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Mutation of DNA polymerase β in esophageal carcinoma of different regions

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Abstract

AIM: To observe the variation of DNA polymerase β (polβ) in esophageal carcinoma.

METHODS: Thirty specimens containing adjacent normal epithelial tissues were collected from patients in Linzhou region (a high risk area for esophageal squamous carcinoma) and 25 specimens were from a non-high risk area. Total RNA was extracted from the samples and reverse transcription polymerase chain reaction (RT-PCR) was performed. PCR products were cloned and sequenced to investigate the polβ gene with DNASIS and OMIGA. Statistical significance was evaluated using the χ^2 test.

RESULTS: High-incidence area group: polβ gene variation was detected in 13 of 30 esophageal carcinoma tissue specimens, and only one variation was found in 30 corresponding adjacent normal tissue specimens. Non high-incidence area group: polβ gene variation was detected in 5 of 25 esophageal carcinoma tissue specimens, and no variation was found in 25 corresponding adjacent normal tissue specimens. The incidence of polβ gene variation observed in the high-incidence area group was significantly higher than in the non-high incidence area group. Two mutation hot spots (454-466 and 648-670 nt) and a 58 bp deletion (177-234 nt) were found.

CONCLUSION: Variations of polβ perform different functions between the high-incidence areas and the other areas, and may play a more important role in the high-incidence areas.

Key words: DNA polymerase β; Esophageal carcinoma; Gene mutation

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INTRODUCTION

Esophageal carcinoma occurs frequently in China, especially in the mountainous Taihang area. Epidemiology and laboratory studies suggest that the carcinogenesis and progression of esophageal carcinoma are probably associated with some gene mutations[1,2]. Some researches indicate that the ability of polβ to repair DNA damage reduces in peripheral blood of esophageal carcinoma patients and that obvious chromosome changes occur in tumor cells[3-5]. Therefore, there must be DNA damage repair in the development of esophageal carcinoma. However, variations of DNA replication and repair enzymes in esophageal carcinoma, especially the mutation of polβ is rare. Thus, we made a preliminary analysis on the mutation of polβ in esophageal carcinoma.

MATERIALS AND METHODS

Specimens

High-incidence area group: Specimens of 30 esophageal squamous carcinomas (serial numbers H1-H30) and matched adjacent normal tissues were obtained from patients in Linzhou region of northern China, a well-recognized high-risk area for esophageal carcinoma.

Non-high incidence area group: Specimens of 25 esophageal squamous carcinomas (serial numbers N1-N25) and corresponding adjacent normal tissues were obtained from patients who underwent surgery at Cancer Hospital of Henan Province and the First Affiliated Hospital of Zhengzhou University.

All patients were histopathologically diagnosed to be infiltrative squamous carcinoma cases. The tissues were frozen in liquid nitrogen immediately after surgery.

RT-PCR

A pair of primers for PCR was designed to amplify the total polβ gene according to the sequence of M13140 in GenBank. Primer P1 (sense): 5' ATGAGCAAACG GAG-GGCGCCG 3'; Primer P2 (antisense): 5' TCATTCGCT-CCGGTCCTTGG 3'. The primer was synthesized by Shanghai Sangon Co., Ltd.

Total RNA was extracted with the QIAGEN RNA extraction kit. Five microliters of total RNA was transcribed into cDNA using 0.2 μmol/L primer P2 , 0.2 μmol/L dNTP,

RNasin 40 U, 1 ×buffer (Promega), and 2 U AMV in a final volume of 30 μL. In PCR assay, the PCR reaction mixture consisted of 1 ×PCR buffer (PE), 200 μmol/L dNTP, 20 pmoL of each primer, 2 U of Golden Taq DNA polymerase (PE). The mixture was pre-incubated for 5 min at 94 ℃, followed by amplification at 94 ℃ for 50 s, 56 ℃ for 50 s, and at 72 ℃ for 60 s, for 30 cycles. A final extension was performed at 72 ℃ for 7 min.

