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Prediction of Exposure to 1763MHz Radiofrequency Radiation Using Support Vector Machine Algorithm in Jurkat Cell Model System

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Abstract

We have investigated biological responses to radiofrequency (RF) radiation in in vitro and in vivo models. By measuring the levels of heat shock proteins as well as the activation of mitogen activated protein kinases (MAPKs), we could not detect any differences upon RF exposure. In this study, we used more sensitive method to find the molecular responses to RF radiation. Jurkat, human T-lymphocyte cells were exposed to 1763 MHz RF radiation at an average specific absorption rate (SAR) of 10 W/kg for one hour and harvested immediately (R0) or after five hours (R5). From the profiles of 30,000 genes, we selected 68 differentially expressed genes among sham (S), R0 and R5 groups using a random-variance F-test. Especially 45 annotated genes were related to metabolism, apoptosis or transcription regulation. Based on support vector machine (SVM) algorithm, we designed prediction model using 68 genes to discriminate three groups. Our prediction model could predict the target class of 19 among 20 examples exactly (95% accuracy). From these data, we could select the 68 biomarkers to predict the RF radiation exposure with high accuracy, which might need to be validated in in vivo models.

Keywords: radiofrequency radiation, mobile phone, gene expression microarray, support vector machine

Introduction

As the total number of mobile phone users has been increased world-widely, the concerns about possible health effect upon RF radiation raised among the public as well as health care providers. Mostly the carcinogenic effects were studied intensively during last several decades on colon cancer (Wu *et al.*, 1994), mammary tumor (Toler *et al.*, 1997), liver cancer (Imaida *et al.*, 1998), lymphoma (Repacholi *et al.*, 1997), brain tumor (Salford *et al.*, 1997) and skin tumorigenesis (Huang *et al.*, 2005). However, the relationship between cancer and RF radiation seems to be not so evident. At the molecular levels, the effects of RF radiation on DNA damage, chromatin conformation (Belyaev *et al.*, 2006), permeability of blood-brain barrier (BBB) (Persson *et al.*, 1997), the concentration of zinc ions (Aksen *et al.*, 2004), and the activities of ornithine decarboxylase (ODC) (Paulraj *et al.*, 2002) were studied and reported to be negative. In our recent study for stress response on RF radiation, 1763MHz RF radiation did not induce the expression of heat shock proteins or activate MAPKs in mice whole-body exposure model (Lee *et al.*, 2005a).

In in vitro studies using C3H101/2 cells, exposure to 835.62 MHz and 847.74 MHz could induce the expression of FOS (Goswami *et al.*, 1999). The up-regulations of heat shock proteins (HSPs) were also reported in human glioma MO54 cells at a relatively high SAR of more than 20 W/kg but not at 5 W/kg (Tian *et al.*, 2002). Leszczynskin *et al.* (2002) also reported the phosphorylation HSP27 upon one hour exposure to 900 MHz RF radiation in human endothelial cells. However, the molecular effect of RF radiation is still debated by reports on the failure to detect any changes in the same targets. No changes in the expression and activation of FOS in C3H101/2 cells at 5 W/kg and 10 W/kg SAR of RF radiations were reported (Whitehead *et al.*, 2005) and no statistical significant difference was detected in the number of cells expressing stress proteins (HSP70 and HSP27) upon 900MHz RF radiation (Lim *et al.*, 2005). Lantow *et al.* (2006) reported altered HSP70 expression level was not observed after co-exposure to RF EMFs+PMA or RF EMFs+LPS.

Microarray technology can provide powerful information on the molecular characteristics of certain physiological and pathological conditions. A number of investigators observed gene expression profiles in ionizing radiation (IR) (Park *et al.*, 2002; Christiansen *et al.*, 2006; Fujimori *et al.*, 2005) to find IR-specific genes. To understand the host responses to RF radiation, Jurkat cells ex-

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posed to 1763 GHz RF radiation were examined their expression patterns to select genes related to RF radiation (Lee *et al.*, 2005b). Radiofrequency radiation; mobile phone; gene expression microarray; support vector machine In this study, we tried to find biomarkers to predict the RF-exposed cells from sham- exposed one using gene expression profiles. Then we developed models to predict the exposure to RF radiation using support vector machine (SVM) algorithm (Vapnik, V.N., 1998) with selected biomarkers based on the Weka environment (Witten and Frank, 2005).

Methods

Cell culture and in vitro radiofrequency radiation exposure system

Jurkat cells were incubated in RPMI 1640 medium supplemented with 10% fetal bovine serum (JBI, Korea), 2 mM glutamine, 125 units/ml penicillin, and 125 μg/ml streptomycin at 37°C in a humidified incubator with 5% CO_2. For the RF-EMFs exposure, cells were grown in 2.5×10^5 cells/ml 16 hours prior to the exposure.

