405: 827-836.
3. Rininger JA, Dipippo VA, Rothberg BE. Differential gene expression technologies for identifying surrogate markers of drug efficacy and toxicity. *Drug Discovery Today* 2000;5: 560-568.
4. Kang CM, Park KP, Song JE, Jeoung EI, Cho CK, Kim TH, Bae S, Lee SJ, Lee YS. Possible biomarkers for ionizing radiation exposure in human peripheral blood lymphocytes. *Radiat Res* 2003;159: 312-3.