Somatic mutations leading to incomplete extinction of HLA class I were associated with replication error phenotype-positive colorectal carcinoma

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Abstract: Hereditary non-polyposis colorectal carcinoma (HNPCC) is one of the prevalent inherited cancers in the general population. Underlying biological process impaired in HNPCC is DNA mismatch repair, which results in microsatellite instability and accumulation of frameshift mutations within the tumor cells. Protein products of the mutant alleles are expected to be altered by the host immune system and become targets for the tumor-specific cytotoxicity. To explore the mechanism for HNPCC tumor cells to escape from the immune surveillance, we investigated the mutations in the beta 2 microglobulin (B2M) and HLA class I genes as well as the microsatellite instabilities in the colorectal cancers. It was found that either a frame-shift mutation of B2M gene or allele loss of HLA class I genes, which would lead to the extinction of HLA class I expression, were more prevalent in the HNPCC tumors than in the non-HNPCC tumors. Interestingly, none of the tumors exhibited complete loss of B2M or HLA class I genes. These observations strongly suggested that the extinction of HLA class I should be kept incomplete, because the complete loss might activate natural killer cells.

Key words: HLA class I, beta 2 microglobulin, colorectal cancer, HNPCC, immune surveillance
INTRODUCTION

Hereditary non-polyposis colorectal carcinoma (HNPCC) is one of inherited cancers in which a profound predisposition to carcinogenesis is transmitted as an autosomal dominant trait (1). HNPCC is clinically defined as a form of colorectal cancer with familial aggregation of at least three cases belonging to two or more successive generations, and about 5% of colorectal cancer are HNPCC (2). Cancer cells in patients with HNPCC usually exhibit a phenotype called as replication error (RER) that lead to the accumulation of multiple mutations in the tumor tissue (3, 4). It has been known that one of six human homologous loci for either *Escherichia coli* (mutHLS pathway) or *Saccharomyces cerevisiae* DNA excision repair genes is semi-inactivated in all body cells by a heterozygous germ-line mutation (5); mutations of any one of *MSH2* (*HNPCC1*, OMIM# 120453), *MLH1* (*HNPCC2*, OMIM# 609310), *PMS1* (*HNPCC3*, OMIM# 600258), *PMS2* (*HNPCC4*, OMIM# 600259), *MSH6* (*HNPCC5*, OMIM# 600678) and *MLH3* (*HNPCC7*, OMIM# 604395) can cause HNPCC, although the majority of HNPCC cases carried mutations in the former two loci (6).

Presence of more than one tumor foci is another characteristic of HNPCC, otherwise very rare in colorectal cancer except for the cases with familial adenomatous polyposis coli that is another inheritable susceptibility to the colorectal cancer. A gene for type II receptor of TGF beta, *TGFBR2*, is one of the most common targets for somatic mutations occurred during the tumorigenesis in the patients with RER-positive phenotype (7). It also is known that a germ line mutation in *TGFBR2* is a cause of non-typical RER-negative HNPCC (*HNPCC6*, OMIM# 190182). Hot spots of somatic mutation found in the RER-positive HNPCC tumors are mono-, di- and tri-nucleotide short tandem repeats (STRs). The RER phenotype has been evaluated with the observation of instability of STRs, also known as microsatellite instability (MSI), in humans as well as in yeasts (3).

There are several protocols for molecular diagnosis for the RER-positive HNPCC, in which a set of microsatellite loci are investigated to detect the MSI, and RER-positive phenotype is usually defined as that MSI was detected in more than one fourth (25%) of tested STR loci (8, 9).