In vitro RF exposure system is specially designed for this study in a rectangular-cavity type (Lee *et al.*, 2005 a). A real CMDA signal 1763 MHz is applied to the chamber maintaining proper environmental conditions like a ventilation, humidity, and temperature in CO_2 incubator. In addition, a cooling device circulating water through the bottom of the exposure chamber is used to prevent the change in temperature upon RF exposure.

RF exposure design

Jurkat cells were exposed to 10 W/kg of 1763 MHz RF radiation for one hour or one hour a day for 7 days. Cells were harvested immediately as R0 groups like sham (SR0) and PCS-exposed (PR0), and cells were incubated for 5 hours to recover from acute response as R5 groups like sham R5 (SR5) and PCS-exposed (PR5). We repeated sets of experiment five times to collect biological triplicates in every sample.

RNA extraction and microarray

Samples in each group were harvested and their total RNAs were extracted by dissolving in TriZol (Sigma). After the fractions containing RNA were collected, total RNAs were purified using Qiagen RNAeasy column again. The array used in this experiment was Applied Biosystems 1700 full genome expression human microarray which includes 30,000 human genes from the public and Celera database (http://www.pantherdb.org/).

Data analysis

Fluorescence intensity was processed and measured using Applied Biosystems 1700 Chemiluminescent Microarray Analyzer. Intensity data were imported to an in-house microarray database. Quantile normalization was applied to remove systematic variance. Quantile normalization is a simple yet powerful method to normalize across arrays by making the distribution of probe intensities for each array in a set of arrays the same, and reduces the variance slightly better than Lowess normalization (Bolstad *et al.*, 2003).

We identified genes that were differentially expressed among the three classes using a random-variance F-test. The random variance F-test is an improvement over the standard separate F-test as it permits sharing information among genes about within-class validation without assuming that all genes have the same variance (Wright, 2003).

Then we identified gene ontology (The Gene Ontology Consortium, 2000) groups of genes whose expression was differentially regulated among the classes. This analysis is different than annotating a gene list using GO categories. The GO analysis is to give information whether or not the list of significant genes selected by the analysis is different from a gene list randomly selected from all genes in the analysis, for a given GO category. This is expressed by the observed vs. expected ratio. The observed is defined as the number of genes in the list of significant genes which fall into a GO category. The expected is defined as the average number of genes which would be expected to fall into that GO category in a subset of genes randomly selected from the genes in the analysis. A GO category is considered to consist of not only the genes which are described by that GO term, but also any gene which is described by any children of that GO term.

Prediction Model

We developed models for utilizing gene expression profile to predict the class of future samples using support vector machine (SVM) algorithm (Vapnik, 1998) based on the Weka environment (Witten and Frank, 2005). Support vector machines have exhibited superb performance in binary classification tasks. Intuitively, SVM aims at searching for a hyperplane that separates the two classes of data with the largest margin between the hyperplane and the point closest to it. There are some studies about multiclass decomposition techniques for SVM such as one-versus-the rest, pairwise comparison and error-correcting output coding (ECOC), and they have showed good performance than other multiclass classification algorithms. We use a sequential minimal optimization algorithm with a logistic regression model and RBF kernel

for training a support vector classifier (Platt, 1998).

Results and Discussion

RF exposure to Jurkat T cells

Upon the exposure to 1763MHz RF radiation, Jurkat cells did not show any change in cell morphologies and growth. We kept the cells in CO_2 incubator while cells were exposed to RF radiation. RF radiation might produce heat in the culture media, but isothermal water at 37°C circulated continuously at the bottom of chamber through the experiment. Because we kept the chamber inside of CO_2 incubator, they were completely shielded from any electromagnetic field radiation generated from other electronic sources. For sham group, we assembled

Table 1. List of annotated genes that significantly changed upon exposure to electromagnetic field radiofrequency radiation

