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Radiation-Sensitivity and Transcription Profiles in Various Mutant p53 Cells

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1. Introduction

The tumor suppressor gene p53 plays an important role in determining radiosensitivity. The normal p53 gene product accumulates after exposure to ionizing radiation, and causes growth arrest or promotes cell death through the apoptosis pathway (Figure 1). Mutation of the p53 gene is the most common genetic alteration observed in human cancers (Nigro et al. 1989). It has been widely reported that cells with mutant p53 are more resistant to ionizing radiation or DNA-damaging agents (Fan et al. 1994; Wattel et al. 1994; Lee et al. 1993; Hamada et al. 1996). On the other hand, there have been reports of cells harboring mutant p53 that are sensitive to ionizing radiation and anticancer drugs (Biard et al. 1994; Fan et al.

Fig. 1. Pathway of p53. From irradiation by ionizing radiation to growth arrest or apoptosis of the cell through p53.
1995), although specific details of the mutations were not discussed. Mutant forms of p53 differ in their properties according to the points of the mutation. For example, Crook et al. using a large series of p53 mutants, found that not all transcriptionally active mutants retained the ability to suppress transformation, and that some tumor-derived point mutations conferred both transforming and transactivating activity (Crook et al. 1994). Some mutant forms of the p53 gene do not merely induce the functional equivalent of p53 loss (Harvey et al. 1995). The radiosensitivity of cells may depend on the type of p53 mutation they harbor. It is important to determine which mutations affect the radiosensitivity of tumor cells, because tumor cell radiosensitivity has substantial clinical relevance in the context of tumor radiotherapy.

2. Mutation in p53

We prepared 15 types of cells harboring mutant forms of p53 (T123A, L130V, Q143A, V157F, H168R, R175H, I195T, C242F, G244C, G245S, R273H, C277F, R280T, R282W and E286K) to examine their radiosensitivity. First, we created various mutations in the p53 gene using a QuikChange site-directed mutagenesis kit (Stratagene, La Jolla, CA) in accordance with the manufacturer’s protocol and integrated them into the LacSwitch inducible mammalian expression system (Stratagene, La Jolla, CA) (Okaichi et al. 1999). These mutant p53 genes were then transformed into the Saos-2 cell line, which is null for p53, and stable transformants were obtained.

3. Radiation sensitivity of cells harboring p53 mutation

Radiation sensitivity may depend on the position at which mutation occurs in p53. We previously examined various p53 mutants for radiation sensitivity (Okaichi et al. 2008). Cells were subjected to γ-ray irradiation and then plated onto dishes. Colonies were examined after about one month to calculate the surviving fraction. The cells with wild-type p53 showed higher radiation sensitivity than Saos-2 (p53-null) cells. Some mutations also resulted in increased radiation sensitivity, but mutations including hot spot mutations (175H, 244C, 245S, 273H and 282W) showed almost no alteration of radiation sensitivity compared with Saos-2. Other mutations conferred an intermediate level of radiation sensitivity (Okaichi et al. 2008).

We then compared the radiosensitivity of these mutants with the frequency of mutation at each point, which is correlated with the tendency for tumorigenesis. Figure 2 shows the relationship between the frequency of p53 mutation in human cells and radiosensitivity of the p53 mutants. We divided these mutants into three groups; R (resistant), M (medium) and S (sensitive). The 175H, 244C, 245S, 273H and 282W transformants were placed in group R, which was radioresistant and included a high frequency of mutation at all hot spots. The 130V, 143A, 168R, 277F and 286K transformants were placed in group M, which showed medium radiosensitivity and a low frequency of mutation. The 123A, 157F, 195T, 242F and 280T transformants were placed in group S, which was radiosensitive and showed a relatively low frequency of mutation.

As the radiosensitivity of these cells may be related to the induced expression of various genes by each type of p53 mutation, we investigated the genes whose expression appeared to be related to the radiosensitivity of cells bearing p53 mutations.
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Fig. 2. Relationship between radiosensitivity of p53 mutant cell lines and the frequency of p53 mutation. The mutant cell lines were divided into three groups; R (radioresistant), M (medium radiosensitivity) and S (radiosensitive).