As a result of mutation in the repetitive sequences, neoplastic cells are expected to possess frame-shift mutations in a number of loci, which, in turn, may cause inactivation of gene function and emerge non-natural polypeptides encoded by the out-of-frame nucleotide sequences. These non-natural polypeptides can be tumor antigens against which the host immune-surveillance system recognizes as the altered-self. Classical HLA class I molecules, HLA-A, B and C, which form heterodimers with beta 2 microglobulin (B2M), serve as presenting molecules of the altered-self peptides to CD8+ cytotoxic T lymphocytes (CTL) as an potent effecter of the tumor immunity. Extinction of the classical HLA class I molecule from the cell surface, then, may be advantageous for tumor cells to escape from the surveillance of CTL. It also is well established that another host defense mechanism, natural killer (NK) cell system, can cope with missing-self neoplasm, for which HLA class I molecules may serve as makers of immunological self. Therefore, we hypothesized that the RER-positive tumor cells should manage balancing of these two host defense systems. In the present study, we examined colorectal cancer specimens for the somatic alterations in genes for HLA class I molecules and found that there was a striking difference in the manner of inactivation of these genes depending on the RER-positive or -negative phenotypes.

MATERIALS AND METHODS

Subjects

Seventy-six unrelated Japanese patients with non-polyposis colorectal cancer were enrolled in the present study. All the patients were received surgical resection at Kyushu University Hospital and the di-
agnosis of each tumor was confirmed by histopathology. Thirty-four of them (through H-01 to H-34; 45%) were either with positive family history in the first- or second-degree relatives and/or having multiple colorectal cancers (one patient carried triple tumors and three patients had double tumors), suggesting the presence of profound genetic predisposition to colorectal cancer including HNPCC. The other forty-two (S-01 to S-42; 55%) were sporadic cases with the solitary tumor. After acquiring written informed consent, tumor tissues were surgically obtained. The neoplastic tissue and adjacent normal mucosa were separated, frozen in liquid nitrogen, and stored at -20°C until preparation of genomic DNA. Experimental protocols were approved by Ethics Reviewing Committee of Medical Research Institute, Tokyo Medical and Dental University and Institutional Review Board of Kyushu University Hospital.

DNA preparation and analysis

Frozen tissue samples were minced by Polytron homogenizer in tissue lysis buffer (50 mM Tris-HCl pH 8.0, 75 mM NaCl, 20 mM EDTA • Na2). Immediately after homogenization, proteinase K (Merck) and SDS were added at 100 µg/ml and 1%, respectively, and incubated at 55°C for 4 hours. After at least three times of extraction with neutralized phenol and chloroform, DNA was salted-out by adding 0.6 volume of isopropanol. Cotton wool-like DNA precipitate was washed twice in 70% ethanol and re-dissolved in 10 mM Tris-HCl pH 8.0, 0.1 mM EDTA • Na2 at 50-200 µg/ml. DNA regions of interest were amplified by polymerase chain reaction (PCR) in a 30 µl reaction with appropriate primer pairs. Nucleotide sequences of the primers are available upon request. For the detection of mutation, single-strand conformation polymorphism (SSCP) analysis was employed. In brief, 3 µl of PCR product was denatured in 50% formamide at 95°C for 5 minutes prior to 8% polyacrylamide-0.8 × TBE (1 × TBE: 44.5 mM Tris-borate, 1 mM EDTA • Na2, pH 8.8) either with or without 10% glycerol. DNA fragments in the gel were visualized by using silver staining kit (Daiichi Chemical). The samples demonstrating aberrant mobility were subjected to direct sequencing using PCR product as a template. Sequencing was performed on both strands using the Big Dye Terminator Cycle sequencing kit and the ABIPRISM 310 capillary sequencer.

Determination of RER phenotype

Polymorphic microsatellite loci were used to study the RER phenotype. Paired tumor and normal DNA samples were genotyped by PCR at 32 microsatellite loci as described previously (10). MSI was detected in tumor DNA where repair error had taken place, and when MSI was found at more than 25% of examined loci, the sample was considered to be RER-positive.

HLA DNA typing

Genotyping of HLA-A and -B loci was performed to investigate the allele loss in tumor as compared with corresponding normal tissue. Reference strand-mediated conformation analysis (RSCA) was the method of choice (11). Paired samples were analyzed in parallel with HLA-A or HLA-B RSCA kit (Pel-Freeze Clinical Systems) optimized for ALFexpress system (Amersham Pharmacia Biotech). Allele assignments were made by ALFwin Software (Amersham Pharmacia Biotech) determining migration values of heteroduplexes formed using the kit reagents and amplified sample DNA.