Gene ID	Genbank Acc.	Gene Symbol	SHAM	PR0	PR5	p-Value
hCG1798475.1	NM_001010883	FAM102B	9.90 ± 0.30	9.25 ± 0.38	9.25 ± 0.40	0.002
hCG1785173.2	NM_001008404	LOC400258	9.72 ± 0.43	9.42 ± 0.55	8.86 ± 0.27	0.005
hCG1980142	U28811	GLG1	16.18 ± 0.16	15.62 ± 0.36	16.04 ± 0.35	0.006
hCG2020065	NM_183006	DLGAP4	11.43 ± 0.17	11.80 ± 0.07	11.66 ± 0.20	0.007
hCG20795.2	NM_025194	ITPKC	10.44 ± 0.44	9.53 ± 0.55	9.96 ± 0.59	0.009
hCG2041317	XM_496693	LOC441016	10.21 ± 0.79	11.25 ± 0.29	11.11 ± 0.65	0.009
hCG1748068.1	NM_024974	FAM106A	10.18 ± 0.48	10.41 ± 0.17	9.61 ± 0.35	0.010
hCG2039732.1	NM_022105	DIDO1	11.96 ± 0.43	11.88 ± 0.27	13.11 ± 1.30	0.011
hCG32158.3	NM_003749	IRS2	10.25 ± 0.37	10.58 ± 0.33	9.51 ± 0.94	0.013
hCG2036819	AF426265	C21orf87	9.61 ± 0.46	8.89 ± 0.86	8.70 ± 0.58	0.015
hCG1786105.2	NM_130810	DYX1C1	10.32 ± 0.17	9.68 ± 0.43	9.67 ± 0.80	0.015
hCG28566.3	NM_003655	CBX4	11.14 ± 0.37	10.96 ± 0.19	11.59 ± 0.31	0.016
hCG2000944	NM_024106	ZNF426	13.51 ± 0.13	13.42 ± 0.18	13.10 ± 0.35	0.017
hCG1997617	NM_033210	ZNF502	10.12 ± 0.27	10.60 ± 0.21	10.29 ± 0.34	0.018
hCG28703.3	NM_006260	DNAJC3	12.01 ± 0.28	11.50 ± 0.22	11.87 ± 0.39	0.020
hCG1787991.1	NM_002867	RAB3B	10.74 ± 0.48	9.94 ± 0.53	10.38 ± 0.53	0.022
hCG2019985	NM_015678	NBEA	10.59 ± 0.35	10.71 ± 0.41	10.06 ± 0.40	0.023
hCG2028915	NM_206886	CCDC18	10.46 ± 0.28	10.33 ± 0.18	10.02 ± 0.26	0.023
hCG38548.4	NM_025132	WDR19	11.08 ± 0.28	11.24 ± 0.30	10.65 ± 0.42	0.024
hCG1812926.1	NM_025211	GKAP1	10.33 ± 0.42	9.76 ± 0.34	10.04 ± 0.16	0.024
hCG2018817	NM_152762	TSGA10IP	10.50 ± 0.38	9.80 ± 0.89	10.69 ± 0.25	0.025
hCG23295.3	XM_170658	EHBP1L1	9.52 ± 0.52	8.98 ± 0.86	8.27 ± 1.24	0.027
hCG2036683	NM_178160	OTOP2	9.62 ± 0.26	10.32 ± 0.74	9.50 ± 0.65	0.028
hCG1783950.2	XM_097977	FAM59B	10.12 ± 0.21	9.29 ± 0.82	9.91 ± 0.69	0.029
hCG1818126.1	NM_018017	C10orf118	10.15 ± 0.69	9.32 ± 0.32	10.19 ± 0.58	0.030
hCG18888.4	NM_025209	EPC1	10.95 ± 0.41	10.20 ± 0.81	10.83 ± 0.19	0.030
hCG1781181.1	NM_015208	ANKRD12	10.92 ± 0.38	10.44 ± 0.24	10.81 ± 0.13	0.033
hCG32740.4	NM_000124	ERCC6	10.07 ± 0.45	9.97 ± 0.40	9.47 ± 0.21	0.034
hCG1784632.2	NM_002316	LMX1B	10.46 ± 0.23	10.79 ± 0.25	10.39 ± 0.16	0.034
hCG1782583.3	Z21966	POU6F1	10.32 ± 0.39	10.33 ± 0.70	9.61 ± 0.53	0.038
hCG28043.2	NM_003042	SLC6A1	9.38 ± 0.44	9.17 ± 0.82	10.08 ± 0.54	0.039
hCG1985127.1	NM_194320	ZNF169	10.50 ± 0.43	10.69 ± 0.41	10.00 ± 0.44	0.040
hCG14997.4	NM_212502	PCTK3	9.73 ± 0.83	10.58 ± 0.46	10.38 ± 0.23	0.042
hCG41586.2	XM_030300	UNC5A	9.43 ± 0.50	9.57 ± 0.55	10.18 ± 0.57	0.044
hCG2044640	NM_021184	C6orf47	12.28 ± 0.30	12.30 ± 0.13	12.64 ± 0.15	0.044
hCG1647586.3	XM_097265	LOC147670	10.15 ± 0.39	10.05 ± 0.19	9.50 ± 0.72	0.044
hCG1749601.2	NM_022076	DUSP21	10.82 ± 0.60	10.13 ± 0.43	10.77 ± 0.33	0.044
hCG2028492.1	BC034618	FLJ31306	13.14 ± 0.28	12.89 ± 0.21	12.76 ± 0.25	0.044
hCG20429.4	NM_153254	TTLL10	9.67 ± 0.45	8.92 ± 0.80	9.64 ± 0.47	0.045
hCG16728.4	NM_024567	HMBOX1	14.42 ± 0.22	14.01 ± 0.44	14.32 ± 0.14	0.045
hCG39984.3	NM_002557	OVGP1	11.65 ± 0.24	11.30 ± 0.57	11.96 ± 0.45	0.045
hCG1983553	NM_144987	U2AF1L4	11.21 ± 0.32	11.20 ± 0.23	10.77 ± 0.35	0.045
hCG1734197.1	NM_152617	RNF168	11.24 ± 0.44	10.64 ± 0.47	11.06 ± 0.33	0.047
hCG2027799	NM_194282	DKFZp686L1814	11.18 ± 0.28	10.93 ± 0.32	11.42 ± 0.26	0.049
hCG1640903.5	NM_145024	CES7	12.98 ± 0.24	12.94 ± 0.18	13.28 ± 0.19	0.050