4. Transcriptional control in cells harboring p53 mutation

We examined the expression of genes in cells harboring p53 mutation that were subjected to γ-ray irradiation. For this we employed a DNA microarray (Gene Chip, Human Genome U133 Plus 2.0 Array; Affymetrix, Santa Clara, CA), containing over 54,000 probe sets, in accordance with the manufacturer’s instructions. We extracted mRNA from each cell type 24 hours after irradiation at 6 Gy, and synthesized the cDNA. After we had synthesized, in turn, cRNA from the cDNA, we labeled the former with biotin and hybridized it with the DNA microarray. After staining and washing, we read the fluorescence using a scanner. The expression value (signal) of each gene was calculated and normalized using GeneSpring (Agilent Technologies, Santa Clara, CA) to adjust for minor differences between the experiments. In order to obtain the mean basal expression level of each gene, the signal values for unirradiated Saos-2 cells were used as the standard for the analysis. The change in value (signal log ratio) for each gene was calculated using Comparison Analysis in the software.

As radiosensitivity is intrinsically related to the apoptosis pathway, we summarized the genes associated with apoptosis, and these are shown in Table 1, where the cells harboring mutant p53 cells are arranged from left to right according to their radiosensitivity, the cells harboring wild-type p53 are located on the far left, and the parent cells, Saos-2, on the far right. We picked up genes showing an increase in gene expression of more than 2-fold, and indicated them by colored column. After irradiation, the cells with wild-type p53 showed more than a 2-fold increase in the expression of 15 genes, whereas Saos-2 did not show any increase in the expression of apoptosis-related genes. Cells harboring mutant p53 lacked...
expression of many genes that were induced in cells harboring wild-type p53, but showed induction of some genes that were not induced in the latter. The 245S mutant cell line showed a particularly marked increase in the expression of many TNF-associated genes upon irradiation. As the expression of TNF-associated genes inhibits apoptosis, this would explain the radioresistance of 245S cells. We also noticed that the expression of TNF-associated apoptosis-inducing genes, such as TNFSF9 (0.15), TNFSF10 (0.18) and TNFSF21 (0.22), was decreased by more than half, in the 245S mutant cell lines. We were unable to explain the radiosensitivity of other mutant cell lines upon induction of apoptosis-related genes.

Table 1. Induction of gene expression in the apoptosis pathway by irradiation at 6 Gy. We listed the apoptosis genes whose expression was increased more than 2-fold in mutant cells. The numbers indicate the gene expression value in comparison with unirradiated Saos-2 cells. The colored columns indicate more than a 2-fold increase.

We speculated that certain genes might play an important role in making some cells radioresistant. In this connection, we listed those genes whose expression was increased more than 2-fold in radioresistant cells. Table 2 shows a list of genes whose expression was increased in more than 4 of the mutant strain of radioresistant cells. We paid attention to the level of gene expression in the radiosensitive mutant cells, because genes that play an important role in conferring radioresistance would be shown lower levels of expression in radiosensitive cells. Expression of the genes CADPS2, DNPEP, NKTR, OVOS2, PSENEN, RASSF4, RBM14 and WTAP was not increased more than 2-fold in almost all of the
radiosensitive cells. CADPS2 acts as a calcium sensor in constitutive vesicle trafficking and secretion (Cisternas et al. 2003), and DNPEP is an aspartyl aminopeptidase that catalyzes the sequential removal of amino acids from the unblocked N termini of peptides and proteins (Nakamura et al. 2011). NKTR plays an important role in NK-cell cytotoxicity (Anderson et al. 1993). OVOS2 is a member of the ovostatin family and possesses trypsin-inhibitory activity (Saxxena and Tayyab, 1997). PSENEN (Presenilin enhancer-2) is a component of the \( \gamma \)-secrectase complex which catalyzes the final cleavage of amyloid precursor protein to generate the toxic amyloid \( \beta \) protein, the major component of plaques in the brain of Alzheimer disease patients, and protects embryos from apoptosis (Zetterberg et al. 2006). RASSF4 binds directly to activated K-Ras in a GTP-dependent manner via the effector domain, thus exhibits the basic nature of a Ras effector and plays an important role in Ras-dependent apoptosis (Eckfeld et al. 2004). RBM14 (CoAA) is a nuclear receptor coactivator protein at the interface of transcriptional coactivation and RNA splicing (Auboeuf et al. 2004). WTAP (Wilms' tumor 1-associating protein) is essential for embryonic development, and appears to exert an antiproliferative effect, inhibiting G1-to-S phase cell cycle transition and also promoting apoptosis (Small et al. 2007).