Statistical analysis

Statistical analysis was performed by Fisher’s exact test. When p value was less than 0.05, the association was considered statistically significant. The strength of association was evaluated by odds ratio (OR) calculated with Woolf’s formula and Haldane’s modification when suitable (12).
RESULTS
RER phenotyping of colorectal cancer

We examined 81 tumor samples from 76 cases, including three double and one triple cancer cases, of colorectal cancer patients for RER phenotype by detecting MSI at 32 polymorphic STR loci. A part of these patients were enrolled in our previous study concerning to mutations in E2F4 target in the RER-positive tumors (10). Nine tumors from eight patients (H-01, H-04, H-05, H-17, H-21, H-26, H-34, and S-11) were positive for RER phenotype, if the RER phenotype was defined as the cases with MSI detected at more than 25% of the examined STR loci (Table 1). Seven out of the eight patients were either with apparent family history of colorectal cancer or carrying multiple colorectal cancers, suggesting the presence of genetic predisposing factor. The frequency of RER phenotype was more prevalent in the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor-ID</th>
<th>%MSI</th>
<th>RER#1</th>
<th>FH#2</th>
<th>MC#3</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-04</td>
<td>G022T</td>
<td>81</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>93ins1</td>
</tr>
<tr>
<td>H-34</td>
<td>K23C</td>
<td>76</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>68del1</td>
</tr>
<tr>
<td>H-26</td>
<td>G106T</td>
<td>74</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>13del2</td>
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<tr>
<td>H-01</td>
<td>G001T</td>
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<td>yes</td>
<td>yes</td>
<td>no</td>
<td>13del2 and Met1Val#4</td>
</tr>
<tr>
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<td>G092T</td>
<td>57</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>13del2</td>
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</tbody>
</table>

(HLA class I LOH mutants)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor-ID</th>
<th>%MSI</th>
<th>RER#1</th>
<th>FH#2</th>
<th>MC#3</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-05</td>
<td>G025T1</td>
<td>62</td>
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<td>yes</td>
<td>yes</td>
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</tr>
<tr>
<td>H-05</td>
<td>G025T2</td>
<td>62</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>HLA-B LOH</td>
</tr>
<tr>
<td>H-17</td>
<td>G070T</td>
<td>56</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>HLA-B LOH</td>
</tr>
<tr>
<td>S-11</td>
<td>G085T</td>
<td>52</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -B, -C LOH</td>
</tr>
<tr>
<td>S-09</td>
<td>G066T</td>
<td>13</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -C LOH</td>
</tr>
<tr>
<td>H-09</td>
<td>G032T</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>HLA-B, -C LOH</td>
</tr>
<tr>
<td>H-24</td>
<td>G101T</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>HLA-B LOH</td>
</tr>
<tr>
<td>S-10</td>
<td>G068T</td>
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<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-B LOH</td>
</tr>
<tr>
<td>S-15</td>
<td>G090T</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -B, -C LOH</td>
</tr>
<tr>
<td>S-16</td>
<td>G093T</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-B, -C LOH</td>
</tr>
<tr>
<td>S-30</td>
<td>K01C</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -C LOH</td>
</tr>
<tr>
<td>S-37</td>
<td>K14C</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -B, -C LOH</td>
</tr>
<tr>
<td>S-38</td>
<td>K15C</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>HLA-A, -B, -C LOH</td>
</tr>
</tbody>
</table>

#1; replication-error phenotype, #2; family history of colon cancer, #3; multiple cancers, #4; Met (ATG) to Val (GTG) mutation
with the genetic predisposition (7 out of 34 cases; 20.6%) than in patients with non-familial solitary tumor (1 out of 42; 2.4%).

