Alterations of the DNA Repair Gene OGG1 in Human Clear Cell Carcinomas of the Kidney

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Abstract

The OGG1 gene, which codes for a DNA repair protein with antimutagenic activity, is located on chromosome 3p25, a frequent site of allelic deletions in many types of human tumors, including renal clear cell cancers. We present the analysis of 99 renal tumors for alterations in the OGG1 gene to determine its association with tumorigenesis. Loss of heterozygosity in the 3p25 region was found for 85% of the informative cases. We detected somatic missense mutations of the OGG1 gene in 4 of the 99 tumor samples. Biochemical analysis of the mutant proteins revealed that a substitution at codon 46 impairs the enzymatic activity. We also describe the occurrence of several polymorphisms as well as aberrantly spliced OGG1 transcripts.

Introduction

Damage to DNA by oxygen free radicals is postulated to cause mutations associated with the initiation and/or progression of human cancers (1, 2). Oxidative damage-induced mutations can activate oncogenes or inactivate TSGs, altering the cell growth control (3). An oxidatively damaged guanine, 8-OxoG, is abundantly produced in DNA as a consequence of cellular oxidative metabolism or exposure to ionizing radiation or chemical carcinogens (4, 5). The presence of 8-OxoG in DNA has been shown to be mutagenic because, although this lesion does not impede DNA chain elongation, it preferentially pairs to adenine during in vitro DNA synthesis (6). Studies using bacterial or yeast mutants defective in the elimination of 8-OxoG have demonstrated that the accumulation of this base generates a mutator phenotype characterized by a high frequency of G:C to T:A transversions (reviewed in Ref. 7). In mammalian cells, the OGG1 gene codes for an 8-OxoG DNA glycosylase/AP lyase that has the capacity to excise this oxidized guanine from DNA. The Ogg1 protein initiates the base excision repair process by recognizing and excising the modified base. Consistent with the yeast findings, mice lacking a functional Ogg1 protein accumulate abnormal levels of 8-OxoG in their genomes and display a moderately elevated spontaneous mutation rate in nonproliferative tissues (8). Because inactivation of the OGG1 gene in mammalian cells causes a mutator phenotype, it can be expected that cells lacking Ogg1 activity could have an enhanced probability of undergoing cancer transformation (9). The validation of this hypothesis requires the identification of human tumors where both alleles of the OGG1 gene are nonfunctional. Analysis of the sequence changes in the p53 suppressor gene showed a bias in favor of GC to TA transversions in lung and kidney cancers (10). This type of mutation would be expected in cells incapable of eliminating 8-OxoG from their DNA and therefore likely to be deficient in the OGG1 gene. Furthermore, the human OGG1 gene has been located on chromosome 3p25 (11). Human chromosome 3p cytogenetic abnormalities and LOH have been observed at high frequency in sporadic forms of RCC. Three loci on chromosome 3p have been shown to be frequently involved in RCCs: (a) 3p14.1–3p14.3; (b) 3p12.2–3p12.3; and (c) 3p25; however, the relative contribution of each locus is not well known. The FHIT gene locus at 3p14.2 covers about 500 kb, including the fragile site FRA3B and the constitutional t(3;8) breakpoint associated with the development of multiple RCCs. Because only a few sporadic nonpapillary RCCs have a deletion breakpoint within the FRA3B/FHIT region and because most renal cell tumors show a normal FHIT transcript, the involvement of the FHIT gene and the FRA3B region can be excluded from the genetics of RCC (12).

Here we analyze a series of 99 clear cell kidney tumors and matched normal tissues for mutations in OGG1 and for LOH in the region of chromosome 3p harboring this gene. The variant alleles of the Ogg1 protein were expressed in Escherichia coli and analyzed for their enzymatic activities.

Materials and Methods

Tissue Samples. This study was conducted on a series of 99 clear cell RCCs and the corresponding normal tissue surrounding each of them obtained after surgery and kept in liquid nitrogen until used. The mean size of the tumors was 6.8 cm (range, 2–23 cm). Twenty-eight percent of patients were stage I tumors, 40% of patients had stage II tumors, 21% of patients had stage III tumors, and 11% of patients had stage IV tumors. RNA and DNA preparations were done using RNAplus and DNAzol extraction kits (Quantum Appliplen, Illkirch, and Life Technology, Cergy-Pontoise, France).