Table 2. A list of the genes induced in radiosensitive cells by irradiation at 6 Gy. We listed the genes that showed more than a 2-fold increase in almost all of the radiosensitive cells. The numbers indicate the gene expression value in comparison with unirradiated Saos-2 cells. The colored columns indicate more than a 2-fold increase.

| Gene       | Wild | Medium | Resistant |
|------------|------|--------|----------|
| ARHGDIA    | 2.26 | 1.78   | 2.33     |
| ATRP0001E1 | 1.39 | 1.84   | 1.72     |
| C9orf56    | 3.04 | 1.49   | 2.00     |
| CADPS2     | 0.65 | 0.73   | 2.6      |
| CUEDC1     | 4.57 | 0.70   | 1.82     |
| DNPEP      | 1.11 | 2.29   | 1.32     |
| EIF4G1     | 2.95 | 0.63   | 1.37     |
| FAM100B    | 4.18 | 3.13   | 1.91     |
| FUS        | 0.75 | 1.84   | 1.34     |
| HREC6      | 15.2 | 3.56   | 1.55     |
| HOME3R3    | 3.22 | 1.51   | 1.40     |
| KSF1       | 0.25 | 2.53   | 1.80     |
| LDLR       | 4.34 | 1.12   | 1.38     |
| MVEF2      | 2.06 | 1.32   | 1.39     |
| NKTR       | 0.66 | 1.64   | 1.54     |
| OVOS2      | 0.56 | 0.80   | 1.96     |
| PSENEN     | 4.48 | 1.44   | 2.74     |
| RASSF4     | 0.53 | 1.47   | 1.13     |
| RBM14      | 10.1 | 1.35   | 1.26     |
| ROHOU      | 0.34 | 0.36   | 0.42     |
| SIRT6      | 2.24 | 1.71   | 1.32     |
| SPAG9      | 2.13 | 1.73   | 1.03     |
| TNRC5B     | 1.41 | 1.51   | 1.96     |
| WTAP       | 0.78 | 0.80   | 3.32     |

Table 2. A list of the genes induced in radioreistant cells by irradiation at 6 Gy. We listed the genes that showed more than a 2-fold increase in almost all of the radioreistant cells. The numbers indicate the gene expression value in comparison with unirradiated Saos-2 cells. The colored columns indicate more than a 2-fold increase.

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Among these genes, RASSF4 and WTAP are related to apoptosis, but exert a negative effect on radioresistance. As PSENEN blocks apoptosis, this gene may play an important role in radioresistance.

We approached this issue from the opposite perspective, and searched for genes that played an important role in conferring radiosensitivity. We listed genes showing more than a 2-fold increase in expression in radiosensitive cells. Table 3 shows a list of genes whose expression was increased in more than 4 of the radiosensitive mutant cell lines. Expression of CBR4, FOXP1, KPNAP5, NEK3, TRIM2 and TRIM38 was not increased more than 2-fold in almost all radioresistant cell lines. CBR4 (carbonyl reductase 4) is a mitochondrial NADPH-dependent quinine reductase that may be involved in the induction of apoptosis by cytotoxic 9, 10-phenanthrenequinone (Endo et al. 2008). FOXP1 is a forkhead transcription factor with functions in tissue and cell-type specific gene expression, and its gene is a direct target of p53-induced microRNA miR-34a (Rao et al. 2010). KPNAP

Table 3. A list of the genes induced in radiosensitive cells by irradiation at 6 Gy.
We listed the genes that showed more than a 2-fold increase of expression in almost all of the radiosensitive cells. The numbers indicate the gene expression value in comparison with unirradiated Saos-2 cells. The colored columns indicate more than a 2-fold increase.

