Gene Activation as a Cell Protection Mechanism Against Gamma-Ray radiation

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Abstract

Introduction: Gamma radiation is accompanied by prominent biological effects and damages. Cell proliferation and tumorigenesis are highlighted as the main resulted effects of gamma radiation on cultured cells. This study aims to assess the dysregulated mode of gene function after gamma radiation in human Jurkat cells.

Methods: Six gene expression profiles from Gene Expression Omnibus (GEO) were analyzed by GEO2R to find the significant differentially expressed genes (DEGs) via gamma radiation. Action map analysis was applied to screen the query DEGs.

Results: Among 108 study genes, 20 critical DEGs including AURKA, AURKB, BORA, CCNB1, CCNB2, CCNF, CDC20, CDCA8, CENPA, CENPE, CENPF, KIF18A, KIF20A, KIF23, BUB1, DLGAP5, ECT2, PLK1, SGO2, and TPX2 were introduced as down-regulated genes by the gamma ray.

Conclusion: Activators of the introduced critical genes may be the cell protector against gamma radiation.

Keywords: Gamma ray; Human Jurkat cell; Activation; Action map; Gene.

Introduction

There are pieces of evidence about various types of damages after exposure to ionized radiation, especially among the survivors of Hiroshima and Nagasaki atomic bombs and the Chernobyl nuclear accident, and studies which are administrated in the treated people after radiotherapy.¹⁻⁴ Different models of damages after ionized radiation have been presented, mostly focused on the DNA and chromosome damages. Effects on protein and lipid molecules have also been investigated to find a clear concept for the mechanism of the radiation effect on biological systems.⁵⁻⁷

Since gene expression profiles in normal and pathological conditions are different, it is reasonable that stress conditions such as radiation can alter gene expression in the irradiated samples.^{8,9} Today advances in proteomics and genomics provide useful methods for assessing the alteration of gene expression profiles after exposure to ionized radiation. In such experiments, the expressional

changes of the genome before and after radiation have been investigated and the dysregulated genes and also the rate of dysregulation have been identified. The results of these types of evaluations indicate that large numbers of genes are dysregulated.^{10,11}

Bioinformatics abilities in the study of complex systems led to widespread penetration of this field in medical investigations. Since gene regulation and genomic study provide complex data, bioinformatics and system biology are a useful approach to analyzing the findings of genomics and proteomics investigations.^{12,13} Network analysis as a bioinformatics and system biology approach is used to analyze large numbers of dysregulated genes, proteins, and metabolites. Such analysis leads to find the critical macromolecules which are related to the studied diseases.^{14,15} Action map analysis can make available valuable information about the biological relationship between the studied genes. In such analysis, activation, inhibition, regulation, binding, catalysis, and reaction

properties of the studied genes relative to the neighbors are determined to elucidate the role of the candidate gene in the interaction with the neighbors.¹⁶ Since protection against ionized radiation is important for human health care, in the present study the gene profiles of human Jurkat cells after being exposed to 10 Gy γ ray relative to the controls from GEO are analyzed via action map analysis to find the critical dysregulated genes and also the mode of damages.

Materials and Methods

GSE10422/GPL6480 was extracted from GEO. GSM2792815-17 were selected as the control sample (in the absence of γ irradiation) and GSM2792818-20 were nominated as irradiated samples with 10 Gy γ -ray. The human Jurkat cells from the T lymphoma cell line were treated with 0 and 10 Gy γ -ray irradiation and after 6 hours they were investigated to find gene expression changes. The samples were prepared from six 14-year-old boys.

Gene expression profiles were matched statistically by the GEO2R program and the 250 top differentially expressed genes (DEGs) considering p-value were assigned for more analysis. 31 uncharacterized DEGs were omitted, and based on the fold change cutoff equal to 1.5, 123 significant DEGs among 219 characterized genes were determined to be investigated in the next steps. If there were several isomers, one of them, which was determined with maximum expression change, was considered for analysis and the others were ignored. 15 isomers were deleted and finally, 108 DEGs were candidates to be assessed. In the case of introducing more than 1 gene for one spot, the first individual was considered. P value < 0.001 was the criterion of statistical analysis.

The action map including regulation, inhibition, and activation actions for the 108 candidate DEGs was provided by CluePedia application of Cytoscape software. The isolated DEGs were separated from the others and the connected DEGs were studied in the form of regulatory networks.

Results

The matched gene expression profiles are shown in Figure 1. Distribution of gene expression amounts of the 6 studied profiles are median center and are comparable in the next steps of analysis. 70 DEGs which are shown in Figure 2 were isolated (without any interaction with the other genes). As it is shown in Figure 3, PDGFA, KIT, LEPR, and SOCS3 formed a limited network and LAMC1, ITGB3, and LAMA3 the other network. PSMC3LIP with DMC1 and UCP1 with SESN2 were paired. These limited networks included 11 DEGs. One of the 27 remained DEGs was not identified by CluePedia and the other 26 individuals were presented as the main connected component (see Figure 4). Since the main action type was activation, the 20 DEGs which were involved in the main connected component

and functioned as activator or activated genes were shown in the separated subnetwork (see Figure 5). The properties of these 20 genes are tabulated in Table 1.

Discussion

Proteomic analysis is performed to discover latent aspects

Figure 1. Six Gene Expression Profiles of Controls (GSM2792815-17) and Irradiated (GSM2792818-20) Samples.

Figure 2. The Isolated DEGs That Were Not Connected to the Other Genes.

Figure 3. The Limited Networks Which Are Formed From PDGFA, KIT, LEPR, SOCS3, LAMC1, ITGB3, LAMA3, PSMC3LIP, DMC1, UCP1, and SESN2. Green, red, and yellow colors refer to activation, inhibition, and regulation actions respectively

Figure 4. The Main Connected Component of the Action Map. Green, red, and yellow colors refer to activation, inhibition, and regulation actions respectively.