**Diagnosis of hereditary non-polyposis colorectal cancer (HNPCC) by mutation analysis**

All 81 tumor DNA and 76 normal tissue DNA samples were subjected to a search for both somatic and germ line mutations in two of the replication error repair genes, *MSH2* and *MLH1*, in order to establish the diagnosis of HNPCC. Three patients (H-04, H-05 and H-17) carried mutations in *MSH2* and other three (H-01, H-26 and S-11) had heterozygous mutations in *MLH1*. Tumors from these 6 patients (9 specimens) consistently exhibited the RER phenotype.

**Mutation patterns of oncogenes in RER-positive and -negative tumors**

It is well-established that the cancerous tissues accumulate somatic mutations in oncogenes and tumor-preventing genes, which both regulate intracellular signaling to promote cell growth, cell-cycle progression, inhibition of apoptotic response in over-stimulated cells or other mechanisms. Both gain-of-function and loss-of-function may take place depending on the function of the genes during the tumor progression. Loss-of-function mutation can in part be detected as a loss of heterozygosity (LOH), which is one of the common mechanisms to get the loss of normal gene function for preventing tumorigenesis. Therefore we sought the mutations in the oncogenes as well as the LOH type mutations in both RER-positive and -negative tumors. The frequencies of *Ki-ras* mutations between the RER-positive and -negative tumors were not significantly different (36.4% vs. 35.2%), suggesting that the gain-of-function type *Ki-ras* mutation was essentially indifferent of the RER phenotype. However, frame-shift mutation due to the insertion or deletion of a single nucleotide or more, another type of gene-inactivation mutation, was almost exclusively found in the RER-positive tumors.

For example, mutations in the type II TGF beta receptor gene (*TGFRB2*) at a hotspot of (A)$_{10}$ corresponding to codons 125–128 (7) were found in 10 of 11 RER-positive tumors (90.9%), while only 2 of 71 RER-negative tumors (2.8%) carried the *TGFRB2* mutations. This observation was in good accordance with the result of the previous study (7).

**Inactivation of beta 2 microglobulin (B2M) gene**

Next we searched for somatic gene alterations which would result in the attenuation of antigen presentation to CTL. As showed in Figure 1, PCR-SSCP analysis demonstrated abnormal band patterns in the single-stranded DNA or double-stranded DNA. Since most of the abnormal band patterns were found in the double-stranded DNA, it was suggested that most of the B2M mutations were insertion or deletion mutations forming heteroduplex which can be easily detected in the analysis. Subsequent sequencing analysis revealed that five tumors indeed carried heterozygous frame-shift mutations due to either insertion or deletion of nucleotide(s) at the repetitive sequences in the protein coding region. Three carried 13del2 (the deletion of one unit of dinucleotide repeat (CT)$_n$, one had 68del1 (one nucleotide deletion at homopolymeric sequence of (A)$_n$, and one showed 93ins1 (one nucleotide insertion at homopolymeric sequence of (A)$_n$) (Table 1). Interestingly, the frame-shift mutations in B2M gene were found exclusively in the RER-positive tumors; 5 of 11 RER-positive tumors (45.5%) carried the B2M mutations, while no mutation was observed in 70 RER-negative tumors (OR = 121.0, P = 1.8 × 10$^{-5}$; Table 2). Another interesting finding was that there was no case which carried B2M frame-shift mutations on both chromosomes, although one tumor (GO01T) had another mutation (Met1Val, missense mutation) on the same chromosome (Table 1).

**LOH of HLA class I heavy chain loci**

We next examined HLA-A, -B and -C loci for LOH in the tumor samples by using SSCP analysis (Figure
Figure 1. SSCP analysis of B2M gene.

Pairs of DNA samples derived from tumor (T) and corresponding normal mucosa (N) were analyzed for polymorphisms in exons side by side. Upper and lower panels showed representative results for the analysis of exon 1 and exon 2, respectively. Both single-stranded DNA (ssDNA) and double-strand DNA (dsDNA) bands were visualized by silver staining. Bands of aberrant mobility due to either SSCP or heteroduplex between mismatched pairing were indicated by arrowheads. Mutations were found in exon 1 in tumor from H-01 and in exon 2 of tumors from H-04 and H-34, and these were confirmed by nucleotide sequencing as noted below the figures.