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(karyopherin-alpha) proteins are responsible for the transport of proteins into and out of the nucleus through the nuclear pore complex, and KPUNA3 contributes genetically to schizophrenia (Wei and Hemmings 2005). MFAP5 (microfibrillar associated protein 5), also known as a microfibril-associated protein (MAGP2), is a highly significant indicator of survival and chemosensitivity of the cells (Spivey and Banyard, 2010). NEK3 is a serine/threonine kinase that contributes to PRL-mediated breast cancer motility through mechanisms involving Rac1 activation and paxillin phosphorylation (Miller et al. 2007). TRIM (tripartite motif-containing) proteins are a family comprising more than 70 members in humans and contain conserved RING, G-box, coiled-coil, and SPRY domains, most of which are involved in protein ubiquitination, but only a few of them have been well studied. TRIM2 mediates the p42/p44 MAPK-dependent ubiquitination of Bim (Bcl-2-interacting mediator of cell death) in rapid ischemic tolerance, and suppression of TRIM2 expression stabilizes the level of Bim protein and blocks neuroprotection (Thompson et al. 2011). TRIM38 has E3 ubiquitin ligase activity and can be degraded during virus infection (Liu et al. 2011).

As CBR4 is involved in the induction of apoptosis, this gene may play an important role in radiosensitivity. However, the precise role of these genes in radiosensitivity remains unknown.

We have attempted to perform hierarchical clustering analysis of RNA expression in these mutant p53 cell lines using Gene Tree software, but were unable to find any clear relationship between radiosensitivity and gene expression.

5. Conclusions

Ionizing radiation is used extensively in medical diagnostic and treatment protocols. With a better understanding of radiation induced molecular processes, it might become possible to identify the radiosensitivity of individuals before the start of radiation therapy, leading to individualization of radiation treatment. Radiation-induced transcriptional responses have been studied using DNA microarray (Kis et al. 2006; Jen and Cheung, 2006). Some previous studies have also examined cells harboring mutant p53 using DNA microarray (Amandson et al. 2003; Scian et al. 2004), but they did not examine each type of mutation.

In the present study, we prepared 15 mutant p53 cell lines, cells harboring wild-type p53 and Saos-2 cells (null for p53). We examined the radiosensitivity of the mutant cell lines and classified them as R (resistant), M (medium) or S (sensitive). We then studied the radiation-induced transcriptional responses in these cell lines, and examined the relationship between their radiation-induced gene expression and radiosensitivity. We found some genes that appeared to have some correlation with radiosensitivity, for example PSENEN and CBR4. However, none of the genes directly determined the radiosensitivity of the cells. Further study will be needed to determine which of these genes is the main determinant of radiosensitivity.

Radiosensitivity may be determined by several genes working in collaboration. Mutation of p53 leads not only to loss of function, but also gain of function. If such functions are related to growth arrest or DNA repair, then loss of function would confer radiosensitivity, and gain of function to radioresistance. On the other hand, if such functions are related to apoptosis, then loss of function would confer radioresistance and gain of function to radiosensitivity. Each mutation of p53 may thus lead to loss of function and gain of some other function at the same time. This makes it very difficult to determine whether a certain
mutation of \( p53 \) leads to the radiosensitivity on the basis of transcriptional analysis alone. Recently it has been reported that many kinds of microRNAs related to tumorigenesis or apoptosis are regulated by \( p53 \) (He et al. 2007; Suzuki et al. 2009). Thus \( p53 \) regulates not only mRNA but also microRNA. The regulation of microRNA in each mutant \( p53 \) cell line would vary the degree of cell radiosensitivity. The available data suggest the importance of determining the type of mutation of \( p53 \) and examining the regulation of overall transcriptional control in individual tumor cells in the context of radiotherapy.

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Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However, people have shortly recognized its harmful aspects through inadvertent uses. Subsequently, people experienced nuclear power plant accidents in Chernobyl and Fukushima, which taught us that the risk of ionizing radiation is closely and seriously involved in the modern society. In this circumstance, it becomes increasingly important that more scientists, engineers, and students get familiar with ionizing radiation research regardless of the research field they are working. Based on this idea, the book “Current Topics in Ionizing Radiation Research” was designed to overview the recent achievements in ionizing radiation research including biological effects, medical uses and principles of radiation measurement.

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