DNA cloning and sequencing

The PCR products from all specimens were excised from 0.8% agarose gels, and the desired fragments were purified using a DNA gel extraction kit (Promega). The purified fragments were cloned into a pGEM-T plasmid vector, and then transformed into *E. coli* JM109 competent cells. Plasmid DNA was extracted from the positive clones and sequenced using a PE 377 sequencer. The sequences were analyzed by DNASIS and OMEGA.

Statistical analysis

Statistical significance was evaluated using the χ^2 test. $P<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 11.0.

RESULTS

PT-PCR analysis of whole polβ gene

In the high-incidence group, PCR products were obviously smaller than 1 008 bp in six carcinoma specimens. The correct length of polβ gene was obtained by amplifying the other specimens (Figure 1).

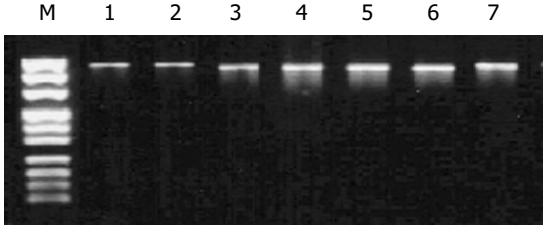

Figure 1 RT-PCR amplification of polβ gene. Lanes 1, 2 and 7: Normal size of PCR products of H1, H2 and H3; lanes 3-6: shorter size of PCR product of H5, H8, H10, and H16; M: DNA marker (from top to bottom: 1 000, 900, 800, 700, 600, 500, 400, 300, 200, 100 bp).

Result of sequencing

Point mutations and deletion of polβ gene were detected in the high-incidence area group (Table 1 and Figure 2). Overall, polβ gene variations were found in 13 of 30 esophageal carcinoma tissue specimens. A 58 bp(177-234 nt) deletion was detected in six tumor tissue specimens (Figure 3). Only one variation was found in the corresponding adjacent normal tissue (Table 1).

Polβ gene point mutations were detected in 5 of 25 esophageal carcinoma tissue specimens, and no variation was found in corresponding adjacent normal tissues in the non-high incidence area group (Table 2).

The incidence of polβ gene variation observed in the high-incidence area group was significantly higher than that in the non-high incidence area group ($P = 0.007$, χ^2 test).

Table 1 Mutation analysis of polβ in high-incidence areas

Specimen	Gene mutation	
	Carcinoma	Corresponding adjacent normal tissue
H1	–	–
H2	–	–
H3	–	–
H4	660 nt A→G	–
H5	462 nt G→T, 177–234 nt deletion	–
H6	–	–
H7	64 nt G→C, 665 nt T→C	–
H8	462 nt G→T, 660 nt A→G, 177–234 nt deletion	660 nt A→G
H9	–	–
H10	177–234 nt deletion, 454 nt T→C 466 nt G→A	–
H11	–	–
H12	375 nt A→G 177–234 nt deletion	–
H13	–	–
H14	–	
H15	454 nt T→C, 466 nt G→A	–
H16	177–234 nt deletion	–
H17	737 nt A→T, 740 nt A→G	–
H18	–	–
H19	–	–
H20	–	–
H21	462 nt G→T	–
H22	–	–
H23	–	–
H24	–	–
H25	177–234 nt deletion, 660 nt A→G	–
H26	177–234 nt deletion	–
H27	–	–
H28	613 nt A→T	–
H29	–	–
H30	–	–

Table 2 Mutation analysis of polβ in low-incidence areas

Specimen	Gene mutation	
	Carcinoma	Corresponding adjacent normal tissue
N1	670 nt A→G	–
N2	660 nt A→G	–
N8	660 nt A→G	–
N16	613 nt A→T	–
N22	670 nt A→G	–

Variation of amino acid caused by gene mutations

Twelve kinds of variation in the polβ gene were found in the present study, including 11 point mutations and a 58 bp deletion (Table 3). The translation of polβ was interrupted due to the emergence of a termination codon at 117 nt caused by 462 nt G→T mutation. Mutations at 665, 737, and 740 nt were synonymous mutations, which would not change the amino acids. The other seven point mutations caused replacement of amino acids.