LOH Analysis. Mapping of the OGG1 gene was performed by amplification from a hybrid radiation panel as described previously (14), using the following OGG1 cDNA-specific oligonucleotides: (a) 5’-GCTGTTCAGTGCACGC-3’; and (b) 5’-AACATGAGACTGGGTGGG-3’ for LOH analysis, 0.2

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3 The abbreviations used are: TSG, tumor suppressor gene; 8-OxoG, 7,8-dihydro-8-oxoguanine; LOH, loss of heterozygosity; RCC, renal cell carcinoma; RT-PCR, reverse transcription-PCR; AP, abasic site; DGGE, denaturing gel electrophoresis.
µg of DNA from each sample was subjected to PCR using primers directed against the following chromosome 3p highly polymorphic microsatellite markers: (a) AFM238wb12; (b) AFM295yc9; and (c) AFM095xc1. The primer sequences and PCR conditions used were those obtained from the Genome Database. For each pair, one of the primers was labeled with Cy5, a fluorescent dye. PCR products were separated on 6% denaturing PAGE. Gels were run and analyzed on an ALFexpress automated sequencer (Amersham Pharmacia Biotech). Homozygosity was classified as noninformative. LOH was calculated by comparing the ratios between the peak areas of the two alleles in the tumor with that in the corresponding normal tissue. Differences larger than 30% were considered to be a LOH.

**Mutation Analysis.** OGG1 mutations were screened by DGGE analysis of RT-PCR-amplified materials as described previously (15). Samples with an altered DGGE profile were then sequenced. Study of the OGG1 cDNA melting domain profile showed that five independent RT-PCRs were mandatory to analyze nucleotides 309-1250. The 3'-end of the cDNA sequence was analyzed systematically by sequencing because alternative splicing occurs within this region. For DGGE analysis, a psoralen clamp was attached at the 5'-end of one of each of the primer pairs, whose sequences are given in Table 1. Each RT-PCR was carried out in a final volume of 100 µl using one-fifth of cDNA template obtained from 1 µg of total RNA mixed with 50 pmol of each forward and reverse primer in 10× PCR buffer containing 27 mM MgCl2. After denaturing for 2 min at 94°C, 32 cycles consisting of 50 s at 94°C, 50 s at the appropriate annealing temperatures (Table 1), and 20 s at 72°C were performed using an automatic DNA thermal cycle (MJ Research). The last cycle was followed by an additional 10 min at 72°C to complete all of the products, and a 10-µl aliquot was electrophoresed on a 1% agarose gel in 1× Tris-borate EDTA and examined by ethidium bromide staining to confirm the presence of the appropriately sized product. Heteroduplex and homoduplex formations were performed by incubating each PCR product for 5 min at 94°C and 45 min at 55°C, and stabilization of the duplexes was obtained by UV irradiation at 365 nm for 20 min, which provokes a covalent link at the 5'-end of both strands of DNA due to the presence of the photoactivatable intercalating psoralen group. Denaturant PAGE of the stabilized duplexes (30 µl) was carried out at 60°C using a thermostated gel apparatus (Prolabo, Paris, France). Gels contained 7% acrylamide in 1× TAE buffer [40 mM tris-acetate, 1 mM EDTA (pH 8.0)] with linearly increasing gradients of the denaturants urea and formamide (100% denaturant corresponds to 40% formamide and 7 m urea). The respective gradients and running conditions for each DGGE are given in Table 1. PCR products of wild-type and known mutants, obtained using point mutated oligonucleotides, were systematically included as controls with each set of test samples. After electrophoresis, the gels were stained with ethidium bromide and photographed under UV illumination at 354 nm. Each sample showing an abnormal electrophoresis profile, as compared with the wild-type migration, was subjected to an independent RT-PCR amplification using the appropriate primers without the psoralen clamp and purified by centrifugation through centricron-100 columns (Amicon). Sequencing reactions were carried out on both strands using the sequencing kit (Perkin-Elmer) on an ABI prism 377A automatic sequencer according to the manufacturer’s protocol. Sequencing reactions were carried out on both strands using the sequencing kit (Perkin-Elmer) on an ABI prism 377A automatic sequencer according to the manufacturer’s protocol. Sequencing reactions were carried out on both strands using the sequencing kit (Perkin-Elmer) on an ABI prism 377A automatic sequencer according to the manufacturer’s protocol. Sequencing reactions were carried out on both strands using the sequencing kit (Perkin-Elmer) on an ABI prism 377A automatic sequencer according to the manufacturer’s protocol. Sequencing reactions were carried out on both strands using the sequencing kit (Perkin-Elmer) on an ABI prism 377A automatic sequencer according to the manufacturer’s protocol. 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strategy, total RNA was extracted from the tissue samples (99 cases) and used as substrates for cDNA synthesis. The cDNAs were analyzed by PCR-DGGE. In the cases where an abnormal migration pattern was observed, an independent PCR was performed, and the product was sequenced. Because of the presence of alternatively spliced forms of OGG1 mRNA (reviewed in Ref. 17), multiple fragments were generated during the amplification of the sequences spanning exons 6 and 7, thus interfering with the interpretation of the results. To circumvent this problem, genomic DNA was isolated, and the region spanning exons 6 and 7 was amplified by PCR and analyzed for the presence of mutations by sequencing both strands of the amplification products.