Figure 5. A Subnetwork of the Main Connected Component Which Includes the Activator and Activated Genes.

of gamma radiation. Network exploration and pathway examination provide detailed information about the effect of gamma radiation on protein expression.¹⁷ In the present study, gene expression changes of human Jurkat cells in the presence and absence 10 Gy gamma-ray irradiation were investigated. As it is shown in Figure 1, the distribution of gene expression values for all samples is statistically comparable. The median centric distribution of the data in the box plot presentation indicates that the studied samples are similar with the different pattern of gene expression which reflects the effect of gamma radiation.^{18,19} As it is shown in Figures 2-5, 107 genes among 108 DEGs were identified by CluePedia and only 37 individuals were connected to each other by three types of actions (activation, inhibition, and regulation) and about 65% of query DEGs remained isolated.

This is a well-established concept that in graph analysis it is possible that several connected components, one of

which is the main connected one, can be formed.²⁰ The most numbers of interacted elements of the constructed network are present in the main connected component. Five connected components including 37 genes are presented in Figures 3 and 4. Since 26 genes among the 37 DEGs (about 70% of the interacted genes) were presented in the main connected component, we focused on the main connected component.

As it is shown in Figure 4, 4 genes (about 15% of the main connected component elements) are linked to the neighbors via regulation action. Similar analysis indicates that 10 genes (about 38% of the linked genes in the main connected component) are related to the nodes of the subnetwork by inhibition action edges. Finally, it appeared that 20 genes (about 77% of DEGs in the studied subnetwork) are connected with activation action. Since the nodes may be linked by multiple types of action edges, the total value of the percentage is more than 100%. It can be concluded that activation is the prominent relationship between the connected elements in Figure 4. In the next step of the analysis, the focus was on the activation action between the related genes, which was dysregulated after gamma-ray irradiation (see Figure 5). The importance of gene activation via certain conditions is considered by researchers in the molecular studies of the living systems.^{21,22}

Title, description, and fold change of the 20 genes that

Table 1. Properties of the 20 Activators and Activated Genes Which Are Involved in the Main Connected Component of the Action Map

Gene Symbol	Gene Title	logFC
<i>AURKA</i>	Aurora kinase A	-1.35
<i>AURKB</i>	Aurora kinase B	-0.62
<i>BORA</i>	Bora, aurora kinase A activator	-0.83
<i>BUB1</i>	BUB1 mitotic checkpoint serine/threonine kinase	-0.65
<i>CCNB1</i>	Cyclin B1	-1.83
<i>CCNB2</i>	Cyclin B2	-1.07
<i>CCNF</i>	Cyclin F	-0.67
<i>CDC20</i>	Cell division cycle 20	-1.47
<i>CDCA8</i>	Cell division cycle associated 8	-0.74
<i>CENPA</i>	Centromere protein A	-1.40
<i>CENPE</i>	Centromere protein E	-1.37
<i>CENPF</i>	Centromere protein F	-1.10
<i>DLGAP5</i>	DLG associated protein 5	-1.43
<i>ECT2</i>	Epithelial cell transforming 2	-0.66
<i>KIF18A</i>	Kinesin family member 18A	-0.88
<i>KIF20A</i>	Kinesin family member 20A	-1.78
<i>KIF23</i>	Kinesin family member 23	-0.65
<i>PLK1</i>	Polo-like kinase 1	-2.80
<i>SGO2</i>	Shugoshin 2	-0.67
<i>TPX2</i>	TPX2, microtubule nucleation factor	-0.86

Note. The genes that belong to a certain family are shown in the same colors.

are related to each other by activation edges are shown in Table 1. Fourteen genes among the 20 individuals are classified as five gene families including aurora kinase, cyclin, cell division cycle, centromere protein, and kinase family. The other 6 genes are determined as BUB1, DLGAP5, ECT2, PLK1, SGO2, and TPX2. Control of cell division and cell proliferation processes are the main functions that are attributed to the 5 introduced gene families.²³⁻²⁷ The importance of SGO2 phosphorylation by aurora B in cell proliferation has been reported by researchers.²⁸ The significant role of BUB1, DLGAP5, ECT2, PLK1, and TPX2 in the cell cycle, cell proliferation, and tumorigenesis is highlighted by investigations in various reports.²⁹⁻³³ The effect of gamma radiation on cell division is a well-known concept established many years ago.³⁴ Based on the findings in Figure 4 and Table 1, there are critical genes, such as CDC20, which are common between the inhibition region and the activation part. This gene is also involved in the cell cycle process. On the other hand, the main part of inhibition action is formed between the genes that are related to the cell cycle and cell proliferation.

As it is depicted in Table 1, all introduced dysregulated genes are downregulated. It is a surprising finding that the cellular damages are induced mainly by gamma radiation via suppressing the activation mode of action which is accompanied by the lack of biochemical normal function in the treated cells. The finding indicates that applying some activators such as metabolites can protect cells against gamma radiation. The role of metabolites in protection against radiation is discussed in more detail in published research studies.³⁵⁻³⁷ It can be suggested that the introduced 20 genes be considered as suitable targets to select proper activator against radiation.

Conclusion

Activation is the main action which the dysregulated genes are suffered from in the irradiated cells by the gamma ray. Aurora kinase, cyclin, cell division cycle, centromere protein, and kinase family together with BUB1, DLGAP5, ECT2, PLK1, SGO2, and TPX2 genes were introduced as the target genes for the activators to protect cells against gamma radiation.

Ethical Considerations

Not applicable.

Conflict of Interests

The authors declare no conflict of interest.

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