Table 2. GO analysis - Molecular Function

GO id	GO classification	Observed in selected subset	Expected in selected subset	Observed / Expected
3700	transcription factor activity	3	1.31	2.29
16301	kinase activity	3	1.47	2.04

Table 3. GO analysis - Biological Process

GO id	GO classification	Observed in selected subset	Expected in selected subset	Observed / Expected
6915	apoptosis	3	0.68	4.43
6355	regulation of transcription, DNA-dependent	7	2.85	2.46
31323	regulation of cellular metabolism	7	3.24	2.16

Table 4. Detailed accuracy by class

Class	TP rate	FP rate	Precision	F-Measure
Sham	1	0.1	0.909	0.952
PR0	1	0	1	1
PR5	0.8	0	1	0.889

exactly same experimental set up for RF exposure without applying the current.

Feature selection to distinguish among Sham, PR0, and PR5

We designed the experiments to identify the genes differentially expressed among the three classes – sham, PR0, and PR5-using a random-variance F-test. Genes whose p-value were less than 0.05 were considered as statistically significant ones. By the statistical analysis, we selected 68 differentially expressed genes and listed fully annotated 45 genes in Table 1. Even though the numbers of genes listed here were quite small, we could detect the transcriptional changes in Jurkat cells upon RF-radiation.

Although there were sizable numbers of un-annotated genes in the feature gene lists, we analyzed GO categories for just annotated genes. Using the GO analysis, we could characterize the biological responses to RF radiation in Jurkat T cells. As we summarized the categories in Table 2 and Table 3, cellular responses require the changes in the expression of transcription factors and kinase enzymes. Especially those genes were related to apoptosis and cellular metabolism.

Prediction Model

The models incorporated 68 genes that were differentially expressed among genes at the 0.05 significance level as assessed by the random variance F-test. We estimated the prediction error of the model with 10-fold cross-validation. Specifically, 10-fold cross-validation means that the available examples are partitioned into 10 disjoint subsets. The cross-validation procedure is then run 10 times, each time using one of the 10 subsets as the test set and the others for training sets.

The performance criteria that we used are as follows:

$$\text{Accuracy} = (TN + TP) \cdot 100 / (TP + FP + FN + TN)$$
$$\text{TP-rate} = (TP) \cdot 100 / (TP + FN)$$
$$\text{FP-rate} = (FP) \cdot 100 / (FP + FN)$$
$$\text{Precision} = (TP) \cdot 100 / (TP + FP)$$
$$\text{F-measure} = 2 \cdot \text{Precision} \cdot \text{Recall} / (\text{Precision} + \text{Recall}) = (2TP) \cdot 100 / (2TP + FP + FN)$$

The accuracy is the proportion of correctly classified examples among total examples. The true positive rate (TP-rate) is the proportion of examples that were classified as class x, among all examples that truly have class x, i.e. how much of the class was captured. It is equivalent to Recall. The false positive rate (FP-rate) is the proportion of examples that were classified as class x, but belong to a different class, among all examples that are not of class x. The precision of the proportion of the examples that truly have class x among all those which were classified as class x. F-measure is a single measure that characterizes recall and precision. Our prediction model predicted the target class of 19 among 20 examples exactly (95% accuracy). One dataset from PR5 class was misclassified as a sham class (Table 4).

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