The combination of these approaches led to the identification of mutations by sequencing both strands of the amplification products. The kidney has an unusually high rate of oxygen metabolism, of mismatch repair genes plays a critical role in the development of tumors. The kidney has an unusually high rate of oxygen metabolism, and it has been shown that the high concentrations of urea frequently present in kidney cells can trigger an oxidative stress (22) and therefore increase the likelihood of DNA damage. The antimutator function of the Ogg1 protein, together with the localization of the gene to chromosome 3p25, renders OGG1 a good candidate as a cancer predisposition gene for kidney tumors. To extend our previous studies on OGG1 gene mutations in human tumors and cell lines and to investigate the role of this gene in tumorigenesis, we searched for the presence of alterations in OGG1 and for LOH in 3p25 in a series of 99 samples of RCC. The finding of LOH in 85% of the cases analyzed risen somatically. The four mutations are missense mutations and affect codons 12, 46, 169, and 232. The amino acids changes generated are described in Table 3. Of those four cases, two show LOH (R36 and R48), one is noninformative (R37), and the remaining one (R16) is heterozygous in the tumor sample.

Characterization of the Mutant OGG1 Proteins. To assess the functional status of the proteins coded by the mutant forms of the OGG1 gene found in the tumor samples, site-directed mutagenesis was performed on a plasmid coding for a glutathione S-transferase-OGG1 fusion (16). The proteins carrying each of the four different amino acid substitutions were subsequently expressed in E. coli and purified. Their 8-OxoG DNA glycosylase activity was tested by determining their capacity to cleave an oligonucleotide harboring a unique 8-OxoG residue. Fig. 1 shows the results of a representative experiment. Using this assay, the mutants in codons 12, 169, and 232 show no difference in their enzymatic activity when compared with the wild-type form. However, in the case of the R46Q mutant, the DNA glycosylase/AP lyase activity is drastically reduced. Its specific activity is 4-fold lower than that of the corresponding wild-type version, suggesting a strong impairment in its DNA repair capacity.

Discussion

The development of a mutator phenotype in a cell has been proposed to be an important factor in the initiation and/or the progression of the carcinogenic process. This hypothesis has been confirmed in the case of hereditary nonpolyposis colorectal cancer, where inactivation of mismatch repair genes plays a critical role in the development of tumors. The kidney has an unusually high rate of oxygen metabolism, and it has been shown that the high concentrations of urea frequently present in kidney cells can trigger an oxidative stress (22) and therefore increase the likelihood of DNA damage. The antimutator function of the Ogg1 protein, together with the localization of the gene to chromosome 3p25, renders OGG1 a good candidate as a cancer predisposition gene for kidney tumors. To extend our previous studies on OGG1 gene mutations in human tumors and cell lines and to investigate the role of this gene in tumorigenesis, we searched for the presence of alterations in OGG1 and for LOH in 3p25 in a series of 99 samples of RCC. The finding of LOH in 85% of the cases analyzed failed to detect any change in the nucleotide sequence of the coding regions. Moreover, no mutations were found in the donor or acceptor sequences of the corresponding intron.