**Table 2.** Beta2 microglobulin mutants were found in RER-POSITIVE tumors (N = 81)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>heterozygous B2M mutants</th>
<th>wild type</th>
<th>OR*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RER-positive</td>
<td>5</td>
<td>6</td>
<td>121.0</td>
<td>1.8x10^-5</td>
</tr>
<tr>
<td>RER-positive</td>
<td>0</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR: odds ratio, calculated with Haldane’s modification of Woolf’s formula

**Table 3.** Mutations which result in HLA class I extinction in RER-POSITIVE tumors (N = 9)

<table>
<thead>
<tr>
<th>HLA LOH</th>
<th>heterozygous B2M mutants</th>
<th>wild type</th>
<th>OR*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent (wild type)</td>
<td>5</td>
<td>0</td>
<td>3.87</td>
<td>0.0079</td>
</tr>
<tr>
<td>Present</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See footnote of Table 2
Figure 2. SSCP analysis of HLA class I genes
Paired samples (T: tumor and N: normal mucosa) were analyzed for polymorphism in exons of HLA class I genes. Representative results are shown for exon 2 of HLA-B (left panels) and exon 2 of HLA-A (right panels) in polyacrylamide gels without (upper panels) and with (lower panels) 10% glycerol. LOH of HLA-B was found in the tumor from H-24 and LOH of HLA-A was observed in the tumor from S-09 as indicated by dots.

Figure 3. Allele loss detected by RSCA of HLA class I loci.
Paired samples were analyzed by using RSCA typing method according to the kit procedures. A part of heteroduplex mobility data used for typing was shown. Allele loss was detected by diminished intensity of signal indicated by arrows. B*4001 was the allele lost in the tumor from H-24, while A*0207 was lost in the tumor from S-09.

2). LOH in at least one of three MHC class I loci was found in 4 out of 11 (36.4%) RER-positive tumors and in 9 out of 70 (12.9%) RER-negative tumors (Table 1). Though the frequency of LOH in MHC loci was increased in the RER-positives, it was not statistically significant (OR = 3.87, P = 0.070). In addition, we determined the type of HLA class I allele that was lost during the tumor progression by using RSCA method as shown in Figure 3, but we found no preference of HLA allele to be lost or retained in the colorectal cancers. The most striking finding was that LOH of HLA class I loci was never coincident with the B2M mutations in the RER-positive tumors (Table 3). A statistical test rejected a null hypothesis that the LOH mutation in the HLA loci and the frame-shift mutations in the B2M gene took place independently.
(P = 0.0079). Consequently, the alternative hypothesis that the occurrence of HLA class I gene mutations and B2M gene mutations was correlated to each other was accepted (OR = 3.87). Finally, either of these mutations account for the majority of RER-positive tumors (9/11 = 81.8%), suggesting the presence of negative selection for the RER-positive tumors against intact HLA class I expression.

DISCUSSION

HNPCC is one of the most prevalent forms of hereditary cancer syndrome, occupying about 5% of primary colorectal cancer (13, 14). Underlying impaired biological process in the patients with HNPCC is in the DNA repair system, known as mismatch repair of replication errors (5, 6). It remains unknown why colon epithelium and endometrium, which is another tissue with prevalent cancers found in the HNPCC pedigrees, are vulnerable to the genetic lesion involving this fundamental cellular activity (15). However, genomic instability at STR is a common phenomenon found in the tumors occurred in HNPCC (6), and the insufficiency of TGFBR2, a putative determinant of malignant transformation (7), is a target of RER in HNPCC, i.e., consecutive (A)$^{10}$ within the protein coding sequence.

Similarly to TGFBR2, tumors in HNPCC are expected to possess a number of mutations in STR sequences all along the genome, which can be accumulated during tumor cell growth due to the defect in mismatch repair. Mutations at STR sequences within the protein coding sequences can result in the impairment of normal gene function and the out-of-frame mutations lead to production of non-natural (altered-self) polypeptides in the cancer cells. Therefore, the tumor cells in HNPCC should be more prone to be recognized as the altered-self by the host surveillance system. Indeed, the correlation between MSI and extent of immune cell infiltration in tumor tissues was reported (16).