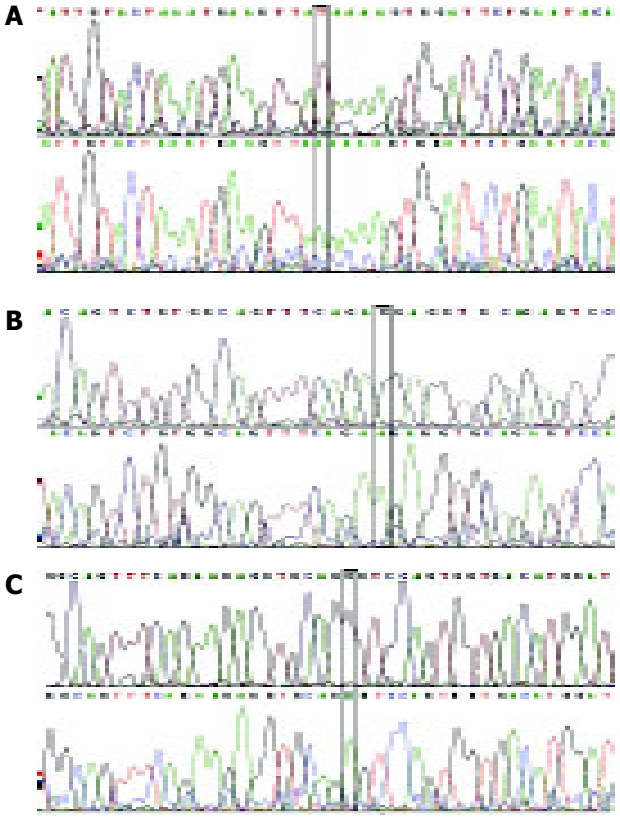

Figure 2 Mutations in the polβ gene. **A**: 660 nt A→G mutation in H4 carcinoma; **B**: 670 nt A→G mutation in N1 carcinoma; **C**: 613 nt A→T mutation in H28 carcinoma.

Table 3 Gene and amino acid variations in polβ

Mutation code	Gene variation	Amino acid variation	Mutation
1	375 nt A→G	88 nt Ile→Val	
2	454 nt T→C	114 nt Phe→Ser	
3	462 nt G→T	117 nt Glu→termination codon	Termination mutation
4	466 nt G→A	118 nt Gly→Glu	
5	613 nt A→T	167 nt Lys→Ile	
6	648 nt G→C	179 nt Gly→Arg	
7	660 nt A→G	183 nt Arg→Gly	
8	665 nt T→C	184 nt Gly→Gly	Synonymous mutation
9	670 nt A→G	186 nt Glu→Gly	
10	737 nt A→T	208 nt Pro→Pro	Synonymous mutation
11	740 nt A→G	209 nt Lys→Lys	Synonymous mutation
12	177–234 nt deletion		Frameshift mutation Termination mutation

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                          110        120        130        140        150
BATE. SEQ  101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H10. SEQ   101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H16. SEQ   101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H25. SEQ   101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H26. SEQ   101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H5. SEQ    101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150
H8. SEQ    101 GGTGCAGGCC GCCATGAGCA AACGGAAGGC GCCGCAGGAG ACTCTCAACG 150

                               160        170        180        190        200
BATE. SEQ  151 GGGGAATCAC CGACATGCTC ACAGAACTCG CAAACTTTGA GAAGAACGTG 200
H10. SEQ   151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200
H16. SEQ   151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200
H25. SEQ   151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200
H26. SEQ   151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200
H5. SEQ    151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200
H8. SEQ    151 GGGGAATCAC CGACATGCTC ACAGAA------ ---------- ---------- 200

                          210        220        230        240        250
BATE. SEQ  201 AGCCAAGCTA TCCACAAGTA CAATGCTTAC AGAAAAGCAG CATCTGTTAT 250
H10. SEQ   201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250
H16. SEQ   201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250
H25. SEQ   201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250
H26. SEQ   201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250
H5. SEQ    201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250
H8. SEQ    201 ---------- ---------- ---------- ------AGCAG CATCTGTTAT 250

                          260        270        280        290        300
BATE. SEQ  251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H10. SEQ   251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H16. SEQ   251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H25. SEQ   251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H26. SEQ   251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H5. SEQ    251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
H8. SEQ    251 AGCAAAATAC CCACACAAAA TAAAGAGTGG AGCTGAAGCT AAGAAATTGC 300
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Figure 3 Comparison between wild type polβ gene fragment and six gene fragments with deletion (177→234 nt).