The second class of alterations corresponds to single-base changes. Four such changes were detected in the tumors and were not found in the corresponding normal tissues, indicating that the mutations had risen somatically. The four mutations are missense mutations and affect codons 12, 46, 169, and 232. The amino acids changes generated are described in Table 3. Of those four cases, two show LOH (R36 and R48), one is noninformative (R37), and the remaining one (R16) is heterozygous in the tumor sample.

Table 2 Polymorphisms of the OGG1 gene found in kidney tumors

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Exon</th>
<th>Codon</th>
<th>cDNA alteration</th>
<th>Amino acid alteration</th>
<th>LOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>R29</td>
<td>2</td>
<td>85</td>
<td>G to T</td>
<td>Ala to Ser</td>
<td>Yes</td>
</tr>
<tr>
<td>R40</td>
<td>7</td>
<td>323</td>
<td>1277 G to A</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>R79</td>
<td>6</td>
<td>308</td>
<td>1231 G to A</td>
<td>Gly to Gln</td>
<td>Yes</td>
</tr>
<tr>
<td>R103</td>
<td>4</td>
<td>220</td>
<td>968 C to T</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>R73</td>
<td>7</td>
<td>326</td>
<td>1285 C to T</td>
<td>Ser to Cys</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* This polymorphism was found in 25% of the cases.

Table 3 Alterations in OGG1 from kidney tumors

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Exon</th>
<th>Codon</th>
<th>cDNA alteration</th>
<th>Amino acid alteration</th>
<th>LOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>R44a</td>
<td>3/4</td>
<td></td>
<td>+GGTGAGTA</td>
<td>Frame shift</td>
<td>Yes</td>
</tr>
<tr>
<td>R57a</td>
<td>5</td>
<td></td>
<td>Δ1056–1085</td>
<td>Δ 250–259</td>
<td>Yes</td>
</tr>
<tr>
<td>R69a</td>
<td>3/4</td>
<td></td>
<td>+GGTGAGTA</td>
<td>Frame shift</td>
<td>Yes</td>
</tr>
<tr>
<td>R71a</td>
<td>5</td>
<td>Δ exon 5</td>
<td>Δ 250–300</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>R94a</td>
<td>5</td>
<td>Δ exon 5</td>
<td>Δ 250–300</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>R106a</td>
<td>5</td>
<td>Δ exon 5</td>
<td>Δ 250–300</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>R16b</td>
<td>4</td>
<td>232</td>
<td>1002 T to C</td>
<td>Ser to Thr</td>
<td>No</td>
</tr>
<tr>
<td>R36b</td>
<td>1</td>
<td>12</td>
<td>343 G to A</td>
<td>Gly to Glu</td>
<td>Yes</td>
</tr>
<tr>
<td>R37b</td>
<td>1/2</td>
<td>46</td>
<td>445 G to A</td>
<td>Arg to Gln</td>
<td>NF</td>
</tr>
<tr>
<td>R48b</td>
<td>3</td>
<td>169</td>
<td>814 G to A</td>
<td>Arg to Gln</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* The alteration found is consistent with an amino acid change.

* Somatic mutations.

* NI, noninformative.

Table 3 Alterations in OGG1 from kidney tumors

Fig. 1. Repair activity of the mutant OGG1 proteins found in kidney tumors. Cleavage of an oligonucleotide harboring a unique 8-OxoG residue. Fourteen ng of each of the hOGG1 proteins were incubated with the 34-mer substrate (S) to yield a 16-mer product (P) of the combined glycosylase/AP lyase activity. Lane 1, no protein; Lane 2, G12E mutant; Lane 3, R46Q mutant; Lane 4, R169Q mutant; Lane 5, S232T mutant; Lane 6, wild type.
OGG1 in Human Kidney Tumors

confirms the results of previous studies (13) and could also be associated with the loss of the VHL TSG. Combining PCR-DGGE and direct DNA sequencing strategies, we found four missense somatic mutations in the coding sequences of OGG1 among 99 RCC tumors analyzed.