HLA-A, -B and -C loci encode for classical human major histocompatibility complex (MHC) class I heavy chains that non-covalently form heterodimers with B2M. Since MHC class I serve as an antigen presenting molecule to antigen-specific CTL, extinction of MHC class I may be a strategy of tumors to escape from antigen-specific CTL (17). In order to down-regulate MHC class I expression, tumors may prone LOH of MHC genes and mutations in B2M gene, as demonstrated in the present study. These events should be rare even in the unstable genomic integrity within the neoplastic cells, because we have never observed any coincidence of LOH mutations in HLA and RER-related B2M mutations. We have not investigated the expression of HLA molecules at the mRNA or protein levels. However, previous reports demonstrated that heterozygous frame-shift mutations of the B2M gene caused lower expression of HLA molecules in colon cancer cell lines as well as in primary colon cancers (18, 19), suggesting that B2M mutations found in this study also lead to decreased HLA expression. Contribution of the possible attenuation in tumor-specific antigen presentation during tumor progression might be underestimated in the present study, because it was reported that several other components involved in antigen presentation such as TAP genes were also impaired during the cancer development (20, 21).

NK cell is another subset of lymphoid cells, which exhibit cytotoxicity against the neoplastic cells. In addition, NK cells possess immune regulatory activities such as gamma-interferon production. So the infiltration of NK cells in the tumor may be a sign of good prognosis (22). MHC class I molecules also serve as ligands for NK cell receptors. Presence of the MHC class I molecules on the target cells suppresses the killing activity of NK cell via killer immunoglobulin receptors, and NK cells are activated upon the loss of MHC class I from the cell surface. Therefore, loss of MHC class I expression which provides tumor cells with a benefit to escape from tumor-specific CTL may be harmful for them to be-
come a target for another host surveillance system enrolling NK cells (23, 24). The incomplete extinction of HLA class I expression found in the present study may be preferable for tumor cells to survive against immune surveillance system in vivo.

In conclusion, neoplastic cells in the colorectal cancer with RER-positive phenotype were shown to possess different subset of gene mutations from those with RER-negative phenotype. The RER-positive tumors were more prone to be recognized as altered-self than the RER-negative tumors, therefore, gained genetic alteration(s) leading to incomplete inactivation of HLA class I expression.

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DNA 複製エラーを呈する大腸がんには HLA クラスⅠ分子の発現異常をもたらす体細胞変異が集積する

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5) 大分医科大学・第一内科

要約: 遺伝性非ポリポーシス大腸がん (HNPCC) は頻度の高い遺伝性高発がん疾患である。HNPCC の原因は DNA ミスマッチ修復酵素の欠損であり、がん細胞においてはマイクロサテライト不安定性とフレームシフト変異が集積することが知られている。このような体細胞変異はがん特異的細胞障害 T 細胞によって非自己として認識されるタンパク産物を生じると考えられる。そこで本研究では、そのような体細胞変異を集積した非自己であるがん細胞が免疫監視機構から逸脱する分子機構を解明するために、大腸がんを対象としてマイクロサテライト不安定性ならびに HLA クラスⅠ遺伝子と β2 ミクログロブリン遺伝子 (B2M) 変異の有無を検討した。その結果、マイクロサテライト不安定性を示す HNPCC 大腸がんにおいては、HLA クラスⅠ分子の発現低下をもたらすと考えられる B2M のフレームシフト変異または
HLAクラスI遺伝子のLOH型変異が非HNPCC大腸がんと比較して有意に多いことが判明した。興味深いことに、B2M変異とHLAクラスI遺伝子変異の両者を同時に有する大腸がんは認められなかった。これらのことから、DNA複製エラーを伴う大腸がんは、HLAクラスI分子の発現欠損を不完全とすることで細胞障害性T細胞とNK細胞のいずれによる認識からも逸脱することが示唆された。
キーワード：HLAクラスI、β2ミクログロブリン、大腸がん、HNPCC、免疫監視機構