DISCUSSION

DNA polβ is one of the four recognized, vertebrate, cellular, DNA polymerizing enzymes. Two features of polβ from various species may play a key role. First, the structure of polβ is highly conserved from the standpoint of both polypeptide size and amino acid sequence. Second, in cultured mammalian cells, the level of polβ enzymatic activity is low and independent of cell-cycle stage[6,7]. Hence, polβ is considered as a constitutively expressed "housekeeping" enzyme required for DNA metabolic events other than replicative synthesis of genomic DNA. DNA synthesis during DNA repair and recombination are examples of such events, and the idea that polβ is involved in some types of DNA repair is supported by various studies with DNA polymerase inhibitors[8-11]. Recent observations have shown that the variation of polβ occurs in some tumors such as colorectal carcinoma, bladder carcinoma, breast carcinoma, prostate carcinoma and non-small cell lung cancer. The variation rate is particularly high in colon carcinoma, being more than 80% (5/6)[12-17,20]. Some studies indicate that the accumulation of proto-oncogene and tumor suppressor gene variations perhaps leads to tumor. However, the initial molecular defects causing accumulated mutations and inducing cancer are not well understood. Interestingly, there is a higher mutation rate of polβ, p53 and ras in colorectal carcinoma. A genetic disease, xeroderma pigmentosum, is associated with ERCC, a kind of DNA repair gene[18-21], and these patients are more susceptible to skin carcinoma[22,23]. The above findings suggest that there is a correlation between human tumors and the damage, maladjustment and defects in the DNA repair system.

The present results showed that some mutations, such as 462 nt G→T and deleting 177-234 nt, could lead to the abnormal amino acid of polβ followed by abnormal protein structure and lack of DNA repair activity. From the histopathological diagnosis, we found that cancer cells involving the two mutations were more malignant. In addition, there were three synonymous mutations at 665 nt (T→G), 737 nt (A→T) and 740 nt (A→G), which may be the single nucleotide polymorphism (SNP)[24-29].

Polβ gene variation in the high-incidence area group was detected in 13 of 30 esophageal carcinoma tissue specimens. The mutation rate of this group was 43.3%. Polβ gene variation in the non-high incidence area group was found in 5 of 25 esophageal carcinoma tissue specimens, and the mutation rate was 20%. Thus, there was a significant difference in mutation rates between these two groups ($P<0.05$). Twelve types of polβ gene variation were found in high-incidence area, but only three types were found in the non-high incidence area, suggesting that damage of the DNA repair system via alteration of this gene may contribute to the development of esophageal carcinoma, and that polβ may play a more important role in the high-incidence area.

By analyzing the variation site of polβ, we found that three point mutations were located in one region (454-466 nt), and four point mutations were located in another region (648-670 nt). The two regions are probably the mutation hot spots of the polβ gene of esophageal carcinoma. Moreover, the deletion of 58 bp was found in 6 of 20 specimens from the high-incidence area (31.6% frequency), but was not found in the non-high incidence area. Hence, this deletion may be one of the main variations of polβ gene in esophageal carcinoma. Our results prove that polβ mutations do exist in esophageal carcinoma, and are probably correlated to the development of esophageal carcinoma.

It is suggested that during such genetic evolution, the DNA repair system plays an important role in cancer development[30-32]. Although the relationship between mutations of polβ and alterations in proto-oncogenes or tumor suppressor genes is currently not clear, polβ gene mutation is involved in a subset of human esophageal carcinoma, especially in the high-incidence area.

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