The substitution in codon 46 corresponds to an amino acid conserved in all of the eukaryotic Ogg1, from yeast to human. The amino acid change shows a marked effect by impairing the in vitro enzymatic activity of the mutant OGG1 protein when expressed in E. coli. For the tumor in which this mutation was detected, homozygosity prevented LOH analysis of the region harboring the OGG1 gene. On the DGGE analysis of the tumor cDNA, a wild-type band was detected, but it could be attributed to contamination with normal host cells, which presented only the wild-type form of OGG1. Interestingly, the same base substitution was reported in the small cell lung carcinoma cell line NCI-H526 (18), suggesting that such a mutation could be associated with the carcinogenic process. Recent elucidation of the crystal structure of hOGG1 shows that residue 46 is located in β-sheet B, not far from Gly-42, which makes direct contact with 8-OxoG (23).

Mutations in codons 12 and 232 affect nonconserved amino acids. Consistent with this is the lack of effect on the in vitro 8-OxoG DNA glycosylase activity of the mutant proteins. Residue 232 maps to the surface of the protein, whereas the position for residue 12 has not been mapped (23). However, this mutation potentially alters the proposed mitochondrial localization sequence. In that case, substitution at position 12 would affect the level of DNA repair activity in mitochondria. As for the amino acid at position 169, it is conserved in the mammalian OGG1 genes, but not in the yeast gene. The substitution of arginine for a glutamine at this position in case R48 does not affect the in vitro enzymatic activity but could interfere with the interaction between OGG1 and other proteins involved in the repair mechanism. Alternatively, the amino acid changes described could have consequences on the stability of the proteins in the cell. A more detailed biochemical characterization of these mutant forms is necessary to evaluate their potential effect on the DNA repair capacity of the cells harboring them.

In this study, several polymorphisms were detected in the OGG1 gene. The amino acid substitution at codon 326 was found at the same frequency reported previously for other types of cancers and in normal individuals. No specific bias was found in the loss of either allele in the RCC cases studied. Two rare polymorphisms leading to amino acid changes at positions 85 and 308 were also detected. These polymorphisms had previously been reported for lung and head and neck cancers, respectively (19, 21). In the in vitro assay, the proteins coded by these variants are functional 8-OxoG DNA glycosylases.

In the analysis of the OGG1 mRNA from the tumor samples, several deletion or insertion modifications were detected. Their location, together with the lack of DNA sequence changes in the OGG1 gene, indicates that they are the result of aberrant splicing of the primary transcript. Four of the six cases involved deletions starting at the 5′-end of exon 5. In all cases, the protein encoded by those messengers is likely to be inactive. Because several alternatively spliced forms of OGG1 have been reported in cell lines and normal tissues, it remains to be determined whether the alternative spliced forms described here are characteristic of the tumor tissue. Such a situation may imply a defect in the RNA processing machinery specific to the tumor cells.

The dissociation between the high frequency of LOH and the inactivation of the OGG1 gene suggests only a minor impact of alterations in the OGG1 gene on the genesis of renal tumors. Similar results were found for gastric, lung, and head and neck cancers (18, 19, 24, 25). However, several possibilities for its involvement in the carcinogenic process remain to be investigated. Because there is loss of one of the alleles in 85% of the RCC cases studied, a dosage effect on the 8-OxoG repair cannot be ruled out. This is underscored by recent studies showing that tumors having lost one OGG1 allele have twice as much 8-OxoG in their DNA (20). This could lead to a weak mutator phenotype. Alternatively, gene silencing could be totally or partially turning off the remaining OGG1 allele through methylation of the promoter CpG island (26). Finally, because of the finding that some of the mutations detected in the original DGGE screen could not be confirmed by a second RT-PCR, the possibility of ongoing mutations having an effect on the progression of the tumor should be considered.

In conclusion, our analysis of 99 cases of renal cancers has identified four somatic mutations in OGG1, along with several polymorphisms. It is important to note that similar studies for other types of cancer failed to identify any mutation in primary tumors. One of the mutations clearly impairs the enzymatic activity of the gene product, whereas the other mutations could have more subtle effects on the DNA repair mechanism, possibly leading to different levels of mutator phenotypes that could contribute to tumorigenesis.

Acknowledgments

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